ISPE®

Baseline®
PHARMACEUTICAL ENGINEERING GUIDE
FOR NEW AND RENOVATED FACILITIES

VOLUME 2

Oral Solid Dosage Forms

Third Edition

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As a contributor to the OSD Baseline Guide Volume 3, CRB is honored to take part in developing a key tool that assists companies in OSD manufacturing. Staying ahead of the ever-changing regulations in the life sciences industry, CRB is committed to finding the right solutions to our clients' most technically challenging problems.

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"The ISPE OSD Baseline Guide is one of the key, go-to international industry documents that provides valuable guidance on topics including, but not limited to: Regulatory Philosophy, Risk Management, Product/Processing, Containment, Architectural, HVAC, Process Utilities, Electrical/I&C, and other. This update highlights the "c" in cGMP and will be a tool everyone involved in OSD facilities will want to have in their tool box."

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Oral Solid Dosage Forms

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Disclaimer:
This Baseline® Guide addresses facilities for the manufacture of Oral Solid Dosage (OSD) Forms, including tablets, capsules, and general powders. It is intended to be used for the planning, design, engineering, construction, commissioning, qualification, and operation of both new and renovated pharmaceutical OSD forms manufacturing facilities. This Guide is solely created and owned by ISPE. It is not a regulation, standard or regulatory guideline document. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

Although many discussions focus on the high-growth area of biopharmaceuticals, Oral Solid Dosage (OSD) forms maintain a large sales volume within the global market. It also continues to be an important segment within the Pharmaceutical Industry. OSD manufacturing is mature and has been slow to change. It is the time to embrace the digital-age technologies for next-generation pharmaceutical manufacture, which should be more efficient, lower cost, and faster to market, while continuing to maintain and improve drug product quality, safety, and efficacy.

This new edition of the ISPE Baseline® Guide on OSD Forms considers both current and new technologies, such as Process Analytical Technology (PAT); continuous manufacturing processes, and other innovative approaches to help meet regulatory requirements and pursue industry best practices. For example, this new edition focuses on product, process, and protection, based on the increased regulatory requirements for OSD forms manufacturing. A new chapter has been added to address containment and cross-contamination in support of the increasing use of highly potent APIs. In addition, this new edition presents an innovative design approach for OSD manufacturing facilities and critical utilities that includes smaller production footprints and space classification considerations and applications.

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This Baseline® Guide was developed and written by an internationally diverse and integrated team, under the leadership and direction of:

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Chapter Leads/Writers/Reviewers

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TO THE USERS OF THIS GUIDE... We hope you find the materials herein useful and of value to you in your OSD activities.

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

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Table of Contents

1 Introduction

1.1 Background

This *ISPE Baseline® Guide: Oral Solid Dosage (OSD) Forms* is intended to offer a tool for consistent framework for regulatory interpretation, while still allowing a flexible, innovative and compliant approach to facility design, construction, commissioning, and qualification. This approach is intended to allow manufacturers to better serve their customers by helping to reduce costs and improve product quality. Additionally, this Guide will provide an overview of potential new technologies, which are being applied selectively in the industry.

The reader should consider this ISPE Baseline® Guide as a tool, to be used in conjunction with other design guides, industry guidance and regulatory requirements that are already available in the industry.

This is the third edition of the ISPE Baseline® Guide for new for new and renovated OSD facilities. It focuses on compliance with the US FDA current Good Manufacturing Practice (cGMP) regulatory expectations, as well as other international regulatory bodies, where applicable.

Some of the major changes/enhancements and revisions to this third edition include:

- Reorganization of the existing chapters and general flow of the document
- Expanded discussion related to Risk Management (see Chapter 3) with content including the topics of: Principles, Processes and Tools
- Significant expansion of Product and Processing (see Chapter 4) including discussion on “ATmospheric EXplosibles (ATEX)”, a European directive focused on equipment intended for use in potentially explosive situations. was created by the European Directive 94/9/EC (ATEX 95) [1], and it applies to both equipment manufacturers and equipment users
- Addition of a new chapter entitled Product Isolation and Containment: Principles of Product, Operator, and Environmental Protection. This chapter provides further detail on the challenges, and considerations relating to containment and cross-contamination issues faced by OSD manufacturers
- Numerous updates and considerations relating to modern OSD forms manufacturing facilities in the areas of Architectural (layout, functional areas, etc.), Process Support Utilities (approach, critical systems, and code issues), Heating, Ventilation, and Air Conditioning (HVAC) (further aligned with the ISPE Good Practice Guide on HVAC [2]), Electrical (classified areas, systems and preventive maintenance), Controls and Instrumentation (Process Analytical Technology (PAT)), Manufacturing Execution Systems (MESs), Electronic Batch Records (EBRs), and Other Considerations (Non-cGMP risks, exposure, life/safety, hazardous operations, environmental, emergency preparedness).
- Addition of easy to use graphics, tables, and visual aids

1.2 Purpose of This Guide

This OSD Baseline® Guide is intended to be used by various industry professionals for the planning, design, engineering, construction, commissioning, qualification, and operation of both new and renovated pharmaceutical OSD facilities. It is intended to be used to develop technically sound and compliant solutions while offering flexibility to meet specific facility and project needs.

The guidance contained herein is neither a set of standards nor is it a commissioning/qualification/regulatory design guide. It is not intended to supersede governing laws or regulations, which apply to facilities of this type, nor is it intended to invalidate existing facilities which may not meet guidelines presented herein or suggest in any way that an existing facility is non-compliant. The use of this document for new facilities and major renovations of existing facilities is at the discretion of the Facility Owner or Operator and is subject to the current codes and standards of governing regulatory bodies and local Good Engineering Practice (GEP).

1.3 Scope of This Guide

The Guide covers pharmaceutical facilities for the manufacture of OSD forms, including tablets, capsules, and general powders. It also may be applied to pilot and clinical supply facilities. The Guide is intended primarily for facilities meeting the regulatory requirements to supply the United States (US) market and follows US standards and references. However, consideration has been given and where applicable, pertinent European and other non-US standards are referenced as appropriate.

The content/idea and concepts proposed constitute a framework from which to proceed, based on each facility's own specific requirements and needs. Other applicable codes, standards, and governing laws still apply and this guide is not intended to supersede GEP, rather it is intended to supplement GEP with suggested approaches to cGMP.

The Guide is not intended to address the manufacture of dietary supplements, excipients, sterile products, topicals, oral liquids, or aerosols. Wherever applicable, references are provided to existing Baseline® Guides for further detail on specific systems or operations.

1.4 Key Features of This Guide

The following key concepts are a basis for this Guide:

- Current and proper application of facility design, engineering and operational procedures to assist with cGMP compliance
- Risk Management, Processes and Tools
- cGMP and non-GMP technology and its impact upon facility design and costs
- Product Isolation and Containment and principles of product, operator and environmental protection
- GEP and proper/enhanced documentation
- Proper balance of facility design and procedures
- It is not necessary to address each cGMP issue only by design; one or more of the following may be applied:
    - Procedural control
    - Demonstrated (or validated) scientific approach
    - Risked-based decision making

This will allow the flexibility to design for appropriate levels of protection or containment, while avoiding costly designs that result in no significant improvement in quality, efficacy of the drug product, or protection of personnel.

A risk-based approach involves using innovative manufacturing science and technology to assess, mitigate, and control the potential hazard in a manufacturing process that affect the quality of the drug product. As an example, utilizing statistical data analysis in conjunction with PAT for continuous process monitoring and control will lead to higher quality product. Sharing such risk mitigation strategies with the FDA may be beneficial. See International Council for Harmonisation (ICH) Q9 "Quality Risk Management" [3].

Non-GMP Technologies: some facility design requirements arise from decisions made to address non-GMP issues or preferences of the manufacturer, such as operator safety or strategic operating decisions. These non-GMP driven technologies often affect facility design features aimed at achieving GMP compliance and are discussed in Chapter 11 of this Guide. With proper planning, both GMP and non-GMP risk assessments can be completed in parallel so that key drivers for capital investment are included in the project scope.

The Level of Protection required is based upon the risk of contamination as assessed by the manufacturer, and assessment criteria include:

- The duration of product exposure
- The product mix and product changeover[1]
- The characteristics of those products, such as potency or toxicity
- Human activities performed during the manufacturing process
- Facility design and performance factors
- Environment in which the plant is located

Operating Conditions are based upon product acceptance criteria, while design set points and conditions are target values for the Engineering Designer to achieve. For example, a blending room may have a set point of 40% Relative Humidity (RH) and a design range of 30% to 50% RH, but the product in that room may be unaffected by humidity in the range of 20% to 70% (validated product acceptance criteria). Therefore, the acceptable operating range for the room is 20% to 70%, not 30% to 50%. Additionally, non-product requirements, such as human comfort, also are criteria for the design. This is discussed further in Chapter 2 of this Guide.

GEP is defined as engineering practices that are applied throughout the business to provide organization and control, balance risk and cost, and ultimately, deliver appropriate and effective solutions.

The term GEP is used to describe an Engineering Management System that is expected in a pharmaceutical enterprise, but not mandated by GxP regulations. GEP recognizes that all systems in a facility undergo some form of commissioning, which includes inspection, testing, and documentation based on agreed protocols, while direct impact systems require enhanced documentation, which include an enhance design review and Quality Assurance inspection and approval that are appropriate and acceptable to regulators. GEP capitalizes upon this by suggesting that manufacturers engage all stakeholders (Engineers, Managers, Operators, Quality Assurance experts, and others) very early in the planning, design, construction, and commissioning and qualification phases to ensure that systems are documented only once. This is discussed further in the following chapters of this Guide.

A key element of GEP is to develop appropriate documentation throughout the life of the project to ensure that the equipment and facility is fit for its intended use. The documentation should be reviewed, approved by appropriate Subject Matter Experts (SMEs), updated in a timely fashion, and stored in a secured location for retrieval.

[1] Product changeover is the frequency of change of product processed in a room or in a piece of equipment.

1.5 How to Use This Guide

This Baseline® Guide for Oral Solid Dosage Forms facility design is organized in a format similar to that followed by other ISPE Baseline® Guides. The reader should consider this Guide a tool to use in conjunction with design guides that are already available in the industry.

An overview of the chapter structure shows the way in which the chapters are grouped:

- Principle Chapters: Chapters 1, 2, and 3 provide the high level guidance of this OSD Baseline® Guide with the emphasis of regulatory compliance, drug product quality, operators' safety and environmental protection by good manufacturing practices, as well as good engineering practices. Chapter 3 discusses the "Risk-Based Approaches to Commissioning and Qualification", with the principles and concepts of ICH Q9 "Quality Risk Management" [3] and ASTM E2500 [4]. This Chapter and Chapter 2 provide the regulatory framework for the design model to follow.

- Foundation Chapters: Chapters 4 through 11 provide the detailed discussion in consideration of good design and construction practice for modern OSD manufacturing facility and equipment application. Further, these chapters explore the opportunities for advancement of the productivity and quality by implementing the new technology and compliance strategy

- Three Appendices (Chapters 12, 13, and 14) have been added to provide more detail on some relevant aspects related to OSD facilities:

    - Appendix 1 contains a discussion and guidance on the life cycle cost analysis relating to optimizing the design of the facility and selection of equipment and system

    - Appendix 2 contains an example of risk assessment for an OSD forms manufacturing facility

    - Appendix 3 contains further information on containment and isolation

- Appendices 4 and 5 provide references and a glossary of useful definitions

2 Concepts and Regulatory Expectations

2.1 Introduction

This chapter is intended to provide guidance on regulatory expectations as applied to the design of OSD process systems and facilities. Understanding and interpretation of regulatory expectations and guidance is key, as the engineering solutions adopted will affect both the initial cost and operating costs throughout the life of the facility. GEP can help to ensure that the products meet the required standards of quality and purity.

2.2 Regulatory Philosophy

The Pharmaceutical Industry faces a number of challenges of a regulatory nature. These can be summarized as:

- Compliance failures of facilities located throughout the world
- Consistent implementation of cGMP concepts, incorporating expectations of all applicable markets
- Counterfeiting
- Drug shortages
- Frequency of inspection based on risk
- Shared facilities and cross-contamination issues

To improve the compliance aspects there is a move to international harmonization by organizations such as the:

- International Council for Harmonisation (ICH)
- Pharmaceutical Inspection Co-Operation Scheme (PIC/S)
- World Health Organization (WHO)

Regional agencies work in collaboration with the international organizations, e.g., the Association of Southeast Asian Nations (ASEAN). In addition, the major regulatory authorities are collaborating so that an inspection by one agency is accepted by other agencies allowing more frequent inspections of a larger number of facilities to take place.

The most significant collaboration is between the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Ministry of Health, Labour, and Welfare (MHLW) in Japan. These agencies are empowered by legislation, such as the Federal Food, Drug, and Cosmetic Act [5] and the EU Commission Directive 2003/94/EC [6]. The legislation requires the pharmaceutical industry to follow cGMP, e.g.:

The FD&C Act, Chapter V, subchapter A, section 501 [5] states: *"A drug …… shall be deemed to be adulterated — (B) if …… the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess; …"*

Paragraph 1 of the EC directive states: *"All medicinal products for human use manufactured or imported into the (European) Community are to be manufactured in accordance with the principles and guidelines of good manufacturing practice."*

cGMP regulations for finished pharmaceuticals are set out in 21 CFR Part 210 [7] and 21 CFR Part 211 [8]. The Center for Drug Evaluation and Research (CDER) also issues guidance documents, which represent the US FDA's current thinking on a particular subject.

In Europe, cGMP is set out in EU GMP Volume 4 Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice [9]. Chapter 3 of the EU GMP Volume 4 [10] covers premises and equipment:

> *"Dedicated facilities are required for manufacturing when a medicinal product presents a risk:*
> *a) Which cannot be adequately controlled by operational and/ or technical measures or*
> *b) Scientific data does not support threshold values (e.g. allergenic potential from highly sensitising materials such as beta lactams) or*
> *c) Threshold values derived from the toxicological evaluation are below the levels of detection"*

EU GMP Volume 4, Chapter 3, (3.6) [10] can be summarized as: undertake a risk assessment starting with a toxicological evaluation of the active.

The proposed toxicological evaluation is completed for each active ingredient. The Permitted Daily Exposure (PDE) is the limit protective of all populations, even if taken daily for life, expressed as weight (mcg or mg per day). This is similar to ISPE's Baseline® Guide on Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP) [11], which uses Allowable Daily Exposure (ADE).

In Japan, GMP is required for manufacturing and marketing approval under Article 14.2, paragraph 4 of the Pharmaceutical Affairs Law [12]. GMP requirements for OSD facility design are provided in the MHLW Ordinance "Regulations for Buildings and Facilities for Pharmacies, etc." [13].

The products manufactured in OSD forms manufacturing facilities may vary in dosage form and degree of product hazard. The equipment used to produce OSD forms can range from open-type manual processing to enclosed, highly automated processing. This can lead to numerous possible facility layouts, but all are governed by the same basic GMP requirements for the design, construction, and validation of OSD forms manufacturing facilities and equipment:

- Should be of suitable size, construction, and layout to allow all required manufacturing operations, personnel, product, and equipment movement, and permit effective cleaning and maintenance
- Should be designed with adequate space and orderly flow to prevent product mix-ups and product cross-contamination
- Should provide protection of the product from chemical, physical, microbiological, and all environmental contamination
- Should be designed and operated with facilities for breaks, toilets, hand washing, and garment changing, provided as appropriate for product protection
- Should include specific precautions to ensure that hazardous materials do not present an unacceptable level of product cross-contamination risk, or a risk to personnel, or the environment
- Elements of the facility and equipment, which are critical to product quality, should be qualified

These general principles represent the regulatory philosophy that drives the basic requirements within OSD forms manufacturing facilities to ensure product quality and operator safety during the manufacturing process.

OSD forms manufacturing facilities have common issues across the different unit operations and product types encountered. Dust containment often presents a design challenge for OSD forms, where highly hazardous active ingredients are becoming more common. This Guide is intended to help establish consistent and minimum parameters for facility design, which address these concerns and meet GMP requirements.

Each manufacturer should define the level of control, protection, and validation appropriate to each manufacturing operation, based upon a sound understanding of both the quality aspects and process requirements. They should determine the risk of product contamination to the product mix within each manufacturing area.

When existing facility renovations or modifications are made or manufacturing procedures are changed, the nature of the changes should be evaluated in advance to determine how they may affect patient safety and product quality. Appropriate change control procedures should be followed in making any change to qualified equipment, systems, or validated processes. In addition, depending upon the extent of the change and its potential to affect patient safety and product quality, the governing regulatory agency may require notification or prior approval of a change before it is implemented. Understanding the potential impact of a proposed change and the corresponding regulatory requirements is critical to maintaining facilities, equipment, and processes in a qualified and validated state. Change management system principles are described in *ISPE Product Quality Lifecycle Implementation (PQLI®) Guide: Part 3 – Change Management System as a Key Element of a Pharmaceutical Quality System* [14].

2.3 Quality Philosophy

2.3.1 Background

There is a mutual goal for governments and corporations to ensure supply of quality product to customers and patients ("ISPE Drug Shortages Prevention Plan, August 2014" [15]). Quality product should be acceptable for its intended use and meet all regulatory requirements, such as identity, strength, purity and other quality characteristics such that it is safe and effective. Quality should be designed into the product through the Quality System since testing alone cannot be relied on to ensure product quality. An appropriately designed and effectively implemented Quality System and Quality Risk Management program support the incorporation of and adherence cGMP. Several government issued documents provide guidance, including the US FDA "Guidance for Industry: Quality Systems Approach to Pharmaceutical cGMP Regulations" [16], European Commission "EudraLex Volume 4, Chapter 1, Pharmaceutical Quality System" [17], and ICH Q10 "Pharmaceutical Quality System" (PQS) [18].

2.3.2 Quality System

Senior Management is responsible and accountable to ensure that an effective Quality System is established and maintained. Leadership and sponsorship of the Quality System by Senior Management reinforces the expectation that personnel at all locations and levels of the organization participate in order to ensure quality product. Personnel should be knowledgeable of applicable cGMP requirements for their specific role in making, testing, and releasing product. Senior Management should ensure the Quality Unit or Quality Organization is appropriately funded, communicate the roles and responsibility, and define the authority. The Quality Unit must report to management independently from other functions for quality and compliance activities.

The Quality Unit is responsible to define, document, implement, monitor, sustain, and continuously improve all Quality Systems. Communication by all functions with the Quality Organization is critical to ensure that Quality Systems are operating as designed. Senior Management should receive timely notification of information that indicates a potential product quality or safety concern.

The Quality System should be described in a Quality Manual, or similar documentation. The FDA describes a Quality System Model which supports adherence to cGMP regulations. The example Quality System Model described has four major factors:

1. Management Responsibilities

2. Resources

3. Manufacturing Operations

4. Evaluation Activities

Each specific area defines the appropriate Quality System elements which support adherence to cGMP regulations.

Another Pharmaceutical Quality System model is described in ICH Q10 “Pharmaceutical Quality System” [18]. This model is based on quality concepts, using Good Manufacturing Practice regulations in conjunction with ICH Q8(R2) [19] and ICH Q9 [3]. The ICH Q10 [18] model should be implemented throughout the product life cycle to support continuous improvement.

Risk Management is inherent in any pharmaceutical process and should be the basis for decision making based on sound scientific knowledge and cross functional discipline input coupled with the organization’s tolerance for risk. For a more detailed discussion on Risk Management, see Chapter 3 of this Guide.

The following Quality Risk Management Process is taken from ICH Q9 [3].

3 Risk Management

The purpose of this chapter is to provide guidance on the principles for establishing an effective Quality Risk Management Process. It also includes an example showing a systematic approach to Risk Management for the design (e.g., new, retrofit), qualification and maintenance of an OSD forms manufacturing facility. When assessing and managing risk for OSD forms manufacturing facilities, the primary factors to consider should include:

1. Product quality and GMP compliance requirements which could have impact on Patient Safety

2. Personnel safety (e.g., operating staff)

3. Business impact (e.g., environmental compliance, schedule, cost)

3.1 Principles of Risk Management for OSD Facilities

The following principles reflect ICH Q9 [3] and should be part of any Quality Risk Management process. Examples are also offered that are specific to OSD forms manufacturing facilities.

Risk assessments should focus on the identification, analysis and evaluation of risks and their associated failure scenarios. Risk assessments may also include both GMP (e.g. product quality, compliance) and Non-GMP (e.g. production personnel safety, business impact) considerations.

For example, there may be inter-dependencies between product quality and production personnel safety considerations when dealing with multi-product or highly hazardous product manufacturing facilities and consequently, both elements require consideration during the design process. An example for consideration is HVAC airflow design between process area and personnel corridors.

Risk control (e.g., reduction, mitigation, acceptance) should be primarily focused on reducing the risk to product quality or personnel safety to an acceptable level.

For example, risk mitigation for a high hazardous manufacturing facility in which it is not technically feasible to provide comprehensive engineering controls for personnel protection, may be ensuring use of Personal Protective Equipment (PPE) for all potentially exposed operating personnel. For a multi-product facility, a risk mitigation to prevent cross-contamination could be increased focus on the HVAC airflow design and process facility and equipment cleanability. Mitigation for identified risks to the business are normally related to business interruption of existing facilities for retrofitting projects, and financial impact for green field projects that may not be started on time to serve a critical product production need.

Risk assessments should be appropriately managed, documented, communicated and periodically reviewed.

Risk assessments should include input from the appropriate SMEs, follow documented procedures, be logically structured for communication to management, and be available for review during regulatory inspections. Where appropriate, they may also be integrated with or referenced from the facility qualification documentation. An effective risk management process should also include some type of periodic review. Some commonly used risk assessment methods are summarized later in the chapter.

3.2 Quality Risk Management Process for OSD Facilities

The prerequisite for any effective quality risk management process is the establishment of the appropriate resources and management sponsorship. Once these are in place, the steps of a risk management process for an OSD forms manufacturing facility may include the following:

1. Determine GMP and Non-GMP design, qualification and maintenance considerations for ensuring project success (e.g., safety, product quality, cycle time, schedule, reliability)

2. Identify the potential GMP and non-GMP risks/hazards for the different design, qualification and maintenance considerations noted in Step 1

3. Initiate identification of potential GMP and non-GMP failure scenarios based on risks/hazards identified in Step 2 and a detailed evaluation of the process

4. Finalize failure scenarios identified in Step 3 and assess their relative risk priority (e.g., Failure Mode Effects Analysis (FMEA) or similar process is recommended). For failure scenarios which exceed your acceptable level of risk (e.g., risk tolerance), apply risk mitigation/reduction and controls. Also consider contingency plans (as required)

5. Ensure on-going performance through maintenance, auditing and review

6. Adopt a continuous improvement philosophy

Table 3.1 details the quality risk management process summarized in this section.

Table 3.1: Quality Risk Management Process

Process Step	GMP Elements (e.g., Patient Safety)	Non-GMP Elements (e.g., Personnel Safety, Business)
1. Determine GMP and Non-GMP design, qualification and maintenance considerations for ensuring project success (e.g., safety, product quality, cycle time, schedule, etc.)	Holistic look at all GMP risk issues which if overlooked can add to capital and operating expense. Some considerations include: • Is the facility multi-product? If yes, facility should assess the vectors (e.g., people, clothing, air currents, pests, raw materials, equipment) that might bring contaminants in contact with the product. The facility will likely require engineered cleaning systems/equipment. The HVAC and processing equipment may also need to be designed to prevent cross-contamination if there will be multiple products produced at the same time • Will the facility need to accommodate highly hazardous compounds or compounds requiring isolation? If yes, the HVAC and other processing equipment will need to be designed to ensure containment and/or prevent cross-contamination. • Are the products microbiologically sensitive? If yes, may need to include the ability to perform micro testing in the facility • Are processing conditions necessary to meet quality standards and ensure patient safety documented? If yes, process equipment (e.g. milling) and controls will need to be designed to reduce process variability to the lowest possible level	Holistic look at all non-GMP risk issues which if overlooked can add to capital and operating expense. Some considerations include: • HSE basic purposes are to prevent or protect against: - Occupational illness or injury - Business interruption or injury from equipment fire, deflagration, overpressure - Unwanted environmental releases If the facility needs to accommodate highly hazardous compounds requiring additional risk control, provisions for protecting workers (e.g., containment, etc.) may be required. If controlled substances are involved, consider the need for transporting Wash In Place (WIP) material to a vault or getting US Drug Enforcement Agency (DEA) approval for storing WIP material within secured Intermediate Bulk Containers (IBCs) in a locked (third-party) monitored manufacturing room.

Table 3.1: Quality Risk Management Process (continued)

Process Step	GMP Elements (e.g., Patient Safety)	Non-GMP Elements (e.g., Personnel Safety, Business)
2. Identify the potential GMP and non-GMP risks/hazards for different design, qualification and maintenance considerations noted in Step 1	Understand "What the GMP Risks/Hazards Are" such as: • Cross-Contamination from a particular vector (e.g., contaminated clothing) • Microbiological contamination (e.g., contaminated shoes) • Non-compliance with regulatory expectations regarding environmental classification zoning • Processing conditions – how can they go out of specification, e.g., Critical Process Parameters (CPPs)	Understand "What the non-GMP Risks/Hazards Are" such as: • Health effects of Active Pharmaceutical Ingredients (APIs) and excipients • Deflagration properties of process powders or solvents • Process equipment pressure or vacuum conditions • Environmental impacts of off property releases of process powders or solvents • Pertinent, legally mandated health or emission limits or fire code requirements
3. Initiate identification of GMP and non-GMP failure scenarios based on risks/hazards identified in Step 2 and a detailed evaluation of the process	Understand through a detailed review of the process flow in order to find "Where the GMP Risks/Hazards Are" such as: • HVAC or processing equipment cross-contamination potential • Mixing or commingling as a result of material flow • Vectors including people, pests, clothing, and air currents that might bring contaminants in contact with product • Processing conditions, residence time, etc.	Understand through a detailed review of the process flow in order to find "Where the non-GMP Risks/Hazards Are" such as: • Potential exposure and release points for highly hazardous or flammable materials due to the variety of operations which require equipment intervention (e.g., equipment adjustment, sampling, cleaning, maintenance operations) • If controlled substances are involved, identify potential points of exposure or release that may contribute to non-reconcilable losses and/or material diversion. • Operating conditions that might cause inadvertent releases in the operating suite or to the environment • Equipment pinch points • Points where the operator may need to be above floor level
4. Finalize failure scenarios identified in Step 3 and assess their relative risk priority (e.g., FMEA or similar process is recommended). For failure scenarios which exceed your acceptable level of risk (e.g. risk tolerance), apply risk mitigation/reduction and controls. Also consider contingency plans (as required)	Using one of the standard evaluation tools such as FMEA, What-If, or Hazard and Operability (HAZOP), etc., rate "How Big the GMP Risks Are" by looking at the potential severity and probability of impact for the scenarios in Step 3 with the participation of the appropriate SMEs Keeping the evaluation process simple (i.e., High, Medium, Low versus a 10-point system) gives a more easily communicated result. For risks/hazards that exceed your acceptable level of risk, decide "How to control the chosen GMP risks." Determine the right combination of engineering controls or procedures or both to mitigate the identified risks/hazards such as: • Process design and PAT • Use of High Efficiency Particulate Air (HEPA) filters to prevent cross-contamination • Cleaning validation (including microbiological considerations if products support microbial growth) • Change control procedures which ensure update of critical process documentation (e.g., Process/Piping Instrument Diagrams (P&IDs) • Use of minimal contact between people and materials through building design • Develop procedural controls to prevent cross-contamination/commingling • Pest controls • Zoning requirements (people and HVAC) • Differential air pressure between zones • Multiple process equipment coupling and vertical stack up to minimize open transfer steps	Using one of the standard evaluation tools such as FMEA, What-If, or HAZOP, etc., rate "How Big the Hazards Are" by looking at the potential severity and probability of impact for the scenarios in Step 3 with the participation of the appropriate SMEs. Keeping the evaluation process simple (i.e., High, Medium, Low versus a 10-point system) gives a more easily communicated result. For risks/hazards that exceed your acceptable level of risk, decide "How to control the chosen hazards." If substitution of less hazardous materials, equipment, or methods is not a feasible option, determine the right combination of engineering controls or procedures or both to mitigate the identified risks/hazards: • Use of Personal Protective Equipment for specific tasks • Machine guards for operator accessible pinch points • Prevent a highly hazardous compound release from dust deflagration or overpressure by specification of 10 or 12 bar rated fluid bed dryer instead of explosion venting • Architectural layout considerations or HVAC zoning Finding additional reasons beyond HSE risk mitigation can increase the justification for engineering controls versus dependence on human procedures. Establish baseline performance and documentation for the HSE mitigation equipment during equipment Commissioning and Qualification.

Table 3.1: Quality Risk Management Process (continued)

Process Step	GMP Elements (e.g., Patient Safety)	Non-GMP Elements (e.g., Personnel Safety, Business)
5. Ensure ongoing performance	Once a system to control the chosen GMP risks is in place, it requires on-going inspections, monitoring, maintenance, and audits to make sure it stays within performance expectations. Elements of the on-going monitoring program include: • GMP auditing including Correction Action Preventative Action (CAPA) • Use of settling plates to ensure containment integrity • Ongoing cleaning validation • Annual review (e.g., statistical process capability, review of change control)	Once a system to control the chosen hazards is in place, it requires on-going inspections, monitoring, maintenance, and audits to make sure it stays within performance expectations. HSE trained resources with adequate time to do the work are also needed over the lifetime of the process. Some elements of the on-going program support include: • Air sampling and monitoring • Relief device inspections/testing • Behavior Observation Systems for compliance with HSE Standard Operating Procedures (SOPs) • Containment and industrial ventilation equipment performance monitoring and maintenance • Environmental wastewater sampling • HSE compliance audits • HSE regulatory agency compliance audits
6. Continuous Improvement Philosophy through maintenance and auditing	Use the data gathered by the Quality System to find opportunities to further minimize the GMP risks.	Use the data gathered by the HSE system to find opportunities to further minimize the risks posed by process hazards.

3.3 Risk Management Tools

Several qualitative and quantitative risk management tools are available. Tools that are routinely used are listed below. Additional references include ICH Q9 “Quality Risk Management” [3] and the ISPE Baseline® Guide on Risk-MaPP [11]. Selection of a specific tool will depend on the rigor level of the data and the criticality of the risk assessment (e.g., higher risks to patient safety may require more in-depth risk analysis tool).

3.3.1 Failure Mode Effects Analysis (FMEA)

- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard and Operability (HAZOP) Analysis
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools
- Basic risk management facilitation methods (flowcharts, check sheets etc.)

Appendix 2 includes an example Risk Assessment for an OSD forms manufacturing facility upgrade.

4 Product and Processing

4.1 Introduction

This chapter presents a guide to process and process equipment. Aspects of commonly used technologies, unit operations, and associated equipment that are pertinent to product quality and facility design are discussed. In addition, material characteristics, material properties, material handling, cleaning, and maintenance are also addressed. This chapter discusses elements of Quality by Design (QbD).

Unit operations are discussed in detail and typical levels of cleaning, containment, enclosure ratings, and electrical classification are presented for each. For further information, see the ISPE Baseline® Guide on Active Pharmaceutical Ingredients [20].

4.2 Quality by Design

QbD was first introduced by the FDA in 2005 and focused on the development, control, and improvement of processes. QbD describes a science and risk-based approach to developing and manufacturing pharmaceutical products based on the principles set forth in the ICH Guidelines used in the EU, US, and Japan for:

- Pharmaceutical Development: ICH Q8(R2) [19]
- Quality Risk Management: ICH Q9 [3]
- Pharmaceutical Quality System: ICH Q10 [18]
- Development and Manufacture of Drug Substances: ICH Q11 [21]

Other regions have also accepted these guidelines, e.g., Canada and Australia. The ICH Guidelines are voluntary, but have set the stage for an alternative way for the pharmaceutical industry to develop and manufacture drug products. It is equally important to generic as well as originator drug manufacturing companies [22].

The concept of QbD is defined in ICH Q8(R2) [19] as:

> *"A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."*

A QbD or "enhanced approach" is a term that ICH uses and is where quality is designed into the process from the onset, using a science and risk basis, as opposed to the traditional approach of end product testing to check that the quality requirements are met. In the past, development of formulations and processes was mainly based on trial and error until a good product was obtained. The QbD approach is a much better concept and well recognized by regulatory authorities [23].

Using a science and risk-based approach to developing a product is not a new concept. Companies have traditionally employed such methodologies during product development, but historically, the output has focused on regulatory compliance which may mean that the science and risk-based information gained at the time was not captured as rigorously as it could have been, or they were more focused on the needs of a patient and developed their products with that in mind. New facilities have historically used tools such as hazard and operability (HAZOP) studies, where risks are evaluated to assure adequacy of engineering designs, particularly for operational safety, and have become established processes.

The science and risk-based approach was further supported and strengthening by the publication of the US FDA GMPs for the 21st Century [24] and their PAT Guidance [25]. The FDA also invited companies to join their pilot program which helped enhance the relationship between regulators and industry. This program encouraged companies to discuss with the FDA their approaches to new product development proposals before a formal submission was made. This program was also extended to include biotechnology products as well.

The European Union (EU) also encourages a science and risk-based approach evidenced by the European Medicines Agency (EMA) (formerly EMEA) instituting their Process Analytical Technology (PAT) team. This team is made up of experts from different parts of Europe, including inspectors, and assessors with a wide range of experience of submissions and inspections. The PAT team and the FDA have now built up a considerable resume of approved submissions that include the QbD principles.

There are several stages in developing a new product using the QbD methodology. These same stages are applied in principle whether the product is small or large molecules.

The principle steps per ICH Q8(R2) [19] starts with the patient safety and efficacy requirements, to ensure the final drug product meets quality requirements. The principle steps are:

- Quality Target Product Profile (QTPP): *"A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product."* ICH Q8(R2) [19]

- Critical Quality Attributes (CQAs): *"A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure product quality."* ICH Q8(R2) [19]

- Critical Process Parameter (CPP): "*A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces desired quality."* ICH Q8(R2) [19] It is important to establish which process parameters for a particular unit operation impact the CQA and the degree of that impact.

- Design Space: *"The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval."* ICH Q8(R2) [19] Many attributes and parameters may have some interrelation with each other and, therefore, the design space should take into account the basis of these interactions and their boundaries.

- Control Strategy: *"A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring or control."* ICH Q10 [18]

- Continual Improvement: to ensure that as more is learned over the life cycle of a product, that this information is utilized to promote improvements to both the products and processes

The implementation of QbD requires using appropriate PAT to monitor CQAs and CPPs during the processing of pharmaceuticals products to ensure that the product meets the desired quality attributes and reduces the risk of poor manufacturing process performance and substandard pharmaceuticals reaching patients. Risk is minimized by reducing variations in the process, while accuracy, repeatability, and reproducibility are increased. There is no single way of implementing QbD in practice. The ICH Guidance documents lay the ground work for a better understanding on how to achieve QbD and improve product and process understanding.

4.3 Preliminary Design Considerations

Preliminary design issues are related to facility, equipment, process, and process support operations that should be considered in the initial stages of a project.

4.3.1 Process Route Selection

The impact of the process methods used on the ability to manufacture product should be considered at the product development stage. Significant benefits can be gained in applying QbD during product development to establish the product life cycle as defined in ICH Q8(R2) [19].

4.3.2 Risk Management Approach for Non-GMP Risks

A considered application of risk management (see Chapter 11 of this Guide) should balance the needs of the process with the cost of various options. The general principles for non-GMP hazards and risk mitigation strategies applied are available as background information:

- Operator Exposure: exposure assessment, containment equipment, personal protective equipment, and administrative procedures
- Physical Injury: noise, heat stress, radiation, ergonomics, machine guarding, lock out tag out, fall prevention/ protection, confined space entry, asphyxiating gases, emergency egress
- Hazardous Operations: process hazard analysis, fire and explosion from combustible or flammable vapors, equipment overpressure and underpressure
- Environmental: permits, air emissions, wastewater, stormwater, groundwater, solid and hazardous waste, transportation of hazardous materials
- Community Response and Emergency Preparedness
- Controlled Substances: government regulated narcotics and other similar materials

For further information, see Chapter 5 of this Guide. Unit operation specific containment and hazardous operations issues are covered in Sections 4.5 and 4.8.

4.3.3 Equipment Safety Certification

Within Europe, all equipment is required to meet certain safety standards and as such should be Conformité Européene (CE) marked as an indication it has met certain design and fabrication criteria. Underwriters Laboratories (UL) is a common standard in the US.

Equipment in which powders are processed further has to be designed to meet the European Directive 94/9/EC (ATEX 95) [1]. In the US, the National Fire Protection Association (NFPA) provides guidance for process equipment and electrical classification [26].

For pressure retaining equipment, the appropriate local standards for design, fabrication inspection, and certification should be applied, such as that provided by the American Society of Mechanical Engineers (ASME). Where welding is required, coded welders and appropriate weld procedures should be used. Supporting documentation, i.e., weld procedure and welder approval certificates, should be available for inspection. Contractors should be aware of and possess a working knowledge of the requirements and certification aspects of the appropriate standards relating to weld/welder approval.

Where it is proposed to protect against explosion by containing the explosion within the equipment, then that equipment should be designed to the appropriate pressure rating, typically 10 bar. Process specific explosion protection issues are addressed in the Table 4.1.

Table 4.1: Process Specific Explosion Protection

Process Step	Process Specific Explosion Protection Issues
Wet Granulation	The dry mixing step of the wet granulation process is the main area of explosion risk due the generation of a dust cloud in the mixer bowl. The chopper is generally not used during the dry mix step for that reason. Care needs to be taken with the ingress of any tramp metal as the impact energy with the impeller may give rise to a spark.
Fluidized Bed Drying	The explosion risk in a fluidized bed dryer comes from the potential for static electric charge ignition of flammable dust clouds generated by the fluidizing air and flammable solvents if used in the granulation step. One additional feature on fluidized beds is the use of electrically conductive filter bags containing either epitropic (anti-static) fibers (carbon threads woven into the filter media) or stainless steel wires to dissipate any static electrical charge from the filter media.
Dry Milling	If the product being milled is a combustible dust, it represents a fire or explosion risk. There may be a need for an explosion containment design to be applied to the mill, particularly impact mills where the energy input during milling is that much greater and frictional heating of the product might cause ignition. Alternatively, nitrogen inerting has been used as a protection measure.
Tablet Coating	If flammable solvents are used in the coating process, a process hazard analysis would indicate the combination of explosion protection and explosion prevention steps to protect the coating equipment, the solvent supply system, and the manufacturing suite in which it operates.

4.3.4 ATEX

The European Directive 94/9/EC (ATEX 95) [1] is focused on equipment intended for use in potentially explosive atmospheres.

ATEX 95 [1] applies to equipment and protective systems in potentially explosive atmospheres, and European Directive 99/92/EC (ATEX 137) [27] applies to the work place. ATEX uses a double digit system of categorization with single digits related to gas environments and double digits related to dust. A comparison between ATEX zones and the US National Electrical Code (NEC) classifications is shown in Table 4.2. This comparison has been utilized by industry, but has not been issued as an official document by either ATEX or NEC.

Table 4.2: Comparison Table for Electrical Classifications between ATEX and NEC

European and IEC ATEX Classification	Definition of Zone or Division	North American NEC Classification
Zone 0 (gases/vapors)	An area in which an explosive mixture is continuously present or present for long periods	Class I Division 1 (gases)
Zone 1 (gases/vapors)	An area in which an explosive mixture is likely to occur in normal operation	Class I Division 1 (gases)
Zone 2 (gases/vapors)	An area in which an explosive mixture is not likely to occur in normal operation and if it occurs it will exist only for a short time	Class I Division 2 (gases)
Zone 20 (dusts)	An area in which an explosive mixture is continuously present or present for long periods	Class II Division 1 (dusts)
Zone 21 (dusts)	An area in which an explosive mixture is likely to occur in normal operation	Class II Division 1 (dusts)
Zone 22 (dusts)	An area in which an explosive mixture is not likely to occur in normal operation and if it occurs it will exist only for a short time	Class II Division 2 (dusts)

ATEX requires a detailed examination testing and assessment of the equipment to be used in potentially hazardous areas. The ATEX certification confirming that the product is deemed safe will be noted by an ATEX approval stamp (Ex inside a hexagon) normally accompanied by a CE stamp.

Table 4.3: Process Operation Containment Issues

Process Step	Process Operation Containment Issues
Dispensing	The weighing of Active Pharmaceutical Ingredients (APIs) before processes that combine API and excipient can produce the highest risk of product and occupational exposure. Open operations will achieve concentrations that may exceed Occupational Exposure Limits (OELs) and cross-contamination limits.
Dry Granulation, Slugging, and Roller Compaction	Containment issues are significantly increased because the particle size is not increased or densified and the only binder effect between API and excipient is inter-particulate friction. Slugging generally produces large densified granules that do not remain airborne and are outside the respiration range. Charging the blend and dust from the process remain challenges. The main issue with roller compactors is powder leakage, both through the roller gap and at the end of the roller between the rotating roll and stationary end plate. Leakage through the roller gap can result in a dusty product, but leakage at the end of the rollers can potentially escape from the machine. To prevent leakage at the end of the roller, improved sealing is required. Where total containment by design proves impracticable, then secondary containment by installing the roller compactor inside a hard or flexible isolator is possible. Pharmaceutical roller compactors being relatively small lend themselves to such isolator installation. Access for maintenance and cleaning inside the isolator should be considered at an early stage.
Wet Granulation	Charging and heel recovery are major containment issues with this process.

Table 4.3: Process Operation Containment Issues (continued)

Process Step	Process Operation Containment Issues
Single Pot Processing	These are preferred systems because a number of processes are contained in a closed process without transfer between processes. Charging and discharging are the major containment issues with this process.
Spray Granulation	Contained spray granulation uses large volumes of air and requires containment design to be effective.
Extrusion Spheronization	Because the process produces (relatively) large spheres, the outcome does not remain in airborne suspension; however, dust related to the process remains a concern.
Drying	One of the worst processes for containment. When not contained, very high concentrations particularly during harvest are possible. Existing non-contained designs present many challenges to occupational exposure. Old fluid bed dryers can be contained, but modern contained designs may be better.
Dry Milling	Due to the high energy and velocity of impact mills, fines may be generated. The “windage” generated by the impeller, especially in impact mills, causes considerable air movement in the milling chamber and may result in the fines being emitted. Occupational exposure is a significant risk. Due to the way conical mills operate and particularly with the under driven design, these mills are more readily contained than impact mills.
Blending	Charging, discharging, sampling, heat, and over pressure during volume to volume transfer are the major containment issues with blending in fixed blenders. Bin blending is basically a contained process so apart from leakages poses no hazard. Bin blending is in theory an inherently contained process, therefore often poses little emission risk. However, it can have some potential emission sources which warrant remediation. They are: • Bin disconnection and reconnection to the rest of the process train • Sampling • Powder additions • At times even the actual bin tumbling itself (for larger bins, the powder’s momentum slamming against the closed bin lid, forcing “minor” leakage through the lid connection) The actual risks embodied in some of these emission sources may or may not prove trivial, depending on the level of the API’s potency and the degree of the emissions. As in other parts of the operation, a risk assessment would indicate that. PAT or a validated process that eliminates the need for opening a vessel (bin, blender, etc.) to check for blend uniformity or other parameters, improves containment. Containment of agitator blenders is problematic.
Compression	The compression process is dusty; however, with increased particle size, density, and the ability of some excipients to lock onto the API, the airborne concentrations of the API are often surprisingly low. Review on a case by case basis should be performed. Cleaning is the main risk and Wash In Place (WIP) presses should be considered.
Encapsulation	The potential for exposure is dependent on the format of the fill. If powder, the exposure is high, while encapsulating tablets is normally low. For tableting, cleaning is a key issue and WIP-able encapsulators should be considered.
Tablet Coating	Charging is a containment issue, but coated tablets do not present a hazard.

These mills are more readily contained than impact mills, due to the way conical mills operate and particularly with the under driven deign.

4.3.4.1 Acceptance Criteria

A containment system is successful if it controls transmissions to a level where they do not cause exposures. The ideal is where control is such that Respiratory Protective Equipment (RPE) is not required.

Gown changing regimes, locations, procedures, and facilities (including airlocks and decontamination provisions) should be driven by a risk assessment process. Such an assessment should include risks to the product (cross-contamination), to the operators (industrial health and hygiene), to the outdoor environment, and to the ongoing business, and should encompass the process and the affected facility.

4.4 Impact of Powder Physical and Chemical Properties on Equipment Design

Many of the issues in the manufacture of OSD forms arise from physical and/or chemical properties of the materials used in the formulation of the product. Consideration is given in this section to the various characteristics and properties of pharmaceutical APIs and excipients that may be affected by the processing environment, such as light sensitivity and hygroscopicity, or those that impact on the ability to process product, such as flowability and compressibility.

The impact of non-quality related material characteristics which affect processability, such as Health, Safety, and Environment (HSE) concerns are addressed in Chapter 11 of this Guide.

The intent is to ensure that these process elements are considered in the facility design and equipment selection. In many cases, pharmaceutical processes are designed out of a need to alter or overcome the limitations of materials and make it easier to process them in subsequent manufacturing steps.

4.4.1 Properties Influenced by the Facility's Processing Environment

4.4.1.1 Temperature and Humidity

Some products may be temperature and/or humidity sensitive and require the use of temperature and humidity control systems to ensure that the product maintains good flow characteristics, as well as maintaining other material properties which could be affected by high or low temperatures and high humidity. The room environment should also be regulated to control the hygroscopicity of a product. Other temperature concerns related to operator comfort are discussed in Chapter 8 of this Guide.

4.4.1.2 Hygroscopicity

If a highly hygroscopic product is exposed to very moist air, the allowable moisture content in the product may be exceeded, which results in the powder material (APIs, excipients, or products) becoming unstable with the onset of depreciative events, such as mold growth and affecting the material's flowability. Facility architectural and HVAC systems require special considerations to address moisture sensitive products. For further information, see Chapters 4 and 8 of this Guide.

4.4.1.3 Light Sensitivity

Many products exhibit a degree of sensitivity to direct sunlight. As a general rule, no pharmaceutical product should be exposed to direct sunlight for extended periods. However, a smaller number of products are classed as light sensitive and may chemically degrade on exposure to moderate levels of light or certain frequencies. Such materials should be protected from exposure to light and light sources by processing in closed equipment. However, this may not assure protection against light, as some exposure is inevitable. Where it is necessary to expose such materials, e.g., during tablet inspection, choosing the correct lighting environment (specific light sources) that minimizes degradation to the materials is recommended.

Appropriate protection based on the sensitivity spectrum should be applied for photo sensitive products.

For some APIs only monochromatic yellow lighting using Sodium Vapor Lamps (SVL) will be appropriate. For other APIs, regular fluorescent lighting with Ultraviolet (UV) filter films may be adequate. SVL lighting can have some design disadvantages, e.g.:

- Infiltration of white light from view panels in walls and doors needs to be evaluated and eliminated, either by blanking off or by providing amber films
- For a multi-product suite with a combination of photo sensitive and regular products, two sets of lighting fixtures may be needed; regular for regular products and SVL fixtures for photo sensitive products
- Working in artificial yellow lighting for long working hours is uncomfortable for operators

Regular fluorescent lighting with UV filter films can have the following advantages:

- Infiltration of white light from view panels in walls and doors can be eliminated by using the same type of UV filter films as used on lighting. Since these are neutral color films, ambient white light is unaffected
- No need for two sets of lighting fixtures in case of a multi-product suite
- Working in white light is much more comfortable for operators

Light Emitting Diode (LED) lighting has become much more cost competitive. With the additional benefits of:

- A more favorable spectral power distribution for light sensitive products, with less emissions at wavelengths of < 500 nm
- Improved color rendering
- Improved efficiency of operation (fewer bulbs provide the same level of light intensity and longer bulb life
- Can be more cost effective for electrically classified areas

4.4.1.4 Oxygen Sensitivity

Many pharmaceutically active compounds (APIs) are sensitive to decomposition caused or accelerated by environmental influences, such as oxygen, humidity, light, heat, and combinations of these. Several approaches have been used to prevent or minimize decomposition caused by atmospheric oxygen. An example used in packaging is the use of blister packaging which incorporates an oxygen scavenger in the portion of the blister package which houses the API. Use of inert gases can also offer another barrier to oxygen exposure of the API.

4.4.2 Properties Influenced by the Process

Product properties that influence the ability to process the product include:

- Particle size
- Size distribution
- Particle shape
- Surface properties

- Particle strength
- Density, porosity, and packing
- Cohesion in powders and powder flow
- Compressibility
- Cleanability
- Operator exposure limitations (see Chapter 5 of this Guide)

4.4.2.1 Particle Size and Size Distribution

The most fundamental of particle properties is that of size. Powders are rarely, if ever, equally sized and the sizes of the particles should be described by a measure of the variation in size, the size distribution, as well as that of a central tendency, e.g., mean. Size distributions by weight, volume, or surface are the most relevant in work related to OSD forms. Frequency or cumulative plots may be used to represent size distributions.

Particle size can have a significant impact on formulation processing, e.g.:

- Particle size of the API can affect the rate of dissolution and ultimately the bioavailability of the drug. The API may need to be processed prior to formulation to control its particle size
- If the percentage of an API in a formulation is small, the particle size can affect the uniformity of the mix
- Particle size may affect the way a product formulates, e.g., it may affect the way a material granulates
- Once formulated, the particle size of the formulated granule can affect many other characteristics, such as flow. Particle sizes in newer formulations can be reduced into the nano/micro particulate ranges
- In a direct compression formulation, selection of excipients with vastly different particle sizes to that of the API can, e.g., significantly increase the risk of segregation.

4.4.2.2 Particle Shape

The shapes of particles comprising a powder can be a very important determinant of the powder's properties, such as flow, bulk density, and compressibility. Particle shape is not necessarily constant in a powder and is likely to vary with particle size. The particle shape can be described by various aspects and is primarily driven by crystal properties rather than particle size.

4.4.2.3 Particle Surface Properties

The particle surface properties will have a significant effect on the bulk powder properties similar to that of particle size and shape, e.g., particles with a very rough surface will have much poorer flow characteristics than smooth particles.

Some particles have an internal surface as well as an external surface due to the presence of pores in the particle. The internal pores will affect the way the bulk material absorbs and releases liquid. If the pores are the correct size, small particulates may become trapped in the pores, which in turn increases the stability of the powder mixture to the risk of segregation but may also affect dissolution if the small absorbed particle is the active.

4.4.2.4 Particle Strength

Comminution and attrition are processes in which particles are broken or damaged. The particle breaks when a force higher than the particle strength is statically applied as in a crushing mechanism, e.g., between rollers or dynamically applied, e.g., impact hammer mill.

Breakage also could occur with lower loads that are applied repeatedly, a phenomenon that is known as fatigue. Fatigue is the real cause for the breakage of particles in many industrial systems, such as grinding or transporting in pneumatic conveying pipelines.

4.4.2.5 Density, Porosity, and Packing

In normal circumstances, a powder will consist of solid particles and inter-particulate air spaces (voids or pores). The true particle density will be the same as the pure solid material. In most cases, the density referred to is the apparent density. The apparent particle density is an average, depending on the pore structure of each particle, and will vary with the manufacturing process.

The apparent density of the powder sample is usually referred to as the bulk density where the volume includes both inter and intra-particulate pores. For a single powder, the bulk density can vary depending on the state of packing of the powder and several values may be quoted:

- Minimum bulk density: when the volume of the powder is at a maximum, caused by aeration, just prior to complete breakup of the bulk
- Poured bulk density: where the volume is measured after pouring powder into a cylinder. This creates a relatively loose structure. This is commonly referred to as the powder “bulk density”
- Tapped bulk density: where the volume is measured after taps the powder in a standard manner

4.4.2.6 Cohesion in Powders and Powder Flow

Cohesion refers to the attraction between the powder particles themselves. Adhesion refers to the attraction between the particles and other surfaces, e.g., a hopper or a tablet punch.

There are several attractive forces responsible for cohesion in powders. These include magnetic, electrostatic, and intermolecular forces.

The magnitude of electrostatic forces is dependent on the nature of the particles and particularly on their electrical conductivity. For most pharmaceuticals, intermolecular forces are important, and of the several types of intermolecular forces, van der Waals forces are the most significant.

Below a certain particle size, cohesive forces dominate and the powder will not be free flowing. As the degree of consolidation increases, i.e., the bulk density increases, then the greater proximity of the particles leads to greater cohesion and the powder is less free flowing.

Moisture, in general, will reduce flow properties by causing a greater cohesion of the particles. However, in very dry powders, a low level of moisture may act as a form of lubricant and improve the flow properties.

4.4.2.7 Compressibility

The compressibility of an individual material is not usually of importance as most products are formulated, i.e., mixed with other ingredients and processed (granulated, milled, and blended) to improve their compression characteristics. The compressibility of a formulation is affected by many factors, including:

- Particle size
- Shape
- Surface roughness
- Strength (friability)
- Bulk density

There are many steps in pharmaceutical processing for which the compressibility of the material should be considered and controlled including:

- Tableting
- Slugging
- Capsule filling (tamping)
- Roller compaction

In these processes, a stable compact of the starting material is required as output from the unit operation. The compact is formed by compressing the particles under a range of compaction forces depending on the strength of the compact required. There will be a rearrangement of particles relative to one another and there may be distortion and fracture of particles, but the mechanism by which the compact holds together is inter-particulate bonding.

Consistent particulate characteristics of the in process blend should be maintained by understanding and controlling the formulation process, because of the complex nature of the compaction process. In the case of a powder mixture, the compressibility property of the predominant component will influence the overall compressibility.

4.4.2.8 Cleanability

In a multi-product facility, the ease with which it is possible to remove all traces of a product from a process equipment train prior to processing a second product can greatly affect the productivity of the facility. The ability to clean the first product, the cleanability, is driven predominantly by the solubility of the formulation in a solvent or aqueous based solution. As API molecules become increasing complex, many are sparingly soluble in water. Removing all traces of such products may require large volumes of aqueous cleaning medium, the use of detergents, and the use of mechanical cleaning, such as manual scrubbing and scraping or, as a last resort, the use of an organic solvent.

During process development, cleaning schemes should be trialed within proof of concept and scale up batches, so that cleaning validations can have a reasonable chance of success, on a ‘right first time’ basis.

4.4.2.9 Explosion Protection of Process Equipment

OSDs are inherently a powder based technology which generates the potential for a dust explosion. Dusts will combust in the presence of oxygen when an ignition source is present; the presence of an ignition source will almost ensure combustion. The intensity of the combustion is largely a function of the:

- Dust composition
- Concentration of the dust in the air
- Particle size

- Other issues which are also part of the overall safety equation, e.g.:
  - Contained space
  - Presence of solvent vapor

Explosions are primarily due to static electrical charges. Grounding of equipment and operators should be provided and routinely checked on a predetermined basis, in order to help to prevent explosions. For further information on the hazards and categorizations associated with dust see Chapter 5 of this Guide.

From an equipment design perspective, once a potential equipment explosion hazard is identified, one or more frequently used explosion mitigation methods should be used to protect the equipment, e.g.:

- Venting
- Suppression
- Containment
- Temperature interlocks
- Inertion

Vented designs may use specially designed explosion bursting discs or panels. There are limits that constrain how long the outlets of these devices can be and there needs to be a free path to safely vent the fire ball. The equipment should have:

- A contained zone that can withstand the force of the explosion
- Isolation valves on any ducts leading into or out of the unit so that the flame front is properly diverted to the safe explosion vent

Where chemical suppression is used, equipment design is generally unchanged, with only minor modifications to accommodate the suppressant tanks and sensors for activating Quick Acting Valves (QAV) that close off and isolate the equipment while holding the suppressant inside the equipment.

Some units are designed on a containment basis; the equipment has been designed to withstand the explosive force. Isolation valves at all ingress and egress points are needed to contain the explosive force.

Oxygen reduction (inertion) can also be an effective tool, although it is less frequently used than venting or suppression. This method uses an inert gas (e.g., nitrogen) as the process gas, so that oxygen is removed from the system in order to eliminate any possible chance of combustion. Controls are required to ensure the maintenance of reduced oxygen levels, as well as any potential for an asphyxiation hazard to operators.

Systems usually require a triggering mechanism, which is bespoke to the application. Triggering mechanisms may include:

- Temperature sensors
- Pressure sensors
- Rate of rise detectors
- QAVs

Rate of rise detectors can provide faster reaction times. QAVs are used for containment or venting.

Constant monitoring systems should signal any upset condition, such as the loss of grounding (which would allow static discharge), detect allowable oxygen level presence in an inert system, and assure minimum suppressant pressure in the storage canisters.

Isolation Valve and Suppression Canister Locations

Isolation valve and suppression canister locations are critical. They should be far enough from the equipment to allow enough time to close or discharge before a flame front can reach that, but if they are too far, pressure piling can occur in ductworks and create a secondary explosion.

Other important safeguards to prevent explosion hazards are good housekeeping practices, which are key to maintaining safe process operations and include:

- Proper ventilation
- Good ductwork design
- Proper electrical area classification
- Proper identification of all potential ignition sources
- Grounding
- Preventive maintenance programs
- Periodic testing of protection systems

Note: for further information, see reference standards such as:

- US:
  - NFPA 654 [28]
  - NFPA 68 [29]
  - NFPA 69 [30]
  - NFPA 70 [31]
- EU:
  - ATEX 137 [27]
- Regulatory expectations for other regions related to this topic

4.5 General Equipment Considerations

This section reviews the quality related equipment design criteria, typically addressed in User Requirement Specifications (URSs), which are common for different unit operations.

4.5.1 Materials of Construction for Equipment Intended for Pharmaceutical Processing

Equipment designated for use in pharmaceutical processing should ensure that materials and product compatibility meet the quality demands of the pharmaceutical industry. In this regard, all equipment that may be used in a pharmaceutical processing area should not contaminate or otherwise impair product quality.

In order to distinguish between different areas of pharmaceutical processing (and the Material of Construction (MOC) demands of these particular areas), it is common to classify material requirement according to duty. The three most common area classifications are:

1. Contact part: a material part that the material comes into contact with during normal processing, such as the inside of a mixer granulator. These materials should be fully inert in the operating environment, including all cleaning regimes and passivation solutions.

2. Non-contact part: a part that is exposed in the process area, which may get coated with product when the processing vessel is opened and will require cleaning at product changeover. The product does not contact these parts during normal processing and no product is recovered from these parts and returned to the process, e.g., the legs or support frame for a mixer granulator.

3. Technical area part: a part of the equipment normally housed in a technical area, which is never exposed to product and should not require cleaning at product changeover, e.g., the main electrical cabinet for the mixer granulator.

4.5.1.1 Metallic Parts

Stainless steel alloys, such as AISI 316L/DIN 1.4404, or higher nickel base alloys are the metallic material typically used for most processing applications, where the item or component comes into direct contact with the product or process. Other materials are acceptable, but should be non-reactive with the process.

For non-contact parts, lower grades of stainless steel, such as AISI 304/DIN 1.4301 or AISI 316/DIN 1.4401, may be used.

For technical area parts, any metallic material may be used as long as it is ‘fit for purpose’ for the particular application.

4.5.1.2 Plastics and Elastomers

In the case of non-metallic plastics and elastomers, there should be no chemical attack of the polymer by the processing environment, and the constituents of the selected polymers should not be extracted into the processing environment during use. The latter is especially true in regard to exposure of plastics and elastomers to organic solvents. For those items/components that will come into direct contact with the processing environment, it is advisable that food grade materials conforming to the appropriate sections of the 21 CFR Part 177.2600 [32], and USP Plastic Class VI [33] criteria are used.

4.5.1.3 Equipment Fabrication

The equipment fabrication should follow the specifications as laid out in the relevant approved engineering documentation.

The method of welding and quality of workmanship are critical to the overall integrity of equipment. Internal welds should be ground smooth and polished to match the surface finish and contours of adjacent parent material. External welds may be ground smooth, but can be left 'as laid' providing carbonization is removed. For all welds, defects such as over penetration, undercut, porosity, and spatter are not allowed and when these occur, they should be dressed and repaired in a manner that is acceptable.

The finished surfaces should be crevice and ledge free and cleanable. This is generally achieved by radiusing all corners and sealing all joins.

During fabrication, for stainless alloys, there should be no contact with ferrous materials, such as carbon steel, owing to the risk of iron pick up and contamination of product/process contacting surfaces.

4.5.1.4 Surface Finish

The quality of finish on product contact surfaces is important during processing, as it impacts on powder flow out of the hopper, but is especially important to the cleanability of that surface, where the goal is a smooth surface, which promotes cleanability.

The roughness/finish requirements should be detailed in the engineering drawing and can be defined by an Ra value (surface roughness measure). Surface finish requirements are application and process dependent. Due to the geometry of equipment and fabrication techniques, achieving the desired surface finish on all surfaces may not be possible. As polishing is a time consuming operation, choosing a particular finish and the degree of smoothness will affect cost. Before selecting a surface finish for process equipment, these points should be considered. For further information on surface roughness requirements see the ASME Bioprocessing Equipment (BPE) Standard Part SF [34], which provides product contact surface finish acceptance criteria for metallic and polymeric materials.

Pickling and passivation is frequently specified for stainless steel components as a final clean of finished components/items and should be performed in accordance with relevant national and international standards. Specifically, ASTM A380 [35]and ASTM A967 [36] are appropriate standards detailing methodologies and practices for carrying out such treatments on 300 series stainless steels, such as 304L and 316L types. It is not necessary to pickle and passivate all stainless steel components post fabrication, and it is not generally required for surfaces routinely exposed to the air, but it is the norm for wetted parts, such as purified water piping.

4.5.1.5 Certification

Material certificates should confirm material types, grades, and suppliers. Certificates of conformity issued by an equipment manufacturer (with an adequate quality system) should be provided for all product contact parts of the equipment, including individual components that form part of an item.

Material certificates or Certificates of Conformity confirm that materials of construction are food grade and of the specified material. These certificates should be provided for all plastic or elastomeric contact parts and any lubricants that may contact the product.

Weld procedures, finish certification, passivation, and electropolishing are also usually expected where applicable.

The origin of all raw materials used in the manufacturing of pharmaceutical products should be known. Certificates of Origin should provide product traceability. Animal component free materials are primarily a concern with respect to Transmissible Spongiform Encephalopathy (TSE) and viral contamination. Bovine Spongiform Encephalopathy (BSE) (i.e., Bovine TSE) is a form of the disease known as "Mad Cow". Certificates of Origin should provide batch or source information about a component or material. This should allow TSE/BSE risk assessments to be performed on the components and materials, based on their intended use.

The European Directorate for the Quality of Medicines (EDQM), the European Medicines Agency (EMA) and the WHO provide guidance documents and directives that should be followed in relation to minimizing the risks of transmitting TSE.

4.5.1.6 *ASME Bioprocessing Equipment*

The ASME Bioprocessing Equipment (BPE) Standard [37] provides requirements for systems and components that are intended to be cleaned, sanitized, or sterilized, including the equipment or systems that provide these processes. The ASTM BPE includes requirements for:

- New system and component design and fabrication
- Definition of system boundaries
- Specific metallic, polymeric, and elastomeric materials of construction (i.e., seals and gaskets)
- Component dimensions and tolerances
- Surface finishes
- Material joining
- Examinations, inspections, and testing
- Sealing components
- Certification

Equipment and components utilized in OSD manufacturing facilities may not need to comply with the ASME BPE [37]. The standard can, however, act as a guide, when no other standard or guide is applicable.

4.5.2 *Product Sampling*

It is required by regulation (e.g., 21 CFR Part 211.165 Testing and Release for Distribution [38], 21 CFR Part 211.110 Sampling and Testing of In-process Materials and Drug Products [39]) to test each batch of drug product to determine conformance to final specifications for the drug product prior to sale. The cGMP regulations require sampling during and/or after each process step when that step may be responsible for causing variability in the material under process. Although sampling from the various process steps assists in their monitoring and control, it is not required to sample routinely from every process step. When this sampling is necessary during process qualification and validation, temporary sampling procedures may be acceptable. When a sample is needed for routine process monitoring and control, it is best to build a sampling device into the equipment so that it is not necessary to open up the equipment and break containment to take the sample. Taking a sample from a fluid bed dryer for moisture testing is such a case. Where product sampling can be replaced by on-line or at-line measurement (PAT), the opportunity to do so should be considered. There may be significant costs and technical challenges in developing and implementing PAT tools and these can present a business risk.

Table 4.4 summarizes some common failure modes and the process control techniques used for each of the major unit operations in OSD manufacturing to prevent them.

Table 4.4: Common Failure Modes and the Process Control Techniques

Unit Operations	Common Failure Modes	Process Control Techniques
Granulation	Fail content uniformity	Feedback control on spray solution flow rate; granulator impeller speed
Drying	Over drying or under drying	Monitoring of outlet drying air moisture content, Near Infrared (NIR) end point determination, and control of inlet air temperature
Milling	Fail particle size distribution	In line sieve analysis, laser particle size analyzer
Tableting	Soft tablet, laminating	Automated tableting force monitoring (precompression and compression) and control, granulation moisture analysis
Encapsulation	Leakage, high moisture, out of specification fills	Proper tuning and set up of encapsulation machine setting, check weighing
Coating	Over spray, low yield, tablet elegance	Proper alignment of spraying nozzles, coating solution flow rate control, temperature control

4.5.3 Cleanability and the Use of CIP

Clean In Place (CIP) is an automated cleaning cycle whereby the contact parts of the equipment are effectively cleaned using jets of water. The CIP cycle may be preceded by manual intervention to remove parts which may be difficult to clean. These parts may be washed off-line and returned to the equipment post CIP. Washing In Place (WIP) is the process by which contact parts of the equipment are wetted down and effectively decontaminated before the equipment is manually stripped down and washed.

Sterile operations may require the sterilization of sterile product equipment and associated piping. For further information on sterile products, see the ISPE Baseline® Guide on Sterile Product Manufacturing Facilities [40].

4.6 Equipment and Parts Cleaning

Risks which should be considered when creating a cleaning process include:

- Cross-contamination that can result from insufficient cleaning
- Contamination due to insufficient rinsing of cleaning agents

4.6.1 Equipment Cleaning

Manual cleaning of major equipment is a risk, as identified in Section 4.6.6 of this Guide. Legacy equipment may exist within a facility that requires manual cleaning, but it is strongly recommended that new or existing process equipment be cleaned with an automated washing procedure if possible. The three typical automated washing procedures utilized in the industry are:

- Clean In Place (CIP)
- Wash In Place (WIP)
- Clean Out of Place (COP)

4.6.1.1 Clean In Place

CIP is a fully automated washing sequence of equipment in situ. Utilizing a CIP skid and auxiliary piping, a programmed washing recipe can be executed to wash completely a piece of equipment with no manual manipulation or additional cleaning required.

4.6.1.2 Wash In Place

WIP is a semi-automated washing sequence of equipment in situ. Utilizing a WIP skid and auxiliary piping, a programmed washing recipe can be executed to wash a piece of equipment with some manual manipulation and additional cleaning required. Typical required interactions include removal of filters and removal of internal baffling or components.

4.6.1.3 Clean Out of Place

COP is a fully automated washing sequence of equipment in an alternate location. Utilizing a COP washing skid and auxiliary piping, a programmed washing recipe can be executed to wash a piece of equipment with no manual manipulation or additional cleaning required. Some tablet presses have encapsulated turrets that can be removed and taken to a remote location to be cleaned, but the most common equipment cleaned via COP are portable solution vessels.

The automated washing sequences should be validated to document repeatable results based on worse case scenarios. As new products are developed, a developmental wash sequence should be created to test the cleanability of the equipment under new conditions.

4.6.2 Parts Cleaning

Parts leaning in OSD forms manufacturing facilities fall into two categories:

1. Manual parts cleaning

2. Automated parts cleaning

4.6.2.1 Manual Parts Cleaning

Manual parts cleaning has been utilized to clean small change parts and small equipment since the inception of OSD manufacturing. As processes and procedures have developed, organizations have identified the inherent risks associated with manual cleaning. Due to observed risks of cross-contamination, consistency, quality, and material handling, manual cleaning has become a much more challenging operation to develop and maintain.

The largest risk with manual cleaning is obtaining repeatable results. Operators should be trained to use the same scrubbing patterns and procedures, soak or rinse the items for the same length of time and determine “visually clean” surfaces accurately. If managed correctly, manual cleaning can be effective and repeatable, but there is risk due to human error.

4.6.2.2 Automatic Parts Cleaning

Automated washing equipment is usually custom designed to accommodate the various sizes and shapes of production equipment. Automated washing equipment can use approved CIP chemicals and multiple rinsing steps to ensure that no trace of pharmacologically active compounds or cleaning agents remain at the conclusion of the wash cycle.

Water systems for automated washing functions usually include hot and cold potable water or Purified Water (PW). Final rinsing should use PW.

When designing a parts washer loading pattern, spray coverage and drainability of each component should be considered. The loading pattern should be documented during cleaning validation. While a parts washer will execute the same washing cycle each time (wash time, flow rate, temperature, etc.), there is still a human aspect to the loading of a washer. Equipment loading should be identical for each recipe and should be documented in SOPs.

Cleaning water must meet the same requirements of the grade of water used for product formulation, as defined in the relevant pharmacopeias.

4.6.3 Room Cleaning

Manual cleaning of OSD forms manufacturing facilities should be performed in order to maintain the cleanliness of the production environment.

Water systems used to facilitate room cleaning usually involve the installation of one or more hose stations within each production room. Hoses can be used to wash down all equipment within the room and the room itself. Water for cleaning in OSD forms manufacturing facilities is normally provided through the hose stations as hot and cold potable water or PW.

Suitable cleaning agents should be determined for the room, depending on the physical characteristics of the bulk materials. Cleaning agents needed for clean rooms should be considered before selecting room finishes.

4.6.4 Designing for Cleanability and CIP

The internal parts of the process equipment should be kept as simple as possible with a minimum number of mechanical intrusions, openings, or areas where product might become trapped and be difficult to remove. All inlets to the equipment should be sloped down into the equipment to facilitate drainage and ensure that there is no possibility of trapped volumes of liquid, which would cause dead legs, where liquid would remain after subsequent air blow and drying steps.

All wash liquid should drain to the lowest point in the body of the equipment. Pressure taps and other instruments, such as temperature or NIR probes, should be mounted to ensure that product is not trapped. It is typical with pressure taps, e.g., to purge the tapped lines with low pressure air during the process step to minimize product ingress. CIP nozzles should be positioned to ensure effective coverage of all parts of the equipment body with care taken to eliminate shadowing, where one mechanical part prevents the water spray from hitting a contaminated surface behind that part.

Typical cleaning cycle example:

1. Once through rinse with process water to wet down parts to be manually cleaned off line
2. Manual intervention to remove difficult to clean parts, such as bag filters on a fluid bed
3. Once through rinse with process water
4. Recirculated wash with process water, including detergent if used
5. Once through rinse with process water
6. Recirculated wash with process water, including second detergent if used
7. Once through rinse with process water
8. Final rinse with purified water
9. Blow through CIP pipe work and nozzles with compressed air to dry the equipment

There are a number of in situ cleanable machines available, such as granulators, fluid bed dryers, and tablet presses, on which design refinements have been made to ensure the equipment can be cleaned using a CIP process without the need for any manual intervention. The use of cleanable metal cartridge filters, instead of the traditional filter socks, has made this possible on fluid bed dryers. Other design enhancements to the standard process equipment to make it a cleanable dryer include:

- Flush fitting sight glasses and openings
- Pinched seals, which protrude slightly into the dryer and so as not create a gap into which product can • be forced
- Inserting nozzles, which lie flush with the machine body during processing and only protrude out into the equipment during cleaning

Process specific cleaning issues are addressed in the Table 4.5.

Table 4.5: Process Specific Cleaning Issues

Process Step	Process Specific Cleaning Issues
IBCs and Bins	When a number of IBCs are being used, it is typical to provide an automated IBC wash booth as an alternative to time consuming manual washing. If the IBC is to be washed in such a booth, this needs to be considered at the design stage. To allow washing of the inside of the IBC and drainage of wash water, it is usually necessary to either remove the charge and discharge valves or to build into the booth a system for actuating the valves. The latter is usually the case when potent products are being handled and there is a need to maintain containment. The IBC also should be designed to eliminate horizontal surfaces both on the top surfaces where pools may form and on lower surfaces where drips may adhere. This will ensure that the wash water can drain off all the IBC surfaces. Any water retained on the surface of the IBC will be difficult to dry during the drying sequence.
Dry Granulation/ Roller Compaction	The roller compactor cannot be regarded as a fully sealed device; it does not lend itself easily to full CIP. It is more usual to use a WIP procedure to decontaminate the machine and then manually strip down and clean the device. The force feeding device, screw(s), or auger also have to be removed for manual cleaning after an initial wet down.
Spray Granulation and Drying	Because of its size and complexity, the fluid bed dryer probably represents the most difficult decontamination challenge in any OSD forms manufacturing facility. Typical steps in a dryer changeover sequence include removal of the internal filter bags, which can be a dusty operation as normal practice is to lower the filter sock and remove it via the bowl opening. In dryers where WIP or CIP spray nozzles are fitted, it is usual to use these to damp down the filters prior to removal so as to minimize the dust hazard. WIP/CIP systems are fitted to most modern dryers. The majority of CIP systems are designed to operate in conjunction with a degree of manual intervention for parts that would prove impossible or impractical to clean with a nozzle. A fluid bed dryer with a batch size of 200kg might have 10 to 12 nozzles in order to provide effective cleaning of all parts of the dryer. Each nozzle may use between 20 and 60 liters/minute. Fixed nozzles will require a lower amount of water than rotating spray balls. In order to reduce the peak flow, it is normal to split the nozzles into three or more groups, which are manifolded separately and operated in sequence. However, during a 20 minute CIP cycle, over 3 to 5 m^3 of water can be used. After the washing cycle, the dryer air handling system is used to dry the machine.

Table 4.5: Process Specific Cleaning Issues (continued)

Process Step	Process Specific Cleaning Issues
Dry Milling	Where milling systems are integrated into the upstream process, such as the fluidized bed drying operation, it is not uncommon for the mill to be integrated into the CIP system for that machine (see above). It is unlikely that a mill would be provided with its own dedicated CIP system, but may have a wet down facility prior to being manually cleaned. Whether CIP or WIP is applied to the mill, it is usually the case that the mill screen will need to be removed from the mill after initial wetting, for cleaning off line.
Compression	Tablet press changeover and cleaning has traditionally been a time consuming process as the press needs to be de-tooled, cleaned, and retooled manually. There have been a number of developments to reduce changeover times and increase press productivity. These include washable, removable turrets, and wettable machines.
Encapsulation	Capsule filling machines have been designed as wettable, which allows manual strip down and cleaning after an initial wet down.
Tablet Coating	Current (at time of publication) practice is to provide a WIP system for the majority of coaters. The WIP system consists of a number of spray devices permanently located inside the coater and associated ductwork that is supplied with washing agents. The WIP cycle can act as a pre-wash prior to dismantling and manual/out of place washing of selected system components. In the more modern installations, no further manual intervention is required to achieve an acceptable cleaning standard. After the washing cycle, the coater air handling system is used to dry the machine.

4.6.5 Validation of Cleaning and CIP

Automated CIP cleaning is preferred as such systems provide more effective and repeatable cleaning action than that which can be obtained manually.

It is possible to examine the effectiveness of a CIP operation by spraying the inside of the equipment with a water soluble indicator material, allowing it to dry and then operating the CIP system. Riboflavin (vitamin B2) is a convenient indicator. After washing, the internal parts can be inspected under ultraviolet light, which causes any remaining traces of riboflavin to fluoresce. However, it should be emphasized that such an examination just indicates the system is operating effectively and does not constitute validation.

Acceptable validation is part of process qualification testing, which involves swab testing of product contact areas in the fluid bed dryer. It is possible to supplement swab testing with analysis of the final CIP rinse water. This test can be repeated at specified intervals to ensure that the cleaning process is repeatable over time. Alternatively, monitoring of the drain water can be a part of the control of the cleaning process with the final rinse continuing until the outlet water attains the desired level of contamination.

4.6.6 Manual Cleaning

Another point to consider is the ability to dismantle equipment easily and without specialist tools. To thoroughly clean any equipment requires a degree of manual intervention, if only for visual inspection after a CIP. It should be possible to access for inspection and, if needed, manual cleaning of all product contact parts.

Where equipment parts are dedicated to a specific product, e.g., cloth filters in a fluid bed dryer, they should be easily removable, to allow cleaning in a separate washing area or cabinet type parts washer.

For validation of manual cleaning of equipment and components, SOPs should be established. These SOPs should provide repeatable procedures that produce clean surfaces. For manual cleaning operations, swab tests are normally used to indicate cleanliness. Two other methods that can demonstrate cleaning effectiveness are:

1. Rinse water analysis

2. Cleaning “coupons”

4.7 Material Handling

Pharmaceutical products are generally manufactured using a batch process. Therefore, it is necessary to transfer the material output from one stage to the next. The transfer can be achieved using an intermediate container or using a direct link between the two process stages.

4.7.1 Indirect Material Transfer

The more traditional approach is to use open or loosely lidded containers for dispensing and material transfer activities. Such containers are not contained and are typically filled through the open top and emptied by tipping or manual scooping. This way of working has material handling implications and because of dust emission, it also has containment implications.

Pharmaceutical materials usually are transported and handled in drums, bags, or Intermediate Bulk Containers (IBCs). The main considerations when designing or selecting an IBC are sizing/capacity, transport (including ensuring the bin does not leak), charging/discharging, and impact on material of being stored in the IBC.

The IBC also may be used for blending of materials and for highly hazardous products that may need to be charged/discharged in a contained way. Consideration should be given to how the IBC is to be cleaned. The information in this Section focuses on rigid wall IBCs. Flexible wall IBCs (also known as FIBCs) with closure systems or active/passive valves are an emerging technology that are gaining in acceptance for pharmaceutical operations.

4.7.1.1 IBC Design

The capacity of the IBC depends on several factors, including the poured bulk density of the powders, granules, or tablets being transported, and whether the material being transported is also to be blended in the IBC. In pharmaceutical applications, IBCs are generally for multi-product use so selection of the IBC volume should be based on the worst case (lowest) density. For purely transport applications, a typical fill factor of 0.8 is used to allow for the formation of a powder cone during charging. As a general rule, poured bulk densities of pharmaceutical powders and granules lie in the range 400 to 600 kg/m^3. Typical tablet poured densities lie in the range 700 to 900 kg/m^3.

If the IBC is to be washed in a wash booth, it should be designed to eliminate horizontal surfaces both on the top surfaces where pools may form and on lower surfaces where drips may adhere. This will ensure that the wash water can drain off all the IBC surfaces. Any water retained on the surface of the IBC will be difficult to dry during the drying sequence.

Critical IBC design considerations include:

- Container closure design
- IBC geometry
- Discharge angle
- Material of construction and surface finishes

- Powder flow assist devices
- Internal configuration (i.e., blending assist technologies)

4.7.1.2 Charging

The IBC may be designed for single point charging/discharging, in which case a means of inverting the IBC, usually at the filling point, needs to be provided.

It is more usual to design the IBC with a charging point at the top and a discharge point at the bottom.

Air displaced from the IBC will need to be vented and it will be necessary to earth the IBC during charging.

4.7.1.3 Transport

The IBC may be mobile and fitted with castors/wheels. Alternatively, the IBC may be transported by pallet truck, in which case suitable channels to accommodate the pallet truck forks should be provided.

If the IBC is lifted by a pillar lift/post hoist, suitable lifting points to accommodate the pillar lift forks should be included in the design.

The discharge valve normally closes off the IBC outlet. It is possible to provide a secondary means of containment by attaching a dust cap or transport cap. It is also possible to fit transport caps to IBC discharge cone valves. The transport cap for cone valves also locks the cone in position, which allows the IBC to be inverted as is necessary for blending.

4.7.1.4 Discharging

The type of discharge should be designed for the worst case material, which typically requires a 200 to 250 mm opening when using a standard butterfly valve.

Where the materials are cohesive and exhibit poor flow characteristics, internal or external activation of the powder may assist discharge. Internal activation is typically achieved with a vibrating probe of some sort, whereas external activation is typically achieved by vibration of the IBC.

An alternative outlet valve for poorly flowing powders may be an activated cone valve. An in built cone lifting/activation device may apply the cone activation. It is more usual on cone valve IBCs to have the cone lifting/activation device built into a discharge station onto which the IBC needs to be docked for discharge.

To assist in the discharge of powders from the IBC, the sidewalls of the IBC should be no more than 30 degrees from the vertical. To ensure that this wall angle is constant on all sides of the IBC, it is usual to construct the IBC such that in cross section it is either square or round. Rectangular cross-sectioned IBCs result in different wall angles on adjacent sides.

If only tablets and/or round pellets (spheroids) are to be handled, wall angles on the discharge cone can be made shallower and may be up to 50 degrees from the vertical.

If tablets are being transported, special designs of discharge valve may be required in order to prevent damage to the tablets in the event of the valve closing during discharge. Typically, for tablet IBCs, flexible membrane iris valves, soft silicone rubber butterfly valves, or specially adapted cone valves may be used.

Air should be vented into the IBC and the IBC should be earthed during discharging.

4.7.2 Direct Transfer

There are alternative ways of directly transferring powders and particulates, but only a limited number are routinely used in the pharmaceutical industry.

4.7.2.1 Gravity

The easiest way to directly transfer material between equipment is via a link using gravity. This is routinely used, e.g., when transferring granules from a mixer granulator to a fluid bed dryer. Ideally, such a discharge chute should be as close to the vertical as the layout of the two pieces of equipment will allow. In such systems, there should be an outlet valve on the upstream equipment and an inlet valve to the downstream process. This will allow the chute to be removed without losing containment.

4.7.2.2 Pneumatic Conveying

Pneumatic conveying is the movement of solids suspended in or forced by a gas stream through conveying lines. The process can be used to transport particles ranging from fine powders to pellets and bulk densities of 16 to 3200 kg/m^3. Dust collectors used with pneumatic conveying of combustible dusts should meet the explosion protection requirements described in Section 11.4 of this Guide. There are two basic pneumatic conveying techniques:

1. Dilute phase

2. Dense phase

Dilute phase pneumatic conveying utilizes a high volume of low pressure (less than 1bar) or vacuum air as the motive force to move powdered and/or granular bulk materials through an enclosed convey line. The high velocity (15 to 45 m/s) airflow typical of a dilute phase system, moves materials through the convey line in an airborne state. Dilute phase pneumatic conveying is extremely cost effective and is well suited for handling non-abrasive, non-fragile, or light materials. Under dilute phase pneumatic conveying conditions, the solid particles behave as individuals, fully suspended in the gas and aerodynamic forces dominate. For that reason, particle properties such as size, shape, density, and size distribution, have the greatest impact on pneumatic conveying. Dilute phase vacuum operation pneumatic conveying is typically chosen for pharmaceutical applications.

Dense phase pneumatic conveying utilizes a small amount of air at a relatively high pressure (above 1 bar) as the motive force to move powdered and/or granular bulk materials through an enclosed convey line. Due to the low conveying velocity (1 to 15 m/s) produced by a dense phase system, materials are gently pushed through the convey line in controlled “slugs”. As a result, dense phase is preferred for moving mixed batches or materials that may be abrasive, fragile, heavy, or hygroscopic in nature.

Dust explosivity is a major concern when transferring explosive powders pneumatically. See the latest edition of the NFPA 69 Standard on Explosion Prevention Systems [30].

4.7.2.3 Flexible Screw Conveyors

The key element in flexible screw conveyors is a rotating spiral within a sealed tube conveying the materials by an Archimedean Screw action. There is no need for any additional equipment, such as filters, because air is not used as the conveying medium, and minimal risk of dust contamination escaping to atmosphere.

During conveying, the rotating spiral is centralized in the tube by the product so there is little product attrition. The action of the screw can provide a degree of remixing, which may be beneficial for product prone to segregation.

For most applications, a standard screw is used, but a range of screw geometries is available for difficult materials. Each screw profile will have a different conveying rate range, but the rate of conveying will be controlled by the screw speed.

4.8 Process Unit Operations

Different routes to the final OSD form are available, including wet granulation, dry granulation, and direct compression. The unit operations utilized in each vary slightly and have advantages and disadvantages, e.g., one process may be more favorable for highly hazardous or non-hazardous compounds. Decision trees, as part of a risk assessment, should be developed to assist with selection of properly designed equipment to meet the process criteria and requirements.

The unit operations described in Table 4.6 present the typical areas in which they occur, cleaning methods, containment levels, electrical classifications, and enclosure ratings. This is intended to be a guide to what is a baseline condition for these typical operations, although there may be exceptions. Users are responsible for determining the proper levels of protection (cleaning, containment, and electrical) required in a facility.

Table 4.6: Unit Operations

Unit Operation	Operation Type	Containment Level	Enclosure Ratings	Electrical Class
Excipient Weigh/ Dispensing	Open Area	> 1,000 µg/m³ < 10,000 µg/m³	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
	Down Flow Booth	< 10,000 µg/m³ > 20 µg/m³	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
	Isolator	< 20 µg/m³	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
API Weigh/ Dispensing	Open Area	> 1,000 µg/m³ < 10,000 µg/m³	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
	Down Flow Booth	< 10,000 µg/m³ > 20 µg/m³	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
	Isolator	< 20 µg/m³	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
Material Transfer	IBC and Docking Stations	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
	Drums with Transfer Systems	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
	Bulk Bag and Docking Stations	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
Blending	Post Hoist/Column IBC	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	Not Applicable
	V Blend	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Double Cone	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2

Table 4.6: Unit Operations (continued)

Unit Operation	Operation Type	Containment Level	Enclosure Ratings	Electrical Class
Blending *(continued)*	Conical Screw	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
Granulation	Roller Compaction	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Low Shear	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	High Shear	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Continuous	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Wet Milling	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Binder Prep	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
Drying	Convection Oven	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Vacuum Tray	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Vacuum Tumble	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Fluidized Bed	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2

Table 4.6: Unit Operations (continued)

Unit Operation	Operation Type	Containment Level	Enclosure Ratings	Electrical Class
Drying *(continued)*	Dry Milling	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Spray Drying	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Filter Dryers	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Vacuum Filter Dryers	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
Milling/Sieving	Hammer and Screen	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Pin Mill	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Conical	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
Compression	Tablet Press Gravity Feed	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Tablet Press Centrifugal Feed	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Roller Compactor	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Extrusion	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2

Table 4.6: Unit Operations (continued)

Unit Operation	Operation Type	Containment Level	Enclosure Ratings	Electrical Class
Coating	Perforated Pan Batch	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Solid Wall Pan Batch	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Pan Coater	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Perforated Continuous	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-1 Div I & II CL-2 Div II ATEX Zone 1 ATEX Zone 2
	Fluidized Wurster	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	
	Fluidized Tangential	< 10,000 µg/m³ to < 1 µg/m³ (see Note)	NEMA4/4X, IP66, or local equivalent	
Note: strategic containment performance can be enhanced with the use of additional engineered controls and devices.				

4.8.1 Equipment Selection Criteria

The conversion of the raw material powders into the final dosage form may involve a number of process operations and require a number of pieces of process equipment. When a process and the equipment to carry it out is being designed or selected, the following points should be considered:

- Processing the ingredients to make the product within the tightest specification range possible for product quality
- Containment, accommodating both operator protection (exposure avoidance) and product protection (cross-contamination avoidance), based on the relative risks to each, as determined by a risk assessment
- Flexibility
- Cleanability
- Maintainability
- High productivity
- Minimized down time
- Minimized unit costs

4.8.2 Dispensing and Material Sampling

Sampling may be required for different purposes, e.g.:

- Prequalification
- Acceptance of consignments
- Batch release testing
- In-process control
- Special controls
- Inspection for customs clearance
- Deterioration or adulteration
- Obtaining a retention sample

The tests to be applied may include verifying the identity, performing complete pharmacopoeial or analogous testing, and performing special or specific tests.

Materials to be sampled usually belong to the following classes:

- Starting materials for use in the manufacturing of finished pharmaceutical products
- Intermediates for use in the manufacturing process (i.e., bulk granules)
- Pharmaceutical products (in-process, as well as before and after packaging)
- Primary and secondary packaging materials
- Cleaning and sanitization agents, compressed gases, and other processing agents

Raw Material Sampling

Raw material sampling should be performed in an area or booth within the weigh and dispensing area that is designed for and dedicated to this purpose. A sample log to record all sampled materials should be maintained. Some sampling may need to be performed in dedicated environments (i.e., hazardous or potent materials which need to be contained from operators or the environment, or where prevention of contamination by dirt or particles from the environment is required). Secured controlled access storage areas may be required for some narcotic type materials.

SOPs should be followed when sampling raw materials. The SOP should provide a documented means of assuring that the changes to raw materials are identified, documented, authorized, and implemented taking into account any required quality, regulatory and validation factors, as well as any environmental and safety issues.

For further guidance on raw material sampling, as well as sampling plans, and other classes of sampling, see the WHO Technical Report Series, No. 929, Annex 4 [41].

Dispensing should have a higher output than downstream steps in the OSD forms manufacturing process to prevent it becoming a bottleneck.

Centralized dispensing areas are usually located near the warehouse to limit the transit of raw material containers through GMP areas. Depending on the output of the production facility, one or more weigh and dispensing units may be required. A multi-product manufacturing facility may have product dedicated dispensing suites, while a pilot plant facility may need only one weigh and dispensing room.

"Local:" dispensaries adjacent to, and dedicated to, a manufacturing area can allow dispensed goods to exit directly into the clean corridor supporting process suites.

Pure API may be handled during dispensing. The dispensary should be constructed and operated under the same GMP and environmental/protection regime as downstream process rooms. Key design considerations for equipment and dispensaries include:

- Containment
- Operator protection
- Prevention of operator exposure
- Cleanability

The containment features and equipment used in a dispensary are a function of the level of risk for the materials and the dispensing methodology.

Solution preparation, particularly of solvent based materials, is usually performed in a separate liquid preparation area.

4.8.2.1 Manual Dispensing and Containment

Manual dispensing in an open environment can achieve concentrations that will be challenging to many OELs and cross-contamination limits. Therefore, a typical approach is to perform weighing in a laminar air down flow booth. Separate booths may be used for active ingredients and excipient materials. For the purpose of this Guide the material OELs should be classified according to guidance given in Table 4.6 of this Guide.

The use of a laminar air down flow booths can provide protection to a level of 100 to 300 µg/m^3. The level of protection can be increased by combining other engineering controls with the Unidirectional Air Flow (UDAF) booth or Airflow Protection Booth (APB). When performing manual handling, improvements in containment using engineering controls are technique dependent.

For potent compounds with OELs between 1 and 10 µg/m^3, the use of a laminar air down flow booth should be combined with another engineering control, such as a ventilated balance enclosure or a 5D rigid barrier. For highly potent compounds with OEL < 1 µg/m^3, the use of only a laminar air down flow booth is not recommended. Highly potent compounds should be handled with isolator technology.

For highly potent compounds, the use of isolators to weigh materials should be considered. Isolators can be of either a solid or a flexible type, each with HEPA filter air and suitably positioned glove ports. Vessels or IBCs may be charged directly from a weigh isolator, but this will require a raised working platform to accommodate the IBC underneath. Alternatively, the isolator may be located in a room on the floor above the IBC charging area. Other containment type equipment typically utilized with contained operations and isolators includes:

- Split butterfly valves
- Beta bags

- Beta type containers
- Alpha-beta ports

Material passing through airlocks should be evaluated and considered when high level containment for product and personnel protection are the goal in the weigh and dispensing operations. Highly potent material dispensing may be located in the manufacturing containment facility. Personnel airlocks may be used to separate these areas and other special areas such as gowning/de-gowning or decontamination which may be required when handling such active ingredients.

4.8.2.2 Automated Dispensing

Automated mechanical dispensing systems are typically based on some method of discharging material from a container or hopper in a controlled way into a receiving container in which the material is weighed. Such systems require that the individual materials be transferred from their primary container into a hopper or similar typically using gravity charging or pneumatic conveying. The controlled discharge from this hopper may involve the use of screw feeders, rotary valves, or pulsed opening of standard valves. The material is collected in a weighed receiving container. When the desired weight of material has been dispensed into the receiving container, the feeding system will be stopped and the next component may be dispensed. When dispensing is based on “loss-in-weight” from the hopper it may be possible to dispense all the components in parallel.

Consideration for the method of data collection and operator instruction must be incorporated into the design.

4.8.2.3 Material Handling and Material Movement

The equipment and method of dispensing should support the material handling and processing philosophy of the facility. Material movements in and out of the dispensary are high, with both raw material and dispensed material intermediate containers being handled. A review of these material flows, including how they integrate with the dispensing equipment, should be performed. Such a review and assessment of risk minimizes the likelihood for cross-contamination, while maximizing the potential for success of this operation and throughput.

Table 4.7 shows the most suited application for the various dispensing or material handling approaches.

Table 4.7: Application for Dispensing or Material Handling Approaches

Category	Dispensing/Material Handling Approach	Most Suited Application
Dispensed Material Container	Disposable Bag	• Small batches • Difficult to clean materials • Low volume
	Rigid Open/Loose Lidded Container*	• Non-potent • Mid to high volume
	IBC	• Potent materials when containment valves are used • Large batches • High volume • Easy to clean materials
Materials Dispensing Methodology	Manual/Hand Scooping*	• Non-potent • Low volume • Difficult to clean materials
	Manual Mechanically Assisted Handling* (drum tipper/drum inverter)	• Non-potent • Mid to high volume • Large batches
	Automated Dispensing*	• Potent materials when containment valves are used • High volume • Less suited to multiple products • Easy to clean materials
Containment	Open Dispensing*	• Non-potent • Easy to clean materials
	Dispensing in Drafted Environment (airflow booth or local exhaust dust extraction systems)	• Midrange potency • Mid to high volume
	Contained Dispensing (isolator)	• Potent materials • Low volume/low dispensed weight • Easy to clean materials • Less suited to multiple products
Material Container Handling	Manual Transport (lift and carry)	• Small batches • Low volume
	Mechanically Assisted Manual Transport (pallet truck), Automated Guided Vehicles (AGVs)	• Mid to large batches • Midrange volumes • Large batches • Large volumes
*Local drum ventilation/dust collection to be considered in these operations.		

4.8.3 Granulation

Pharmaceutical granulation is the process of joining several powder particles together into one larger particle, known as a granule. These granules can be composed of particles of either the same or dissimilar materials, depending upon the formulation. Granules are joined together using either wet or dry granulation processes. Wet granulation may use a binder solution. For materials that are water soluble, wet granulation does not need a binder. No liquid is used for dry granulation roller compaction; mechanical forces are used to press the particles together into a granule.

Granulation is performed for various reasons, including:

- Particle size and uniformity: final granule size can be predetermined with the proper process parameters
- Segregation: prevents the segregation of the constituents of the powder mix, due to differences in the size or density of the components of the mix
- Robustness: the binder solution adheres the powder particles together, reducing friability
- Flowability: enhance flowability since many powders, because of their morphology, are cohesive and do not flow well
- Compaction: a binder solution helps hold the granules together when they are compressed into a tablet. Uniform size particles and flowability also help tablet press operation
- Dust: many powders are fine and prone to dust during processing. Granules are larger and avoid dust issues

4.8.3.1 Wet Massing/Extrusion Granulation

The traditional pharmaceutical process made use of a planetary mixer for mixing of a binding liquid into a mixture of powders, one of which is the API. This wet massing and extrusion process is still commonly used at development scale and for pellet manufacture at production scale. There is considerable manual handling of the product, and therefore, great potential for contamination and exposure of the operator.

The dispensed powders are charged to the mixer bowl of the planetary mixer, dry mixed, and the liquid binder added. Liquid addition into planetary mixers is less critical than for high shear mixers. It is unlikely that the classical granule growth mechanisms will be evident, as the wet mass is subjected to a considerable amount of work by pressure between the wall and mixer blades or between the mixer blades. This creates a reasonably “heavy” doughy mass that is suitable for external granulation in a granulator/extruder. The consistency of this wet mass depends on the dry particle properties, the amount and type of binding liquid, the mixing time, and agitator speed.

Because of the poor handling characteristics of the wet mass, it is difficult to operate the discharge of the mixer bowl in any automated way. Therefore, it is usual to manually transfer the wet mass from the mixer bowl to the external sizing equipment.

There are many alternative designs of extrusion granulators that can be used for sizing of the granules, but all operate on the same principal where the wet mass is forced through a screen or through a roller. The granulate particulate size is controlled by the aperture size in the screen or drilled hole size in a roller extruder. The smaller the hole size, the greater the degree of densification of the wet mass. This densification may result in the extrudate becoming too paste like, rather than granular. Therefore, it is necessary to optimize the amount of work done in the mixer and during extrusion.

Densification of the wet mass reduces the amount of liquid required to granulate the powders with obvious benefits to any downstream drying operation. However, over densification reduces granule friability and this may impact on granule compression into tablets and on dissolution of those tablets.

4.8.3.2 High Shear Granulation

High shear granulation is used when larger amounts of energy and shear are required to create granules, to reduce cycle time and to reduce particle size distribution.

Material flows into and out of the high shear granulator dictate the layout of the facility and vice versa. The use of manual charging of the granulator is limited by the inherent dustiness of this operation. It is more likely, in a production environment in which closed material transfers with IBCs or direct connections will be used.

Other considerations for high shear granulation systems include preparation and delivery of the binding liquid and automation and control of the process. To wet granulate the dry powder requires the delivery of a binding liquid into the mixer bowl. When using dry binders, the dry material is a mixture which also includes a binding liquid consisting of either purified water or a solvent.

Where the binder materials are included in the binding liquid, a binder preparation system needs to be provided. Some of the more traditional binding agents, such as starch and gelatin, require heating in order to get them to gel. For such materials, a jacket heated binder preparation vessel is required.

High shear granulation formulation development is challenging due to the complex interactions between a number of operating parameters and the granule quality in terms of API content, API distribution, particle size, particle size distribution, and granule density. Typically, a number of fixed control parameters, such as impeller speed, binder addition rate, binding liquid droplet size, and dry mixing time, which allow a limited number of other parameters to vary until a desired process end point is attained. For example, the amount of binding liquid and the time for which the wet mass is granulated may be allowed to vary until a desired impeller load or torque is reached. Because achieving the desired granule quality is important to the success of subsequent processing steps, such as tablet compression, the control of granulation processes is an area where the application of PAT technologies could be beneficial.

4.8.3.3 "Single Pot" Processing

The most common method for producing pharmaceutical granules via a wet granulation route remains the combination of a high shear mixer-granulator and fluid bed dryer. An alternative means of providing better containment, and providing a more ideal process for handling solvents, is to granulate and dry in the mixer-granulator, the so called "single pot" process. Single pot processing is the name given to the process where the powders are wet granulated and dried in a single piece of process equipment.

The wet granulation step in a single pot process is very similar to that carried out in a mixer granulator, but lends itself to particular types of granulation process, including solvent granulated formulations and effervescent tablet formulations.

An additional benefit of single pot processors concerns space, as the single pot process takes up less than half the size of the traditional two story configuration of a mixer-granulator and fluid bed dryer, and considerably smaller than a single process fluid bed spray granulator. Another potential benefit is containment, because at least one transfer step between unit operations has been eliminated. The single pot approach has not been universally adopted mainly because of the existing large installed portfolio of mixer-granulator and fluid bed dryers and the length of drying time required by the single pots.

Drying time is the single longest step in wet granulation. It is crucial to productivity, and a process at which fluid bed dryers are highly efficient. Drying in single pot processors under vacuum and using jacket heating tends to be less efficient than a fluid bed dryer, but can be improved by the enhancements described below, which may or may not be available on a particular design of machine:

- Oscillating the bowl so that it tips from side to side
- Injection of a carrier gas into the product during drying ("gas stripping")
- Application of microwaves

4.8.3.4 Spray Granulation

Spray granulation is a wet granulation process utilizing a fluid bed processor where atomized binder or water droplets are sprayed onto a fluidized powder mass. As the powder moves vertically through the processing chamber it encounters the droplets, particles within the powder mass are wetted and collide with each other to form granules. The fluid bed granulations are more porous than those created by high shear granulators, where the mixing energy produces a denser granule.

Traditionally, fluid bed granulators have used a top spray configuration, with the nozzle mounted well above the bottom screen spraying down onto the fluidized bed. More recent designs have been introduced with the nozzles mounted tangentially in the side wall of the processing chamber or spraying up from the bottom of the process chamber at an angle. The core operating principle is the same: an atomized liquid spraying into the fluidized bed of product to be formed into a granule.

One of the main advantages of fluid bed granulators is the ability to granulate and dry within the same piece of equipment. In addition, by varying key process parameters, the final granule size and density can be consistently controlled. Fluid bed granulators need little floor space but do need extra ceiling height.

Control parameters interact with each other and impact processing characteristics, which in turn affects product quality. Dynamics of fluid bed granulators include:

- Air volume: this higher the air volume, the faster the particles will rise through the fluid bed, therefore minimizing contact time in the atomized droplet zone with less contact and consequently, smaller granules. Higher air volume can mean more drying capacity, allowing higher spray rates. Excessive velocity can cause particle attrition and excessive dust

- Liquid spray rate: higher spray rates can cause a denser atomization zone which causes higher moisture and denser granules

- Atomization air pressure: this determines the droplet size, with higher pressure resulting in smaller droplets

- Air temperature: this determines the evaporation rate within the processing chamber, which will affect particle size, density and brittleness

- Air humidity: this sets the air's ability to absorb moisture and the evaporation rate so the impact is similar to that of air temperature

- Exhaust filter: the porosity and permeability contribute to airflow as well as to fines retention. In general, the tightest filter is best in terms of preventing excess dust from entering the atmosphere as well as returning fines to the product bed to maintain higher yields. However, prevention of an excessive pressure drop should be considered, as this could interfere with proper fluidization

- Bottom screen: this creates a base pressure drop to establish a uniform air stream through the bed. In some cases, it also imparts a slight directional movement to the fluidization pattern to enhance processing

In a typical fluidized bed, the powder sits on a screen at the bottom of the processing chamber with air drawn in from below to create the fluidization pattern. Rotor based fluid beds utilize a spinning disk at the bottom of the processing chamber with an airstream flowing around the edge of the disk to lift the powder. This system combines the high shear aspect of mechanical energy input into the product bed, along with the drying capability of a fluidized bed. Such processors can create extremely dense granules, although they are more often used to create spheres ("spheronziation") or to layer successive coatings onto non-pareil beads.

Spray granulation is a wet granulation process in which the dry powder is contacted with the binding liquid in the processing chamber of a fluid bed processor. There are two ways of introducing the binding liquid. In top spray granulation, the binding liquid is sprayed through nozzle(s) down on to the top of the fluidized powders. In bottom spray granulation, the binding liquid is sprayed upward through a nozzle at the base of a draft tube (Wurster column), which ensures a regular passage of powder through the spray zone.

Bottom spray systems utilizing a Wurster column are usually used for pellet coating applications. The main benefits of the fluid bed spray granulation process compared to conventional wet granulation are lower space utilization and lower capital cost for an equivalent output. In terms of product quality, the granules will be less dusty and have improved flowability, compressibility, and dispersibility. The disadvantages of spray granulation are that the process is not suitable for as wide a range of products as conventional wet granulation, and it is also more difficult to control.

A fluid bed processor can be used to produce a range of granule forms by fitting different inserts. For example, the high shear imparted by the rotor granulator insert within the fluid bed processor chamber results in a denser granule than produced in a conventional (top spray) fluid bed granulator. The granules are smoother and rounder as a result of the toroidal particle movement.

4.8.3.5 Extrusion/Speronization

For some controlled drug release products, it may be desirable to have a dense, spherical pellet suitable enteric coating, typically using a Wurster coating process. A commonly used process to manufacture such spherical particles or pellets is extrusion/spheronization. This is a multi-step process and involves the separate processes of wet massing, followed by extrusion of this wet mass into rod shaped cylinders and subsequent spheronization of these cylinders into spheroids. The product itself is not a dust exposure issue, because the process produces relatively large spherical particles. However, the fraction of residual dust not agglomerated into the spheres can be a containment concern.

Less uniformly sized rounded pellets also may be prepared by varying the process parameters used for granulation in a high shear granulator to obtain a high humidity within the processing chamber. Imparting a high shear on the particles and material physical properties play a role in forming the pellets.

A major difference in the wet massing step for pellets, compared with granulation for compaction into tablets, is the amount of granulation fluid needed to achieve spheres of uniform size and sphericity.

A second difference is the importance of achieving a uniform dispersion of fluid to ensure good quality product. The wet mass should be subjected to a considerable amount of work in the mixer to improve liquid distribution. This creates a reasonably “heavy” doughy mass that is suitable for external extrusion. The wet mass is extruded by being forced through dies and shaped into small cylindrical particles with uniform diameter. The extrudate particles break at similar lengths under their own weight.

The properties of the extrudate and the resulting spheres are highly dependent on the plasticity and cohesiveness of the wet mass. In general, an extrudable wet mass needs to be wetter than that appropriate for conventional granulation by wet massing.

Spheronization rounds off and densifies the rods produced by extrusion into spherical particles. This is carried out in a spheronizer; the working part of which consists of a bowl with fixed sidewalls and a rapidly rotating bottom plate or disk. The rounding of the extrudate into spheres is dependent on frictional forces generated by particle-particle and particle-equipment collisions. The bottom disk has a grooved surface to increase these forces.

For any formulation, there is an optimum rotational speed. Below this speed, there is no change in shape or densification with time. Above this speed densification is so rapid that the process quickly becomes unstable with the formation of large agglomerates if the formulation is wet or dust if the formulation is dry. If the mass is too dry, spheres will not be formed.

A drying stage is normally required after spheronization in order to achieve the desired moisture content. This may be the final step in the process. The pellets can be dried in any drier that can be used for conventional wet granulations, including tray dryers and fluidized bed driers. Both may be used successfully for extrusion/spheronization. Solute migration may occur during drying of the wet spheres and this may result in an increased initial rate of dissolution, stronger pellets, and modified surfaces that might reduce the adhesion of any added film coats.

4.8.3.6 Hot Melt Extrusion

Hot Melt Extrusion (HME) is a technology used in pharmaceutical formulation development, where poorly soluble and poorly permeable APIs are utilized. The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization, and particle size reduction have been used to increase dissolution rates and, therefore, oral absorption and bioavailability of such drugs, there are limitations to these techniques.

Solid dispersion has been developed as a formulation approach for overcoming challenging solubility issues. HME and spray drying have been used to generate these dispersions. In HME, drug, polymers, and occasionally surfactants are melted, mixed, and then cooled. The drug is finely dispersed within the polymer matrix. The amorphous solid dispersion can then be milled and processed in the same manner as crystalline APIs, or subjected to advanced techniques such as calendaring or pelletization. The amorphous form of the drug is released as very fine colloidal particles when exposed to water. The dissolution rate and extent, as well as bioavailability, are greatly improved because of the greatly enhanced surface area and the non-crystalline state.

Hot melt extruders can be used to continuously melt, mix, and cool the drug and polymers to produce a solid dispersion suitable for further processing into oral dosage forms. A major advantage of HME is that no solvents are required, which eliminates residual amounts of solvent and reduces the stability risk during the shelf life of the formulation.

4.8.4 Drying

4.8.4.1 Tray Drying

Tray drying has applications in, e.g., product development, when drug substance can be scarce and expensive. Tray drying is the only drying technology that allows total recovery of the product with minimum losses. One of the main disadvantages of tray drying is drying time, which can range between 8 and 24 hours. Another disadvantage is developing ergonomic equipment and methods to contain product as the trays are being emptied to recover the product. The potential for a combustible dust explosion also should be addressed.

Two types of tray dryers are available, one pass and recirculating air (where about 90% of the air is recirculated and 10% is replenished with fresh air).

Operating temperatures of up to 60°C (140°F) are sufficient for most pharmaceutical processes. The temperature is generally controlled thermostatically. Tray dryers can be heated electrically or with steam, a common energy source, particularly for drying inflammable solvents.

Tray dryers are fabricated on a steel framework covered with double walled insulation-filled steel panels at least of a grade 304 stainless.

Tray dryers are notoriously difficult and time consuming to qualify and demonstrate that the temperature within the oven is reasonably consistent and close to the operating set point. A well-designed dryer should show only ΔT within ± 2°C to 3°C (± 3.6°F to 5.4°F) difference from the set temperature with the trays in position.

4.8.4.2 Fluidized Bed Drying

Drying in batch fluidized bed dryers is very efficient with process times typically under an hour. This effective drying is based on suspension and movement of particles in an air stream resulting in efficient heat transfer from the gas to the bed of particles and efficient mass transfer of the liquid vapor into the gas stream. The behavior of the bed is highly dependent on the properties of solid materials and the velocity of the inlet gas. From a containment perspective, this can be one of the most difficult processes to contain, particularly when manually removing product from the equipment which can cause very high operator exposures. Modern FBDs may be available with proven containment designs, including CIP.

Dryer Design

Critical aspects of dryer design include:

- The dryer bowl, which has a perforated base or distributor plate to ensure a more even distribution of air across the particle bed. Fluid bed dryers may use a single piece perforated plate as the distributor with perforations that are angled imparting direction to the airflow.

- The inlet air, which is heated and HEPA filtered in two stages typically EU 7 or 8 and then typically EU 12, 13, or 14 (see “International Classifications of Air Filters of Atmospheric Dust” EN 779 [42] and EN 1822 [43]). The drying process is affected by the ambient air humidity and temperature; therefore, repeatability of drying is improved if the inlet air is also humidity controlled.

- The internal product retention filter, which should retain all of the product particles, but allow process air to pass through. A typical specification for a multi-product fluid bed dryer would be 95% retention at 5 µm. Traditionally mechanically shaken fabric filter socks have served as product retention filters. More recently, the trend has been to stainless steel cartridge filters. These are available as a pleated mesh filter or as a sintered particle filter. Particle release from the filter is usually by a reverse jet of compressed air back through the filter.

- As the volume of air passing through the equipment is significant, and there is a risk of passage fine airborne particulate product through the internal filters, it is normal practice to fit the equipment with two stage outlet air HEPA filters. The filter should be specified according to the relevant standards, EN 779 [42] and EN 1822 [43].

- The fan is generally downstream of the police filter to prevent dust buildup on the vanes; this also generates a negative pressure in the dryer body, which ensures minimal dust leakage from the dryer. The air is then vented to atmosphere usually via a noise reduction silencer.

- Although the use of organic solvent for granulation purposes has reduced, they are still employed mainly in fluidized bed coating applications. Typically, systems for solvent recovery based on a closed loop or vacuum operation of the fluid bed are used in such cases.

Note: for filter ratings and comparisons, see table in Section 8.2 of this Guide.

Dryer Operation

The typical stages in a fluid bed drying process include:

- Charging wet granules, which will typically be transferred directly from the granulator. When it is necessary to charge dry powders or pellets directly to the dryer for spray granulation or coating processes, typically from an intermediate container, this transfer may be achieved by vacuum conveying or by gravity.

- The drying step is conveniently divided into three distinct phases. In the bed warming phase, the material heats up from ambient to approximately the wet bulb temperature and the rate of moisture loss slowly increases. In the constant rate period, the layer of air adjacent to the particle surface is saturated so the drying rate is determined

by the humidity and flow rate of the air stream. During this period, the temperature of the particle surface remains constant at the wet bulb temperature of the saturated air, which is usually in the region of 30°C (86°F). The falling rate drying phase has two regions due to the free water and the bound water. During this phase, moisture migration is not sufficient to keep the layer of air adjacent to the particle surface saturated. The drying rate depends on the pore structure of the material and on the mechanism of moisture migration. Therefore, the bed temperature is no longer maintained at the wet bulb temperature, but starts to approach the inlet air temperature.

Typically, the end points of drying processes are determined on time combined with off-line sample analysis using gravimetric or Karl Fischer tests. It may be possible to continuously monitor the product moisture during drying rather than infer it from indirect measurements, such as product temperature, outlet air temperature, and humidity. As these parameters essentially remain constant for most of the drying cycle and only start to vary in the falling rate period, it may prove difficult to identify a condition at which the desired product moisture has been attained. This may lead to under drying, over drying, or lengthening of the cycle time. The development of NIR methods offers a fast real time technique for control of product moisture in fluid bed dryers. Product moisture changes during the complete processing cycle can be followed using NIR and critical process endpoints can be determined accurately.

Dryer discharge may be carried out manually on smaller scale machines where automated discharge is impractical. On production scale dryers the dried product is usually discharged with the bowl in situ either vertically through the bottom of the bowl by gravity or vacuum transferred through the side of the bowl typically assisted by the centrifugal force generated by the distributor mesh.

Qualification of Fluidized Bed Dryers

- Product moisture control, airflow rate control, and ensuring the quality of the inlet air in terms of filtration standard, temperature, and humidity form a major part of fluid bed dryer qualification
- Performance qualification concentrates on the batch-to-batch accuracy, consistency of drying, and moisture content uniformity across the product bed. This is true whether the drying end point is determined by time, the relationship between product or exhaust gas temperature and moisture content of the product, or NIR
- The final moisture content of the granules may be critical to its successful compaction into tablets, and therefore, may have a marked effect on the final quality of the product

4.8.4.3 Spray Drying

The spray drying process is designed to turn a pumpable liquid (solution, suspension, slurry, or melt) into a free flowing powder with the desired powder characteristics (particle size distribution, residual solvent content, dissolution profile, flow ability, etc.).

Spray drying is also a very fast method of drying, due to the very large surface area created by the atomization of the liquid feed and high heat transfer coefficients generated. The short drying time, and consequently fast stabilization of feed material at moderate temperatures, means spray drying is also suitable for heat-sensitive materials. In the pharmaceutical industry, spray drying is mainly used:

- To enhance the solubility of poorly soluble APIs
- To facilitate modified release of APIs (enteric or sustained)
- For taste masking of bitter APIs
- To create particles for inhalation
- As an alternative to lyophilization (freeze drying) by aseptic spray drying

As a technique, spray drying generally consists of four basic stages:

1. Atomization: a liquid feed stock is atomized into droplets by means of a nozzle or rotary atomizer. Nozzles use pressure or compressed gas to atomize the feed while rotary atomizers employ an atomizer wheel rotating at high speed

2. Drying: hot process gas (air or Nitrogen) is brought into contact with the atomized feed guided by a gas disperser, and evaporation (or congealing) begins. The balance between temperature, flow rate, and droplet size controls the drying process. For a melt process, cold or room temperature gas is used.

3. Particle formation: as the liquid rapidly evaporates (or congeals), a solid particle forms and falls to the bottom of the drying chamber

4. Recovery: the powder is recovered from the exhaust gas using a cyclone or a bag filter. The whole process generally takes no more than a few seconds

Spray drying starts with the atomization of a liquid feedstock into a spray of droplets (as an example 1 L of concentrate is atomized to 1.5 times generating ~1000 droplets. Each droplet has an average diameter of 50 microns for a total surface of 120 m^2. The evaporation takes place from the surface of all these droplet particles). The small droplets are created by an atomizer, either a rotary wheel or a two fluid or high pressure nozzle. The droplets are introduced into a hot airstream, which is cooled down due to the evaporation of the water or a chemical solvent from the concentrate. This now colder and humid air is discharged from the dryer through a cyclone, bag filter, or a combination of the two. After separation of the now dry particles, the air is discharged into the atmosphere. The dry particles can be cooled and bagged off after separation from the process air.

Spray drying is suited to QbD process development, as it is a continuous process with a high degree of repeatability, with the ability to integrate PAT technologies such as particle size distribution, residual solvent content, and content uniformity measurements of the powders in-line. A spray drying process may be used to eliminate one or more batch processes in a traditional pharmaceutical manufacturing train. Solvent and or dust explosivity is a major concern when spray drying solvents/explosive powders.

4.8.5 Milling

Milling (sometimes referred to as dry milling or dry granulation) is the stage in the process after size enlargement (granulation), when the size of particles is reduced to a size several orders of magnitude smaller than the final dosage form. There are various types of mills available, the choice depending on the degree of size reduction required and the friability of the starting material. This Section does not cover jet milling or micronization, as these techniques are limited to milling of an API. Dust explosivity is a major concern when milling explosive powders (see NFPA 69 [30]).

4.8.5.1 Impact Mills (hammer mills)

Impact mills are more commonly used in the size reduction of API. In this type of mill, the product is struck (impacted) by a series of blades on a horizontal rotating shaft. The product is reduced in size by the impact of the blade and by collisions with the cylindrical chamber walls. The milled product eventually passes through the screen at the base of the chamber and is discharged at a size that is always smaller than the hole size of the screen. The particle size of the milled product is controlled by the blade type (knife or flat), the shaft speed (3000 to 7200 rpm), and screen size.

4.8.5.2 Conical Mills

Conical mills are now one of the most commonly used size reduction devices in OSD manufacture. In this type of mill, a vertical rotating impeller imparts a vortex flow pattern to the product entering the conical screen chamber. The product is forced toward the screen by the centrifugal force ensuring continuous delivery to the active zone between the impeller and screen. In this zone, the particles are sized and pass tangentially through the screen. The finished product is discharged at the base of the chamber. The particle size of the milled product is controlled by the blade type (round, square, or triangular), the shaft speed (400 to 1000 rpm), impeller to screen distance, and screen size.

4.8.5.3 Horizontal Screens (oscillating)

The more traditional milling device is a flatbed screen/mesh onto which the product is fed and forced through by an oscillating horizontal blade. The blade profile is normally triangular. The blade configuration and blade speed are normally fixed so the only variable to control particle size is screen size.

4.8.6 Tableting/Compression

Tablets formed by compressing uniform volumes of particles inside a fixed die between two punches are manufactured in many permutations of size and shape and may be formulated to be chewable, dispersible, effervescent, or for sublingual administration.

4.8.6.1 Machine Design

Tableting machines include various features and options depending on the machine type and supplier. Machine types are defined by their compression action mechanism:

- Single stroke/single punch presses, including hand operated laboratory models, are more commonly used for research and development purposes.

- Slow speed single rotary machines with outputs of 200 to 2,500 tablets per hour have one powder feed station and produce a single tablet per station for each revolution of the turret. The slower machines use a tray feeder, which is best suited to granules and good flowing powders.

- High speed single rotary presses achieve outputs of 2,000 to 4,000 tablets per minute by using larger diameter turrets with an increased number of stations. These faster machines typically have forced flow (rotary paddle) feeders.

- Centrifugal rotary presses are a more recent development, which employ filling of the die through the side of the die by centrifugal force. The design allows for cleaning in place of the machine more easily than can be achieved with the more conventional machines.

- Double sided rotary machines produce two tablets per station for each revolution of the turret. Tablet take off is often from opposite sides of the machine. Tablet outputs can be more than 1,000,000 per hour. Special tablets with up to three layers or with a tablet embedded between two tablets can be produced using enhanced double sided rotary presses.

- From a containment perspective, tablet presses can be designed to handle non potent and highly potent products. Tablet presses can be the isolator type or with exchangeable modules with high containment. Special consideration should be given to ancillary equipment (i.e., sampling, tablet deduster, metal detector, and connections at feeder, at the outlet to the tablet container, to rejected tablets and also to the dedusting system).

4.8.6.2 Tooling

Tooling is one of the most critical elements of the tablet press. Controlling and maintaining the dimensions of the punches and dies is a critical aspect of any tableting operation. The condition of punches and dies has to be checked on a scheduled basis and a careful record kept of all actions taken.

The majority of tooling falls into one of two configurations with several options of die size available. Great care should be taken in selecting tooling for machines supplied from different countries. The US uses the Tableting Specification Manual (TSM – formerly the IPT category) [44] tooling which has a few dimensional differences, including the head angles and the head flat diameter.

For CIP tablet presses, there is continuing development of higher chromium tooling steels, which can still be hardened.

4.8.6.3 Press Operations

During the press operation, a number of parameters are controlled in order to maintain the tablet quality, including:

- Weight control in order to maintain a target weight is established to deliver the stated dose of active material. In order to minimize fluctuations in tablet weight, the granule size distribution should be tailored to suit the finished tablet size and weight

- Tablet thickness assists in establishing a target hardness value. The thickness may need to be controlled for packaging reasons, e.g., blister packing and rigid tube packs

Tablet hardness values are established using a specific hardness testing machine. The formulation should be designed to form a robust tablet, which maintains the registered bioavailability profile.

Tablet disintegration testing is performed in a specially designed piece of equipment, which involves lowering and raising a tablet in water maintained at 37°C (98°F). The tablet rests on a wire mesh. Each test unit comprises six cells so that six individual tests can run concurrently. The tablet should disintegrate and fall through the mesh within a defined time.

Friability is a simulated rough handling test to predict how tablets will behave during coating, packaging, and transportation. It also should detect any potential “capping” or lamination issues.

Granule Feeding and Tablet Collection

One important feature of tablet compression that has a significant effect on tablet quality is the granule or powder feeding system. Slower machines are often fed manually using a hand scoop. Feed mechanisms for faster machines include pneumatic transfer or gravity feeding.

After compression, tablets are sampled for quality checks, typically weight, friability, and disintegrations. Depending on the tablet press being used, automated checking of the weight, thickness, and hardness of a random sample of tablets also may take place with automatic feedback from such weight checkers to the press control system. Prior to collection, the tablets are dedusted, typically using a spiral brush or vibratory deduster and passed through a metal detector, which will identify ferrous particles down to 130 µm, non-ferrous metal contamination to 300 µm and austenitic stainless steel down to 500 µm.

Traditionally, tablets have been collected in small lots, placed in polythene bags within stackable rigid containers. For higher output machines, automated systems of collection are available by weight or count. Collection systems include IBCs specifically designed for tablet collection, including an offset inlet port and a soft seat discharge valve.

Continuous on-line weight checking using NIR techniques may ultimately provide an alternative to off-line sampling.

4.8.7 Encapsulation

Capsules are composed of hard or soft gelatin shells of various shapes and sizes. They can be filled with powders, granules, pellets, oils, and tablets. Hard shell capsules are generally dry filled. It is possible to fill liquid into hard capsules, but this usually requires an additional banding step to seal the capsules and prevent leakage. It is more likely that liquids and pastes would be filled into soft shell capsules. From a containment perspective, the potential for exposure is completely dependent on the format of the fill. If powder, the exposure is high, particularly when feeding powder to the encapsulator, while encapsulated tablets are a lower exposure. Similar to tableting, cleaning is a key issue and WIP-able encapsulators have demonstrated lower exposures.

Filling into hard gelatin capsules has some advantages over tablets, but a lower production rate is a major limit on its wider use.

4.8.7.1 Encapsulation Process

Capsule filling machines should carry out four operations:

- Rectify the capsules, i.e., position the cap uppermost in the machine
- Separate the body from the cap
- Fill the body
- Replace the cap before ejection

Powder Filling

A powder formulation used for capsule filling is a homogeneous blend of the drug, fillers, flow aid (e.g., aerosols), lubricant (e.g., magnesium stearate), and surface-active agent. The characteristics of the powders are particularly relevant to the product quality from the capsule filling process and need to be understood to comply with pharmacopoeial weight variation limits. For high-speed capsule filling with filling rates of up to 3,000 capsules per minute, the formulation should be free flowing with some cohesive properties. Other powder characteristics that are fundamental to dry fill capsule production include:

- Bulk and tapped density
- Particle size and distribution
- Particle shape and geometry
- Inter-particulate forces of attraction
- Moisture content

There are various ways of filling the powder into the capsule. The most critical aspect of the filling process is to control the volume of powder filled into the capsule and by that means the powder weight. For the dose weight to be controlled by the dose volume, a consistent powder density is needed. To achieve a consistent density, it is usual to provide a tapping force to the powder prior to or during the filling step. This powder compaction may be achieved by an auger type feed system or more commonly by a single or multiple tamping rods.

Pellet and Tablet Filling

A common product filled into hard gelatin capsules is pellets or spheroids. Unlike a powder fill, such products are free flowing and require no densification or tamping, which might result in breakage of the pellet or damage to the coat if enteric coated. As with powder filling, the pellet fill into the capsule is controlled on volume.

Tablet Filling into Capsules

Ordinary compressed tablets and small capsules can be filled into hard gelatin capsules. There is a limit on the size of the contents relative to the diameter of the capsule. The tolerance on these measurements is ± 0.1 mm. For a spherical shape, the diameter should be 0.4 to 0.5 mm less than the internal diameter of the capsule to be filled.

Multi-Component Filling

Many capsule filling machines have the possibility of filling one component or multiple components into the capsule. A separate filling station may be required for each component.

Capsule Closure and Sealing

Filling machines normally replace the original cap onto the body without any axial movement so that any print is correctly aligned. Usually, a metal finger pushes the filled body into the cap. The whole capsule is raised until the cap comes into contact with a stop. On some machines, this distance can be accurately set; on others, the closing fingers are spring loaded so that movement is more dependent on the capsule fill and speed of operation.

Most gelatin capsule manufacturers make the cap and body to be self-locking. The possibility of reopening and deliberately contaminating a product has led manufacturers to seek methods to permanently sealing capsules. Spot welding or banding with gelatin may be used to secure the overlapping portion of the capsule.

Capsule Sorting and Check Weighing

Because of the limitations of the capsule filling process, capsule sorting and check weighing is considered a critical step in the filling process. It is usual to sort and 100% check weigh the filled capsules after the capsule filling step.

Capsule sorting removes half and empty capsules as well as any powder from capsules which may have split. The sorting is generally achieved by passing a flow of air through the capsules being fed down a chute. The lighter component (waste) is carried away by the airflow; the good capsules are recovered at the base of the chute. The waste, which may contain active substance, should be collected safely in a contained dust collection system.

Sorted capsules may then be check weighed. Typically, the capsules are fed onto a balance and the capsule weighed. Air jets are used to blow the capsule off the balance, either toward the reject chute if the capsule weight is outside the limits or toward the product collection chute if the weight is within specification. Check weighing is normally a slower process than filling and so has historically been carried out off-line. However, devices are available that can sort and check weigh at speeds comparable with capsule fillers.

4.8.7.2 Soft Gelatin Capsules

Capsules suitable for liquid or paste fill are composed of gelatin with the addition of a plasticizer. Other optional ingredients include preservatives, colorants, pacifiers, and flavorings.

4.8.7.3 Capsule Storage

Capsule processing facilities should conform to cGMP, but the handling of gelatin capsules also brings an additional requirement for climate control for storage and processing of empty and filled capsules.

Capsules are sensitive to extremes of temperature and humidity. At low humidity, they lose moisture and become brittle. At high humidity, they gain moisture and soften. Their optimum moisture content is between 12.5% and 16%. Storage areas should be designed to control ambient temperatures between 10°C and 30°C (50°F and 86°F) with relative humidity between 30% and 70%. The gain or loss in moisture, apart from causing changes in the nature of the gelatin film, also has an effect on the dimensions. It has been calculated that for every 1% change in moisture away from the optimum value, there is a 0.5% change in dimension.

Empty capsule shells occupy a significant storage volume. Although production campaigns are planned to minimize stocks, the warehouse should have sufficient environmentally controlled storage to cover manufacturing output with some reserve capacity.

Capsules also can be damaged by a sudden temperature change or localized heat sources, such as radiators or direct sunlight.

4.8.8 Tablet Coating

4.8.8.1 Aqueous Coating

Coating may be applied to tablet cores for both functional and non-functional reasons, including:

- Protection of the active ingredient from light or moisture ingress
- To increase the robustness of the core
- To seal in the active agent as for potent products

Additionally, the coat may act as a glidant and improve the aesthetic quality of the tablet.

Two main types of aqueous coating may be applied to tablets, i.e., sugar coating, generally applied in pan coaters, and film coating generally carried out in side vented drum coaters.

Drum Coater Design

Drum coaters generally include the following features in the design:

- A horizontal, rotating, perforated, vented drum arranged so as to allow heating/drying air to be supplied from one side and “wet/dusty” air to be extracted at the opposite side
- Inlet air filtration, temperature, and humidity control similar to that described for fluid bed dryers
- Outlet air handling unit through which the air is extracted and treated
- Coating solution spray system, this is used to spray the solution onto the tablets in the coater

Coating Process

The tablet coating process begins with tablet core loading typically manually from small containers or bulk container via the loading door. Alternatively, the tablets may be pneumatically transferred via the front door. For contained charging, the cores may be charged into the rear or the side of the coater via a hard connection.

The charged tablets are warmed by a flow of heated, filtered air passing through the coater, while the drum rotates. Once the tablets are pre-warmed, the application of the coating solution onto the tablet bed can begin. During spraying, the heated airflow is maintained and the rotation of the drum imparts constant motion to the tablet cores. The drum speed is a critical control parameter and is set to minimize tablet damage, while maximizing the tablet movement in the drum and the number of passages each tablet has through the spray zone.

The method of application of the spray needs to be designed around the requirements of the coating solution to be applied to the tablet substrate. Pneumatic spray nozzles are generally used for aqueous solutions. The nozzle based application systems should fulfill the following requirements:

- Be capable of producing a droplet size spectrum of low mean diameter
- Be able to handle a range of low viscous suspensions with a solid content of between 8% and 20% by weight
- Be of simple construction
- Have simple controls for altering the spray angle

- Be constructed of materials that would not adulterate the product (GMP)

In air atomized sprays, the coating solution is fed to the spray gun at relatively low pressures and low application rates in order to match the evaporation rate. Typically, multi-head peristaltic pumps are used with one pump head serving one spray nozzle. The critical aspects of the spray addition systems to control are the atomizing air pressure, which controls the droplet size, and the spray fan width. It is also critical to control the positioning of the nozzles by setting nozzle to bed distance and the spray direction to bed surface angle.

Film coating relies on tablets passing through a spray zone, after which the adherent material is dried before the next portion of coating is added. This activity is repeated many times before the coating is fully applied. The thickness of such a coating is usually between 20 µm and 100 µm. The film structure tends to be relatively non-homogeneous as a result of the deliberate addition of insoluble ingredients, such as pigments and because the film itself is built up in an intermittent fashion.

There should be some means of drawing the air through the bed of tablets. The volume of air exhausted will vary with the evaporation rate required and the total pressure drop will depend upon the resistance of the tablet bed, exhaust ducting, and any additional equipment, such as filters or dust collectors. There should be a Control and Instrumentation (C&I) system that will monitor and control the exhaust air to maintain constant conditions in the coater drum and not affect the quality of the coating.

The exhaust air will contain a percentage of particulates ranging in size from sub-micron to 200 µm to 300 µm. The particulates will come from both the tablets and from spray dried coating solution. Systems for removing particulates from the exhaust gases include cyclones, filters, dust collectors, and wet scrubbers.

The coated tablets are then discharged using one of the discharging options, which include:

- Manual scooping out of the drum by an operator
- Pneumatic transfer using a vacuum lance through the front door
- Gravity discharged, through doors in the base of the coater
- Forward drum rotation discharge using a discharge scoop insert that picks up tablets and directs them down a chute projecting out of the coater door. The tablets are collected in a container standing in front of the coater
- Reverse drum rotation discharge, which utilizes fixed baffles in the drum that only pick up tablets when the drum is rotating in the reverse direction. The tablets are directed down a closed chute at the front of the coater. Reverse drum discharge is the only discharge technique that can be operated in a contained way with the coater door closed.

4.8.8.2 Enteric (solvent-based) Coating

Coating pellets with different films of specific properties can allow the product to match a certain release profile and duration and for release in a specific area of the stomach and intestines. For example, a resistant film (enteric coat) can be used to prevent the active substance from being released in the stomach and in so doing prevent it from irritating the mucous membrane.

It is of great importance that the pellets cores are flawless and that their firmness is good to achieve the correct function in the coat. In addition to pellet quality, poor control of coating may result from incomplete dissolution of coating materials, over-wetting of the pellets, or spray drying of coating solution droplets before they hit the pellet bed.

Typical materials used for enteric coating are hydroxypropyl methylcellulose (HPMC) as film former and ethylcellulose for its controlled release properties. The ethylcellulose requires a solvent and typically mixed methanol and methylene chloride solution is used.

It is important to know the physical properties of the coating solution in order to be able to coat in an appropriate way and as a result obtain good film formation.

The properties of the coating solution that have the greatest effect on the coating process include:

- Density
- Surface tension
- Dry material content
- Viscosity

How the physical properties of the coating solution influence the atomization process and the transport of droplets between the spray nozzle and pellets and the wetting of the pellets should be understood.

How the physical properties of the coating solution influence the appearance and function in the finished film also should be understood.

Equipment for Pellet Coating

The most commonly used technique for coating pellets is bottom spray fluid bed coating, (Wurster coating).

This technique employs nozzles mounted in the distributor plate, facing the top of the equipment. Above each nozzle, there is a Wurster tube positioned so that there is a narrow slit between the bottom of the tube and the distributor plate allowing for pellets to pass through. There are extra-large perforations in the distributor plate underneath the Wurster tubes creating an extra strong airflow through the Wurster tubes allowing for pellets to be entrained through the Wurster tubes. Once the pellets have passed through the Wurster tubes, they fall back down to the bottom; the coating solution spray flow is directed upward inside the Wurster tubes at the same time as the pellets in the bed are entrained by the flowing air.

Dust Collection

When pellets or large uniformly sized particles are being dried or coated, there is no need for an internal fine particle retention filter as in granule drying. In this case, an external bag filter may be used to collect dust from the fluid bed and a coarse mesh used to retain particulates in the dryer body. The external bag filter is backed up with a police filter unit.

4.8.8.3 Active Over Coating

Besides pellet coating, fluid bed processors can be used to generate a range of special formulations. To manufacture such dosage forms may require different inserts to be installed on the fluidized bed. For example, dry powder layering, where dry powders are layered onto the surface of seed pellets, is carried out in a ‘rotor coater insert.

4.8.9 Dry Granulation

Dry granulation processes are those in which a blend of raw material ingredients (excipients and API) is formed into granules in the dry state without addition of a liquid binder.

In the dry granulation process, there is no scope for further inter particle dispersive mixing after the preliminary powder blending, which makes this step more critical than in wet granulation processes.

Where the ingredients in the formulation are in even proportions, a simple tumble blending process may suffice. If the API is present at less than 10% of the mixture, it is usual to carry out the dry powder mixing in a more intensive mixing device.

4.8.9.1 Slugging

In the slugging process, dry powders are compressed using either a conventional tablet press or more often, a large heavy duty rotary press. The compact made in the process (typically 25 mm diameter by about 10 to 15 mm thick) is called a “slug”. The same issues apply to the slugging process as apply to normal tablet compression. In order to prevent picking on sticking to the punches and dies, it is necessary to include a lubricant in the dry blend.

A heavy duty milling step is needed to break up the slugs into granules, and typically, a hammer mill or similar is suitable for this purpose.

4.8.9.2 Roller Compaction

The use of roller compaction is increasing on the grounds of throughput and lower manufacturing costs.

The dry powder characteristics affect the viability of the roller compaction process. When formulating a product for roller compaction, it is it important to consider attributes, such as particle characteristics, e.g., size, shape, and morphology. Bulk powder properties, such as density, compressibility, angle of internal friction, and angle of wall friction, are also important.

In the roller compaction process, the powder mix is squeezed between two counter rotating rollers to form a dense compact, typically, a sheet or briquette. Briquettes typically require the same level of milling as slugs, but the sheets, being more brittle, break easily and can be milled using a screening type mill.

There is no universal guidance on how to select appropriate processing parameters for the operation of a roller compaction process. The key roller parameters, which may impact on sheet formation to be considered include:

- Type
- Diameter
- Speed
- Pressure
- Surface friction

Powder handling also has an impact, including the feed screw speed and whether there is vacuum deaeration of the feed.

It is important to identify and optimize the critical process variables above based on key sheet and granule attributes and characteristics, including:

- Sheet properties
- Powder leakage/compact ratio
- Porosity (the ratio of the volume of voids in the sheet to total volume of the sheet)
- Thickness
- Degree of densification
- Micro structure

- Breakage properties
- Granule properties
- Degree of flow enhancement
- Recompressibility, which can be determined by comparing tensile strength of tablets made of roller compacted granules and primary material using a low to high roll pressure study
- Effect on disintegration and dissolution of the final products

When the roller compacted granules are used for tableting, the granule's property to be optimized is it's recompressibility. It is important to retain an ability in the material to form strong compacts (tablets) after a second compaction (tablet compression) process. To minimize the detrimental impact of roller compaction on recompressibility, a compaction force that is as low as possible should be used, provided that it is sufficient to densify the powder materials.

During formulation for roller compaction, types of intra granular components should be selected and their ratios balanced in order to maximize the reworkability of the roller compacted granules. If low recompressibility remains an issue even after careful selection of process conditions and intra granular excipients adding a sufficient binder, such as Microcrystalline Cellulose (MCC), in the extra granular portion, to provide acceptable tablet bonding strength should be considered. A sound understanding on how to balance intra extra granular components helps maximize reworkability after roller compaction.

Powder Compaction Process

Robust roller compaction processes require powder materials to feed consistently. It is critical to spread the powder evenly across the full width of the rollers so that there is an even flow of material into the draw-in zone to the rollers. Starting material characteristics impact significantly on how a material feeds and typically candidate products for dry granulation tend to have low bulk densities and poor flow properties. Such materials require force feeding with screws to deliver the materials to the rolls at a uniform rate. Force feeding not only conveys material to the rolls, but also serves as a mini compactor to pre-compress material prior to the roller compaction. Even though there is slippage at the roller in the feed zone causing powder to recirculate, which distributes the powder across the roller width, an inconsistent feed rate will result in particles leaking through the gap between the rollers without being compacted. This effect can be made worse if the rollers are running too quickly or there is excess powder slippage. In both cases, there is little opportunity for the powder to distribute itself evenly on the draw in side of the rollers. Powder leakage also tends to be more problematic for materials with a bulk density lower than 0.3g/cc. In addition to force feeding, vacuum deaeration is another way to ensure uniform powder feed to the rolls as this removes entrapped air from the powder bed prior to the roller compaction step. Entrapped air can cause powder fluidization and a non-uniform powder feed at the roll gap, resulting in a high powder leakage rate and a non-uniform compact density.

If the powder is not delivered adequately and evenly to the draw-in and compressing zones leakage rates as high as 15% are possible. Such significant powder leakage leads to excess fines and granules that are suboptimal for downstream processing. Although fines could be recycled to improve the product yield, extensive recycling reduces product throughput, increases the manufacturing cost, and is less acceptable as a routine way of working.

As the roller starts to grip (nip) the powder, it is forced between the rollers. The angle between the point at which the rollers grip the powder and release the sheet is called the 'nip angle.' Once the powder material is drawn into the nip angle, powder to roller surface friction imparts motion to the powder moving it through the compaction zone. In this zone, the powder undergoes a densification process by which particles may be deformed or fragmented to eventually form a sheet at the narrowest gap between the rollers.

It is usual to include a dry lubricant, such as magnesium stearate, in the powder blend as an effective way to minimize sticking. It is critical to optimize the level of lubrication as it reduces the frictional angle between particles and roll surface, thereby reducing the roller compaction efficiency.

The sheet will normally start to break up on release from the rollers, but an additional sizing step is usually required. Most proprietary rollers compactors have an integral dry milling/screening device.

4.8.10 Blending

The objective of blending is to secure uniformity of composition, so that any sample removed from the bulk will contain the same relative proportion of components that comprise the bulk as a whole. Mixing occurs after granulation to add excipients, such as a lubricant, a flow aid, and a disintegrant prior to compression.

Typically, mixers employed in the pharmaceutical industry are batch, as they produce material in discrete lots. Charging, discharging, sampling, heat, and over pressure during volume to volume transfer are the major containment issues with blending in fixed blenders.

4.8.10.1 Tumble Blending

The diversity of form among tumbling mixers ranges from cubes through “Y” to oblicone shapes. Since they operate mainly by diffusive mechanisms, they are used to blend free flowing or granular materials. As the mixer rotates about a central axis, the components flow in a continual rolling action. The V-shaped, Y-shaped, and the double cone mixers are the most common examples.

During the rotational cycle of a V-shaped blender, the load is split as it descends into the two arms and then recombines in the single arm. Both shear and diffusive mixing mechanisms operate during the recombination phase.

In double cone blenders, disrupter bars/baffles are often incorporated into the walls of the vessel to increase convective/shear mixing.

An optimum operating speed exists for tumbling mixers. Low rotational speeds may not provide sufficient shear forces to produce effective mixing. On the other hand, excessive speeds can enhance segregation within the mix and in the extreme, oppose the gravitational forces on which this type of mixer relies to blend the mix.

Load size relative to mixer volume is particularly important in tumbling mixers/blenders. An insufficient load will tend to slide *en masse* with little movement within the bed itself. Material flow of excessive loads is physically restricted. Typically, tumble blenders should be operated with a two thirds fill.

A modified form of tumble mixer has been developed, which incorporates the action of an agitator blade in the center of the vessel. This intensifier bar increases the shear action available within the mixer and as a result allows the mixing of cohesive/wet materials. However, this is at the expense of increased attrition to friable materials.

4.8.10.2 Bin Blending

The bin blender is a modification on the tumble blender by which the materials handling container also becomes the blender container.

The bin should be sized with the appropriate amount of free space so as to allow for free movement of the powders within the IBC, typically a two thirds fill.

During blending, the IBC is rotated about its vertical axis. When a square or rectangular bin is being used, the rotation should give a corner-to-corner blending motion. As it is inverted during blending, the IBC should not leak so that powder containment is maintained when in the inverted position.

The IBC rotation may be achieved in a pillar lift type blender or a cage type blender. The dimensional tolerance of the IBC should fall within the acceptable tolerances allowed for in the design of the blender unit.

4.8.10.3 Agitator Mixers

This class of machine relies on the action of a blade/paddle moving through a powder bed. Obviously, the first stage of the granulation process is a dry powder blend, but the ribbon blender and conical screw mixer are the two main types of machine used solely for powder blending in the pharmaceutical industry.

In the ribbon blender, helical blades of one or more configurations rotate in a hemispherical vessel. This type of mixer has a relatively low shearing action compared to the planetary and sigma blade mixers and it has a tendency to form dead spots within the mixing space (particularly at the ends and corners of the machine). In practice, machines may have to be stopped during the mixing process in order for the vessel walls to be scraped down.

The design of the conical screw mixer is such that the presence of dead spots is avoided. A rotating screw shaft, fixed at the base of a conical vessel, is gradually drawn around the periphery of the vessel. Material is thus continually brought up to the top of the vessel and deposited at the surface of the mix. Such an action employs all three mixing mechanisms. A major advantage of this design is that the mixing action is constant no matter how high the powder level is within the vessel.

4.9 Supporting Unit Operations

4.9.1 Introduction

This Section discusses supporting systems and equipment, such as fluid bed processor filter bag washing, CIP systems, and wash stations. Process air handling systems and dust collection as they relate to OSD process equipment air handling systems are also discussed; however, for additional process supporting systems, see Chapter 7 of this Guide.

4.9.2 Process Air Handling Systems

Air Handling Units (AHUs) or air handlers are used to precondition the air which is used inside processing chambers, e.g., of fluid bed processors and coating pans. There is intimate and sustained contact between the air and the final pharmaceutical product. The air used as a heat transfer fluid and its quality can have a direct impact on final product contamination. Air handlers should control temperature, humidity and air quality for drying, granulating or coating. Appropriate air handler design is needed to provide the appropriate level of filtration to prevent potential contamination. For further information on Process Air Handling System Design, see Chapter 8 of this Guide.

4.9.3 Dust Collection

Most OSD unit operations create dust, and dust production should be minimized. Many process equipment designs are capable of returning dust or fines into the process; however, some dust inevitably gets into the exhaust duct work. In order to prevent this material from release into the atmosphere, post processing dust mitigation is needed usually using dust collectors and as a two-step process. Depending upon the toxicity of the materials, a “police filter” or “final HEPA” is used to ensure that particle emissions are kept to an absolute minimum. A dust collector (i.e., a bag house) can be provided upstream to remove the majority of the dust from the airstream to prevent blinding the HEPA filter, as HEPAs are extremely high efficiency devices. Dust collectors are well suited to this task because they are capable of removing high volumes of solids from an airstream over an extended period of time.

The dust collector is essentially a large plenum with either cartridge filters or bag type filters and a collection hopper. The airstream from the process flows through the filter media which entraps the solid particles so the air can either exhaust directly to the atmosphere or first pass through a final HEPA filter enclosure. The filters are cleaned while the

system is operating. Cartridge filters and filters bags can both be cleaned by a reverse air pulse or while filter shaking is only applicable for sock type filter designs. The filters are mounted in the upper portion of the dust collector and the entrapped particles thus obtained are collected in the lower section of the dust collector before periodic removal and disposal.

Note: the WHO TRS 961 Annex 5 [45] requires that the final filter for any exhaust from the facility be at least EN 779 F9 [42].

When specifying a dust collector, the key issue is the air volume passing through the unit, with the air to cloth ratio being a critical design parameter. Other issues to consider are the air temperature, vacuum created by the fan drawing the air, dust explosion rating, and indoor versus outdoor location. Dust collector manufacturers should consider these factors in order to properly size the unit.

Another critical issue is explosion containment (see NFPA 68 [29]) which requires explosion protection). There are two basic approaches: venting or suppression. The NFPA [26] provides clear calculations that determine the explosion relief area for a vented unit. In some cases, venting may not be practical due to size constraints or layout issues with the explosion venting path. While a vented unit is less expensive, a suppression system is a viable alternative for non-vented designs. These systems utilize high pressurized bottles of explosion/flame retardant chemicals which are triggered by a rate of rise pressure sensor. Vented systems require explosion isolation valves on the inlet and exhaust ducts if the explosion path through those ducts is to be blocked. On non-vented systems, isolation valves are less critical, serving to prevent chemical suppressant from being blown into the upstream process equipment or downstream exhaust fan.

4.9.4 Vacuum Systems

Vacuum systems utilized include process vacuum and house vacuum systems. House vacuum systems are used for facility housekeeping and are discussed in Chapter 7 of this Guide.

Process vacuum systems are used in a variety of pharmaceutical applications such as dust collection, tablet presses, tablet coating, crystallization, deaeration of suspensions or low density powders, vacuum drying of temperature sensitive products in fluid bed drying and spray drying, also in blending, granulation, bottling and filling equipment, packaging equipment, capsule separation in encapsulators, and in general room ventilation. Suitable vacuum pumps should be chosen to provide the required vacuum pressure, provide any filtration system required, suitable for gas temperatures, be compatible with solvents (if applicable) as well as discharging the evacuated gas (air or other) to a safe discharge location.

There are many types of vacuum pumps. The most common types of pumps are the rotary pump for reaching rough vacuum, and the diffusion pump for reaching high vacuum. Considerations for selecting a pump include:

- How it operates
- What pressure range it operates in
- Its pumping speed
- Type of gas flow (viscous or molecular)
- Effects of pumping on different types of gas
- Advantages and disadvantages

In OSD processes, vacuum pumps are mainly used in the low to medium vacuum ranges, with some exceptions. Typically, vacuum pressures achieved by each type of pump are:

- Low (rough) vacuum: 10^{-1} to 10^{-2} (*Pa*) or 10^{-3} to 1 Torr (conventional units)
  - Vane, claw, screw, liquid ring, blowers, etc.
- Medium (or fine) vacuum: 10^{-4} to 10^{-1} (*Pa*) or 10^{-6} to 10^{-3} Torr (conventional units)
  - Metal degassing, semicon, crystallization, freeze drying
  - Vane, screw, piston, roots, absorption, etc.
- High vacuum: 10^{-7} to 10^{-4} (*Pa*) or 10^{-9} to 10^{-6} Torr (conventional units)
  - Thin films, research, space simulation
  - Scroll, diffusion, turbo, etc.
- Ultrahigh vacuum: < 1×10^{-9} to 1×10^{-12} Torr
  - Thin films, research, space simulation
  - Turbo, sublimation, cryo, etc.

Vacuum pressure is measured in different units throughout the industry. Common conversions that may be helpful, when working with vacuum systems include:

1 inch Hg = .49 psi
25.4 Torr
25.4 mm
33.9 mbar
3.39 kPa
33.9 hPa

For additional conversions, see Table 4.8.

Table 4.8: Vacuum Conversion Table

Torr	mm Hga	Mbar	" Hgv	" Hga	PSIA	% Vacuum
760.00	760.00	1013.00	0.00	29.92	14.70	0.00
750.00	750.00	999.67	0.39	29.53"	14.50	1.32
700.00	700.00	933.03	2.36	27.56	13.54	7.89
600.00	600.00	799.74	6.30	23.62	11.60	21.05
500.00	500.00	666.45	10.24	19.69	9.67	34.21
400.00	400.00	533.18	14.17	15.75	7.74	47.37
380.00	380.00	506.50	14.96	14.96	7.35	50.00
300.00	300.00	399.87	18.11	11.81	5.80	60.53
200.00	200.00	266.58	22.05	7.87	3.87	73.68
150.00	150.00	199.93	24.02	5.91	2.90	80.36
100.00	100.00	133.29	25.98	3.94	1.93	86.84
90.00	90.00	199.96	26.38	3.54	1.74	88.16
80.00	80.00	106.63	26.77	3.15	1.55	89.47
70.00	70.00	93.30	27.17	2.76	1.35	90.79
60.00	60.00	79.97	27.56	2.36	1.16	92.11
50.00	50.00	66.64	27.95	1.97	0.97	93.42
40.00	40.00	53.32	28.35	1.58	0.77	94.74
30.00	30.00	39.99	28.74	1.18	0.58	96.05
25.40	25.40	33.86	28.92	1.00	0.49	96.66
20.00	20.00	26.66	29.13	0.79	0.39	97.37
10.00	10.00	13.33	29.53	0.39	0.19	98.68
7.60	7.60	10.13	29.62	0.30	0.15	99.00
1.00	1.00	1.33	29.88	0.04	0.02	99.87
0.75	0.75	1.00	29.89	0.03	0.01	99.90
0.50	0.50	0.67	29.90	0.02	0.01	99.93
0.10	0.10	0.13	29.92	0.00	0.00	99.99
0.01	0.01	0.01	29.92	0.00	0.00	100.00
0.00	0.00	0.00	29.92	0.00	0.00	100.00

4.10 Supporting Management Systems

Supporting quality management systems include change controls, preventive maintenance, and calibration of critical equipment and instrumentations. Quality management should ensure that all critical equipment and instrumentations are maintained in a qualified state.

4.10.1 Change Controls

Organizations should establish change control procedures prior to manufacturing drugs. Any change made to a manufacturing facility and process equipment should be documented and the record maintained for a minimum number of years, as required by the regulatory authorities. Change controls can be classified into three categories:

- In kind replacement of manufacturing equipment: like to like replacement, e.g., replacement of existing HEPA filters in a facility HVAC system. This action does not normally require a formal change control procedure. However, for business purposes, a traceable work order or purchase order should be obtained for system life cycle cost and/or equipment inventory management

- Not in kind changes to a non-critical component: this applies to manufacturing equipment that does not have a critical aspect to the quality of product, such as for equipment performance improvement, e.g., adding a branch shutoff valve for a washer machine, which will isolate manufacturing systems to minimize unnecessary downtime. It allows a localized utility shutdown without affecting other equipment that needs to remain in service. No change control is required, however, other key documentation may need to be revised, i.e., general arrangement drawings, process and instrumentation drawings, manuals, etc.

An Equipment Modification Request (EMR) may be recommended for traceability of the equipment history and service records. The EMR will add value to the system life cycle cost analysis and asset/inventory management

- Changes to qualified equipment having a critical aspect on the quality of product: a formal change control procedure should be used prior to making any changes to the system/equipment, e.g., changing the process HVAC discharge air dew point. Therefore, a written change control document should be issued for review and approval prior to implementing the change

For further information, please see the *ISPE PQLI® Guide: Part 1 – Product Realization using Quality by Design (QbD): Concepts and Principles, including Overview, Criticality, Design Space, and Control Strategy* [46].

4.10.2 Preventive Maintenance

Preventive maintenance is prescheduled periodic maintenance work used to minimize expensive/damaging/time consuming equipment failures and ensure uniform equipment performance throughout its life cycle, and increase equipment life expectancy by mitigating part damage. See the ISPE Good Practice Guide on Maintenance [47].

4.10.3 Calibration Critical Component

Calibration is a comparison of process instrumentation against a standard instrument of higher accuracy to detect, correlate, adjust, rectify, and document the accuracy of the instrument being compared. See the ISPE GAMP® Good Practice Guide on Calibration Management [48].

4.11 Considerations for Post-Approval Equipment Changes

A particular consideration when selecting process equipment is its equivalence to similar technology in use in the company and whether a product can be transferred from one piece of equipment to another without additional regulatory approval implications. The Scale-Up and Post-Approval Changes (SUPAC) guidance for industry from the FDA “SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms” [49] lists the various unit operations and identifies equipment used for those unit operations as equivalent or not equivalent.

Regulatory requirements and regulations for OSD forms manufacturing facilities are discussed in Chapters 2 and 3 of this Guide.

4.12 Emerging Technologies

This Section considers emerging technologies, such as modular processes, continuous processing, and measuring and controlling key process parameters.

4.12.1 Continuous Processing

The advantages of continuous processing to manufacture OSD products include:

- Consistent product quality: continuous processing utilizes continuous monitoring, by way of a validated method, so the entire batch is assured to be within acceptable process limits. Batch process only monitors at specific points in the process based on statistics; the continuous process provides consistent product quality over the whole production period.

- Production quantity is controlled by operating time: the process is completed when the required production quantity has been reached. Scale up of a product during the commercialization process is based on the same process but varying time. Batch processing scale up should utilize individual equipment platforms for commercial scale up.

- Smaller machines: a continuous processing system is much smaller in size when throughput and staging requirements associated with the equivalent batch process are considered. There is no need for storage of work in progress. The amount of space required to accommodate a continuous process is much less than batch, thus saving facility capital costs and ongoing operating cost.

- There is less product in a continuous machine than in a batch machine, a smaller drum and drive are needed for the same throughput.

- Less manual product handling: continuous machines can be easily integrated in comprehensive units with automatic feeding. This can eliminate some working steps and WIP storage requirements, which further reduces the risk of accidental contaminations.

- Operational safety: operators are less exposed to the product ensuring safety at work

- Less manpower: with the reduction of the handling, storage, and transfer steps, fewer operators are required

- Less cleaning: cleaning frequencies of batch processing can be quite high. In extreme cases a cleaning will be required after each batch. Continuous units only require cleaning when the product is changed. With highly integrated equipment cleaning times can become extensive, so change parts become a way to reduce change over cycle times.

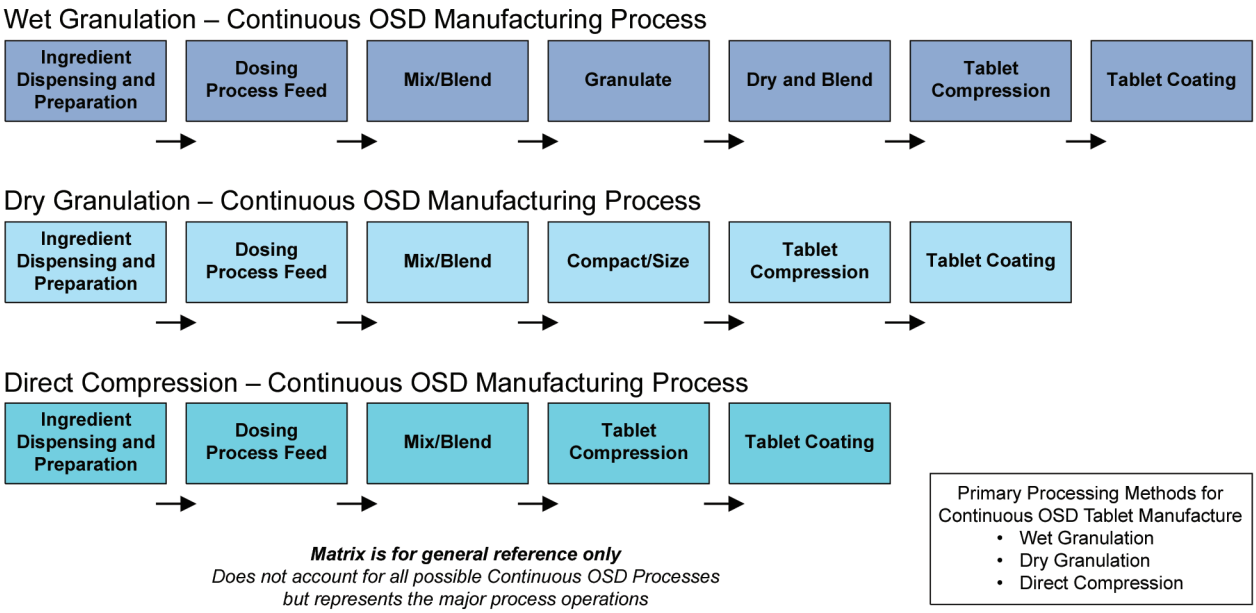
- Lower product cost: compared to a batch process, a continuous process reduces the production cost while maintaining the same or better product quality.

Continuous processing also offers improved containment and has the ability to apply lean manufacturing principles. Economical production of larger product quantity has been the most predominant justification of continuous processes; however, running smaller flexible batches and savings during the commercialization process can be used to justify continuous granulation.

Process development in a continuous process is much easier and quicker than in a batch process. Issues associated with technical transfer of a batch process from platform to platform during commercialization can be eliminated, as commercialization of continuous products use the same equipment platform. The process can run longer to produce additional amounts rather than employ larger equipment. The steady state operation of a continuous process is monitored in real time and offers a more viable way of controlling the process to ensure a more consistent product quality. While a number of OSD process unit operations could already be classified as continuous/pseudo continuous, e.g., roller compaction, hot melt extrusion tableting, milling and encapsulation, they have usually been preceded or succeeded by a batch step. The common batch operations such as granulation, drying and coating are now available as a continuous unit procedure. This allows for a fully continuous manufacturing stream to be applied. Equipment vendors can offer a fully integrated line or continuous unit procedures that can be integrated to form a continuous processing line.

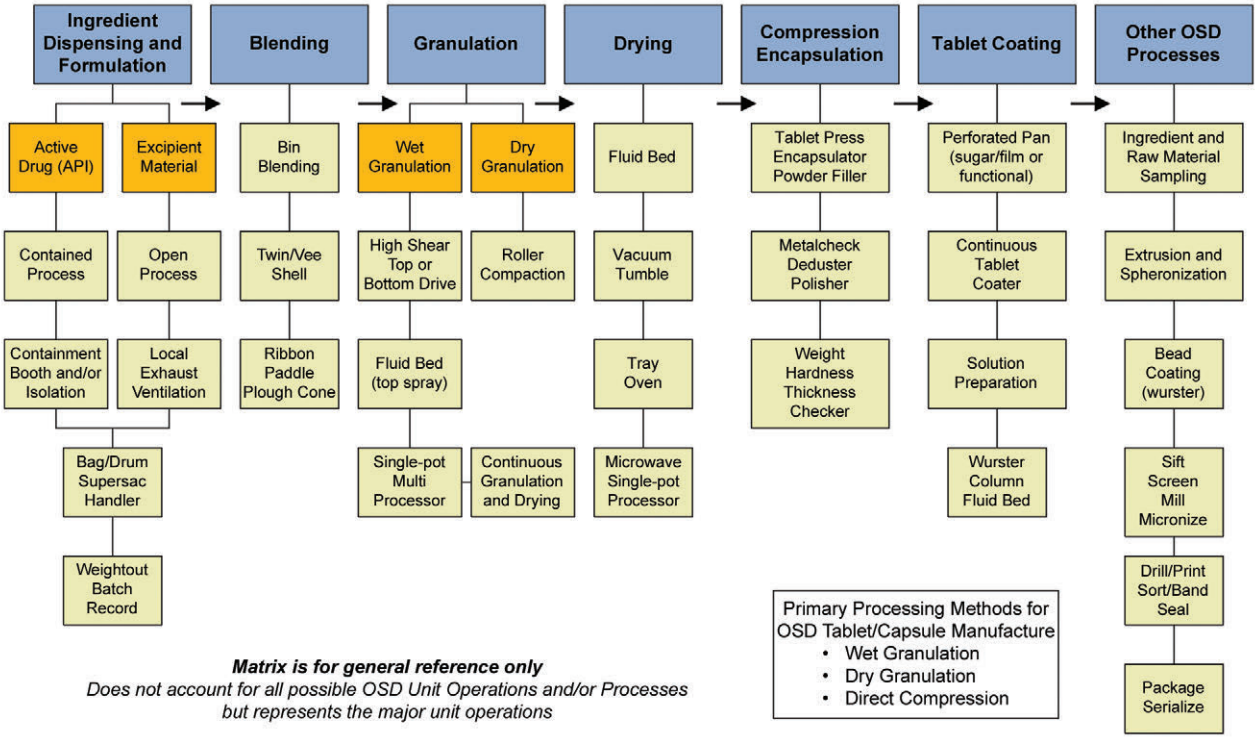
Figure 4.1 compares batch and continuous processes and typical in-process test points. Batch process requiring discrete testing versus on line PAT monitoring and control, PAT and its role in continuous processing are discussed in Chapter 10 of this Guide.

Figure 4.1: Batch versus Continuous Processes



For further information on determining whether to use continuous processing see the ISPE website [50] and the ISPE Oral Solid Dosage Community of Practice.

Figure 4.2: Unit Operations-based Batch Process



5 Product Isolation and Containment: Principles of Product, Operator, and Environmental Protection

5.1 Concepts, Risks, Requirements, and Interactions

This chapter describes containment considerations for OSD manufacturing. A pragmatic approach, coupled with good engineering judgment, should be used when choosing appropriate designs, procedures, and testing protocols.

Note: examples provided are intended only for illustrative purposes and points to consider. The specific process, the materials handled, their toxicity, potency or other hazard, and the facility should be specifically understood in order to make appropriate design decisions for any application, which is beyond the scope of this chapter.

5.1.1 Definitions and Discussion

The primary philosophy for effective isolation and containment should focus on the object or source to be contained or isolated, as much as is practical. This "source containment" approach[2] is reflected throughout the chapter.

The manufacturing function may be considered to involve three components:

1. The pharmaceutical ingredients
2. The personnel
3. The surrounding area or environment

Isolation and containment consists of controlling, to a given, tolerable level, the interaction of the pharmaceutical ingredients component with both the personnel and the surrounding area components.

The first step for isolation and containment is to clarify what needs to be contained or isolated from what, and why:

- Product (or "patient") protection: contamination is 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 [51]. The product (e.g., raw materials, intermediates, or finished formulation) needs to be protected from contamination by the surrounding environment. Limits have been developed which can be used as a partial basis to aid in determining required levels of product protection from the surrounding environment. Two such limits are:
    - Permitted Daily Exposure (PDE) in ICH Q3A(R2) [52] (used for residual solvents, but proposed by the EMA in Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities [53]) as a basis for a limit for cross-contamination in shared facilities.
    - Allowable Daily Exposure (ADE) is a dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below that dose every day for a lifetime.

[2] Also referred to by other names, e.g., closed processing, source isolation.

- Contained or isolated processing operations should protect the integrity of the product and minimize the potential for mix up and cross contamination, including from other non-contained operations. Product protection is generally the concern of quality professionals and involves ensuring that products that are manufactured are safe, pure, and unadulterated, as generally required by cGMP.

- Personnel protection: personnel need to be protected from ingredients or product emitted by handling, transfer, and production steps of the process. Personnel protection is generally the specific concern of industrial hygienists and/or other safety professionals. It involves ensuring the segregation or suitable isolation and control between a route of exposure and individuals

- Outdoor environmental protection: the outdoor environment needs to be protected from process emissions that could otherwise cause harm to the ecosystem. Chapter 11 describes various sources of environmental issues, comparisons of issues, and typical risk mitigation approaches. In the context of containment and isolation of production processes, the philosophy of containing potential emissions within the process equipment can often yield similar advantages of reduced post-emissions mitigation that is environmentally driven as it can for personnel and product protection driven rationale

Typically, an emissions concentration threshold or similar criterion will be set. Below this criterion the quantity of emitted/uncontained ingredients or product will be deemed tolerably “contained” or “isolated” from its surrounding environment.

Emissions concentration thresholds, or similar criteria, are usually set by functional areas, e.g.:

- Quality

- Toxicology

- Industrial Hygiene

- Environmental Affairs

- Other functional areas[3]

In the context of this Chapter, contained/isolated/protected are not defined as an absolute,[4] but as meeting the threshold values of the various containment or isolation criteria which exist for a given compound and situation.

This definition is consistent with the following three points made elsewhere in this Guide:

1. Personnel should be protected from exposure to excessive doses of any materials from the process or supporting areas by all potential exposure routes

2. The environment should be protected against the release of damaging quantities of hazardous agents from the process or supporting activities

3. The ingredients/product should be protected from contaminating agents or undesirable material originating from the surrounding environment

[3] Larger organizations typically have Health, Safety, and Environmental departments staffed with trained SMEs. Organizations which do not have such in-house capability or suitably qualified personnel should consider utilizing qualified outside resources.

[4] In this respect, an “absolutely contained” condition is not possible. Emissions and exposure potential are often defined on a logarithmic scale which, by its nature, has no zero point.

ISPE defines highly hazardous drugs as [11]:[5]

> *"Genotoxic compounds that are known to be, or highly likely to be, carcinogenic to humans, compounds that can produce reproductive and/or developmental effects at low dosages, and compounds that can produce serious target organ toxicity or other significant adverse effects at low dosages."*

5.1.2 Reasons for Product Containment/Isolation

The previous Section provides three reasons for isolation and containment of products:

1. Product protection[6]
2. Personnel protection
3. Outdoor environmental protection

These are grouped separately because they each have associated compliance related imperatives.

There is a fourth reason for effective isolation and containment. It relates to productivity and can be thought of as "business protection". Business protection generally refers to the desire to maintain the maximum yield possible from production while minimizing operating costs, which involves minimizing losses or downtime (product or timing waste of any nature) during or between processing, packaging, distribution, and cleaning/decontamination.

Improved containment at the source of emissions can:

- Decrease room cleaning times during switchovers
- Decrease solid and liquid waste streams coming from room decontamination and cleaning (subsequently reducing hazardous waste, collection, and treatment capacity requirements)
- Reduce changing and decontamination time and equipment when PPE requirements are lessened or eliminated[7]

A source containment solution can enhance the performance in all four areas of concern: protection of people, product, the environment, and the business.

Additionally, the further upstream source containment can begin in a manufacturing process, the more secondary benefits increase further downstream in the process, in terms of legacy or residual emissions. Conversely, any emissions contamination residual left unattended is driven downstream in the process chain, as well as being spread around the rest of the physical facility surrounding the process.

5.1.3 Containment/Isolation and the Relationship with Other Disciplines

The inputs into a complete containment design should include links into functional areas, e.g.:

1. Quality

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[5] The industry has, in the past, also made wide reference to "potent compounds", from which evolved a consensus to mean compounds with biological activity of approximately 15 µg/kg of body weight, or with an OEL below 10 µg/m^3, or a compound with high selectivity or a potential to cause cancer. According to the ISPE Baseline® Guide on Risk-MaPP: "Terms such as potent, cytotoxic, cytostatic, and steroid are not precise when categorizing specific API hazard potential, and conclusions based on a reactive response, rather than specific scientific data, should be avoided." [11]

[6] Reliance on a containment system as the basis of cross contamination control may entail some requirement to validate system performance.

[7] Containment of laboratories in quality, research, and development operations are often managed very differently from manufacturing due to lack of knowledge of materials, extensive user interaction, frequency of cleaning, difficulty of containing at source with small equipment, requirement for flexibility in process routes, and/or common use of standard systems and personnel interface requirements for such equipment as fume hoods/fume cupboards and similar equipment.

2. Operator health and safety and/or industrial hygiene

3. Outdoor environmental considerations

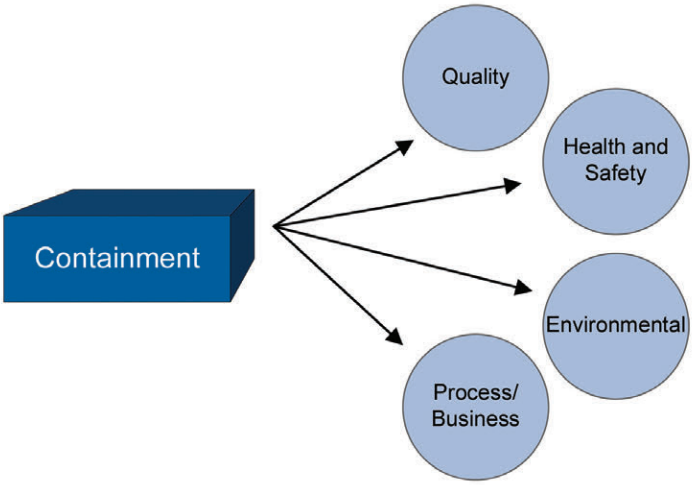
4. Process/operations

As mentioned earlier, the first three functional areas are compliance driven imperatives. The fourth, Process/ Operations, is the remaining broad category which includes the actual process design and ongoing business productivity improvements which effective containment can generate. These business-related attributes of effective containment include cost elements, e.g.:

- Downtime reduction
- Yield increases
- Cost savings from less clean up and decontamination time and consumables used
- Reducing the frequency of quality related product rejection
- Ease of contained maintenance and repair
- Other elements which drive business metrics and increase profitability

Some of these elements are influenced by other indirect considerations, e.g., ease of maintenance and repair would be influenced by the technical capability of the labor force in the local, surrounding geographic area.

Figure 5.1: Containment/Isolation Stakeholders



The outputs of an effective containment approach are multi-disciplinary, or cross-functional, in nature. Successful containment may be achieved through physical design elements, e.g.:

- Process operations and process equipment (process/chemical engineering disciplines)
- Facility architectural layouts (architectural discipline)
- Mechanical, HVAC, extract, and filtration systems (mechanical engineering discipline)
- Effective drainage, collection and/or treatment systems (mechanical/civil engineering disciplines)

Containment/isolation may be viewed as a distinct topic and addressed throughout a project life cycle. Functional areas and disciplines should remain engaged to ensure a comprehensive containment approach throughout the design and development of the process, facility, and procedures that meet the intent of the project requirements.

Stakeholders may have conflicting perspectives regarding the project's containment/isolation requirements. Health and Safety may want controls that keep product emissions within the room in which they are generated, i.e., a negative room pressurization to keep the product captive within the production zone. At the same time, Quality may want controls that create an environment where contaminants cannot reach the product, and one of those controls could be positive room pressurization to push away external particles and contaminants. Methods to accommodate such apparently contradictory requirements are discussed later in this chapter.

Some high hazard product groups can include hormones, Selective Estrogen Receptor Modulators (SERMs), teratogens, beta lactams, cephalosporins antibiotics, and low ADE/PDE materials. Regulations of appropriate agencies should be consulted for guidance on the manufacture and handling of such identified groups when designing new or assessing existing systems.

5.1.4 Risks/Gaps

An analysis of an individual product, process, and design, can yield a set of gaps, or risks, in which containment or isolation of the product may be deemed inadequate by one or more of the containment stakeholders.[8] (The various tolerable limits for each of the different stakeholders may be different, but are likely to be based on similar toxicology data.)

Typically, a risk assessment is used to identify and evaluate gaps, enabling the determination of which physical design elements (selection of control equipment, facility accommodations, and other containment-based provisions) are implemented, and how the system is operated. A risk assessment may consist of:

A. Identifying the tolerable exposure criteria (Quality, Health and Safety, Environmental, etc.)

B. Assessing the exposure or anticipated exposure for all relevant activities, processes, and materials

C. Comparison of A and B:

- If B < A then the (real or anticipated) condition is tolerable and no further control is indicated
- If B > A select control system to reduce exposure, then reiterate from B.

For information on Risk Management see Chapter 3 of this Guide.

Evaluations of risk should include:

- Process hazards
- Compound handling requirements
- History of operation and incident review
- Engineering and administrative controls utilized for hazards detection, mitigation, and control interlocks, sensors, alarms, etc.
- Consequence of failures of hazard controls, engineering and administrative controls

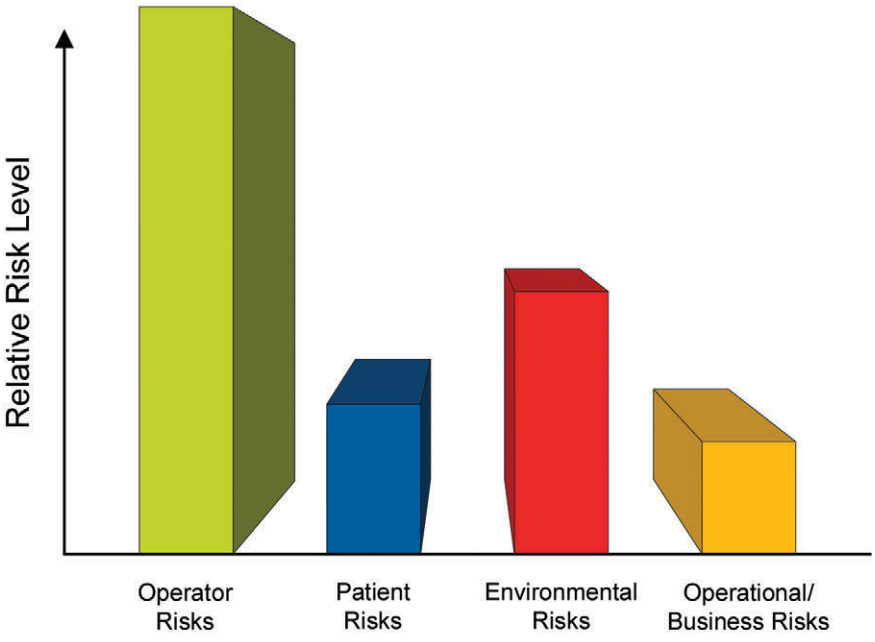
[8] Inadequate, gaps, stakeholders: an inability (qualitatively or quantitatively) for an exposure to meet the tolerability criteria defined by the individual groups (Industrial Hygiene, Quality, Environmental, Operations) to meet their specific requirements.

- Facility setting
- Human factors[9]
- Consequence analysis of failures identified during hazard evaluation in relation to:
  - Number of employees and neighbors affected
  - Equipment and property involved
  - Size and complexity of the process
  - Number of hazardous chemicals involved

Different types of operations will tend to have characteristic risk profiles. For example:

1. A single-product OSD forms manufacturing facility formulating a low ADE compound may have an increased operator safety risk (due to a more stringent OEL, the powder form of the product being more prone to become airborne, etc.[10]) and increased outdoor environmental scrutiny (e.g., potential for external liquid effluent from process/facility cleaning waste streams impacting aquatic reproductive cycles). At the same time the exposure threshold for product contamination and cross contamination (patient risk) might be met relatively easily due to the product being an oral dosage form versus parenteral, and being processed in a single product building. See Figure 5.2.

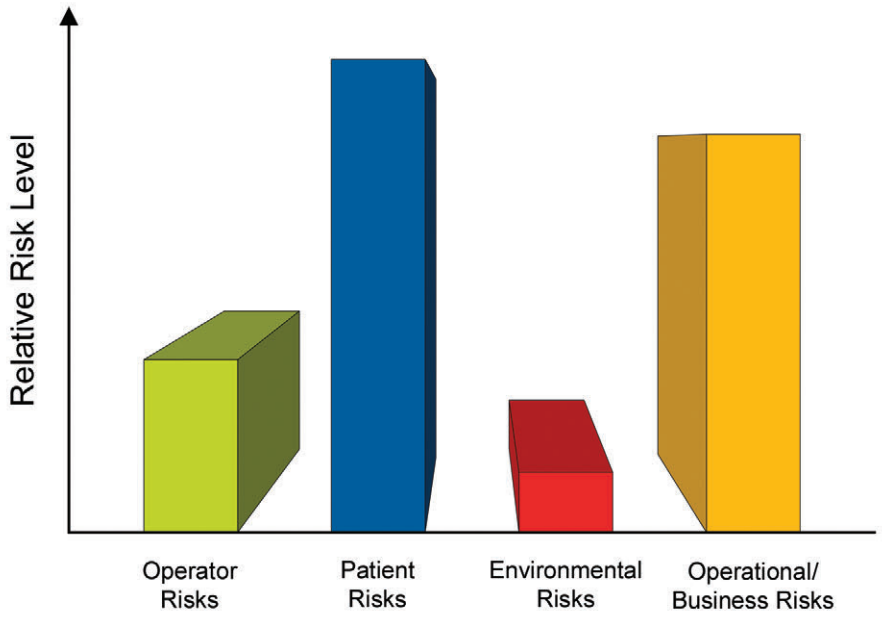
Figure 5.2: A Hypothetical Risk Profile of a Single-Product OSD Facility Formulating as Low ADE (low OEL) Compound



[9] Human factors may make a marginal containment system perform or render the system ineffective.
[10] Various compound formulations can have a pronounced effect on the level or percentage of API that becomes airborne. The continuum runs from solids/powders to semi-solids (e.g., Polyethylene Glycol (PEG)), to creams and liquids.

2. A hypothetical parenteral process[11] which fills multiple products of relatively high OEL compounds into syringes or cartridges could have a higher quality related threshold than OSDs (due to the aseptic imperative of parenterals and an increased risk of cross contamination via multiple products in one building), and a lower threshold to meet for operator risks, due to a higher/less stringent OEL and the liquid form of the product, or at least of the initial API state. (Liquid form is generally, but not always, less aerosolizable than dry/solid states).[12] See Figure 5.3.

Figure 5.3: A Hypothetical Risk Profile of a Parenteral Process in a Facility Which Fills Multiple Products of Relatively High (less stringent) OEL Compounds



Note: Figures 5.2 and 5.3 represent hypothetical processes and are also merely qualitative in nature and are included here to help articulate the concept of differing risk profiles. Assessments of specific processes would be done to determine their specific risk profiles.

For the purposes of containment, risk can be determined in several ways. For example, when utilizing an FMEA based approach, risk is ranked by quantifying the impact, probability and detectability of a hazard, while the hazard is a direct function of the properties of the molecule, and the amount and type of potential exposure to that molecule. Variations of the FMEA approach can also be used to "quantify" risks, on a relative scale, becoming a tool to help determine which risks to mitigate. Managing the risk of potential product contamination, operator exposure, and environmental release is achieved by controlling the nature and degree of the exposure.

Continuing in an FMEA-based context with containment/isolation of drug substances, risk is a function of hazard and potential exposure, and in some cases, detectability.

- Hazard is due to the inherent pharmacologic and toxicological properties of a substance to produce adverse effects on people, environment, process, or product

- Exposure is contact with the substance, and is a function of the process, formulation, equipment, residence time, or period of contact

[11] While a *parenteral* process does not have a direct connection with OSD facilities, it is included here to broaden the example to make the larger point that risk profiles vary from process to process. The same, if subtler, risk profile difference may occur in a process involving an OSD compound with, for example, relatively lower dustiness characteristics (Dustiness Index), compared with that in Figure 5.2.

[12] A multi-product plant is also likely to have more frequent cleaning and changeover, due to its nature, which in some cases might present the greatest exposure risks of all. A risk assessment is needed for the specific situation.

- Detectability is the ability to discover or determine the existence, presence, or fact of a harmful or potentially harmful situation in this context
- Risk is the likelihood of an identified harmful consequence [11]

Different unit operation steps in an OSD process will yield different probabilities of API emissions above the user's threshold level. The probability of API escaping from a process depends on several variables, most of them difficult to quantify with precision. The probable level of API emissions is generally a function of factors such as:

- Openness of the process (including the degree of operator interface needed throughout)
- Percentage of API making up the material being handled at that point in the process
- Friability/dustiness index of the material
- Nature or type (design/configuration) of the equipment
- Adequacy and level of procedures, ongoing training, and expertise of operations personnel
- Age and relative degree of maintenance of the equipment
- Energy input into the material during the process step
- Volume of material handled/scale of operations
- Degree of manual/local versus automatic/remote activities and control
- Ambient temperature and humidity
- Position and orientation of the emission source relative to personnel

Historically, it was thought possible to construct charts or tables showing containment control methods as dictated by an exposure band (i.e., a defined range of allowable exposure concentrations in which a given chemical entity fit). Exposure bands are a convenient shorthand tool to quickly communicate the approximate hazard inherent in a given compound. However, engineering for the actual risk which might be associated with a specific compound in a specific process can be much more complex. See Section 5.1.6.

While there will be exceptions with individual processing steps, in general the probability of API emissions exceeding the user's threshold tends to reduce as the compound proceeds downstream. This is because:

- The material is diluted from 100% API with excipients[13]
- The process steps do not require as much direct operator interface
- Primary packaging serves as a primary containment method for the compound

Figure 5.4 and Figure 5.5 are intended for illustrative purposes only and should not be interpreted as definitive emission levels. Specific and relative emission levels will vary for different compounds, processes, and equipment kits.

[13] The API may be the dustiest component in the drug mix. The combination of excipients with APIs may have an effect of lowering the overall challenge to the containment system relative to API emissions.

Figure 5.4: A Hypothetical Set of Production Steps (Example 1)

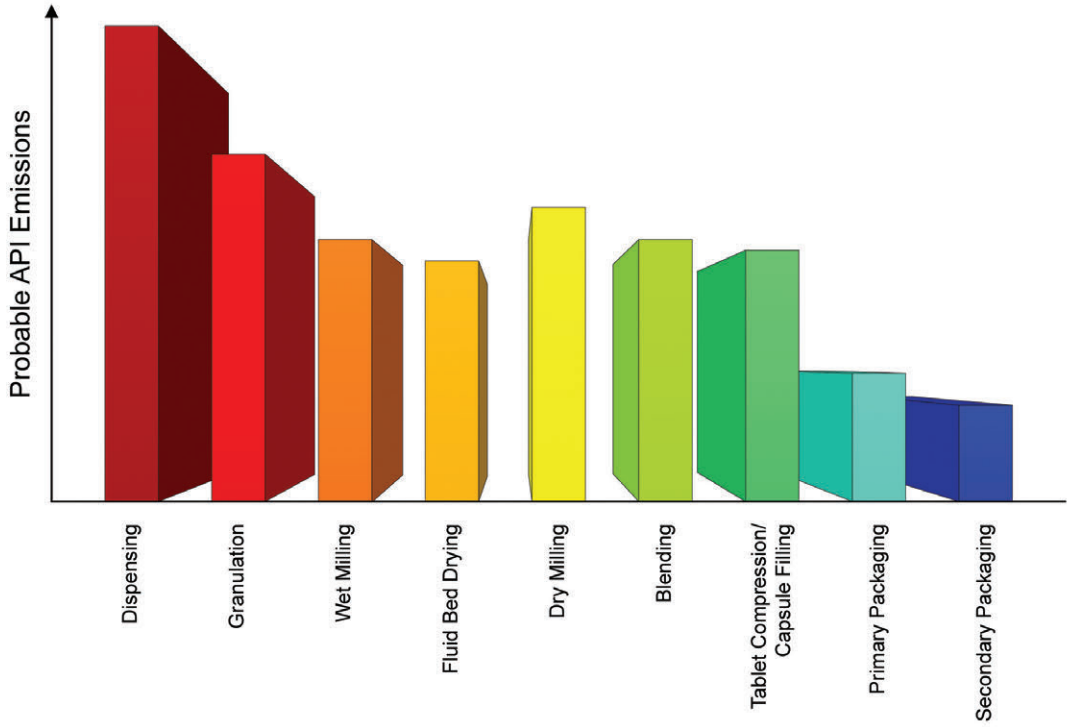
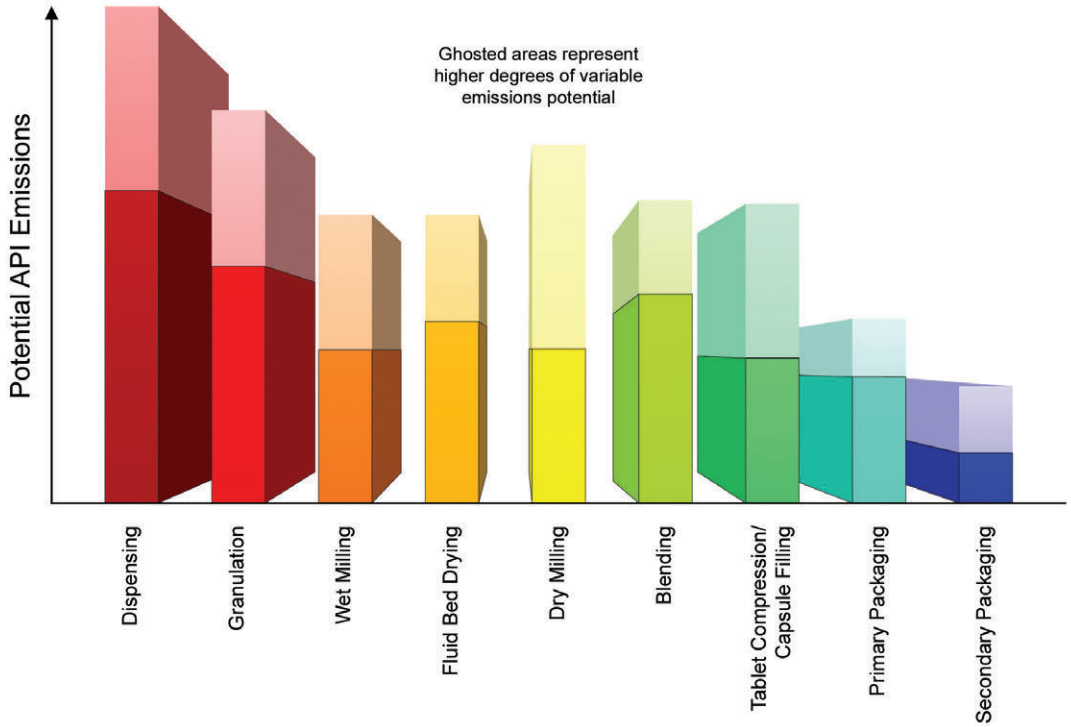


Figure 5.5: A Hypothetical Set of Production Steps (Example 2)



Note: the vertical axis in each of Figures 5.4 and 5.5 is a relative scale.

5.1.5 Dilution

The dilution factor refers to the percentage of API making up the material being handled at that point in the process. For example:

- Where an API being handled at point A with a 100% concentration, and again being handled at point B after excipient additions have diluted the mix to a 10% concentration of API, a case can be made that (in some cases) the degree of containment controls can be lessened once that dilution occurs.

- The argument could be that the energy input to the specific API is diluted, a proportion being used to make the non-API components airborne. In practice, multicomponent solid blends may not behave like perfectly miscible liquids and small API particles can 'stick' to larger excipient particles and, therefore, become less likely to become airborne. They should be considered on a case by case basis.

Note: such reduction in controls should be based on risk assessments.

The OEL of the active ingredient remains unchanged, as long as the API remains unchanged. The percentage of API making up the overall mix escaping from a given process leak may be lower than if it were undiluted API at that point, but the API's exposure limit has not been reduced due to dilution.

5.1.6 Banding

Banding was originally developed by toxicologists to classify materials for which a quantified OEL had not been established. Over time, the approach has been adapted by some organizations to define containment solutions against bands where materials of known OEL are fitted into nominal OEL band ranges taken from that original toxicology approach. These bands are then used to define minimum criteria for control, design, or process review teams to adhere to during design development. While this is an organized methodology, it can cause the design to leapfrog over the risk assessment process of allowing specific risks to drive specific (frequently, more optimal) solutions, i.e., the same containment method will not always yield the same containment results. Alternatively, an assortment of containment methods (or technologies) may yield similar results. See Figure 5.7 and associated text.

Where a risk assessment has not been performed prior to a new process or compound arriving at a site, a banding approach can serve as a quick, first-pass template for approximating potential containment approaches. In such a case, it is recommended that a follow up risk assessment should be performed and, if its results are at variance with that of the banding template, the risk assessment (being more reflective of the operation's actual inputs and variables) should supersede the banding approach. For further information on a risk management strategy to evaluate the level of risk for a specific product which allows the team to determine the appropriate containment strategy see the ISPE Baseline® Guide on Risk-MaPP [11].

5.2 User Requirements

5.2.1 Topics Covered in a Containment System URS

Topics covered by the containment system URS may vary, depending on the operational needs of the specific process and the physical constraints of the surrounding area. Early planning at this stage, however, both ensures accuracy of procurement and can also help to streamline later validation activities.

User Requirements should:

1. Define what the system is intended to contain/isolate/protect against

2. Determine the tolerable threshold/measurable criteria within which the system is expected to maintain conditions

3. State what the control measures are, defining what is safety/quality/environmentally critical

4. Identify how and when performance is to be verified

The most fundamental requirement of a containment system is how contained or isolated it needs to be. Determining this may be complicated for two reasons:

1. The end user requirements are usually not emissions based but exposure based (see Figure 5.6). For example, the industrial hygienist measures for airborne concentrations of compound in the breathing zone of the worker (i.e., a potential exposure). These are different measurements of different things, at different locations, taken in different ways compared with measurements of emissions. For further information on comparisons of equipment emissions see the *ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment* [54].

2. There is not a precise 1:1 correspondence of emission levels to exposure levels. There is a multitude of variables between the emission and the exposure, with which an emission interacts as it moves toward becoming a potential exposure (see Figures 5.6 and 5.7). It is impractical, and usually indeterminate, to devise a precise relationship between those variables and their influence on an initial emission as it goes on to become a potential exposure. However, some of the variables can be referenced in a general way in the URS. For example, particle sizes and density, the required throughput rate, and the expected operator interfaces can be important for the supplier, engineer, and industrial hygienist to improve matching the containment features of a piece of equipment to the user's needs:

Suppliers can speak only to how contained their own equipment can be, with the other variables (e.g., operator interface, procedures, product dustiness) either normalized out or otherwise discounted. For further information, see the *ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment* [54].

A sufficiently contained piece of equipment can enable an operation to run contained, assuming the other variables are adequately controlled as well. There should be a common understanding between the user and the supplier about an approximation of how the variables will manifest in the actual operations, i.e., how they may affect, positively or negatively, the containment capability of the equipment.

Figure 5.6: Emissions versus Exposures

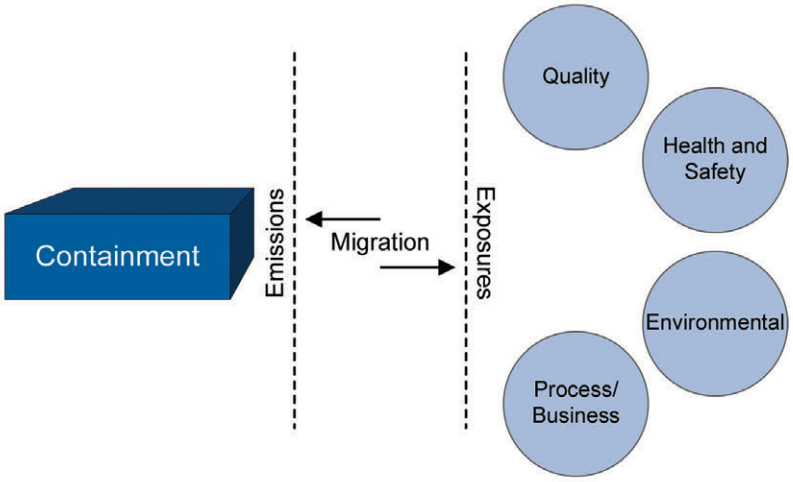
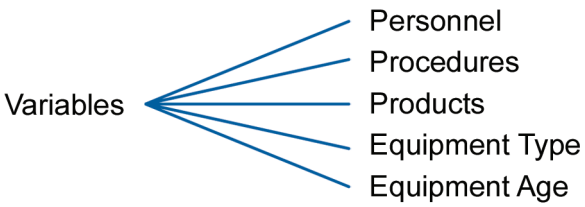


Figure 5.7: Isolation Variables Beyond the Containment Technology Utilized



Another consequence of the variables depicted in Figure 5.7 is that the same containment method will not always yield the same containment results. Alternatively, an assortment of containment methods (or technologies) can sometimes yield similar results. While these observations can be disconcerting due to precluding cookbook recipes for matching a predetermined isolation technology with a given OEL or process type, it can yield alternative solutions and approaches for individual situations. This can allow the engineer to optimize ergonomic, economic, and compliance factors into a more holistic final approach.

Beyond the containment or isolation capability of a system, additional elements that should be captured in user requirements for a containment system may include:

- Materials of construction of a system
- Size or specific dimensional constraints
- Overall configuration and orientation needs of the system relative to process or other hardware
- Equipment, including the process being contained or isolated, and details of the equipment related to it
- Operator interface needs
- Cleaning and maintenance expectations (frequency, access, ancillary equipment, materials used)

5.2.2 Product, People, and Environmental Protection Confusion

The success criteria or tolerable level of emissions containment/isolation is often different between the different stakeholders.

Industrial Hygiene (IH) and Quality (cGMP) considerations tend to be linked, in that they share the same underlying toxicological data. It should be noted, however, that the individual target populations (workers versus patients, respectively), the typical routes of exposure (inhalation/dermal versus oral or intravenous), and the acceptability criteria are different. There is no direct correlation between IH concentration data and cross contamination determinations. Similarly, those breathing zone concentration levels and potential cross contamination thresholds will be fundamentally different to outdoor environmental questions. Individual containment stakeholder areas will have individual sets of criteria by which to judge the effectiveness of the design.

Depending on the specific reasons for containing a process, therefore, the measurement of containment effectiveness for the various stakeholders could be in terms of:

- OEL/Short Term Exposure Limit (STEL) values (for operator protection):
    - There are several routes by which an active pharmaceutical compound or a hazardous material can enter the human body, depending on the material's physical, chemical, or pharmacological properties. There may be several potential routes of exposure, including:
        > Inhalation: direct breathing in of airborne particulates

- > Eyes: direct contact by airborne particulates or indirect contact with a contaminated hand
- > Dermal: direct contact with the skin or indirect contact with contaminated hands, feet, or equipment
- > Ingestion: transfer to the mouth by contaminated hands or other objects
- > Intravenously: sharp object contaminated with the product penetrating the skin

- Compound migration through areas, and residuals on surfaces (for quality/cross contamination potential)
- Emissions from a stack or liquid stream (for outdoor environmental concerns)
- Potential product losses or risk to business interruption (Production/Operations concerns)

Note: each of the above requirements or specifications is different from an equivalence standpoint. For example, the OEL and surface residual of a compound measure very different things, yielding different types of information to the Industrial Hygienist or Quality professional respectively. Similarly, outdoor environmental emissions data track parameters different from the other two and are used to answer other specialized questions.

5.2.3 Timing

Depending on how early in the design process the effort is, it may be beneficial to delay detailing some user requirements rather than constrain the design prematurely. For example, if a process requires an operator to manually interface with it once a day, as opposed to twice an hour, that could be an initial consideration suitable to capture immediately in the user requirements. Conversely, if the only size constraint of a containment system is that it fits into a given room, its specific orientation to the process equipment might stay reasonably undefined until further development of engineering alternatives.

5.3 Containment Philosophy and Approaches

Improved containment at the source of emissions usually enhances the containment and isolation performance to some extent in each area of concern (i.e., Health and Safety, Quality, Environmental, Operations). Containment and isolation needs should be assessed for all manufacturing operations including:

- Material and personnel flow
- Operator activity and product interaction
- Batch components
- Sample handling
- Waste management
- Maintenance and repair operations
- Utility operations

There are many different techniques, applications, and hardware components designed to reduce emissions. Identifying the optimal mix or combination of available choices for a specific operation, therefore, becomes a key activity. This section discusses an organizing principle to begin logical analysis of alternatives.

Generally, the recommended design target is to focus primarily on containment at the source before an emission can occur, e.g., within the process equipment. Additional containment provisions may also be needed further out from the process. However, the required overall level of containment should be achieved as close to the source of emissions as practical.

5.3.1 Choosing the Most Suitable Containment Approach

The rationale for containment for the specific project (quality, health and safety, outdoor environmental, productivity/financial, etc.) should be determined.

The production process should be analyzed in the context of the optimal overall approach to address the following:

- Where does the critical step occur in the process train, how many open steps are tolerable?
- What is the risk downstream of the critical step?
- What is the cost of relatively higher levels of protection needed for more open versus closed processes?
- What will the short-term cost increases and long term cost savings be for higher levels of source containment?

A part of the overall question is:

- What other risks may have been increased through specific selections?

For example, isolators may minimize exposure risks, but increase cycle times and present significant ergonomic issues, or “Business Operations” risk.

Containment system selection can be a balance of multiple factors, e.g.:

- Containment performance
- Process operability
- Ergonomics
- Financial impacts
- Lean manufacturing objectives
- Local maintenance resources capability
- Equipment supplier support in-country

5.4 Hierarchy of Containment/Isolation Controls

A hierarchy of containment controls exists. It utilizes an integrated approach of engineering, administrative, and procedural control measures, and generally represents what has become an industry consensus for strategies and approaches to reduce or eliminate emissions. As quantitative data becomes available for each process step or technology, the combination of controls utilized should be reviewed and their adequacy confirmed, to demonstrate containment and isolation effectiveness during set up, operation, upset, product transfer, and clean up.

The hierarchy is a tool to help organize and then prioritize the options for controlling emissions. The prioritization reflects the philosophy toward containing at the source first, and exploring other options progressively further away from the source location. The hierarchy can be described in the broad categories of (in descending order of impact):

- Elimination
- Substitution
- Product modification
- Process modification
- Process equipment modification
- Local containment provisions
- Facility provisions
- Procedural and administrative controls

Details of the implementation of the upper tiers of the hierarchy (specifically, elimination through process modification) tend to be product specific and so are described here only at a high level. Beginning with the process equipment modification tier and beyond, additional design concepts for containment and isolation begin to be added to the description, as applicable.

5.4.1 Elimination

Elimination refers to omitting or excluding the hazard, either the task or specific material, from the process. (Changes to the material or the task can also logically be considered as examples of product modification or process modification. However, assessing whether the hazard can be eliminated is a logical first step.)

5.4.2 Substitution

Substitution refers to replacing a low OEL or hazardous ingredient with a less hazardous one. This may not be feasible in the pharmaceutical arena, as the API's chemical parameters have been finely tuned and explicitly designed for a desired patient response; many/most changes to the chemical entity could invalidate that design. However, occasionally some reaction chemicals or intermediate compounds might be substituted by less hazardous ones. When this can be achieved, it can yield the most significant impact for the lowest relative cost.

5.4.3 Product Modification

Product modification usually refers to modifying a compound's physical attributes, to make it less of a containment challenge, rather than modifying the product chemically, e.g.:

- Making the API's particle size as large as possible while still accommodating formulation requirements
- Making the particles as spherical as possible
- Increasing particle densities

Modifying these and other physical parameters can decrease the propensity of the API to become or remain airborne; therefore, reducing the challenge to the containment measures put in place. The window of opportunity to affect product modification (i.e., physical attributes) is usually limited to early upstream in the product's development phase, because all process chemistry should be defined before the regulatory submission for a new drug.

5.4.4 Process Modification

Process modification is the modification of the planned or existing manufacturing process itself.

It maximizes the degree to which process attributes and characteristics can contain and isolate the compound. Examples run along the spectrum from the complex (e.g., eliminating transfer points by reducing /combining process steps, such as utilizing single pot processing) to the more routine (e.g., changing the order of powder addition constituents such that the highly hazardous ingredient is added last). Considerations include:

- Designing a process to utilize closed equipment for all steps and transfers
- Minimizing the need for direct operator handling
- Increasing batch size/reducing batch numbers (and therefore reducing disconnections and cleanings)
- Extending campaigns to reduce changeover frequency

For example, continuous manufacturing is a logical extension of process modification that in concept has improved containment potential, and can be worth considering rather than batch type operations.

5.4.5 Process Equipment Modification

Process equipment modification refers to making all process equipment and transfers closed and self-contained. Specific pieces of equipment can be designed with increased containment capability to prevent emissions between the process and the workplace. The process equipment itself can be designed tighter, as well as being designed for access into it in a more contained fashion. In addition, partial barriers (rigid or flexible) can be integrated into the equipment for isolation during running and/or cleaning and maintenance access. Such designs leave the product contact elements inside the containment boundary, with the mechanical housing and controls outside the containment boundary. For OSD facilities, this includes equipment such as:

- Transfer equipment and connections (and more importantly, disconnections), such as Rapid Transfer Ports (RTPs)
- Dispensing equipment and provisions. These include such devices as Split Butterfly Valves (SBVs) and cone and septum devices:
    - SBV: the basic principle consists of two parts of a valve occluding the exposed closure faces during material transfer. In selecting a valve, simplicity and performance are key factors.
    - Cone and septum: a cone with a butterfly valve and a short tube is placed over an open drum. It is inserted into a silicone septum at the point of charge and the valve opened. A potential emissions point is generated where the cone is withdrawn from the septum and the recovered for re-use. Performance can be improved with the addition of LEV at the critical points.
- Sieves
- Blenders
- Granulators
- Driers
- Coating machines
- Mills

- Tablet presses and capsule fillers
- Dedusters
- Exhaust/extract filters
- Vacuum transfer systems[14]

The aim is to contain at source. The focus in this case is to modify the hardware to make the process equipment and transfers inherently self-contained. It is common to work with the equipment manufacturer for such modifications.

The process modification and process equipment modification activities above represent opportunities to influence which process steps are deemed critical or open. These modifications target potential process breach points directly, enhancing levels of quality assurance, while reducing facility costs, as they drive the level of protection. For further information, see Chapter 6 of this Guide.

5.4.6 Local Containment Provisions

Local containment provisions refer to specific pieces of equipment that are used to contain emissions directly at their site of generation (hence the term “local), as they are initially escaping from the process. Local containment provisions can become necessary when process equipment modifications are unable to effect the desired isolation level. Such provisions generally fall into one of two categories:

1. Enclosed, physical barriers
2. Air based methods

Enclosed physical barriers can be further subdivided into rigid or flexible material designs and combinations. In addition, hybrid combinations of rigid and flexible designs may be used, as well as mixing air based methods with them. The strengths and limitations of each type of rigid and flexible design should be understood individually, in order to create an effective overall design.

5.4.6.1 Enclosed Physical Barriers

A key advantage with barriers (rigid or flexible) over an air based approach is that being a physical barrier, there is typically a greater degree of assurance that contaminants are allowed neither into, nor out of, the control volume. In addition, the defined volume of air to be isolated or controlled is relatively small.

Rigid Physical Barriers

This equipment is fabricated from solid materials such as stainless steel, acrylic sheeting, and glass or similar. 316L stainless and/or polycarbonate are materials commonly used. Generally, such barriers can be integrated within and around the process equipment.

These barriers are less susceptible to punctures or other sources of catastrophic damage than their flexible counterparts. Gloveboxes and isolators are common examples of this equipment.

Disadvantages of a rigid barrier approach can include:

- Delivery schedule (design including long prototype periods, fabrication, commissioning)

[14] Vacuum systems may be unsuitable for blended materials of a particular size and density heterogeneity, due to the risk of segregation. The issue should be checked for the specific application. A wanding station can also be considered to reduce emissions during drum to next process transfers.

- Cost
- Ergonomics
- Periodic decontamination and cleaning requirements

Prototyping is advised prior to final design approval and fabrication. The cost of the material used to fabricate, as well as the machining expertise to yield the appropriate finishes, flush surfaces, and coved corners for cleaning/decontamination can elevate over the course of the design development. Ergonomics are constrained to the final dimensions of the enclosure and should be optimized as much as possible during design.

Rapid fluctuations in the internal pressurization of the barrier should be anticipated and accommodated. While typically much less sensitive to pressurization changes than flexible barriers, a failure can be catastrophic; an improperly pressurized barrier can shock release its contents outward when opened, or the barrier itself can implode or explode if a pressure relief system is not in place. With adequate process definition and planning for human interface, such operational considerations can typically be accommodated during the detailed engineering design of the rigid barrier.

Flexible Physical Barriers

This equipment is relatively inexpensive, readily available, often in appearance translucent or transparent, tactile, and flexible. Its geometry is not as rigidly fixed or confined. It is highly operator adaptable, and conducive to rapid prototyping and deployment, often in the field. These features counter disadvantages of more rigidity, longer prototype time periods and higher costs of rigid systems. Ergonomics may also be less of an issue (although they remain a critically important factor). In addition, a requirement for periodic cleaning may be avoided if each flexible device is disposed of and replaced with a new one, i.e., the single use approach. This necessitates an ongoing cost of barrier replacement, as well as disposal costs of the used barrier, a cost sometimes higher due to the hazardous compound residual in the discarded barrier. However, the cost of a flexible barrier replacement should be compared against the cost savings of reduced (or no) cleaning or decontamination of the barrier. The economics (i.e., the true cost of cleaning) should be considered when making the analysis.

Examples of flexible barriers include glove bags and FIBCs. These are usually made of flexible film and fitted with aspirating filters (HEPA or otherwise, depending on the application) for pressurization relief. The glove bag can be connected to a fan/filter system. The filter(s) allow airflow in the event air turnover is desired within the control volume. It also allows the bag to be compressed, or vacuumed down through the pressure relief filter, for disposal after usage. Glove bags need supplemental support, which can be provided by the equipment being contained and/or by a framing system. The framing system can be internal or external to the glove bag; however, if it is internal it will also be contaminated with compound after use. Generally, external framing (an exoskeleton) is utilized for its ease of reuse. Gloves, sleeves for utility connections, and bag-in/bag-out provisions can also be incorporated.

Disadvantages include significantly less tolerance for pressurization changes than rigid systems, requiring secondary support structures to maintain shape, and less robustness against physical wear, impaction, sharp instrument punctures, etc. As with other engineering controls to one degree or another, successful operation is generally procedurally dependent and should be compliant with SOPs.

Hybrid Designs

Hybrid designs can incorporate both rigid and flexible approaches to local containment. Many diverse combinational design approaches may be used, e.g.:

- Barriers (partial gloveboxes or glove bags) fabricated onto the side of process equipment at required access points
- Stand-alone barriers where some walls are rigid and others are flexible

- Various containment components (sleeves, continuous liners, chutes, etc.) that are utilized entirely independent from larger barrier systems

5.4.6.2 Air Based Approaches

Air based approaches rely primarily on control of airflow direction and pressure differentials. The underlying principle of air based containment is that of positive pressure inducing an outward airflow pattern from the area to protect the product (quality concerns), or negative pressure/inward flow for the area to be contained (health and safety/environmental concerns). Examples of air based containment approaches include:

- Local exhaust or purge systems
- Unidirectional airflow devices or areas[15]
- Localized push-pull air systems
- Ventilated enclosures (fume hoods, biosafety cabinets, balance enclosures, laminar flow booths, etc.)

Advantages

A significant advantage to air based containment methods is ergonomics; air based approaches are typically one of the least restrictive of containment approaches for the operator. Depending on the ergonomic and access requirements, this advantage alone can be significant.

Disadvantages and Considerations

Air is an inherently unstable (easily affected) system. Every personal interaction or mechanical change in or around the containment zone can radically affect the intended airflow pattern, as well as performance. In addition, the dimensional relationship and orientation between the emission source and the airflow device can be unforgiving, with small shifts in equipment position or personnel orientation causing significant degradation in containment performance. Operators' orientation to the airflow and emission source is also critical to effective performance. Consequently, the approach is highly technique dependent. Operator procedure, along with the ergonomics and anticipated interaction with the process step, can have a significant impact in its design and effectiveness.

Another disadvantage, depending on the alternative under consideration, can be the owning and operating cost. When in operation, exhaust air uses energy in both fan power and increasing the demand for heating, cooling, filtering, and other conditioning of fresh make up air into the facility. The facility's geographic location determines both the cost of power (local energy rates) and the amount of conditioning for fresh outdoor make up air (local climatic conditions).

Successful operation of air based systems relies significantly on commissioning, validation (if applicable), maintenance, and record keeping.

Exhaust systems may accumulate contamination of internal surfaces, such as connecting ductwork and filter media, and may themselves need additional contained methods of maintenance and replacement.

There are several guidance documents on the effective design, operation and maintenance of exhaust/extract systems, e.g., the HSG258 (UK) [55].

Some air based methods can also be used in conjunction with rigid or flexible barrier hybrids, increasing the potential design options for local containment approaches.

[15] Depending on the size, volume, and degree of airflow targeting, this method could also be categorized as a "facility provision".

5.4.7 Facility Provisions[16]

Facility provisions refer to design elements that are built in to the facility.

Architectural examples include physically separated production, cleaning, or equipment spaces, such as by area/zone/room or containment zones and airlocks as applicable. Such layouts can enable, e.g., unidirectional traffic flow of personnel, material, equipment, and waste through the building. Functional areas should include provisions such as gown/de-gown/decontamination facilities when needed.

Mechanically, facility containment provisions are comprised of HVAC airflow turnover, zoning of environmental control, appropriate filtration, effective use of area pressurization differentials, and similar elements.

Two phenomena which should be well understood in order to utilize facility based features to help achieve containment effectively are:

1. Compound migration

2. Types of movement within a building

5.4.7.1 Compound Migration

Compound migration may occur by many different means, such as aerosolized emissions escaping from a unidirectional hood, operator tracking product out on shoe covers or uniform, filter changing operations with uncontained dirty filter disposal, etc. However, compound migration occurs in only two modes, either separately or in combination:

1. Airborne distribution/transfer

2. Mechanical transfer, which includes:

    - physical tracking: compound being tracked out on equipment, uniforms, or containers

    - transfer in liquid form: e.g., a liquid mixture spilled onto the floor, partially run under the room door's undercut and into a general corridor

Analysis of containment features at the facility level can highlight potential gaps in a design. For example, an air lock can be placed between a process room housing emission sources and a general corridor. Theoretically, the airlock can mitigate airborne emissions from getting out into the hallway; however, the airflow alone may be inadequate to control the compound from being physically tracked through the airlock. Both modes of migration, the airborne distribution and the mechanically transferred, should be adequately accommodated, ideally in the same place and at the same time[17] for maximum control of emissions.

5.4.7.2 Airlocks

Airlocks are hybrids of the architectural, mechanical, and (at times) procedural control disciplines:

- Architecturally

    An airlock is simply an intermediary buffer space connecting two or more other spaces. Doors connecting the other spaces to the airlock are interlocked such that only one can be open at a time. This is to maintain a desired pressure differential between the spaces divided by the airlock.

[16] In this context, "facility" is taken to be the physical, stationary, "built into the building" infrastructure; typically, these are mainly the architectural/adjacencies layouts and HVAC elements.

[17] From a containment perspective, this is the rationale for decontamination showering within a negative or "pressure-sink", airlock.

Traditionally airlocks are not pressure-controlled; they are allowed to "float" between the areas to which they are connected. The small volume of the airlock relative to the larger connecting areas causes the pressure in the airlock to immediately equilibrate, rising or falling, to that of the area which its door opens onto, while having negligible effect on the larger area's pressure. Pressure differentials between the various larger areas remain undisturbed, because the airlock's multiple doors are never open simultaneously.

- Mechanically (HVAC)

  Technically speaking, for an airlock to be an airlock, no HVAC is needed; the airlock can achieve its function of maintaining pressurization differentials by architectural elements only (walls and interlocked doors). However, the pharmaceutical industry presents additional requirements of, and opportunities for, airlocks. These can be achieved by added HVAC applications:

  - Sufficient air turnover rates and filtration levels may be needed to maintain required cleanliness levels (e.g., ISO standards [56]) which may prevail due to the cleanliness levels of the rooms which the airlock is opening out onto.

  - Often, some activity is intended to occur within the airlock, frequently gowning and/or de-gowning. In addition, decontamination may be required along with the de-gowning function, therefore having additional activities (and risks) associated with it. In addition, if airlocks are required and a unidirectional traffic flow pattern exists, there may be separate airlocks for entering (and gowning) and exiting (and de-gowning/ decontamination) the production space.

  - Quality, health, safety, and environmental imperatives are sometimes contradictory in terms of airflow direction. HVAC design can enable airlocks to provide a ready response. An airlock can be balanced and controlled to be more highly pressurized than its surrounding connected areas (becoming a pressure bubble), or conversely less pressurized than its surrounding connected areas (becoming a pressure sink). Doing so may solve both compliance and technical performance issues:

    > Compliance: can allow the process room to be either more positively or negatively pressurized relative to an adjacent (major) area without appreciable airflow between those areas through the airlock

    > Technical performance: as a practical matter, it is usual for specific functions to be performed within an airlock. For example, personnel exit from a production area, if through an airlock, might also include decontamination and/or de-gowning activities within that exit airlock. Such an application may be accommodated by that space being a pressure-sink:

      ○ Regardless of the direction of air flow between the production area and the airlock, the operator will still have the tendency to physically track out API and contaminant on the uniform and other instruments and components. (In terms of the model this chapter describes: while airlocks can be good protection against the airborne distribution method of migration, they are less effective with mechanical transfer, or physical tracking.) The default should be to make sure that the airflow between the airlock and the less protected non-production area is directionally into the airlock, as there will plausibly be contaminant within the exit airlock, regardless of airflow direction relative to the production room. Assuming for quality reasons it is unacceptable to balance the airflow such that it cascades in a single direction throughout (i.e., from the non-production area through the airlock, into the production area) this pressure sink balance approach, which pulls air from the production area into the airlock, is an alternative.

    > For entrance from a less clean space into a production room that has seemingly competing pressure differential preferences between Quality and Health and Safety, a pressure bubble may provide a way to accommodate both.

- It can also provide isolation between the production room and the general non-production area, while acknowledging the different risk profile of entering the room instead of exiting it. When an operator first enters the entry airlock, it is presumed (different from exiting) that there is no API being tracked in on the uniform, etc.; therefore, no material is being tracked through into the production area through the entryway, regardless of airflow direction. However, when there is airborne API within the production room from ongoing operations, the positive pressurization of the entry airlock will aid pushing back the airborne API from migrating into that airlock. At the same time, the airlock will be in clean mode by being positive to the adjacent non-production (e.g., non-controlled) space.

Airlocks, and hybrid variations of them, do not by themselves necessarily provide positive isolation or containment across areas. Other design elements and procedural controls are often integrated into an overall approach. However, effective utilization of airlocks, used in conjunction with a clear understanding of the risk profile, specific compliance requirements (if any), and the modes of contaminant migration (airborne and physical tracking) can enable effective isolation control.

5.4.7.3 Movement within a Building

Facility design should focus on controlling three types of movement or motion within a building:

- Personnel
- Material (includes equipment, compounds, waste products, and reusables)
- Air

The main facility infrastructural elements through which emissions are normally spread fall under the architectural and HVAC disciplines.

Layout/Architectural

Personnel and material flow can have an impact on the mechanical transfer (or tracking) of compounds within a facility. Simple, more direct (and closer) routing for access and transport has a greater probability of maintaining containment than more complex routing. Layout considerations are also three dimensional; height is another key consideration. For example, a room that is sufficiently high can accommodate a gravity fed transfer mode, while a lower ceiling may limit available options to vacuum transfer as the only transfer mode. In addition, a contained receiver may be located in a room directly below a transfer vessel, allowing an architectural separation between a contained versus a dusty operation, effectively minimizing the amount of space which might become contaminated during the transfer.

Depending on risk assessment outcome, mechanical equipment areas housing HVAC and other fan/filter equipment can be separated or isolated from other mechanical areas to prevent migration of emitted compound (e.g., compound emitting during access for cleaning and maintenance, if self-contained features of the equipment prove insufficient by themselves) from contaminating systems serving other areas of the building. Personnel accessibility and isolation of such a contained mechanical space should be given similar consideration as other contained process spaces.

HVAC

Airflow should be controlled in order to work in concert with other containment/isolation methods and the user requirements. Components which should be analyzed in regard to migration modes (airborne versus mechanical transfer) and control of movement within a facility include:

- Zoning

- Area pressurization regimes
- Degree of filtration
- Means of contained maintenance

5.4.8 Procedural and Administrative Controls

These include the extensive body of procedures, job aids, and other defined work practice direction and techniques required for the operator to appropriately interface with the process and equipment so as to complement the system's overall efficacy. Additionally, administrative controls refer to job rotation and other exposure limiting policies. SOPs for operating equipment are another form of control in this category. These include SOPs for the use of Personal Protective Equipment (PPE) and Respiratory Protective Equipment (RPE).

5.4.8.1 Importance of Procedure and Training

Operator technique and interface is considered critical as it has the potential to counteract physical design and layout. Procedures are normally used to control or direct operator techniques and interface. Procedures may also be critical to minimizing variability in emissions and containment system performance, e.g., with Local Exhaust Ventilation (LEV) type systems:

- Procedures should be developed and clearly workable. A robust training program should be established
- Adherence to procedures should be followed long term to verify continued compliance
- Verification of overall system and procedure effectiveness should be via emissions monitoring techniques, air sampling

5.4.9 Administrative Controls and Work Practices

5.4.9.1 Importance of Administrative Controls and Practice

Administrative procedures are intended to ensure that personnel understand what the hazards are, how those hazards are addressed, and the reasons for management expectations. SOPs may describe, e.g., the proper use of engineering controls or PPE to enter and operate equipment. Training in relation to an SOP is a major activity in administrative control to ensure that personnel understand risks and how to perform tasks safely. Attention should be focused on behavior management, air monitoring, and medical surveillance, as procedural success is dependent upon compliance.

5.4.9.2 Behavior Management

Behavioral based safety management may be used to ensure compliance of personnel with policies and procedures. The safety culture of an organization may be described as:

1. Employees do not follow SOPs and safety rules even when directly supervised
2. Employees follow rules only when directly supervised
3. Employees follow procedures when not directly supervised
4. Employees correct the behavior of a coworker in the absence of a supervisor. This is considered the ideal behavior based safety culture

A safety culture tends to progress through these steps in direct proportion to the perception by personnel of management commitment to safety and is considered a valuable indicator of overall program success.

Management should provide visible support and resources for proper training and reinforcement of SOPs, etc. Feedback that assists in achieving world class behavior management compliance may be provided by:

- Well communicated and visible management commitment
- Capable HSE staff
- Well written policies and procedures, incorporating operator input

5.4.9.3 De-gowning

PPE worn in a manufacturing suite can become contaminated with hazardous materials. Facilities and equipment should be provided and procedures established allowing operators an appropriate, safe means to remove contaminated PPE. During de-gowning, operators should be protected from inhaling contaminants. Contaminants dislodged from PPE should be prevented from re-aerosolizing, potentially ending up in the breathing zone of the operator and/or spreading over a wider area.

Fog or mist showers may be used to encapsulate and hold dusty contaminants to external uniforms and room/equipment surfaces. This can minimize or, in some cases, effectively eliminate re-aerosolization of contaminant during PPE removal. The water volume should be minimized to avoid exposing operators through a non-waterproof coverall. Minimizing water spray (via fog or mist methods of delivery) also reduces the chance for overspray and the amount of liquid waste from showering requiring treatment. Where PPE components, such as RPE, are to be reused, facilities for cleaning and maintenance should be part of the de-gowning area.

5.5 Other Considerations

5.5.1 Equipment Monitoring and Maintenance

Performance of containment equipment should be included in normal predictive maintenance activities. Materials that include physical barriers, such as elastomers, may lose their flexibility or degrade from chemical exposure over time. Swipe tests and air sampling may be used for routine monitoring of containment capability, in addition to maintenance recommended by the equipment manufacturer. Routine analysis of deposition plates positioned around a manufacturing area also may be used to reveal containment problems.

Ventilation system performance may degrade over time due to causes such as duct or filter plugging, or fan belt failure [57]. There may be a high potential for exposure during maintenance. Exposure assessments should be completed and appropriate procedures established before maintenance work is performed. Operating and maintenance personnel should be trained prior to equipment startup. Industrial hygiene personnel should be experienced in sampling and should be involved in developing testing protocols.

5.5.1.1 Controlled Substances (security/general public protection)

Controlled substances or controlled drugs are narcotic drugs and psychotropic substances regulated by provisions of national drug laws [58].

Controlled substances or controlled drugs may (but not necessarily) be low OEL in nature and are usually the concern of security professionals who are interested in maintaining tight restriction of access to the product (or raw material, or intermediate), largely due to its high market value in unregulated environments.

Generally, there should be a physical barrier (containment/isolation) between anyone potentially considering diversion during manufacturing, packaging, and distribution of low OEL compounds or highly hazardous drugs. During operations where open processing occurs, additional physical security measures should be considered.

There are physical security measures to secure product. Generally, these are regulated by local jurisdictions and may include the use of secured cages for specific controlled substances, or vaults for products susceptible to diversion or theft. Some of these measures may need to be coordinated with specific containment and isolation needs. Controlled substance design considerations include:

- How accessible is the product to the operator?
- What methods of diversion can be employed and prevented?
- Are there any hidden areas from view that could be exploited for diversion attempts?
- What is the strategy for maintaining a security guard presence?

Special design considerations can include:

- Enhanced building structures (wire cages, vaults, thickened and reinforced floors and walls etc.)
- Secure and limited access to areas processing or storing controlled substances
- Lockable product/material containers
- Security cameras (internal and external)
- Security personnel/product escorts
- Physical sensors (motion, high heat, light beams and curtains etc.)
- Audio and visual local alarms systems
- Remote monitoring of alarms
- Minimized movement or controlled substance material
- Adequate lighting

Procedures should be developed for the handling of controlled substances and all employees should be trained in the handling and manufacture of controlled substances.

5.5.2 Containment Technology Cost Implications

Engineering controls have traditionally been perceived as expensive in comparison to PPE, RPE, and expanded cleaning requirements. A complete life cycle analysis of containment capital costs versus ongoing operating costs may indicate that greater capital costs have an improved return on investment over PPE, RPE, and cleaning. Aspects that should be considered include:

- Ongoing replacement expense for RPE/PPE, including cost of space to store
- Management effort required to achieve behavioral compliance of RPE/PPE use

- Productivity and housekeeping cleaning to prevent both cross contamination and sub threshold levels which might build up over time to create operator exposure situations
- Reduced HVAC operating expense
- Reduced electrical costs for equipment in areas with combustible dusts or flammable liquids
- Reduced clean up and room turnover times (i.e., the true internal cost of downtime)
- Reduced cost of contaminated waste treatment (liquid, solids for landfill/incineration)

5.5.3 Facility Renovations and Facility Demolition Considerations

Normal demolition considerations for facilities, as listed below, can take on additional dimensions when increased containment or isolation is emphasized, e.g., when there is a risk of residual hazardous compounds present.

- Identification of resources and their required skills to establish a project team needed to effectively manage and execute the many elements and phases of a demolition project
- Development of the upfront engineering costs associated with the environmental characterization, utility relocation, and hazard abatement that is associated with the planning and site characterization phase of the project
- Execution of a comprehensive planning and site characterization phase that includes risk assessment, process equipment planning, and all demolition preparatory operations
- Development of final engineering project costs and scopes of work for decontamination
- Implement effective, safe, and verifiable equipment and building demolition and decontamination processes
- Management of the final disposition of all out of service process equipment and related ancillary equipment located within the building or structure scheduled for demolition or strip out
- Implementation of effective and safe demolition and decontamination of operations and activities
- Management of the handling, transportation, and disposal of all associated special wastes (especially low OEL and highly hazardous compounds) and demolition debris
- Ensuring that that appropriate implementation documents are developed and records of implementation are retained
- Execution of an effective project closure reporting and record keeping system

6 Architectural

6.1 Introduction

This chapter discusses the requirements for architectural design considerations of new and/or renovated OSD manufacturing facilities. Generally, the process architect translates the process requirements into a facility layout based on the manufacturing process, people flow, material flow, equipment (dirty and clean) flow, and waste flow. These aspects of the manufacturing processes should be developed in the context of GMP requirements, risk assessment, process requirements, and CQA of drug substance and product substance to establish facility's design and layout.

6.2 High Level Considerations

The architectural design of an OSD forms manufacturing facility, both in layout and detail, is influenced by key product and process fundamentals. These fundamental requirements can have a significant impact on the design of the facility. They should be understood and addressed in a facility and unit operation context when developing the facility design concept. High level considerations include, but not limited to:

- Product quality risk
- Product, chemical, and physical characteristics
- Material and equipment flows
- Personnel and waste flows
- HSE aspects of the process and product
- Building Code requirements

6.2.1 Product Protection

The ISPE Baseline® Guide on Risk-MaPP [11] describes a scientific risk-based approach based on ICH Q9 [3] to manage the risk of cross contamination to maintain product quality and operator safety. This approach will aid in the determination of the need or otherwise for dedicated or segregated facilities in the manufacture of pharmaceutical products.

Note: see ISPE Baseline® Guide: Risk-MaPP [11] for other methods of risk determination.

6.3 Product Protection Requirements

It is a regulatory requirement that OSD forms manufacturing facilities protect the product from chemical, physical, or biological contamination during all phases of the manufacturing process. This chapter considers product protection through the design of the facility.

The need for product protection should be evaluated during risk assessment at the process design stage. Product protection requirements are typically evaluated at each step of the design process. Suitable preventative methods, which reduce risk of contamination to an acceptable level, should be identified.

6.3.1 Levels of Protection

The level of protection requirements should be soundly based on a detailed risk assessment with appropriate application of risk level and risk mitigation (refer to Chapter 3 of this Guide). There are three main levels of protection categories which are based on potential product exposure, defined as follows:

- Level 1 General (Low Risk): areas of the facility that have no potential for product or product contact surface exposure and the environment or activities in these areas have no direct or indirect impact on the product
- Level 2 Protected (Medium Risk): areas of the facility that have a no potential for product or product contact surface exposure, however the environment or activities in these areas may have direct or indirect impact on the product
- Level 3 Controlled (High Risk): areas of the facility that include open processes where the product or product contact surfaces are exposed and the environment or activities in these areas have direct impact on the product

The risks to the product may include, but are not limited to:

- Contamination (foreign matter or viable organisms)
- Cross-contamination (other products contaminating a product)
- Mix-up (other products being mistaken for the subject product, e.g., rogue tablets, incorrect labels)

Risk factors should be considered during discussion of risk mitigation plan. Typical risk factors should include:

- Potency of materials
- Dustiness (e.g., ability of the process to create an aerosol of powder which can cross contaminate)
- Volume of product handled (the larger the product volume, the greater the risk from emissions of a short duration)
- Duration of operations (the longer the duration the greater the probability of contamination or cross-contamination)
- Openness of the process (exposure of the product or process to the room environment). This can be more significant during charging and discharging

Risk mitigation plans may consider the following:

- Process closure/equipment integration (product not exposed to the space)
- Process enclosure (isolator and containment systems)
- Room environmental control
- Adequate space and separation (hard walls, transition spaces such as airlocks)
- Personnel controls (appropriate growing and gowning rooms, PPE)
- Administrative controls (campaign operation, frequency of operation)

For further information on levels of protection see the ISPE Baseline® Guide on Risk-MaPP [11].

Table 6.1 outlines risk levels and frequently associated levels of protection, as well as some common industry terms.

Table 6.1: Risk Levels and Frequently Associated Levels of Protection

Risk Level	Description	Risk Mitigation	Level of Protection	Current Industry Common Terminology	Purpose
High	Open and exposed product is present in the space. This may include unit operations such as: • Incoming raw material sampling • Weigh/dispense • Formulation • Granulation • Solution preparation primary packaging (where is product is exposed to the space) • Transition spaces and corridors (where there may be exposed product)	Typically, within these areas, environmental conditions which may apply include: • Temperature • Humidity • Air filtration quality These should be specified and validated, as well as personnel protection	Level 3 Controlled	White Zone, or primary, controlled	To protect product (quality)
Medium	Spaces where manufacturing processes are closed (not exposed) and where there is the potential for accidental product exposures. These spaces may include: • Secondary packaging • Primary packaging, if the product is enclosed • Manufacturing, if the product is not exposed	Typically, within these areas, environmental conditions include: • Temperature • Humidity • Air filtration quality These should be specified and validated, as well as personnel protection.	Level 2 Protected	Grey Zone, or secondary controlled	To control the migration of product if accidently released, and to control the migration of contaminants into spaces where the product is exposed
Low	There is minimal risk for product or product contact surface exposure. Spaces may include areas where raw materials and packaging components are in their received packaging. Final product is fully contained and protected by its completed shipping packaging. Areas may include warehouse, shipping/receiving, palletizing, pallet wash, and equipment maintenance.	Typically, within these areas, environmental conditions which may include temperature and humidity are controlled. Gowning may include facility uniforms and access control.	Level 1 General	Black Zone, or Tertiary controlled	To provide control and accountability of product (chain of custody)
Spaces outside the cGMP manufacturing areas	These areas are physically separated from GMP manufacturing areas. These are typically support functions (e.g., offices, laboratories, break rooms) for the facility.	Not Applicable (N/A)	N/A	N/A	Support of the manufacturing operation

6.3.2 Product Quality Risk

The degree of product quality risk is related to the:

- Level of material and product exposure
- Potential for cross contamination

- Material and product hazard characteristics
- Single versus multiple product

Multi-product facility versus single product facility:

- Level of production activity
- Product change over controls
- Equipment and facility cleaning procedures
- Frequency of facility and equipment cleaning
- Cleaning validation

Risk may be mitigated architecturally by:

- Providing appropriate and adequate space
- Designing for logical material, product, equipment, and personnel flows
- Designing for appropriate segregation within the manufacturing facility layout
- Providing appropriate materials of construction and finishes

Appropriate space can be established by test layouts of spaces to determine if there is adequate space for equipment as well as movable pallets, IBCs, drums, and equipment access, etc. The appropriate space should accommodate manufacturing unit operations, manufacturing support functions, staging, storage requirements, and service and maintenance. In addition, space may be needed for amenity, administration and operational support spaces, and gowning provisions. The facility design should provide for cleaning and maintenance operations based on the level of protection.

Operationally, the flow of materials, including waste, parts, equipment, and personnel through the building, should be achieved by a logical and efficient design. The flow should promote product control and necessary segregation, as well as operational efficiencies. Segregation and control requirements may become more stringent as the level of product quality risk increases.

The facility layout should accommodate suitable locker, gowning, toilet rooms, corridors, doorways, and airlock arrangements, providing controlled access and necessary segregation between GMP areas and non GMP areas, and also between GMP areas of different levels of risk. The level of gowning needs to be appropriate for each area based on its level of protection. Airlocks are usually used between changes in different level of protection areas. De-gowning or over gowning are recommended. Toilet and break rooms are typically outside of the manufacturing areas.

At a minimum, architectural requirements and construction control for the facility materials and components should be established to support space segregation, prevention of cross contamination, and cleaning requirements.

6.3.3 Material Flow

A Process Flow Diagram (PFD) should be established prior to the facility concept design. Material flow should be based on the process flows of the facility that will influence the architectural design and layout. CPPs that can affect layout detail include the:

- Types of material transfer technologies employed

- Frequency of transfer
- Quantities of materials transferred

Material transfer technologies include gravity transfer, pneumatic/vacuum transfer, and bin/container transfer. Facility designs are normally driven by the primary method of material flow, but may incorporate other transfer options within the overall design. Material flows should be built around the selected technologies.

Specific attributes of facilities designed to a governing material transfer technology, which affect the facility layout and configuration, may be as follows:

- Gravity transfer: facilities designed to accommodate gravity transfer are developed as vertical facility arrangements with high bay or multi-floor designs and stacked process operations. The direct gravity flow of materials avoids material handling operations between process unit operations where they are not restrained by intermediate batch or staging requirements. Adequate vertical space needs to be available to accommodate this approach
- Pneumatic/vacuum transfer: pneumatic/vacuum transfer of materials provides opportunity to limit material movement space requirements and reduce operator presence, transfer time, and works well within horizontal facility arrangements. Limiting factors in the use of these technologies include the process concerns of cleaning and material segregation
- Bins/containers: where materials are transferred in containers, a key decision is whether to provide IBCs in which the material can be subject to particular unit operations (e.g., bin blending), or to provide transfer only containers, such as drums. The container movement and manipulation, staging, storage, charging, discharging, blending, and cleaning requirements should be integrated into the overall facility design. The staging requirements and number of bins should be reflected in the layout

The material tracking strategy should be incorporated into the facility design. The material within the bin/container and state of the bin/container may be tracked through paper based procedures or electronically through the use of bar code or tagging systems. The staging and docking space should be coordinated with the tracking system and related protocols. If a MES has been implemented, the material tracking strategy should be part of the MES system.

Key design and cGMP criteria associated with the material flow and building arrangement include:

- Provision of logical, direct, and sequential flow, minimizing the potential for mix-up of materials and products
- Provision of logical flow of dirty and clean equipment and components and avoid common staging areas
- Minimize movement distance

Adequate space and access for maintenance should be provided and should consider:

- Provision of adequate protection against cross contamination
- Minimization of material handling steps
- Provision of adequate staging and access
- Provision for airlocks between areas with different levels of protection
- Provision of adequate space to facilitate ergonomic material movement, e.g., lifting of bins, corridors, and door widths

6.3.4 Product/Process Characteristics

Chemical properties and process characteristics will have architectural impact that includes:

- Product hazard characteristic
- Potency
- Explosivity
- Flammability
- Light/UV sensitivity
- Hygroscopicity
- Flowability
- Particle size and distribution
- Adhesive and cohesive
- Cleanability
- Chemical reactivity

Product/process characteristics may vary through the process steps and should be addressed at the appropriate unit operations. These characteristics are integral to the process and can impact overall facility design and detail.

Product hazard characteristics: affect layout by the requirement for specific features. These should be identified in a risk assessment and may include:

- Additional material and personnel airlocks
- Gowning rooms
- Spatial requirements for equipment, or environmental sampling and testing

Material explosivity and flammability: affects layout by the potential requirement for hazardous facility design which may include:

- Deflagration design
- Containment of spills
- Building code implications on occupancy classification

The specific requirements for each facility and system will be defined by the building code, referenced codes, guidelines such as NFPA [26], and insurance requirements. The quantities of hazardous and flammable materials can affect the type of construction and allowable areas of the facility. For further information, see Chapter 5 of this Guide.

Light/UV sensitivity: has an effect on both natural lighting and building lighting systems and should be incorporated into the layout, lighting design, and detail aspects of the building.

Hygroscopic sensitive materials: have an effect on architectural detail and layout arrangement. This includes providing appropriate vapor barriers, as well as necessary airlocks to segregate low humidity areas from higher humidity areas. Construction details should be specially designed and reviewed for separate low humidity areas.

Cleanability: may affect the architectural room design. Production rooms should be subject to a cleaning routine. The greater the exposure of materials to the room environment, the greater the risk of room contamination, the greater the likelihood of a more demanding cleaning routine. Materials and details should be selected to support and withstand the prescribed cleaning materials and methods. Decisions on cleaning should determine if an area will be:

- a hose down area, requiring water and drains
- a wipe down area, due to impact on the selection of appropriate finishes

Chemical reactivity of production materials: should be understood at the room level. The compatibility of appropriate finish and substrate should resist degradation. Finishes that will require periodic repair and replacement should be avoided. Where repair and replacement are needed, the effect on ongoing operations should be understood.

6.3.5 Environmental, Health, and Safety

Items to consider in HSE assessments include:

- Highly hazardous materials
- Controlled substances
- Hazardous operations
- Environmental protection

Each of these aspects should be understood and assessed and the facility designed appropriately.

When designing for the processing of highly hazardous materials, such as potent compounds, a risk assessment should be performed to determine the containment and segregation requirements. Risk assessments may determine the OELs. Facility layouts may need to allow for containment equipment, while considering safe and ergonomic operation. There may also be a requirement for secondary protection measures. Secondary protection measures could include:

- Specific segregation requirements for materials, personnel, equipment, and waste
- Additional airlocks for personnel and material
- Mist showers
- Gowning rooms (gown and de-gown)
- Safety shower and eye washer

These measures should help to prevent migration of airborne or surface contamination from process areas into non process areas. Requirements for support facilities, such as occupational health and PPE/RPE storage rooms, may also affect layout.

In addition to GMP requirements, the controlled substances are classified and regulated under other regulatory agencies (e.g., the DEA in the US). There are specific design requirements for the storage of controlled substances based on federal and regional requirements. Security and control may involve space monitoring and surveillance, access restrictions, and specialized storage requirements. Process contact waste handling and exhaust systems may require specialized control and capture detailing. A specific control and process procedure should be established and implemented, including qualification and training of operators.

Hazardous operations involving the use of solvents and flammable materials involve design considerations of individual pieces of equipment, a room, a portion of a building, or a complete building and are governed by local and national building and referenced codes. Design details are required to address areas of hazard, including fire separation, spill control, firewater containment, and damage limiting construction.

Most insurance companies and/or insurance underwriter companies have additional requirements for maintaining facilities and reducing the risk of business interruption. The appropriate insurance carrier should be consulted during the early part of the design stage in order to incorporate specific requirements.

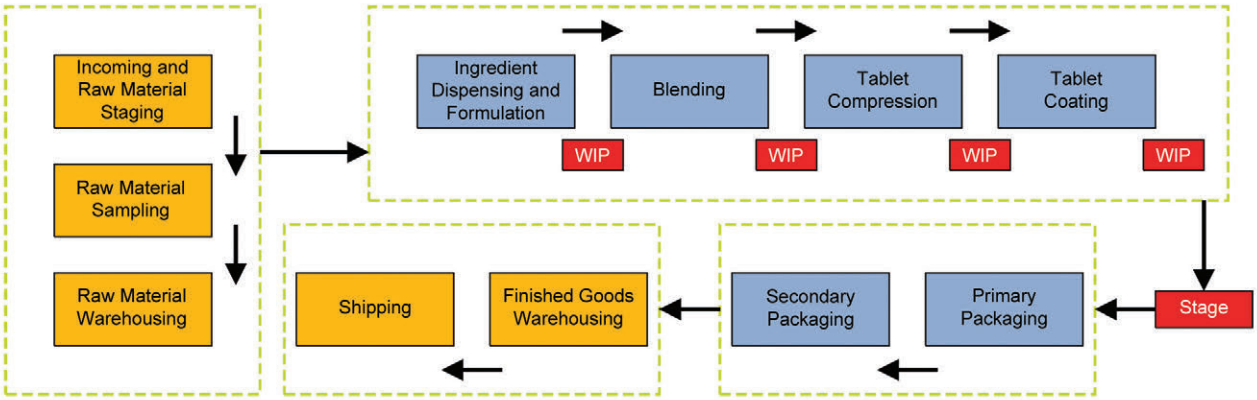
For an overview of HSE and controlled substance considerations, see Chapter 11 of this Guide.

6.3.6 Block Flow Diagrams

Block Flow Diagrams (BFDs) serve as the critical transfer of process flow information to the designer in the early development of a facility. They are the initial diagrams produced during programming, and are distinct from process flow diagrams which are used in equipment development. BFDs outline each unit operation within a given process in a logical, direct, and sequential order. They also identify intermediate steps between unit operations (i.e., WIP) and should follow a process from beginning to end, devoid of any relationship to a building or space. A separate BFD should be produced for each product within a facility, and for each separate process which may exist for production of the same product.

BFDs should be used in identifying the total number of unit operations (or other process steps) which require physical space within the facility, acting as a key programming tool. In addition, they identify critical adjacencies between unit operations and allow the opportunity to discover efficiencies in layout which will minimize movements and potential for mix up. BFDs should be referred to throughout the design process to ensure that facility design is appropriate for the production process.

Figure 6.1: OSD Block Flow Diagram



6.4 Functional Areas

OSD forms manufacturing facilities contain different types of functional areas. This Section of the Guide addresses issues that affect architectural design related to the operations that occur in these functional areas, which are subdivided into:

1. Unit operations: process
2. Unit operations: process support
3. Unit operations: material handling and storage/staging
4. Personnel support spaces
5. Utility spaces and maintenance shops

Manufacturers should review their specific situation and determine an appropriate level of protection, based upon the criteria and process described in earlier Chapters.

6.4.1 Unit Operations: Process

This Section discusses the architectural features relating to each unit operation, such as proper layout, adjacency, and space requirements to prevent cross contamination and provide proper containment of the product within the OSD forms manufacturing facility.

6.4.1.1 Dispensing

Dispensing are areas in an OSD forms manufacturing facility where specific quantities of materials are transferred from bulk containers to batch size containers according to batch requirements. They are typically located either near the warehouse or the materials receiving entrance to the facility to enhance material flows, or adjacent to a manufacturing area.

Proper dust control should be considered for weighing and dispensing areas. These spaces normally contain equipment, such as weigh/dispense booths and weigh/dispense isolators, and ventilation to contain the powders being dispensed and to protect the open product. Dispensing areas are typically Level 3 areas because product is exposed but may be Level 2 areas with localized Level 3 areas. The risk of product exposure and personnel exposure to the product can vary greatly depending upon the type of dispensing equipment provided. The requirements for the room environment outside of the booth or isolator should be evaluated to determine the Level of Protection based upon risk. Areas where active ingredients or excipients are dispensed directly in the room without booths or isolators, and are exposed are typically Level 3 areas. The architectural finishes for these areas should follow the requirements for Level 3 areas, as discussed in Chapter 5 of this Guide.

Dispensing areas handling highly hazardous compounds have additional considerations for operator safety. Containment equipment, such as fixed or portable weigh/dispense isolators, is typically used in these areas. In the selection of materials of construction, manufacturers may consider hard, cleanable surfaces so that the rooms can be decontaminated in the event of a breach of containment. Additionally, decontamination showers at the exit to the dispensary may be considered for operator protection as well as separate gown and de-gown areas.

6.4.1.2 Granulation

Granulation is a closed process operation and may be performed in a Level 2 area however a typical granulation room is a Level 3 area because there is product exposure for charging. The product transfer may be open or closed. If the product transfer is open, a Level 3 area is required. Cleanability of surface finishes should be considered for areas where dusts can be liberated during product transfer operations. Where combustible dusts or flammable liquids are present, appropriate safety measures may be required as determined by the relevant codes and industrial insurance requirements. Area classifications can be determined by quantities of flammable liquids and dust.

See Chapter 4 for information on the effect of granulation technology selection on layout and Chapter 5 for code requirements.

6.4.1.3 Extrusion/Spheronization

Spheronization is similar to granulation and has similar architectural considerations.

6.4.1.4 Drying

Drying is often performed in fluid bed dryers. While this is normally a closed operation, open charging and discharging may be required. Therefore, drying rooms are typically Level 3 areas.

Although explosion proof fluid bed dryers are available which provide flexibility in terms of layout location, non-explosion proof fluid bed dryers are frequently outfitted with explosion vents that should be accommodated. The explosion vents may be directed horizontally through an exterior wall or vertically through the roof, and the location of these vents should be taken into consideration when locating drying rooms.

6.4.1.5 Milling

Milling is often an open operation and can be a very dusty. Thus, milling areas are typically Level 3 areas. Careful consideration should be given to both the protection of the product and the operators. Milling of highly hazardous compounds can take place inside an isolator, significantly reducing the risk of product and operator exposure, and potentially requiring a lower level of protection in the general room area.

Under certain circumstances, milling may generate combustible dusts and produce a room explosion hazard. A safety analysis and risk assessment should be performed to determine if an explosion hazard is present, and if measures such as room explosion venting or alternative methods determined by the governing codes are required.

6.4.1.6 Compression/Encapsulation

Compression and encapsulation rooms typically have exposed product. They are typically located in Level 3 areas, depending on the potential for product or operator exposure. For compression rooms, additional equipment for metal checks and dedusting should be accommodated.

Inspection/check weighing is a testing operation performed on tablets and capsules. The equipment for this operation is often located inside the processing rooms. Space for this operation should be considered when programming the relevant areas. Charging of the encapsulators and tablet compression machines may be from a mezzanine, platform, or from the same floor level.

6.4.1.7 Tablet Coating

Tablet coating rooms typically contain exposed product. They are typically Level 3 environments. Where solvent based coating processes are used, requirements for the use of flammable liquids should be considered. A safety analysis and risk assessment should be performed to determine appropriate safety features.

6.4.1.8 Solution Preparation

Solution preparation areas normally are located either near granulation or coating operations. If solvent based processes are used, requirements for the use of flammable liquids must be considered. A safety analysis based upon code requirements should be performed, and the design should incorporate appropriate safeguards.

If solution preparation operations are closed, the area may be Level 2, if product is exposed in the area it is a Level 3 area.

6.4.1.9 Packaging Overview: Primary and Secondary

Primary packaging usually is performed in a room adjacent to the final processing room. As product is exposed, a Level 3 environment is required. The Level 3 environment may be in the general room area or localized above the point of fill. Areas for staging of primary packaging materials (labeling, bottle blowing equipment, etc.), are generally required to be accommodated within the program. These areas may be located on a mezzanine to provide separation

Once primary packaging is complete, the product is normally no longer exposed. Level 2 environments are typically suitable for secondary packaging areas. It is considered good practice to separate primary and secondary packaging areas to prevent contamination of the primary area with a pass through from the primary to the secondary area. Areas for inventory control equipment (corrugated boxes, etc.), should be planned for secondary packaging areas. These areas can be significant and should be considered early in the design. Secondary packaging areas are typically located adjacent to shipping warehouses.

6.4.2 Unit Operations: Process Support

6.4.2.1 Bin Washers, Equipment, and Component Wash Rooms

Wash areas should be designed with a clean dirty flow through the room, though it may be fed from a common corridor. Wash areas should be located either locally to specific process operations to minimize travel distance of dirty parts or centrally to maximize operational efficiency. The room should provide sufficient space to support staging of clean and dirty items in segregated areas and should be located along the material flow path with access from the production area. Pass through bin washers are also available, with the bin washer located in the wall between the dirty and clean areas. The wash area is generally Level 2 on the dirty side and Level 3 on the clean side. In addition, consideration should be given to the spatial requirements of the CIP package and delivery, and storage of detergents.

6.4.2.2 Bin Charge/Discharge Stations

Bin charge/discharge stations may be located in or outside production rooms. In vertically integrated, high volume facilities, production floors can be located between discharging and charging floors. This segregates material transport operations from process unit operations. Bin charge/discharge station level of product exposure is dependent on the technology utilized and level of containment achieved. The area of charge/discharge is typically Level 3. Where full containment is provided, Level 2 protection is considered appropriate.

In locating charge/discharge stations, consideration should be given to the mechanics and ergonomics of bin maneuvering for docking and undocking (i.e., the use of pallet jacks, AGVs, or overhead rails).

6.4.2.3 In Process Testing Laboratories

In process testing laboratories are provided within the GMP area to support local testing advantages. The laboratory area may be accessed from within the production space or may be located outside of the production space, with pass through from the production spaces. Materials are to suit a GMP environment, see the ISPE Good Practice Guide: Quality Laboratory Facilities [58].

6.4.2.4 Process Control Room

The process control room may be embedded in, or located outside, the production space dependent on operational requirements and preferences. Control rooms within production areas should have materials and detailing to suit a GMP environment. The area is considered a non-product space with Level 1 protection. The level of gowning in the process control room should match the area in which it is located, and have gowning and de-gowning.

6.4.3 Unit Operations: Material Handling and Storage/Staging

6.4.3.1 Quality Assurance Sampling

Quality Assurance (QA) sampling areas are typically located conveniently to the incoming materials area. Booths are often used for the sampling areas to reduce the risk of operator and product exposure. The QA sampling areas are typically Level 3, but may be Level 2 areas with localized Level 3 protection at the point of exposure.

6.4.3.2 Repalletize

Wooden pallets should not enter production areas. An area will be required to provide transfer of materials to a captive metal or plastic pallet. Space may be required to clean pallets according to established SOPs. When, where, and how re-palletization is performed is important in establishing the appropriate flow and spatial requirements within a facility. A pallet washer may be required.

6.4.3.3 Elevators

For multi-story operations, elevators may be required to be planned into the program. The location, function, and finishes of these elevators will depend on their use. Depending on layout, it may be appropriate to incorporate an airlock between the elevator and the production area and areas of levels of protection. Separate elevators may be required for materials, equipment, and personnel movement. Elevators may be required for multi-story operations to meet disability accessibility requirements.

6.4.3.4 Warehouse: Materials

Shipping and Receiving Areas

Shipping and receiving areas should be separate spaces, and should be separated from the warehouse. Trucker toilets and break areas should be accessible directly, and only from, the exterior of the warehouse. Exterior doors on the loading docks and the interior doors separating the shipping/receiving areas from the warehouse should never be open at the same time. This should be controlled procedurally or by interlocks.

Raw materials, components, and finished goods, both quarantined and released, require warehousing and storage. Space for rejected or returned goods should be considered. Specialized, independent storage may be needed for specific materials, due to their environmental needs, health or safety hazards, or regulated status, such as DEA controlled substances.

Materials, compounds, and products in a multi-purpose facility may be identified using:

- Conventional warehousing with a system to individually label and identify material by type, quality, and quantity:
  - This identification system can be manual, semiautomatic, or automated, including bar coding.
- Conventional warehousing can use either standard or Very Narrow Aisle (VNA) equipment:
  - VNA warehouses may provide more dense storage than conventional warehouses, but generally have a higher initial cost.
- Automated Storage and Retrieval Systems (ASRSs):
  - ASRS warehouses can often provide more dense storage than conventional warehouses, but generally have a higher initial cost.

The appropriate selection of warehousing and storage systems can be affected by:

- The amount of storage required
- Density of storage within the storage system
- Through put requirements
- The construction and operating cost advantages and disadvantages of each system

6.4.3.5 Warehouse: Waste and Non-cGMP Materials

The storage of non-cGMP materials is typically required for OSD facilities. These materials may include gowning supplies, secondary packaging materials, waste, and cleaning supplies. It may be desirable to separate warehousing of non-cGMP materials from warehousing of raw materials and finished goods to reduce the size and cost of the controlled storage areas.

6.4.3.6 Equipment Storage

Provision should be made for the storage of cleaned equipment, as well as product dedicated equipment, such as dryer filters, and also duplicate equipment, such as a spare product bowl. The store should include an area for assembling/testing of parts prior to use within production.

6.4.4 Personnel Support Spaces

Personnel support spaces, such as offices, lavatories, break rooms, conference rooms, and locker rooms etc., are normally required in OSD facilities. Such spaces are normally separated from the manufacturing areas and require protocols for gowning and de-gowning to access these areas. They are typically separated from manufacturing areas by airlocks. Employee support spaces need to be included in space considerations when planning an OSD forms manufacturing facility.

6.4.5 Utility Spaces and Maintenance Shops

There are generally three types of utilities required in an OSD manufacturing facility:

1. Process systems
2. Process support systems
3. Facility support systems

Procedures for utility generation should be reviewed and the required level of protection determined. Process systems and process support systems may be located in Level 2 or Level 1 areas, depending upon the risk of exposure. Facility support systems are generally located in Level 1 areas. Maintenance access should be considered when designing utility spaces as well as consideration for interstitial and walkable ceilings.

6.5 Layout

The development of the layout should be developed in an organized and structured manner defining operations and arrangements through accommodation schedules, adjacencies matrix, conceptual layouts, equipment arrangements, and all material and personnel flows. This information is tied to process block flow diagrams. Key elements of layout development include:

- Sequential and logical flow of unit operations
- Appropriate segregation to avoid cross contamination
- Space for containment equipment and barriers for necessary space segregation
- Space for room and equipment cleaning

The layout considerations will need to harmonize with the concepts and regulatory and risk-based assessments.

Design tools may include accommodation schedules, conceptual layouts, equipment arrangements.

6.5.1 Design Tools

6.5.1.1 Room Card

Room cards contain the specific datasheet to confirm CQA and CPP, and operational special requirements.

Figure 6.2: Typical Example of Room Card

Room Attributes					
General			**Utility Services**		
Room Name	Compression/Encapsulation		Ambient WFI		
Room Function			Control Air		
Normal Occupancy			Hot WFI		
Room Area	1937 S.F.		Nitrogen		
Room Dimensions	52'0" × 37'3"		Emerg. Tempered Water		
Design Noise Level			Process Air		
Architectural			Process Glycol		
Wall Construction			Process Waste		
Wall Finish			Process Vent		
Wall Bumper System			Clean In Place (CIP		
Lab Casework			Utility Notes:		
Base Finish			**Floor Drains**		Process
Wall/Ceiling Cove					Sanitary
Floor Finish			Drainage Notes:		
Ceiling Type			**Fire**		
Ceiling Height			Suppression Type		Dry Pipe
High-hat Areas					Wet Pipe
Overhead Hoist					Preaction
Door (W × H)			Sprinkler Coverage		100%
Door Type			Special Conditions		
Door Activation			Fire Alarm		Smoke/Heat Detection
Door Finish					Audio
Door Glazing					Visual
Door Interlocks			Extinguisher		As required.
Panels		Control	Fire Hose		
		Electrical	Fire Notes:		
		Transfer	**Safety**		
		Utility	Breathing Air		
Architectural Notes:			Eye Wash		
Electrical			Clock		
Electrical Classification	Unclassified		Safety Shower		
Power Requirements		Emergency	Safety Notes:		
		UPS	**Security**		
		Normal	Card Readers		
Lighting	Type		Interlock		
Required as per plan.			Intercom		
		Dimmer	Electric Door		
Electrical Notes:			Motion Sensor		
HVAC			CCTV		
HVAC Classifiecation			Security Notes:		
Air Change per Hour			**Communication**		Voice (telephone)
Minimum Ventilation					Data
Room Conditions					Announcement Speaker
Summer					Radio Speaker
Winter			Communication Notes		
Filtration		Supply	**GENERAL NOTES:**		
		Exhaust			
Pressurization					
Night Setback		Yes			
		No			
Monitoring		Temperature			
		Humidity			
		Pressure			
HVAC Notes:					

6.5.1.2 *Accommodation Schedule*

The accommodation schedule identifies all areas that can affect or influence required space or unit operations, defines their interrelationships, and establishes the flow pattern that best represent the GMP and operator requirements. This also can be used as a basis to test developed design. The overall flow pattern should be taken into account in the development of an integrated design.

Note: requirements of airlocks should be determined by a risk assessment identifying containment and segregation measures.

6.5.1.3 *Adjacency Matrix*

To assist with the establishment of links between the different areas, an adjacency matrix can be used to define the priority of the relationship between different areas. For example, areas requiring a close adjacency are given a high rating, whereas those with no particular adjacency are given a low rating. The number and type of ratings used will depend upon the complexity of the project.

6.5.1.4 *Conceptual Layout*

Building blocks are developed to show equipment and operation size, and allow space for utility connections and operator access.

The process flow diagram and accommodation schedule should be used to determine equipment relationships, allowing building blocks to be assembled. Obtaining typical equipment dimensions will assist in this task.

A conceptual layout is developed by combining the necessary building blocks in an arrangement that meets the accommodation schedule requirements. This should integrate equipment needs and access and movement requirements for people, and components, etc., to permit development of an efficient layout. Figure 6.3 gives a typical example.

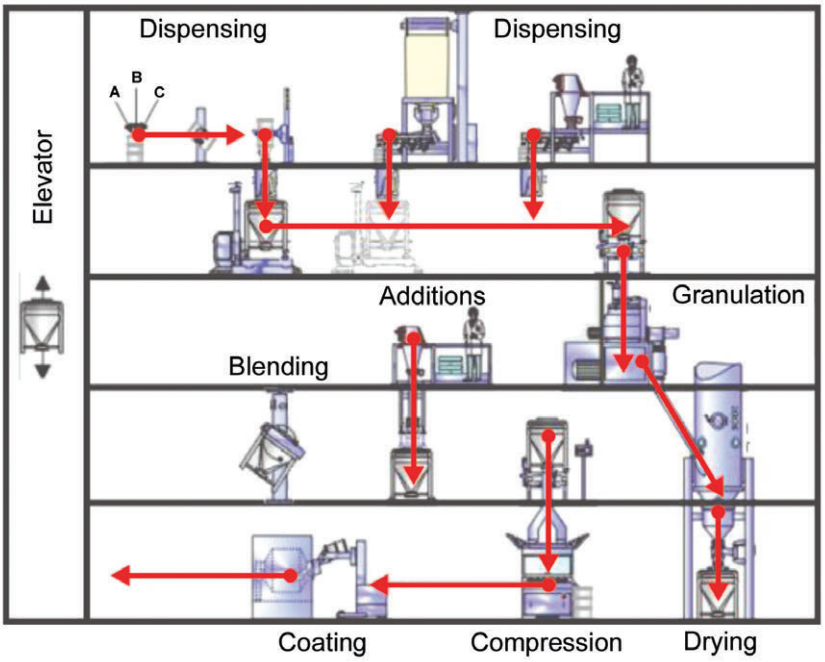
Figure 6.3: Example of a Typical Conceptual Layout

Note: requirement of airlocks should be determined by a risk assessment identifying containment and segregation measures.

6.5.2 *Product Capacity, Process, Scale, and Technologies (material transfer technologies)*

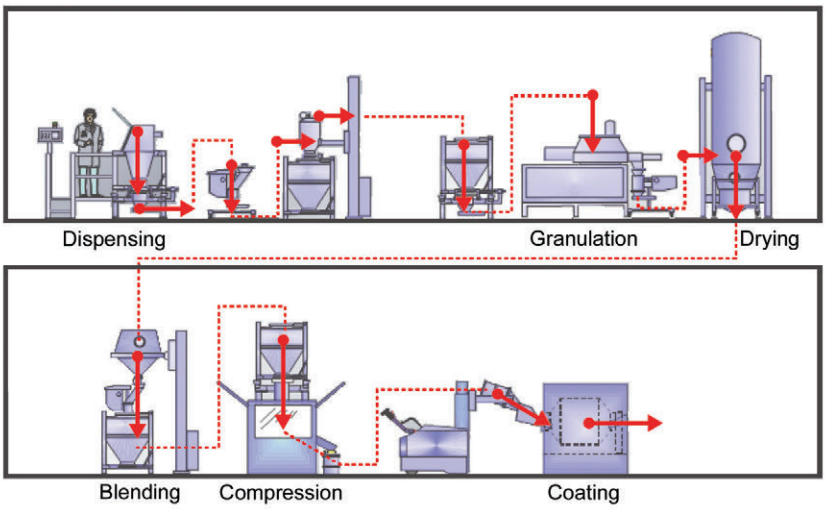
6.5.2.1 *Gravity/Vertical Transfers*

Figure 6.4: Vertical Production Flow Example



6.5.2.2 *Pneumatic/Vacuum/Horizontal Transfers*

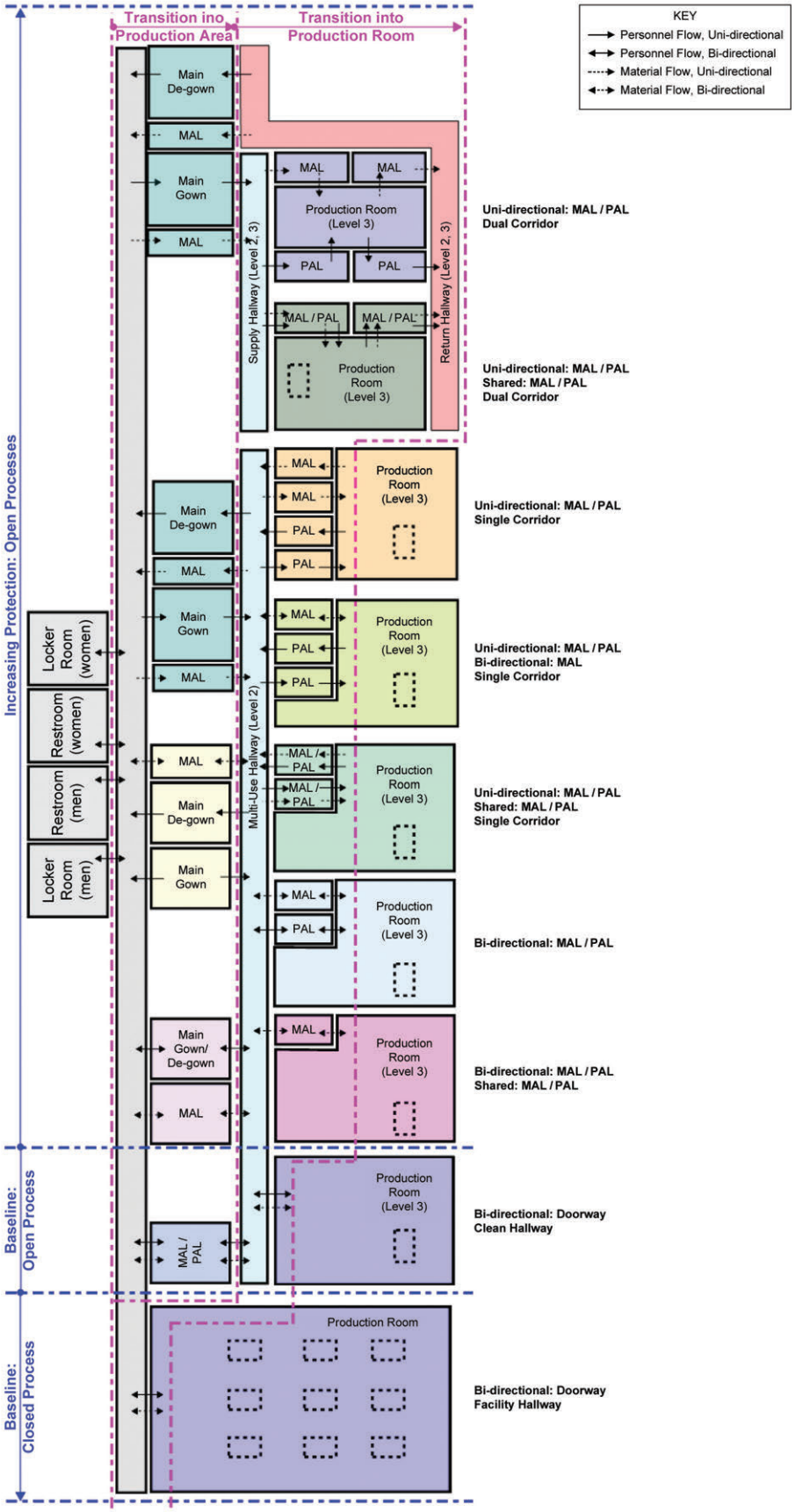
Figure 6.5: Horizontal Production Flow Example



6.5.2.3 *Bins/Containers*

- IBCs
- Disposables

Figure 6.6: Physical Segregation Diagram



6.5.3 Product Protection and Segregation

Preventing product contamination may be achieved by segregating sources of product contamination from the product. The main sources of product contamination include:

- Environmental: preventing environmental contamination is achieved by physical barriers which can be by way of facility design (room separation) and/or by equipment design (closed processes)
- Crossover: preventing cross-contamination between two exposed products is typically achieved by physical barriers
- Carryover: cleaning methods (product contact parts, equipment, rooms, etc.) should be sufficient to prevent carryover contamination
- Raw Material: preventing contaminated materials from entering the process can be assisted by proper material testing

An exposed product should have environmental protection, such as an appropriate room environment.

6.5.3.1 Segregation Concepts

Preventing product contamination by environmental and crossover sources of product contamination, can have a significant impact on facility design. These sources of product contamination can be addressed using primary and secondary segregation. Primary segregation focuses on the facility design aspects required to protect an exposed product. Secondary segregation focuses on non-critical facility aspects which result from the use of closed processing.

Both primary and secondary segregation consist of four basic segregation concepts, which apply to cGMP facility design, utility design and process design:

Physical Segregation

Physical segregation involves a physical barrier which can prevent both environmental and crossover contamination. The space inside a closed container/process is physically segregated from the space outside the container/process.

Closed System: in closed systems, non-exposed product is physically segregated from the room environment. Process closure is an application of physical segregation.

Open System: in open systems, exposed products require both a physical segregation and environmental protection from other open processes to prevent cross-contamination. Physical separation for open processing is typically achieved by using separate rooms. This can result in dividing open process steps into a series of separate processing cleanrooms. These cleanrooms can be surrounded by airlocks, and use the concept of nesting and facility flows that are designed and arranged to reduce the environmental challenge to the cleanroom.

Environmental Segregation

Environmental segregation utilizes clean air to protect exposed product and product contact surfaces that cannot be functionally closed. Environmental segregation is primarily used for open systems. A typical application is a cleanroom. The level of the room environment relates to the degree and the criticality of the product or surface exposure.

Local Environmental Protection: a locally protected process is a subset of environmental segregation. Local environmental protection is designed to provide a higher level of clean air protection for a specific purpose within the cleanroom background.

Chronological (Temporal) Segregation

Temporal or time based segregation can be applied to both open and closed processing, and can be a factor in maintaining control of materials. Time based segregation involves using the same physical area for more than one function but activities are separated by time, e.g., campaigned manufacturing. Two open processing production lines occupying the same room and operating concurrently will be at risk from cross-contamination. Separating the processing activities by time (i.e., campaigning) can mitigate the risk.

Closed processing can involve concurrent processing or campaigned processing of several products within the same processing area or room.

Procedural Segregation

Procedural or SOP based segregation is typically applied to preventing mix ups, but it also has open processing or exposed surface aspects. An example is manual equipment cleaning in a washroom with many components from different products being handled in the same area concurrently, but segregated by procedures. This may involve using the same area for different open functions (possibly handled concurrently), but using procedures to prevent equipment contamination.

Example facility applications of procedural segregation include:

- Preventing mix ups
- Washing components and equipment, while exposed to the room environment
- A closed process that briefly exposes product to the room environment that requires special SOPs to protect the product. Operator action may be needed when the process closure technology does not address all aspects of a functionally closed system

6.5.4 Gowning

The risk assessment of the various process operations will determine the gowning procedures required in the facility. Areas with higher risk assessments will require more and varied levels of gown changes. As personnel move from common areas to process operation areas the level of product protection and personnel protection will increase. The more interaction that the personnel have with the product will increase the Level of Protection. Minimizing the level of interaction that personnel will have with the product, through closed or semi closed operations will decrease the level of gowning required.

The de-gowning operation should not violate the cross-contamination control condition achieved in common areas. Procedures also should address employee movement during the course of the day to toilet facilities, and areas such as the cafeteria and offices.

Mirrors, signage for instructions on gowning procedures, storage of gowns, trash for gowns, and benches are typical components of a gowning area.

Gowning practices should match the room level of protection and HVAC design capabilities. HVAC design criteria should match product and process requirements, and could be affected by the number of operators required in selected spaces. For example, gowning practices generally have a greater impact on Controlled Not Classified (CNC) spaces with monitoring or microbial limits than CNC spaces with no monitoring. The higher the room classification, the greater the impact gowning has on meeting environmental acceptance criteria.

In production spaces, laboratory coats are typically used with hair nets, shoe covers or facility dedicated shoes, gloves, and face masks at the highest area classifications. Where engineering controls cannot be employed to reduce personal risk adequately, organizations should ensure that appropriate PPE is used, e.g.:

- Safety glasses
- Safety shoes
- Goggles and or face shields
- Protective gloves
- Respirators

Closed Systems: closed processes allow for relaxed gowning practices, e.g., use of laboratory coats or scrubs as a worker uniform to enhance operator comfort. Gloves, shoe covers or dedicated facility shoes, and hair nets may be worn. Gloves should be worn when working in Biological Safety Cabinets (BSC)s.

Organizations may require disrobing/removing street clothes before gowning. This may contribute to improved comfort while gowned (less layers of clothing) and adds another level of disconnection between production environments and the environment outside. The associated facility design may need to include more locker space and privacy requirements.

Costs associated with high levels of gowning include:

- Investment in airlocks, changing spaces, and gowning materials
- Time spent performing the gowning and de-gowning procedures
- Higher cooling demand for operator comfort
- Performance issues working while gowned

6.5.5 Airlocks

Reasons to consider airlocks include:

- Low humidity rooms
- Product segregation (multi-product, food grade versus Over The Counter (OTC) grade)
- Level of protection segregation
- High hazard operations
- Regional regulations
- Cross contamination
- Containment

Airlocks are a tool used in the layout of a facility to control, segregate, and protect both the product and personnel in the design of an OSD forms manufacturing facility. While airlocks require significant space within a production area, they can provide a solution to many of the issues that are presented through the risk assessment of the facility. Airlocks can be used to separate and protect the various unit operations within a facility. They can act as a buffer zone to minimize cross contamination and maximize protection.

In facilities with multi-products or highly hazardous compounds, airlocks can mitigate issues of cross contamination and maintain product integrity, as well as help to ensure personnel protection. Airlocks serve for both personnel and material/product. While it is not required to have separate gown and de-gown for personnel and material airlocks, the level of risk associated with the facility may lead to consideration of various opportunities in the development of the layout.

Personnel Air Lock (PAL): personnel airlocks serve several purposes including:

- Create a separation/transition between production rooms
- Allow for additional layers of gowning, PPE, etc., to be applied prior to entering a production space.

Material Air Lock (MAL): material airlocks can serve several purposes including:

- Pallet exchange: allows for transfer of materials from a warehouse pallet to a clean pallet before materials enter the production/clean environment
- Inspection: allows for inspection of materials before entering the production/clean environment
- Surface cleaning: allows space for cleaning/wipe down of materials prior to entering the production/clean environment

Clean and dirty hallways: this approach incorporates unidirectional flows for personnel, materials, equipment, and waste etc., throughout the production area. This solution can need more building area for gowning, airlocks, and corridors which may limit available area for production space.

Note: requirement of airlocks should be determined by a risk assessment identifying containment and segregation measures.

6.5.6 Facility and Process Flows

Plan flow diagrams are a critical tool in the development of an OSD forms manufacturing facility. Understanding the flows is critical to the development of a facility where product and personnel protection are maximized and the potential for cross contamination is minimized. All types of flows in a facility should be accounted for to minimize the risks of the facility. The flows of a facility should be studied from the moment an element enters the facility, how it moves throughout the facility, and how it exits the facility. There are many levels of flows that need to be examined to design and OSD forms manufacturing facility.

Flows may not be unidirectional. In multi-product facilities or facilities with highly hazardous compounds unidirectional flows may help to protect the product and personnel.

Facility and process flows are designated paths of travel for:

- Personnel
- Materials
- Product
- Equipment cleaning
- Solid waste
- Maintenance and service personnel

The purpose of these flows can be categorized into three categories:

- Demonstrating a logical production process
- Avoiding mix ups
- Protecting the room environment

6.5.7 *Material/Equipment Block Flow Diagrams*

Material and equipment flows are critical elements that drive the overall OSD forms manufacturing facility design and design detail. Material flows and the basic types of material transfer will drive the facility design. It is important to understand how the equipment will be cleaned and maintained to properly layout the facility.

Material flows should describe the flow of the raw materials as they enter the OSD forms manufacturing facility and follow them to whatever level of completion they will achieve in this facility and exit the facility. The waste flows are a byproduct of the material flows that also should be considered. It is important to understand both how and when these flows migrate through the facility.

In addition to proper material flow, the flows of the equipment that are associated with the handling, cleaning, and storing of clean and dirty equipment should be identified. Adequate staging should be provided within the layout of the facility for clean and dirty equipment. In a facility where IBCs are used, the storage of clean and dirty IBCs can be a significant factor in the allocation of space in the facility.

Provisions should be made for the maintenance of equipment in terms of access and space, as well as the transport of the equipment items and components through the facility.

6.5.8 *Personnel Flows*

Personnel flows should be developed to protect the product, personnel, and the environment, while addressing site security and control issues. There are several types of personnel flows that should be examined based upon the risk assessment characteristics of the facility:

- Employees
- Operators
- Visitors
- Mechanical or service personnel
- Emergency egress

While this list does not address all types of personnel flows in a facility, it does highlight the major groups that will impact the development of the facility. The control of personnel flow by type may offer product and personnel protection and security advantages. Methods include badging, uniforms, and procedures, either at site or facility level.

Personnel flows are not typically required to be unidirectional. Special consideration should be given to multi-product facilities and highly hazardous operations where appropriate procedures to prevent contamination may be required.

Segregated entrances and exits may be necessary to protect against contamination and allow gowning or decontamination procedures. If the same entrance and exits are used, simultaneous entrance and exiting should not occur. Acceptable methods for preventing this include administrative controls, interlocking of doors and signaling systems, such as lights indicating gowning, decontamination, or other activity. Controlled access, physical barriers, or signs should be used to prevent unprotected and unauthorized personnel from entering areas where they may be exposed directly to materials or products.

6.5.9 Working Environment, Touring, and Inspection

Maximizing the use of viewing windows into production spaces can allow for non-production personnel, visitors, business partners, and inspectors etc., to experience the production process without the need for gowning.

Examples include:

- Full glass views can be provided into processing areas from adjacent production administrative spaces.
- Daylight and/or outside views into the processing areas or adjacent non-classified support space can be provided.

6.5.10 Maintenance and Servicing

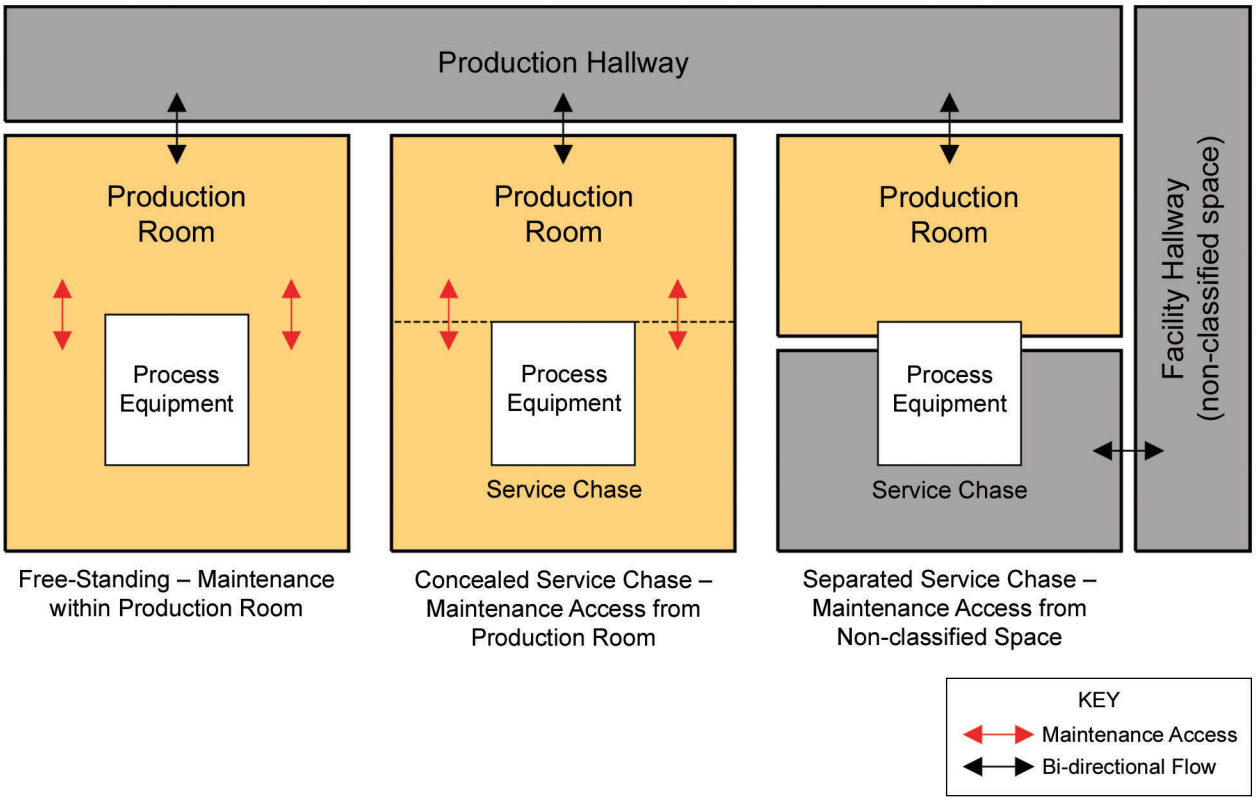
Maintenance and servicing considerations have a significant impact on the development of the layout of an OSD forms manufacturing facility. How equipment is serviced, as well as understanding the routine maintenance issues associated with the equipment, influence the design of an OSD forms manufacturing facility. The relationship between the operational side of the process equipment and the service side of the equipment should be reviewed. There may be opportunities to integrate the equipment with the facility so that the clean and technical sides of the rooms are associated with the clean and technical sides of the equipment. The connection can be provided by “pass through” locks. This can provide operational benefits, such as reduced HVAC utility loads due to smaller clean production areas in the building.

It is critical to understand the flows, access issues, and ergonomics of the maintenance operations to allow maintenance activities to be undertaken in a safe, efficient, and reliable manner, while minimizing impact to production areas.

Equipment Integration

Equipment may be integrated into the fabric of the building or be free standing within a room; opportunities presented in the development of the layout for either option should be examined. There is potential for the equipment to be located in both classified and non-classified spaces concurrently. The process function of the equipment would be located in a classified space, while the technical side of the equipment would be located in a non-classified environment. Integrating equipment with the building fabric can increase the accessibility to the equipment, while potentially minimizing the size of the classified space. This has several advantages, such as reduced facility cost and operational benefits such as reduced utility loads and cleaning requirements.

Figure 6.7: Equipment Integration Concepts Diagram



6.5.11 Additional Layout Considerations

There are several additional layout considerations that can influence the development of the layout of an OSD forms manufacturing facility, including:

- Multi-product/multi-use facility
- Highly hazardous operations

6.6 Surface Finishes and Materials of Construction

Operating and cleaning requirements are critical parameters in the selection of finishes and materials. It is important to understand the operating philosophy in regard to personnel, material and product movement. The cleaning and sanitizing philosophy should be documented and understood. This will affect the selection of finishes. Cleaning and sanitizing agents may be harmful to finishes used in an OSD forms manufacturing facility.

It is important to understand if a facility is wipe down or wash down, and the difference associated with design implications. In a wash down facility, the substrate of the finish material should be able to withstand wash down, as well as the surface finish. The finish material has the potential to be consistently saturated and is mostly in a wet environment. There should also be a plan in place for drainage in a wash down area. If solvents or hazardous materials are being used, the drainage system should be designed based on the requirements of local authorities. In a wipe down area, the environment is typically moist but does not require a completely sealed, water resistive construction. A variety of finishes and construction methods can help provide the appropriate built environment for a wipe down or wash down area.

Performance criteria for durability, cleanability, functionality, and maintainability should be established. These are used to select finish and substrate materials, which successfully meet performance and cost requirements. Finish requirements and the detailed elements of architectural designs depend on the level of protection (see Chapters 2 and 3 of this Guide). Both cross contamination and material/finish wear or degradation should be addressed in the design phase.

6.6.1 Cleanability

Cleanability in a Level 1 protection area requires regular removal of debris, such as papers and cardboard, dusting, and sweeping.

Cleanability in a Level 2 protection requires access to primary surfaces. Primary surfaces are the solid surfaces closest to an exposed product. In a room, this includes the walls, floors, ceilings, and doors, the room side of air diffusers, and floor drain covers. The duct side of air diffusers and drainage piping systems are not included. This type of area should have a clean and neat appearance. This can be achieved by avoiding wall mounted elements such as conduits and minimizing ledges.

Barriers or enclosures around the exposed material may provide the primary surfaces. In such cases, room surfaces require only Level 1 protection.

Primary surfaces, as determined by a risk assessment, do not need to be washed or wiped down on a frequent basis. However, the level of cleaning may be affected by materials selected. If wash downs are required, integral floor bases may be beneficial. Horizontal surfaces should be accessible for cleaning.

Cleanability in a Level 3 protection area is the same as that for a Level 2 protection area; however, wipe down or wash down may be expected on a more regular basis. Surfaces in these areas should be non-porous and smooth with detailing that minimizes areas of dust collection, such as sloped ledges. Coved intersection details and integral floor base flushness will enhance cleanability. Horizontal surfaces should be accessible for cleaning. Floor based equipment or furniture should be movable or have an integral floor base around its perimeter to enhance accessibility for cleaning.

6.6.2 Durability

All finishes should be able to withstand appropriate traffic types. This includes maintenance, repair, or replacement of the product/system within acceptable limits. For example, in a warehouse, a sealed concrete floor is recommended. It is generally less expensive and easier to maintain compared to a rolled industrial coating which tends to lift over time. Durability is most important in areas where degradation of finishes can cause product contamination. Finished floors should be capable of withstanding rolling wheel load of vehicles, such as fork trucks, pallet jacks, and tanks. In addition, floors should be able to withstand impact from dropped tools and parts.

Chemical resistance to process ingredients and cleaning materials, particularly solvents that damage many types of systems, should be considered. Abuse resistant wall construction is recommended in manufacturing, packaging, warehouse, and support spaces. The process of patching and ease of replacement of the chosen product system in an operating facility should be understood.

6.6.3 Functionality

Specialized functions, independent or unrelated to product exposure and contamination risk, often required of a finish system. For example, maintaining design airflow direction through air pressurization, maintaining low humidity conditions, conductivity, or antistatic requirements may depend on the finish, substrate, and detail.

The risk of slipping should be minimized on floors where wash down is part of the cleaning philosophy. Eliminating slipping by use of texture should not compromise an anti-microbial environment. Test samples should be installed on site to be evaluated by facilities maintenance and operations staff.

The color of the finishes can be a tool used in the clarification of operations within the facility. Different types of operations, or identification of traffic paths and safety equipment can be differentiated by different colors or texture of finishes. Furthermore, the darkness of the color or pattern schemes can be used to detect materials on walls and floors, and be used to visibly indicate the cleanliness of the area. Depending on what a facility is producing, colors and patterns can mask tablets and other materials, potentially making it harder to see if an area is unclean. Material attributes should be known for materials which are processed within a facility in order to make proper finish selections.

Other factors affecting selection of materials and finish systems include:

- The ability for transition to adjoining surfaces
- Repair
- Renovation
- Replacement

Health or environmental issues, such as Volatile Organic Compounds (VOCs) compliance, may be a concern if repairs are adjacent to operating areas. Sustainable finishes are becoming more prevalent in pharmaceutical manufacturing as a facility standard. Product lines have made sustainable options affordable and readily available for traditional and new types of finish systems.

6.6.4 Architectural Detailing

Table 6.2 provides guidance on the selection of acceptable materials and finishes. In general, the use of higher quality, more durable, or more cleanable materials and finishes is acceptable. The ultimate selection should be in keeping with the level of risk associated with the specific project and space.

Table 6.2: Material and Finish Selection Guidance

Architectural Element	Level 1	Level 2	Level 3
Floors	Typical recommended materials include: • Sealed concrete • Resinous coatings with a high level of wear resistance • Vinyl Composition Tile (VCT)	Typical recommended materials include: • Resinous coatings • VCT • Sheet vinyl with welded seams Surfaces should be smooth and cleanable.	Typical recommended materials include: • Resinous coatings • Sheet vinyl with welded seams • Chemically resistive coatings Surfaces should be smooth and cleanable.
Interior Walls	Typical recommended substrate/wall construction materials include: • Gypsum board (may be abuse or water resistant) • Concrete Masonry Unit (CMU) • Wire metal cages • Hollow metal and storefront wall glazing systems • Sealed butt glazing wall systems • Ceramic tile Recommended finishes: • Paint as related to use	Typical recommended substrate/wall construction materials include: • Gypsum board (may be abuse or water resistant) • CMU • Hollow metal and storefront wall glazing systems • Sealed butt glazing wall systems Recommended finishes: • Semi-gloss latex paint • Epoxy paint • Resinous coatings Appropriate finish materials should align with durability and cleanability requirements. Hollow metal and storefront system frames should minimize ledges. Butt glazing rail systems should minimize ledges. Provide metal framing and blocking only.	Typical recommended substrate/wall construction materials include: • Gypsum board (may be abuse or water resistant) • CMU • Hollow metal and storefront wall glazing systems Recommended finishes: • Epoxy paint • Resinous coatings • Clean room type panels with smooth transitions • Stainless steel metal panel with smooth transitions Appropriate finish materials should align with durability and cleanability requirements. Hollow metal and storefront wall glazing should be flush with frames. Wall finish construction should provide a solid, non-porous surface. Provide metal framing and blocking only.
Ceilings (Areas which are to retain pressure differentials can be maintained by selecting the appropriate architectural element)	Ceilings are generally recommended to provide a more finished appearance/ environment. Although ceilings are generally recommended, depending on use, ceilings are not required in these areas if material or product is not exposed. Typical materials include: • Acoustical ceiling panel systems with a suspended grid • Gypsum board Recommended finishes: • Paint as related to use	Ceilings are typically required in these areas. Typical materials include: • Cleanable acoustical ceiling panel systems with a suspended grid • Gypsum board Recommended finishes: • Semi-gloss latex paint • Epoxy paint • Resinous coatings • Cleanable panel systems Provide metal framing and blocking only.	Ceilings are typically required in these areas. Gasket ceilings with hold down clips should be evaluated to confirm seal meets pressurization requirements. Wash down surfaces are seamless. Typical materials include: • Cleanable sheetrock ceiling panel systems with a suspended grid (gasketed as required) • Gypsum board Recommended finishes: • Epoxy paint • Resinous coatings • Cleanable panel systems with sealed smooth transition seams • Stainless steel metal panels Provide metal framing and blocking only.

Table 6.2: Material and Finish Selection Guidance (continued)

Architectural Element	Level 1	Level 2	Level 3
Intersection Details: wall/wall-wall/ceiling- wall/floor	• Vinyl/rubber bases are typically recommended. • Coved or splayed integral floor bases are typically not required. Rounded wall/wall and wall/ceiling details are typically not required.	Coved or splayed integral floor bases are typically recommended but not required to protect wall bases, particularly when materials such as gypsum board are used. Rounded wall/wall and wall/ceiling details are typically not required.	Coved or splayed integral floor bases are recommended to enhance cleaning ease and to protect wall bases particularly when materials, such as gypsum board are used. Rounded wall/wall and wall/ceiling details are recommended to enhance cleaning ease.
Interior Roof	• Decking or structural members can be exposed. • Should present a neat appearance	• No exposed decking or structural members Ceilings should be installed in these areas, see ceiling conditions.	• No exposed decking or structural members Ceilings should be installed in these areas, see ceiling conditions.
Exposed Structural Members	• Decking or structural members can be exposed • Should present a neat appearance It is not recommended that non-durable finishes such as non-cementitious fireproofing be exposed.	• No exposed decking or structural members • Non-exposed structural members should be painted or enclosed for cleanliness above the ceiling which is located below. Access for cleanability should be taken into consideration.	• No exposed decking or structural members • Non-exposed structural members should be painted or enclosed for cleanliness above the ceiling which is located below • Tube steel is recommended for cleanability Access for cleanability should be taken into consideration.
Doors and Windows	Should meet general building code, facility, and use requirements.	• Hollow metal and storefront system frames should minimize ledges. • Butt glazing rail systems should minimize ledges. • Glazing type should be chosen based on code, facility, and use requirements. • Exposed ledges and tracks that are a part of equipment roll up, hi-speed fabric, sliding, and swinging doors including shrouds, conduits, and operators should be concealed, or sloped to provide a clean appearance and help avoid non-particle generation. This is recommended but not required. • Provide metal framing and blocking only.	• Hollow metal and storefront glazing is recommended to be flush with frames but not required. • Butt glazing rail systems are not recommended. • Glazing type should be chosen based on code, facility, and use requirements. • Exposed ledges and tracks that are a part of hi-speed fabric, sliding, and swinging doors including shrouds, conduits, and operators should be concealed to provide a clean appearance and help avoid non particle generation. This is recommended but not required. • Provide metal framing and blocking only.
Hardware	Hardware that complies with the facility uses and building codes and references are required. Using facility standards is recommended if applicable.	• Hardware that complies with the facility uses and building codes and references are required. Using facility standards is recommended if applicable. • Hardware designed to promote and provide access for cleaning is recommended but not required.	• Hardware that complies with the facility uses and building codes and references are required. Using facility standards is recommended if applicable. • Hardware designed to promote and provide access for cleaning. Typically, plated metals or stainless steel are recommended but not required.

Table 6.2: Material and Finish Selection Guidance (continued)

Architectural Element	Level 1	Level 2	Level 3
Platforms (structural members and walking surfaces)	Acceptable materials include Fiberglass Reinforced Plastic (FRP) grating, aluminum, steel, or stainless steel. The use of tube steel is not required.	• Acceptable materials include FRP grating, aluminum, steel (painted), or stainless steel. The use of tube steel is recommended but not required • Wide flange beam sections or similar open steel shapes can be used if accessible for cleaning.	• Acceptable materials include FRP grating, aluminum, steel (painted), or stainless steel. The use of tube steel is recommended but not required. • Wide flange beam sections or similar open steel shapes can be used if accessible for cleaning, but are not recommended.
Penetrations through walls, floors, or ceilings into the space	Sealing is generally not required, except as necessary for fire resistance and thermal requirements.	• Should be sealed with caulk to prevent contamination between areas • Escutcheon plates and service panels at exposed penetrations and fixtures are typically provided for a clean appearance and ease of cleaning but, are not required.	• Should be sealed with caulk to prevent contamination between areas • Escutcheon plates and service panels at exposed penetrations and fixtures are typically required for a clean appearance and ease of cleaning If fire resistant sealant is required, it should also be covered by an escutcheon plate if exposed within the room.
Fixtures and Diffusers	• Fixtures including lighting, safety devices, and diffusers can be exposed or surface mounted.	• Fixtures including lighting, safety devices, HEPA filters, access panels, and diffusers should be recessed mounted with exposed flanges allowed. • Fixtures should be mostly concealed within the ceiling system.	• Fixtures including lighting, safety devices, HEPA filters, access panels and diffusers should be recessed and flush mounted. • Exposed flanges are not recommended and should be mostly concealed within the ceiling system.
Built-in Furniture and Equipment			

6.6.5 Modular Building Components

Modular construction provides a prefabricated wall panel and ceiling system of factory finished metal panels and metal channel core, which also may integrate building components, such as:

- Utility panels
- Doors
- Windows
- Hardware
- Return air chases

The system offers advantages of factory control of quality and workmanship, allowing for clean and precise detailing. The module should be established early and the plan layout developed in the context of the module to achieve most benefit and minimize the cost of the modular system.

The initial cost of the modular system should be reviewed in context with the life cycle costs. Proper design of the demountable system will allow for future adaptability and flexibility, while minimizing dust and disturbance during renovations. This advantage should be reviewed in terms of full facility effects as the details, equipment, utilities, and HVAC system design may impede the demountable aspects of the modular partition and ceiling system.

Modular ceiling systems may be integrated with the wall panels working to the same established grid. The option for walkable ceilings provides a key advantage of accessibility outside of GMP, controlled, or contaminated areas. This allows for maintenance access and facilitates renovations with minimum impact to ongoing operations. Specialized lighting also may allow the relamping of fixtures from above.

A walkable ceiling grid and suspension system could impose coordination and constructability restrictions on the overall construction effort and should be integrated with the utility distribution. Panelized joints may be a concern in wash down areas and those areas where aggressive cleaning is performed. In these cases, a ceiling covering material may be required to provide a uniform surface.

6.7 Other Considerations

6.7.1 Accessible Design

Accessible design ensures access to the built environment for people with disabilities. The documents that guide accessible design and their application may vary depending upon region. In principal the design should take account of:

- Floors and ground surfaces:
    - Specifications for floor and ground surfaces address surface characteristics, carpeting, openings, and changes in level.
- Clear floor or ground space and turning space:
    - Sufficient clear floor or ground space is required at accessible controls, operable parts, drinking fountains, lavatories and sinks, Automated Teller Machines (ATMs) and fare machines, appliances, beds, and other elements.
- Operable parts:
    - Compliance is required for operable parts located in accessible spaces and along accessible routes. Operable parts include light switches, electrical and communication receptacles, thermostats, alarm pulls, automatic door controls, and other elements used by facility occupants.
- Protruding objects:
    - To prevent hazards to people with vision impairments, the standards limit the projection of objects into circulation paths. These requirements apply to all circulation paths and are not limited to accessible routes. Circulation paths include interior and exterior walks, paths, hallways, courtyards, elevators, platform lifts, ramps, stairways, and landings.

These guidelines apply to both interior and exterior spaces, and to both new and renovated facilities. Support areas within a facility, offices, laboratories etc., would usually need to provide accessible design.

Refer to local and country codes and guides for the authority having jurisdiction where the project is being designed.

6.7.2 Pest Infestation and Control

GMP facilities should have a program and design features to prevent the access and infestation of any pests into the facility. Managing and controlling pest incursions into the facility are a continuous process. Insects and rodents are of particular concern.

There are several areas that require focus and attention in managing pest infestation:

- Early soil treatment for the control of termites and other insect pests.
- The building perimeter should be clear of vegetation to prevent rodent nesting and hiding, near the building.
- Locate traps around the perimeter of the facility.
- Limit the number of entrances to the facility and protect them with vestibules.
- Insect exterminating devices should be considered for areas exposed to the exterior environment.
- Loading docks should include a vestibule to minimize direct exposure to the exterior environment.
- All exterior doors should include complete seals at the hinges and threshold.

6.7.3 Security/Control

GMP facilities should limit access of personnel to production areas. This control is typically provided by biometrics or ID card to a production suite or area. Areas of sensitive documentation and production material storage also should be under controlled access.

6.7.4 Acoustics

Management of acoustic levels in OSD manufacturing facilities is becoming an important factor in the design and comfort of the processing suites. Disturbing noises can cause fatigue, stress, and communication problems. The regulations of the authority having jurisdiction for the project should be understood and the acoustic levels should be designed accordingly.

The finishes in GMP manufacturing facilities are typically hard surfaces that can amplify the noise levels within the working environment.

There are several ways to mitigate the acoustic levels within the working environment:

- Establish an acceptable equipment and HVAC acoustic level at the onset of the project
- Require the equipment manufacturers to comply with the established noise levels by enclosing noise generation components, minimizing vibration, or selecting high performance materials of fabrication
- Where appropriate use sound absorbing materials to help moderate the noise levels

As a last resort provide appropriate PPE that does not interfere with the job requirements

6.7.5 Utilities

6.7.5.1 Utility Generation

Utility generation equipment is typically located outside of processing areas. Level 1 areas are typically suitable for these spaces. To minimize maintenance and service traffic within cGMP areas, consider the use of adjacent unclassified service chase/corridors which are accessible from outside the manufacturing core. Flush detailing is typically provided to promote cleanability.

6.7.5.2 Utility Interface

Within the GMP spaces of OSD forms manufacturing facilities are many opportunities for utility interface with the processing equipment. This becomes a significant design implication in the layout of the processing suites since most of the equipment is set in the center of the room. There are several ways to get the utilities from the perimeter of the room to the equipment:

- Extending an enclosed floor trench from the utility chase to the equipment. This can increase flexibility by properly sizing the trench and making it extendable.
- Locating the utility connections in enclosed cabinets on the nearest perimeter walls. Utilities should be extended via flexible hosing from the cabinet to the equipment. Flexible hosing lengths should be properly designed to avoid tripping hazards and ensure a neat appearance in the process suite. This is the most flexible option for changing the operation within the suite, the only difference will be the length of the connections.
- Run the utilities above the ceiling and drop directly to the process equipment via a stainless steel shroud. Penetrate the stainless steel shroud with piping to make equipment connections.

Drains

Drains should be limited in GMP spaces. However, where it is necessary to install drains in the process space, drains should be sealed and traps kept primed.

6.7.6 Renovations

There are several concerns with renovation work in an ongoing manufacturing facility:

- None or minimal interruption to ongoing manufacturing
- Containment of dust, debris, and construction personnel so that there will be minimum impact to the manufacturing personnel and facility
- Maintaining a construction envelope to eliminate any contamination from construction to manufacturing or manufacturing to construction. Air pressure differentials are required to contain dust and odor from entering the manufacturing areas.

7 Process Support Systems and Utility Systems

7.1 Introduction

This chapter discusses two broad categories of mechanical systems used in OSD pharmaceutical manufacturing:

1. Process support systems
2. Utility systems

The categorization of mechanical systems using a risk-based approach is considered. This provides a robust methodology for the identification of process support and utility systems. The chapter focuses on GEP for utility system design. It also provides a method for the determination of system applications and the selection of commissioning and qualification strategies.

The basic principle for the design of OSD process support and utility systems is to ensure that products manufactured by using these systems are fit for use. Specifications and quality attributes of intended products should be understood in order to determine Critical Process Parameters (CPPs) and the parameters of associated process support and utility systems.

This approach described applies a science and risk-based life cycle analysis to the design and qualification of OSD manufacturing process support and utility systems that are subject to cGMP regulations. Design and qualification activities that occur throughout the project life cycle are addressed. For further discussion of a science and risk-based approach see Chapter 3.

Process support and utility systems can be complex in their specific application to an OSD forms manufacturing facility and may have unique engineering and design attributes that are outside the scope of this Guide.

7.2 Water Systems

Typical OSD forms manufacturing facilities use a variety of water systems to provide ingredients for formulations and maintaining a suitably clean environment for a product. This may include potable water in both its raw form and with a variety of treatment steps until it meets the quality requirements for purified water, including:

- Filtration
- Softening
- Dechlorination
- Reverse Osmosis (RO)
- Deionization

The specific need for and use of these various types of water is generally based on the manufacturing and cleaning methods to be used and the specific needs of a particular drug product. The ISPE Baseline® Guide on Water and Steam Systems [59] contains a decision tree to assist in the selection of the appropriate grade of water. For further information on grades and types of purified water and their specifications see:

- European Pharmacopoeia (EP) [60], Japanese Pharmacopoeia (JP) [61], or US Pharmacopeia (USP) [62]

- Clinical and Laboratory Standards Institute® (CLSI) [63]
- ASTM [64]
- ISO Standards [56]

7.2.1 Purified Water Systems

Purified water is usually required to be used in formulations or as part of a drug product and for cleaning. Purified water generally needs to meet the water quality standards as defined by applicable pharmacopoeias, e.g., the USP, EP, or JP.

Purified water systems usually require the installation of treatment systems, storage vessels and distribution systems to deliver purified water to each Point Of Use (POU) in the manufacturing process area. For further information, see the ISPE Baseline® Guide on Water and Steam Systems [59].

Purified systems are normally operated at room temperature (68°F to 72°F (20°C to 22°C)) and are, therefore, not self-sanitizing. Frequent sanitization of the entire system should be performed, during which time the use of the water for production purposes may be interrupted. This can significantly affect the facility and should be considered when selecting the desired type of piping system and sanitization method.

Depending on the level of acceptable risk, low capital generations systems that use service exchange bottles for filtration and deionization can deliver high quality purified water. The quality of these systems is highly dependent on monitoring and maintenance. These systems are only viable where regular deliveries of filter and resin materials are available.

An example of a lower risk option is a generation system that has automated sanitization and regeneration cycles of carbon bed filtration, RO, and continuous Electro-Deionization (EDI) units. These units usually have a higher capital cost, but once set up and qualified, can run self-sufficiently with minimal maintenance.

7.2.1.1 Typical Purified Water Generation System

Purified water systems should be properly maintained and can typically provide water of an acceptable quality for operations. For additional information on options, recommended system set-points and standard operations, see the ISPE Baseline® Guide on Water and Steam Systems [59].

Pre-Treatment Generation

Potable water supplied to a pretreatment system should be treated by filtration or chemical addition to remove or remediate problem contaminants typically found in potable water, e.g.:

- Particulate contaminants (generally > 10 µm nominal size)
- Hardness (generally > 1 ppm, particularly Hardness)
- Chlorine (generally > 1 ppm, antimicrobial oxidizer)

Potable water should be evaluated for the presence of other, less common contaminants or conditions that could compromise the product or system integrity. Potable water may also need to be modified in response to source water chemistry, e.g., the presence of:

- Silica
- Chloramines

- Organic compounds
- Seasonal variation and/or multiple water sources

Unit operations employed in a pretreatment system should use proven technologies that are robust, reliable, and serviceable.

Typical pre-treatment systems consist of the following components:

- Multi-media filter
- Water softeners
- 5 µm cartridge pre-filters
- Hot water sanitized activated carbon filter (or service exchange filter)
- Break tank with immersion heater (if hot water sanitized)
- Circulation pump
- Programmable Logic Controller (PLC) control system

Purified Water Generation

RO technology can reliably purify water with approximately 25% of the energy input of distillation technology and can help to establish higher overall system recovery. Good practice for a purified water generation system includes a multi-pass RO system which can efficiently reduce dissolved solids by > 98%, typically yielding a water purity of < 20 µS/cm^2.

In order to generate compendial purified water, polishing with ion-exchange technology should be incorporated into the purified water generation system to increase water purity to < 1 µS/cm^2.

Typical generation systems consist of the following components:

- Pre-filters
- Single pass RO Unit
- EDI unit (or service exchange bottles)
- UV light
- Final filters
- PLC control system

The RO system is a relatively complex unit operation and should be subject to regular cleaning and maintenance operations. A degree of redundancy for this system is recommended, to ensure that purified water is reliably delivered in sufficient quantity to support uninterrupted manufacturing operations.

Table 7.1: Minimum Criteria for a US Pharmacopoeia Purified Water System

Containment	USP Specification
TOC	< 500 ppb
Microbial Count	< 10,000 cfu/100 ml
Conductivity	< 1.3 µS/cm @ 25°C ± 1°C < 2.7 µS/cm @ 80°C ± 1°C
pH	5.0 to 7.0
General Properties	Meets the latest EPA, USP, TGA, EU, and WHO requirements and regulations for Purified Water

7.2.1.2 Distribution System

Purified Water Storage and Distribution

To control bioburden, the storage distribution loop/system should be chemically sanitized on a scheduled basis, as a minimum. However, if all the chemical is not removed or purged during the sanitization process, chemical sanitization can present a risk to the quality and integrity of the system.

Higher cost options that have reduced risk include heat sanitization and ozone sanitization.

Example approach for chemically cleaning a distribution and storage system:

Cleaning Solution: a suitable cleaning solution should be used.

Cleaning of a System:

1. Fill system with the cleaning solution
2. Allow the system to circulate
3. Using appropriate safety equipment, draw solution from each POU
4. Allow the system to soak in the cleaning solution
5. Flush the system with deionized or purified water and allow water to flush through each POU
6. Check for cleaning solution concentration at each POU, e.g., using test strips
7. Drain the system and place into operation

The system capacity and equipment sizes should be defined during detail design and should be based on instantaneous usage requirements and daily usage requirements. The system capacity and equipment sizes should, as a minimum, typically include:

- One (1) 316L Stainless Steel USP storage vessel:
  - Free Draining
  - Pressure Rated
  - Cleanable Surface Finish

Polypropylene can be a lower cost option, but has limitations to heat sanitization and ozone sanitization.

- USP tank:
  - Sanitary vent filter housing
  - Sanitary level monitoring device
  - Sanitary safety relief device
  - Spray-ball(s) to provide full top head coverage (not a requirement for an ozone system)
  - Ozone destruct vent heater (if the system is ozone sanitized)
- USP distribution system:
  - PLC based control system
  - Sanitary centrifugal distribution pump and Variable Frequency Drive (VFD) to maintain loop pressure
  - Loop cooling heat exchanger (trim cooler)
  - Loop sanitization heat exchanger (if the system is heat sanitized)
  - Ozone generator (if the system is ozone sanitized)
  - UV destruct light (if the system is ozone sanitized)
- Distribution loop instrumentation:
  - Loop supply instrumentation including temperature and conductivity
  - Loop return instrumentation including pressure, temperature, conductivity, and Total Organic Carbon (TOC)
- Distribution loop piping:
  - Polyvinylidene difluoride (PVDF) (chemical or ozone sanitized)
  - 316L stainless tubing (heat sanitized)

7.3 Process Heating and Cooling Systems

Process heat transfer systems can be used to cause a change or chemical reaction within a formulation tank or heat exchanger that contains APIs. These systems form an integral part of the drug formulation process, but typically the heat transfer medium will not directly contact the drug product. Types of heat transfer systems include:

- Process heating water systems
- Process cooling water and glycol mix systems
- Steam systems

Two types of water systems typically used in the formulation of drug products are process heating and process cooling water systems. Process heating and cooling water systems are not required to comply with any specific water quality requirements. These systems may contain propylene glycol and other additives to enhance the overall performance of the heat exchange process. Process heating and cooling water systems are typically dedicated generating and distribution systems and are not influenced by less critical HVAC or other utility systems. The reliability of process heating and cooling water systems may be critical to the reliability of the formulation process; therefore, these systems will normally include redundant components and connection to emergency power systems.

7.3.1 Process Heating Water

Process heating hot water and process heating hot glycol are found primarily on process air handling equipment applications. Propylene glycol can provide additional safeguards against freezing during low ambient conditions. Process heating water/glycol offers improved set point control over steam only systems that employ air bypass and mixing schemes to maintain set point. When possible the process heating/glycol system should be inhibited to prevent system corrosion.

7.3.2 Process Cooling Water and Glycol Mix Systems

In some cases, potable water can be used as process cooling water or as a backup cooling medium to the process cooling water. The potable water is directly connected from potable water main to the equipment and other control devices; and it is discharged from the equipment to the drain after performing its heat transfer function. Building code requirements may mandate the use of backflow prevention and vacuum relief devices to prevent contaminants from entering the domestic water supply system. In addition, the building code may require that the potable water discharges from the equipment should have an air gap between the discharge point and the sanitary connection to prevent contamination from the sanitary gas and wastewater backflow.

Process heating and cooling water systems are also frequently used in heating and cooling coils associated with process air handling equipment. In this case, the process heating and cooling water would have a source identical to that described above for use with formulation related heat transfer equipment.

Process cooling loads can have significant variation in size (tonnage) and duration. Process chilled water system design and equipment selection should account for variations in the process load profile to reduce equipment cycling and optimize runtime. This can only be accomplished by understanding the system load profile as a whole at an early stage in the design process.

7.4 Steam Systems

7.4.1 Plant Steam

Plant steam is a commonplace utility in the OSD production environment. When the CPPs or processing time requirements dictate the need for a reliable source of high temperature heat transfer media, there is generally no cost effective alternative to steam.

The generation and distribution of plant steam should be performed in a manner that maintains steam quality. Good practices should be followed with regards to trap placement, line sizing, condensate recovery and overall system design. Use of plant steam is very common for non-process HVAC humidification and for non-process contact heating applications. Any application used to heat product contact materials should use safeguards to prevent process contamination.

Plant steam may be used for process contact applications when the appropriate risk assessment has been completed. Plant steam created with boiler additives provided in accordance with 21 CFR Section 173.310 [65] requiring FDA approval and are Generally Recognized As Safe (GRAS) compliant may be used in GMP areas.

7.4.2 Clean Steam Generation/Distribution Systems

Pharmaceutical steam generation and distribution systems are normally distinguished from plant steam systems by the quality (dryness, non-condensables and superheat) of the steam and the cleanliness of the piping distribution system. These systems are characterized by distribution systems that use orbital welded stainless steel tubing, sterile service valves and in-line devices, as well as installation techniques that ensure the system meets the requirements for sterility. See the ISPE Baseline® Guide on Water and Steam Systems [59].

Clean steam use in OSD forms manufacturing facilities usually occurs where the steam comes into direct contact with the pharmaceutical product. These instances would include humidification within process HVAC equipment or where steam is introduced directly into a formulation vessel. The steam delivery system should be designed to avoid dead legs and effectively discharge condensed steam to ensure self-sanitizing temperatures are maintained throughout the system at all times.

7.5 Compressed Air and Other Specialty Gases

OSD manufacturing requires the use of compressed gases within production rooms, as well as in the mechanical rooms supporting production operations. These gases may include:

- Compressed air
- Nitrogen

Compressed gases that are considered part of a pharmaceutical product must meet minimum quality and purity requirements as defined in the relevant pharmacopoeias. In addition, these applications are required by regulatory agencies to be supported by testing and documentation against written purity, strength and quality specifications developed by the pharmaceutical manufacturer.

7.5.1 Compressed Air

Compressed air may be used in applications, such as the motive force for drum or other equipment lifting equipment, as long as the compressed air does not come in direct contact with product. It is generally not cost effective to generate and distribute two types of compressed air within a facility. Consequently, compressed air systems in OSD forms manufacturing facilities are generally designed to deliver clean compressed air although some of it may be used in applications where industrial quality compressed air would be acceptable.

7.5.1.1 Clean Compressed Air

Clean compressed air may be defined as compressed air that meets US, EU, and Japanese pharmaceutical manufacturer established quality requirements. Typically, this air is generated by an oil-free compressor, dried using a desiccant dryer to control microbial growth and condensation, and terminally filtered before entering distribution piping. The distribution piping is usually copper or stainless steel, and along with valves and other in-line devices, should be fabricated to meet the requirements of medical gas systems. All tubing and materials used in clean compressed air systems should be oil free and cleaned for oxygen use, e.g., according to NFPA 99 [66].

Care should be taken when selecting the compressed air dryer on systems with large demand turn-down. Heated and/or purge type air dryers may be required to maintain effective dew point control under low load conditions. A dew point temperature of -40ºF (-40ºC) is typical for OSD applications.

7.5.2 Instrument Air

Generally clean compressed air and instrument air will be generated by a common front end oil-free air compressor with a dryer. In these applications a separate instrument air header does not require additional filtration and is typically supplied at or above 90 psig to the POU.

7.5.3 Breathing Air

Compressed air also may be used as the source material for breathing air systems when required by manufacturing operations. When clean compressed air is used as the source for breathing air, it may require additional air quality treatment to ensure air quality for human consumption. Breathing air systems should have redundancy or reliability enhancements, including connection to emergency power systems or use of backup cylinders with automatic changeover controls. These systems should include alarms and other safety devices to alert operators to potential problems with the breathing air system so that manufacturing activities can be suspended safely and operators exit the area in the event of an interruption in the breathing air supply.

There are HSE regulatory requirements in the US and the EU that apply to supplying safe breathable air for personnel use.

7.5.4 Nitrogen

Nitrogen is the second most common compressed gas used in OSD manufacturing. It is used extensively as an "inert" agent for operations involving flammable solvents, usually to blanket the vapor space of vessels containing flammable liquids. Nitrogen displaces air, therefore eliminating the likelihood of an explosion. Nitrogen also may be used as a blanketing agent for compounds that require controlled exposure to oxygen or that are sensitive to high levels of humidity. Installation procedures and materials are similar to clean compressed air, where all tubing and materials are oil free and cleaned for oxygen use, e.g., according to NFPA 99 [66].

Nitrogen leakage into the work place will lower the space oxygen concentration level and may cause an asphyxiation hazard to personnel.

Low demand nitrogen systems may simply involve the use of a single compressed gas cylinder located in close proximity to the production area with a short run of distribution piping. As nitrogen demand increases or additional reliability is required, larger scale systems may include multiple gas cylinders and automatic changeover manifolds. Nitrogen systems that serve entire facilities may use cryogenic liquid nitrogen storage tanks and vaporizers to meet facility requirements.

Bulk feed liquid storage type nitrogen systems generally require a dedicated open air equipment pad for the tank, vaporizer and reducing station assemblies. The bulk tank should be located in an area that can be accessed by a tanker truck for refilling.

There are usually specific operator safety criteria that need to be met when nitrogen is used, such as oxygen depletion sensors and alarms.

Nitrogen quality should meet established quality requirements in the US, EU, and Japan.

7.6 Solvent Supply Systems

In the OSD manufacturing environment, solvents are used to facilitate chemical reactions and to convey coatings for OSD finished products. Solvents are usually alcohol based. These may present significant combustibility and flammability hazards. Solvents that are considered part of a pharmaceutical product are required by regulatory agencies to be supported by testing and documentation against written purity, strength, and quality specifications developed by the pharmaceutical manufacturer.

7.6.1 Solvent Recovery/Abatement Systems

Pharmaceutical manufacturing is one of the most solvent intensive chemical processes. In lieu of recycling spent solvents, manufacturers typically incinerate a large amount of the solvents as a means to generate energy. The decision to incinerate rather than recycle is driven by a simple financial analysis and the Return On Investment (ROI).

The main driving force worldwide for the recovery and recycle or alternative disposal has been the stringent pollution laws. As more governments establish mandates for gas emissions, organizations may change their typical approach to dealing with solvents as legislation may begin to increase the cost of spent solvent incineration. Manufacturing may determine that recovering these solvents has the best impact on an organization's ROI.

7.6.1.1 VOC Abatement Systems

Volatile Organic Compound (VOC) abatement systems are described in two major categories:

1. Destruction
2. Recovery

Destruction technologies consist of oxidation of the VOCs to their most oxidized form, carbon dioxide, and water. Recovery technologies simply remove the containment from the exhaust stream for recovery or additional treatment.

VOC emissions occur from many sources, such as:

- Storage vents
- Distillation vents
- Reactor vents
- Mixers
- Pan coolers
- Spray dryers/granulators
- Coating, printing, and laminating machines can give low concentration of vapors

Destructive Technologies

Destructive technologies are broken down into two subdivisions:

1. Thermal oxidation
2. Biological oxidation

Thermal Oxidizer

Thermal oxidation, or incineration, is the process of increasing and maintaining the temperature of a combustible material above its auto-ignition temperature in an oxygen laden environment to allow the complete conversion to carbon dioxide and water. The process is considered to be moderately effective and can be used safely on any gaseous organic stream given the proper design, engineering, and maintenance conditions. Thermal oxidation can be an attractive VOC abatement option because it can be used for complex mixtures of compounds and it can provide very high levels of control. These systems are designed for a specific residence time, flow rate range, and contaminant type, which makes the system relatively inflexible.

Biological Oxidation

Biological oxidation processes utilize microbial populations that are able to utilize VOCs as the primary source for both their catabolic (respiration) and anabolic (growth) requirements. The basic concept is to immobilize microorganisms (bacteria and fungi) in a packed porous bed or media through which nutrients and pollutants may flow. The immobilized microbial pollutants utilize the pollutants as their primary carbon source for growth and metabolism, oxidizing the VOC compounds to carbon dioxide, water, nitrogen oxides, and salts. Biological oxidation can be highly cost effective provided the system is properly designed.

VOC Abatement Recovery Systems

VOC recovery systems are divided into two types based on whether it is high concentration or low concentration. The recovery systems could be categorized as below:

- Refrigeration based systems
- Absorption based systems
- Adsorption based systems

Refrigeration Systems

The refrigeration based systems depend upon the cooling of the effluent gas to a temperature sufficiently low so that the VOC is condensed out to the desired extent. The temperature for mechanical refrigerated systems can be as low as -70°C (-94°F); beyond this temperature a combination of mechanical and cryoscopic cooling can be used. Refrigeration systems can achieve liquid nitrogen temperatures as low as -180°C (-292°F) to execute condensation.

Refrigeration systems are mainly used for concentrated gases such as emission from storage tanks and filling systems process vents.

- It does away with one step of separation of the VOC from the inert compounds
- The refrigeration load goes up considerably as concentration of non-condensable increases
- To some extent this is mitigated by heat interchange between inlet and outlet gases
- As the gas becomes leaner the temperature of condensation reduces
- The system is inherently safe as it operates at very low temperatures
- The system pressure drop is very low
- It has high turn down ratio from 0 to 100%
- Ease of performance monitoring
- Does not require concentration measurement
- Low power cost as the units consume power on demand
- Low maintenance – only preventive maintenance is required
- No cost of carbon replacement or solvent replacement
- System can take care of water content in influent stream

- Systems are pre-engineered and come in modules

Absorption Systems

In absorption systems, VOCs are absorbed in a suitable high boiling solvent at low temperature in an absorption tower and are then desorbed by heating the solvent directly or indirectly. The desorbed gases, which have high concentration of VOCs, are then condensed; it may become necessary to use a refrigerated condensing system to meet emission standards from the condenser vents.

Absorption systems consists of:

- Choice of correct absorbent is required so that the absorbent losses are low and equilibrium concentration is high
- System operates continuously at all loads
- Can use low concentrations of VOC, typically 0.5%
- High concentration of VOC would require high circulating volumes due to equilibrium requirements
- System requires some on site engineering and erection etc.
- System is fully automatic
- Requires outlet gas concentration measurement
- System can be engineered for small foot print
- Permits partial separation of components
- Requires vacuum to limit temperature of desorption

Adsorption Systems

The VOC is adsorbed onto a suitable adsorbent, usually activated carbon. When the bed is saturated the gases are switched to another bed and the VOC matter is then desorbed by heating the bed of activated carbon, directly or indirectly.

The concentrated gases that come out are condensed. Refrigeration systems can be added in series to meet emission standards if required. This is batch process.

A typical solvent recovery process consists of an activated carbon adsorption unit and, if necessary, an air stripper or distillation unit. In a carbon adsorption system, solvent enriched air passes through an adsorber vessel in parallel, or in series, to flow where the solvent vapors are adsorbed by the activated carbon. Once the carbon is saturated and solvent is detected, the solvent laden air is routed to a newly generated standby adsorber unit while the other solvent laden carbon adsorption unit is regenerated.

Solvents are recovered by regenerating the activated carbon via steam or hot nitrogen. Steam heats the carbon and strips the solvent from it. The steam or hot nitrogen is then condensed in a water or an air cooled condenser and drained into a separator. Water immiscible solvents may be separated from water by a simple decanting or distilling process to purify them further if they are intended to be returned to the process for reuse, resale or disposal. Solvents that are miscible are separated from the water and purified in a distillation system. Where heated nitrogen is used to strip solvents from the carbon, the solvent is condensed from the nitrogen stream at low temperature (approximately -20°C (-4°F)).

Adsorption systems are:

- Used for low concentration of VOC, typically 0.5%
- Requires large number of beds
- It is batch process requiring switching of streams form bed to bed
- Periodic replacement of activated carbon
- Large volumes of organics are kept in process presenting a safety hazard
- Periodic regeneration of beds with steam or inert air
- Large installation cost
- Requires condensation of outlet gases
- Requires measurement of concentration of outlet gas
- Limit to size of activated carbon beds due to heat transfer considerations
- Because of large size of installation, possibility of air ingress and explosions – as the unit has to operate above ignition temperature
- Activated carbon quality can vary between manufacturers and the size of equipment, etc., will also vary.

Carbon adsorption can be a highly cost effective alternative to VOC emission systems for manufacturing processes that emit halogenated or nitrogenated solvents. When oxidized, these solvents can lead to the production of acid gases, such as HCl, HF, NOX, or dioxins which are pollutants that would require additional equipment to remove them from the oxidizer exhaust gas before venting to the atmosphere. The equipment required to process these byproducts would require an additional capital investment.

7.6.2 Solvent Code Issues

Formulation operations using solvents usually involve the dispensing of solvents into blenders or other vessels, followed by mixing and drying of the formulated product. Such activities generally require the room in which they occur to be classified as hazardous by the US National Electrical Code (NEC) [31], the US National Fire Protection Association (NFPA) [26], the EU ATEX 95 Directive [1], the Japanese Industrial Standards (JISs) [67], and other recognized standards. These standards, as well as International Building Codes [68], place many restrictions on manufacturing operations using hazardous materials. For example, an entire manufacturing facility may be limited to just four relatively small “control areas” in which solvent dispensing and use is allowed. Solvent processing areas also will require explosion proof equipment and special electrical wiring provisions for all devices within a room. The full impact of operations involving solvent based processing can be costly. A detailed evaluation of building codes should be performed prior to planning or budgeting for new solvent based processing operations or expansion of existing operations.

Solvents must meet appropriate HSE regulatory requirements for flammable or combustible liquids. For further information, see Chapters 3 and 11 of this Guide.

8 HVAC

8.1 Introduction

This chapter focuses on the cGMP requirements for HVAC systems for OSD forms manufacturing facilities. It provides guidance on the establishment of clearly defined user requirements (e.g., level of product protection, product and process requirements, and architectural design).

Non-cGMP requirements, such as operator protection, environmental protection, energy efficiency, and personnel safety are also addressed, as they may be associated with and influence, cGMP requirements.

HVAC can have a significant impact on the quality of product and the safety of the working environment. Control of the processing environment HVAC can help to mitigate risks both to the product and to operators.

8.1.1 cGMP Risks

cGMP risks that may be mitigated include:

- Protecting the product from ambient particulate contaminants
- Assuring product stability by protection from excess temperature
- Assuring product stability, machinability, flow-ability, and potency by protection from excess humidity
- Protecting the product from cross contamination with other products

8.1.2 Non-cGMP Risks

Non-cGMP risks that may be mitigated include:

- Protecting operators from excessive exposure to active ingredients
- Protecting operators from excessive exposure to hazardous chemicals used in processing
- Protecting operators from risks of fire and explosion due to processing of flammable mixtures
- Protecting the surrounding community from the above risks

See Chapter 3 for further discussion of risk management.

The relationship between HVAC and these risks is influenced by the configuration of processing equipment and the closure of processes.

- Where open processing is used, the surrounding environment of the room where the process takes place, forms the background for processing and is critical to controlling these processing risks.
- Closure of the process separates the surrounding environment from the process, thus reducing its importance in controlling processing risks.

Process closure can mitigate both cGMP and non-cGMP risks by placing a barrier between operators, the room, and product. Process closure can also save energy by making the critical process background environment smaller than the surrounding room.

HVAC engineers should understand applicable cGMP regulatory requirements and should be familiar with industrial HVAC as defined in various documents by the:

- American Society of Heating, Refrigeration and Air-Conditioning Engineers (ASHRAE) [69]
- American Conference of Governmental Industrial Hygienists (ACGIH®) [70]

HVAC engineers should have knowledge of local and national construction codes, including fire safety (e.g., NFPA [26]) standards, environmental regulations, and occupational safety and health (e.g., Occupational Safety and Health Administration (OSHA) [71]) regulations. The design and installation of HVAC systems should comply with these and applicable building, safety, hygiene, and environmental regulations.

8.2 General Principles

The role of HVAC in OSD processing is to manage airborne particulate (both product and contaminant) and to provide an environment with temperature and humidity suitable for the product being processed.

8.2.1 Environmental Control Considerations

For operator comfort, ASHRAE Standard 55 [72], ASHRAE Standard 62.1 [73], and ISO 7730 [74] should be followed. Conditions may need to be adjusted for workers in protective clothing (e.g., coveralls, full-face respirators, or air supplied full body suits).

Specific conditions needed for products (e.g., hygroscopic or temperature sensitive products) during the manufacturing process should be defined prior to selecting and sizing the HVAC system.

In OSD facilities, the most prevalent contaminant is pharmaceutical powder (dust) from handling and manipulation of the product and raw materials. Dust containment methods should be employed to protect both the operators from exposure to potentially hazardous compounds and to avoid cross contamination of product.

A risk analysis should be performed in production areas (e.g., dispensing, granulation, mixing, drying, encapsulation, and compression) in order to determine whether a once through (100% exhausted) air systems or a filtered return air system is appropriate for the application:

- Once through air systems can ensure that product or material is not inadvertently distributed to other spaces via the HVAC system; however, these systems are costly to operate and may increase the risk of contamination with dirt.
- Filtered recirculating systems can provide containment of powders at lower cost, but usually require regular monitoring to assure correct operation.
- Airstreams which contain high concentrations of product (e.g. dust collection) are not recommended for recirculation, even with filtration.

HVAC systems may also be used to reduce the concentrations of airborne contaminants emitted from the processes.

8.2.2 HVAC Regulation

Key issues in regulation and guidance impacting HVAC design qualification and maintenance in OSD manufacturing include:

- Contamination control and cross-contamination control:
  - Control of pharmaceutical dust (from processing)

  - Filtration
  - Recirculation
  - Pressurization
  - Control of contaminants from personnel

- Environmental control of critical parameters:
  - Temperature
  - Humidity
  - Pressurization
  - Filtration
- Risk Assessment:
  - By processing zone
  - Product/process specific
  - Qualitative or quantitative

Citations are included from the EU GMP Volume 4 Chapter 3 [10] and EU GMP Volume 4 Chapter 5 [75]; as well as excerpts from: 21 CFR Part 210 [7], 21 CFR Part 211 [8]; WHO TRS 937 [76], WHO TRS 961 [77], and ISO 14644 [78]. The content of these citations is also typical for regulations from:

- China (CFDA)
- Australia (TGA)
- Brazil (ANVISA)
- Mexico (COFEPRIS)
- Japan (MHLW)

8.2.2.1 Contamination Control

Common among regulations is a requirement that the environment be appropriate to the drug processed:

> *"5.10 At every stage of processing, products and materials should be protected from microbial and other contamination."* [75]

In OSD products, potential contamination may be the contamination of one drug by another. Regulations predominantly suggest that this is related to the dissemination of pharmaceutical dust and active product must be controlled. This requirement for control of pharmaceutical dust includes minimizing the escape of dust from the process and the control of fugitive dust within the room:

> *"3.14 In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross contamination…* [10]

5.11 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing material. [75]

5.18 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapors, sprays… from active substances… [75]

5.21.vi…• Controlled removal of dust close to source of the contaminant e.g. through localized extraction" [75]

Control of pharmaceutical dust in the surrounding environment is a key environmental control in the processing of oral dosage products. Regulations typically call for *"minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air…"* (EU GMP Volume 4 Chapter 5.19 [75]. However, these same regulations point to an evaluation of cross contamination potential in lieu of an across-the-board ban on recirculation of air in multi-product facilities *"An evaluation of potential for cross-contamination via HVAC should be part of the risk assessment in multi-product facilities."* (WHO TRS 961 Annex 5 [79]).

8.2.2.2 Environmental Control of Critical Parameters

cGMP regulations commonly require that the environment is appropriate to the drug processed. The determination of critical HVAC parameters is part of the design of OSD forms manufacturing facilities.

OSD processing may require control of the space temperature (for drug stability and operator comfort), humidity (for stability, machinability and flowability of powders), and pressurization (for contamination and cross-contamination control). Filtration may also be a key parameter to assure that the environment is sufficiently clean, this may done in lieu of counting particles since "in-operation" particle counting is not typically practical in facilities where powders are handled.

Parameters may be required by regulation in order assure that an environment is appropriate for the product being manufactured. A risk-based process for determining critical parameters is suggested by most regulations. The list of parameters that may be judged as critical can be broad. For instance, the following citation from WHO TRS 961 Annex 5 [79] suggests a long list of parameters that may need to be qualified in an OSD forms manufacturing facility:

"8.2.13 For a pharmaceutical facility, based on a risk assessment, some of the typical HVAC system parameters that may be qualified can include:

- *Temperature*
- *Relative humidity*
- *Supply air quantities for all diffusers*
- *Return air or exhaust air quantities*
- *Room air change rates*
- *Room pressures (pressure differentials)*
- *Room airflow patterns*
- *Unidirectional flow velocities*
- *Containment system velocities*
- *HEPA filter penetration tests*
- *Room particle counts*
- *Room clean-up rates*
- *Microbiological air and surface counts where appropriate*
- *Operation of de-dusting*
- *Warning/alarm systems, where applicable."*

For OSD forms manufacturing facilities that class 100,000 (ISO 8) in the "at rest" state (similar to EU Grade D) is a suitable background environment for OSD forms manufacture. As an example, the following is a citation from WHO TRS 961 Annex 5 [79]:

> *"Many open product zones of OSD form facilities are capable of meeting ISO 14644-1 Class 8 or Grade D, "at-rest" condition, measured against particle sizes of 0.5 µ and 5 µ… "*

Note: The required degree of air cleanliness in most OSD forms manufacturing facilities can normally be achieved without the use of HEPA filters provided the air is not recirculated.

8.2.2.3 Risk Assessment

A risk-based approach should be used in the establishment of critical parameters and the design of HVAC systems. Other expectations for HVAC and environmental control will be influenced by assessment of the risks inherent to the product and process. The following is a citation from the 2013 draft update to Chapter 3 of the EU GMP Volume 4 (updated and issued in summer 2014) [10]:

> *"3.6 …The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks."*

Risk assessment should include a toxicological evaluation of the products being manufactured. For further information on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities see the ISPE Baseline® Guide on Risk-MaPP [11].

The principles outlined in the EU GMP Volume 4 Chapter 5 [75] and the WHO TRS 961 Annex 6 [80] suggest that cross-contamination risk is the product of the risk inherent in the contaminating material and the risk inherent in the item becoming contaminated.

Amongst the highest risk potential contaminants in OSD forms manufacturing are those which are highly potent (OEL < 1.0 mg/m^3) or highly sensitizing (e.g., penicillin).

In relation to OSD products, the highest risk dosages which might become contaminated are those which are taken in large volume or over long periods of time:

> *"5.18 Contamination of a starting material or of a product by another material or product must be avoided... The significance of this risk varies with the type of contaminant and of product being contaminated. Products in which cross contamination is likely to be most significant are those administered by injection and those given over a long time…"* [75]

This suggests that cross-contamination must be most closely controlled when handling potent products to prevent the contamination of those given in large doses or over long periods of time, such as cardiovascular and metabolic control drugs.

Risk assessment can be used to determine the correct level of environmental control (Zone 1, 2 or 3), the appropriateness of a system configuration, or the quantitative risk of cross-contamination between products. WHO TRS 961 Annex 5 [79] suggests that risk tools should also be used to help set critical parameters, rather than observing prescriptive requirements.

The assessment of risks in HVAC for oral drug processing is further discussed in Section 8.2.4 of this Chapter.

8.2.3 HVAC Risk

This section builds upon the discussion of risk in the regulation section to give guidance on the typical application of risk management tools to HVAC.

8.2.3.1 Contamination and Cross-Contamination

The control of contamination and cross-contamination typically comes down to an assessment of the effectiveness of filtration in removing the offending particles. Assessment of filtration efficiency has often been done by assuming that filters reduce the amount of airborne particulate by an amount equal to their ASHRAE efficiency rating. This method is flawed in that it is exceptionally conservative. As can be seen in the following table, the "Arrestance" or "ability of a filter to remove mass" exceeds its ASHRAE efficiency rating.

Table 8.1: Filter Comparison – Pre-filters
These comparisons of filter rating systems are only approximate as the test methods are different.

ASHRAE 52.2	ASHRAE 52.1		EU Type	EN 779
MERV Designation	**Arrestance (Gravimetric Efficiency)**	**Dust Spot (Colorimetric Efficiency)**	**Designation**	**Designation**
1	< 65%	< 20%	EU 1	G 1
2	65 – 70%	< 20%	EU 2	G 2
3	70 – 75%	< 20%	EU 2	G 2
4	70 – 80%	< 20%	EU 2	G 2
5	80 – 85%	< 20%	EU 3	G 3
6	85 – 90%	< 20%	EU 4	G 4
7	> 90%	25 – 30%	EU 4	G 4
8	> 90%	30 – 35%	EU 5	F 5
9	> 90%	40 – 45%	EU 5	F 5
10	> 95%	50 – 55%	EU 5	F 5
11	> 95%	60 – 65%	EU 6	F 6
12	> 95%	70 – 75%	EU 6	F 6
13	> 98%	80 – 90%	EU 7	F 7
14	> 98%	90 – 95%	EU 8	F 8
15	< 100%	> 95%	EU 9	F 9
16	< 100%	> 95%	EU 9	F 9
				EN 1822 *
16			EU 10	H10
* All EN 1822 tests at MPPS		H = HEPA; U = ULPA		

Add to this the fact that most pharmaceutical oral API are sized to be in the range of 10 to 50 microns, a range where medium and high efficiency filters are very efficient (see Figure 8.1) coupled with the fact that most HVAC systems possess an array of filters in series, which work together to remove contaminants and it becomes clear that filtration can be an effective solution to issues of contamination and cross-contamination.

Figure 8.1: Prefilter Efficiencies for MERV Rated Filters
Used with permission from the National Air Filtration Association (NAFA), www.nafahq.org (source: Summer 2002 issue of Air Media, Figure 4 Composite of all MERV filter models, based on initial conditions, Author(s): W.J. Kowalski, PE, PhD; W.P. Bahnfleth, PE, PhD, The Pennsylvania State University)

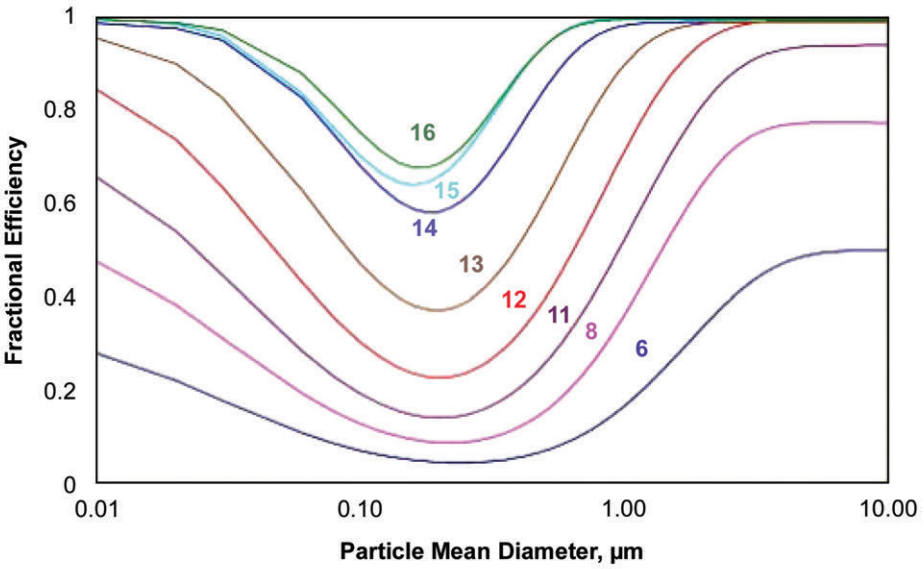
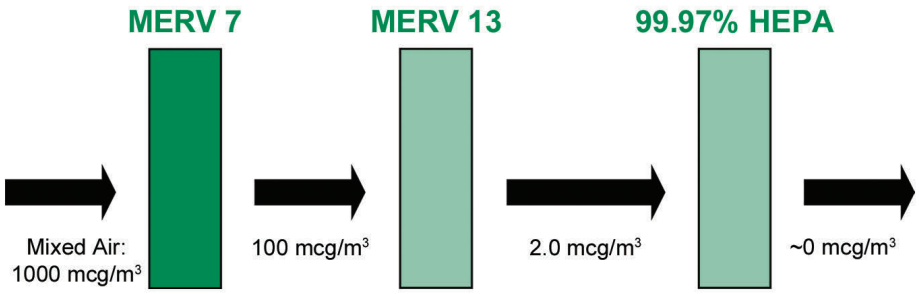


Figure 8.2: Average Mass Removal of a Filter Array
Used with permission from Genesis Engineers, Inc., http://www.geieng.com/



Methods for quantification of risk using a numerical model of airborne product concentration and fractional filter efficiencies are suggested.

Steps that may be taken to assess the risk of cross-contamination in an HVAC system include:

- Evaluating the mass or volume of airborne “contaminant” product in its environment
  - HSE monitoring is usually a good source of data
  - Where HSE data is not available, historical or SME data on typical process emissions may be used.
  - Where neither of these are available, a total particle count may be taken and a uniform poly-dispersed aerosol may be assumed for the purposes of modeling.

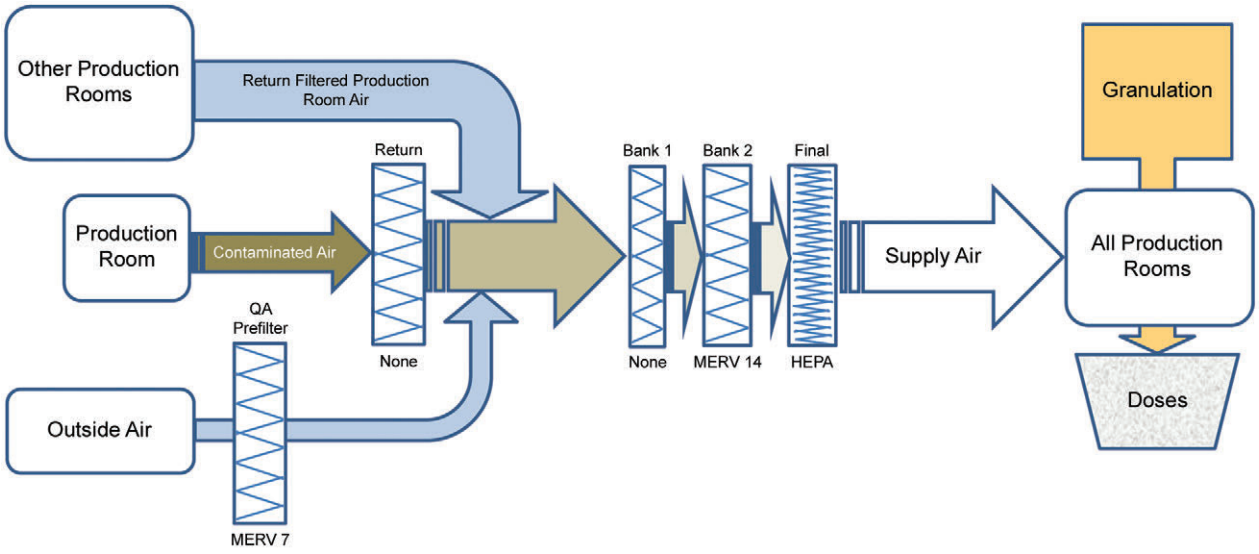
- Evaluating the reduction in airborne contaminant in the HVAC system (using ASHRAE 52.1 [81] and 52.2 [82] filter performance data).

  a. Evaluating dilution inherent in the system

  b. Comparing the contaminant mass to the processed product mass and number of doses to determine potential concentration per unit dose

Figure 8.3 gives an example of this methodology.

Figure 8.3: Quantitative Evaluation of HVAC Cross-Contamination Potential
Used with permission from Genesis Engineers, Inc., http://www.geieng.com/



Cross-Contamination Assessment

Case	Room Classification (mcg/m³)	Gravimetric Filter Efficiency (arrestance)				Post-Filtration Contamination (mcg/m³)	Room Airflow (M³/hr)	System Airflow (M³/hr)	Daily Hours of Operation	Total Contaminant Contributed (mcg/day)	Room vs. Total Airflow Dilution	Potential Contamination/ Room (mcg/day)	Production (units/day assumed)	Potential Contamination per Unit (ng/unit)
		Return NONE	Bank 1: NONE	Bank 2: MERV 14	Final HEPA									
Case 1: Proper Containment	2	100%	100%	0.10%	10%	2.0E-04	3,279	20,535	8	5.2E+00	16%	8.4E-01	30,000	2.8E-02

This method can be modified by the use of fractional efficiencies, particle size based efficiency ratings.

8.2.4 *Critical Parameters*

In OSD forms manufacturing facilities the common critical parameters are temperature, relative humidity, and differential pressure.

Acceptance criteria for critical parameters are product dependent and should be determined in advance, to ensure the proper control equipment is designed. Monitoring of critical parameters can indicate when acceptable ranges are exceeded and potential mitigation is required.

8.2.4.1 *Temperature*

Room temperature will be a critical parameter for both the operating personnel working in the space and the product present in the room (opened or closed). Both occupant comfort and the potential for particulate generation at temperature extremes should be considered. Depending on the exposure time, most products can deal with a wide range of temperature variations.

The USP excursion limits for Controlled Room Temperature (CRT) finished product storage are 59°F to 86°F (15°C to 30°C) with a maximum Mean Kinetic Temperature (MKT) of 77°F (25°C). However, individual products may differ and require a more stringently controlled environment. Product temperature monitoring may be performed as an alternative to room temperature monitoring.

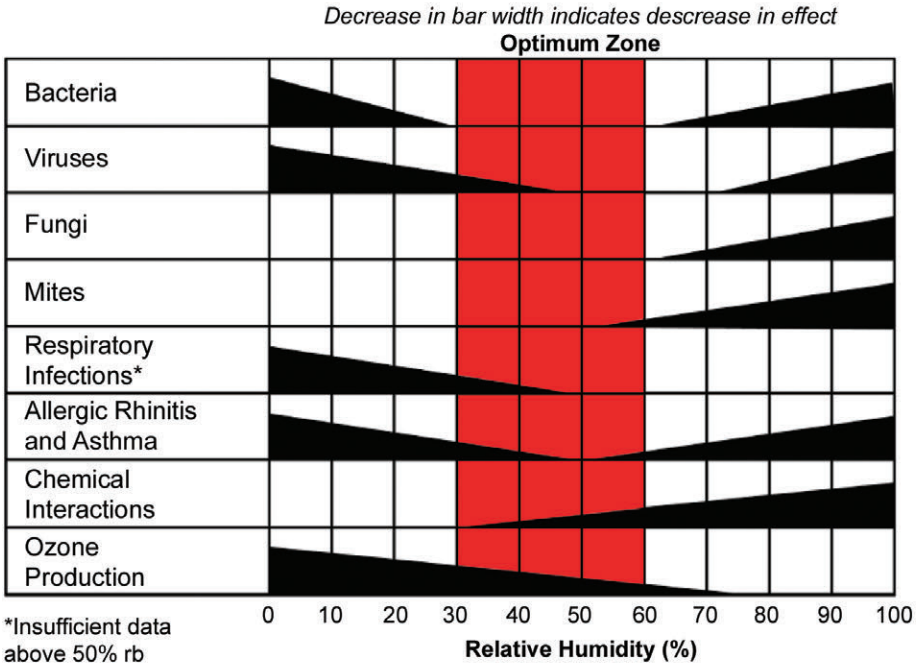
Room temperature can be monitored by return/exhaust duct mounted sensors or wall mounted sensors that relay information to the Building Automation System (BAS) and/or to an independent Environmental Monitoring System (EMS). Typically, a relatively tight control range is specified (i.e., 20°C to 22°C (68°F to 72°F)), with an "Alert" occurring when a wider range is exceeded (i.e., 18°C to 24°C (65°F to 75°F)), before an action "Alarm" occurs when a maximum range is exceeded (16°C to 26°C (60°F to 79°F)). All values being equal to the USP excursion limits, corrected for instrument error.

Note: Temperature and room Relative Humidity (RH) are interdependent and an excessive value in one may adversely affect the other (i.e., a room designed for 21°C (70°F)/50% RH but being maintained at 17°C (62°F) will actually be at > 62% RH).

8.2.4.2 Relative Humidity

Room RH will be a critical parameter for both the operating personnel working in the space and the product present in the room (opened or closed). Depending on the type of product (solid, powder, liquid) varying moisture content in the room will cause different reactions.

Figure 8.4: Optimum Humidity Range for Human Comfort and Health
Source: Arundel, A.V., E.M. Sterling, E.M., J.H. Biggin, and T.D. Sterling, "Indirect Health Effects of Relative Humidity in Indoor Environments," Environmental Health Perspectives, Vol. 65, March 1986, pp. 351-361.



Typically, room RH is maintained in the 30% to 60% range. Room RH above this level will promote problems with the occupants as well as the product:

- High viable contaminant growth is typically observed above 80% RH (see ASHRAE Systems 2012 [83])
- Occupants will generate particulate as they are likely to perspire in high humidity areas (> 60% RH)

- Powder clumping, improper flow characteristics, and poor machinability may be observed at lower RH depending on product composition
- Hygroscopic products may absorb water causing incorrect formulation or negatively impacting physical characteristics at > 30% RH
- Highly moisture sensitive products, such as effervescent and rapid dissolving tablets, may be negatively impacted by > 10 to 15% RH

For these reasons, room RH may need to be controlled in the 15 to 45% RH range, depending on the product. This will usually require a medium better than mechanical cooling (i.e., chilled water, Direct Expansion (DX), etc.) such as brine, low temperature glycol water, or desiccant.

RH below 20 to 30% greatly increases the risk due to electrostatic discharge (ESD). Static electricity charges can also cause damage to electronics and provide a spark leading to fire or explosion due to ignition of gasses, explosive dusts and/or volatile liquids. The dust deflagration index (Kst) and Minimum Ignition Energy (MIE) of powders being handled impact this risk.

Table 8.2: Static Buildup versus Relative Humidity

Activity (@ 21°C (70°F))	Static Voltages	
	20% RH	80% RH
Walking across vinyl floor	12 kV	250 V
Walking across synthetic carpet	35 kV	1.5 kV
Arising from foam cushion	18 kV	1.5 kV
Picking up polyethylene bag	20 kV	600 V

8.2.4.3 Classification

The term “Classification” within HVAC and environmental control of pharmaceutical facilities refers to ISO 14644 [78]. This standard defines classifications by the count and size of airborne particulate found in the space. For pharmaceutical facilities, we typically focus on particles with a mass mean of 0.5 µ and 5.0 µ. Sterile product guidance utilizes these same airborne particle sizes and counts, but adds fixed limits for viable particulate and surfaces. It should be noted that sterile product guidance is not normally applicable to oral products due to the tremendous difference in risk between these dosage forms.

As discussed in “Environmental Control” (Section 8.2.2.2) classification of oral product manufacturing spaces is not typically required by regulation. However, guidance documents (such as WHO TRS 961 [77]) suggest that classification according to ISO 14644 [78] as ISO 8 for 0.5 µ and 5.0 µ airborne particles in the “at-rest” state is appropriate for OSD forms.

The use of an ISO 14644 [78] classification of room performance for the design of OSD forms manufacturing facilities provides an independent and verifiable standard for acceptance of designs and eliminates the need for highly suspect and limited acceptance criteria such as air exchange rates (air change rates).

8.2.4.4 Differential Pressure and Flow Direction

Where airborne contamination, cross-contamination, or potent/hazardous material containment are a concern, one tool for control of airborne particulate is to control the differential pressure or direction of airflow between spaces.

The velocity and direction of airflow between spaces should be satisfactory to reduce the transfer of airborne particulates or vapor. While there is not a numerical value for pressurization required in regulation, a number of suggestions do exist in guidance documents.

Where mass flow is used for control, a velocity of 100 to 200 fpm is desirable to control light powders moving across a work area. This principle is used for containment in weighing booths, dryer discharges, and similar open containment devices.

Where direction of airflow across a door is used for control, a velocity of 100 to 200 fpm is desirable to control light powders moving across the opening. Generally, smoke tests and Baulin tubes may be used as indication in this type of control.

Where airflows are variable, higher levels of containment are required, or containment requires continuous monitoring, differential pressure measurement can be used. In these cases, a minimum pressure difference of 5.0 Pa (0.02"WC) is suggested to allow for repeatable control. For better control and higher containment, a value of 12.5 Pa (0.05"WC) is common.

8.2.4.5 Air Change Rate

Air flow supplied and exhausted from a space must be based on that required for adequately providing heating and cooling. Factors such as room pressurization, exhaust flows, and ventilation may increase the values.

While air exchange rates (air change rates) are a common design parameter, it has little value as an acceptance criterion for OSD facilities. There commonly is no minimum air change rate requirement in regulation for OSD facilities. Successful and licensed OSD forms manufacturing facilities operate across a broad range of air exchange rates, typically from 6 to 20 ACH. The minimum rate of 6 ACH cited has more to do with code requirements and heat load than with space cleanliness.

The basic deficiency of air exchange rate as an acceptance criterion is that it assumes that particle generation and infiltration rates vary with room volume; however, the rate at which particles are generated is actually based on process and personnel. Consequently, we get the incorrect impression that reducing room size without changing process or personnel will reduce the airflow demand. See the ISPE Good Practice Guide on HVAC [2] for further discussion of the deficiencies of ACH and the basic science of cleanroom HVAC design.

By contrast, recovery rate, as defined in ISO 14644-3 [78] provides an additional independent and verifiable parameter to be considered in the design of pharmaceutical facilities. Recovery rate testing determines the period of time needed for a cleanroom to reduce a contamination event, or “clean up”, by 1 or 2 log. This test determines actual cleanroom performance, rather than an assumption made via ACH. It also is indicative of the time needed for the environment within a room to recover between batches of products to maintain separation.

In lieu of utilizing ACH as an acceptance criterion for oral product production spaces, we recommend utilizing ISO Standards 14644-1, 2, 3 [78] to establish HVAC acceptance criteria and proof of environmental control.

8.2.5 Humidity Control

Room RH may need to be controlled anywhere from 15 to 60% RH, depending on the product and process.

Single product, or single RH requirement plants, may utilize a central dehumidification control strategy, with room RH or dew point controlled at a central station air handling unit (AHU). This control can be via chilled water, low temperature chilled brine, or desiccant. Typically, these technologies are applied as follows:

- > 45% max RH @ 22°C (48°F dew point) – Chilled Water
- > 30% max RH @ 22°C (37°F dew point) – Low Temperature Chilled Brine

- < 30% max RH @ 22°C (72°F) – Desiccant

Flexible production plants may benefit from dedicated room dehumidification equipment to allow adjustment of RH according to product needs. This can be achieved with either an “after cooling” coil or a desiccant dehumidifier.

In areas where low RH is required, the design team should consider:

- Airlocks to slow the ingress of moisture
- Tight room construction with vapor barriers to slow the ingress of moisture
- Use of a recirculation system to enhance RH control
- Use of air tight return ductwork to slow the ingress of moisture
- Careful grounding and control of powder explosion risks

8.2.5.1 Dry Desiccant

Desiccant bed and wheel technology are well developed and reliable. An array of dry desiccants, including silica gel, lithium chloride and molecular sieves, are available to address a wide range of room humidity levels and moisture loads.

The dry desiccant technologies all utilize a mechanism to move a bed of solid desiccant from the process air stream into a warmer reactivation airstream. Filtration of the air to and from these beds is critical.

8.2.5.2 Liquid Desiccant

Liquid desiccant is a similar technology to dry desiccant, but has the added advantage of being biocidal due to the high osmotic pressures within the concentrated salt solution. These systems can also be arranged to combine cooling with desiccant effect, eliminating the need for an after cooling coil to remove the sensible heat gained during drying.

There are a smaller range of desiccants available in liquid systems (typically lithium chloride), but the concentrations can be varied to address a range of applications.

Liquid desiccant is highly corrosive and the equipment handling it should be carefully selected. Furthermore, control of desiccant concentration is critical to proper functioning of the process and life cycle of the equipment.

8.3 HVAC Air Distribution Principles

Dilution ventilation is the use of room HVAC systems to disperse and exhaust contaminants emitted from the process, whether by normal operation or by upset conditions. Issues which should be considered include:

- High number of air changes to dilute on-going sources of contaminants to low concentrations. This should only be used as a secondary means of control and represents a major HVAC system expense considering the volume of high quality conditioned air being thrown away.
- Dispersion of peak exposures due to upset or emergency conditions to limits where respiratory protection would not be required takes time. The recommendation is to assess the time to dilute from concentration X to concentration Y using the dilution equations in Industrial Ventilation: A Manual of Recommended Practice for Design [84], to determine whether a dispersion strategy can meet the need
- HVAC room air velocities are typically too low to act as a primary means of containing heavy 10 to 100 µ pharmaceutical dusts. These dusts will settle onto the floor or equipment rather than be conveyed

- HVAC can be used as a secondary means of containment, managing the smaller, lighter, fugitive dust emissions from closed or contained pharmaceutical operations. Room air currents should be arranged to sweep light dust and fumes from the point of emission, away from doors and operators, to the returns

- Low returns are advisable due to the comparatively low velocities in room HVAC and the heavy particle size of any pharmaceutical dust

Local Exhaust Ventilation (LEV) is contaminant point source control by the use of shaped airflow patterns to capture dusts or vapors emitted from process operations, such as granulation, mixing, weighing, or tableting. A risk assessment should be performed to determine if LEV is acceptable for the application. Issues which should be considered include:

- Hoods or enclosures should be designed with operator input to successfully interface with the process unit operation in a way that will not introduce contaminants into the process. Hood airflow patterns should not pull the contaminants into the operator's breathing zone. Hood performance is highly dependent upon operator technique.

- Ductwork will need a higher conveying velocity in all branches than HVAC systems, due to the requirement to convey particulate. If the collected contaminants are a dust or vapor deflagration hazard, the air pollution control device may need to be located so that it can be vented to the roof. An alternative explosion suppression or containment strategy may need to be chosen if the contaminant is a highly hazardous compound.

- The exhaust for LEV systems affects the room air balance for the HVAC systems. LEV exhausts should not be considered for recirculation back into process areas without additional safeguards. For guidance on recirculation of LEV exhaust, refer to the *Industrial Ventilation: A Manual of Recommended Practice for Design* [84] and ANSI/AIHA Standard Z9.7, Recirculation of Air from Industrial Process Exhaust Systems [85].

- If the LEV is not operated while the process room exhaust system is operated, then steps may need to be taken to prevent reverse airflow through the idle LEV

8.4 Process Specific HVAC

Containment strategies for pharmaceutical powders or hazardous materials vary within processing rooms. The choice of containment strategy depends on a variety of factors, including:

- Material characteristics

- Process equipment design

- Balance between equipment and operator procedure

- Business needs

This section discusses the typical critical parameters and issues associated with typical OSD unit operations. The categories of unit operations are discussed.

8.4.1 Raw Material Storage

Written procedures should be available describing the receipt, identification, storage, handling, sampling, testing, and approval or rejection of incoming goods.

As soon as raw materials are transferred to a storage area, they will start to adopt the room temperature as a result of the heat transfer between surrounding air and stored material. The temperature and humidity selected for storage areas are dependent on the material requirements. Typically, raw materials are stored at 15°C to 25°C (59°F to 77°F) and 25 to 80% RH. Individual raw materials may have more stringent requirements. It should be noted that most plastics do NOT prevent the migration of moisture over long periods of time, which may require the further control of RH.

HVAC systems for storage areas should be designed to maintain temperature uniformity throughout the space to ensure compliance with desired storage conditions. Ductwork design and sensor locations are important as warehouse design can vary from single story to multi-story structures and uniformity is desirable throughout the space. Ductwork should be designed so as not to interfere with crane or pallet lifter equipment operation and have the air distribution velocity to reach all areas. Destratification means may be required to ensure the desired temperature conditions at all storage locations. Sensors must be located to properly represent storage space(s) geometry and storage rack layout(s). The relationship between storage conditions and sensor readings should be establish by temperature mapping during qualification.

Truck docks require special attention to ensure their operation does not impact the storage areas temperature and humidity uniformity. Air curtains or strip curtains are generally used above truck dock doors to provide an air wash to separate the outdoors from the storage area. Segregating walls and doors between shipping/receiving and storage areas are desirable to enhance this separation.

8.4.2 Sampling

Sampling should be undertaken in a segregated area adjacent to the storage area before being brought to the laboratory for testing. Some regulations explicitly require this segregation and it has been the subject of citations on inspection. Depending on the original container of the raw materials, the sampling room may be designed with separate material and personnel airlocks, or with smaller transfer boxes for materials and personnel airlocks. In either case, the proper air pressure differentials must be set up so as to prevent contamination of samples. Within the sample area, a unidirectional flow hood or similar dust control device may be used to remove samples from the primary container. The unidirectional flow hood may be used to duplicate the cleanliness level of the production suites, or the room itself may be designed to mimic manufacturing room conditions.

8.4.3 Dispensing

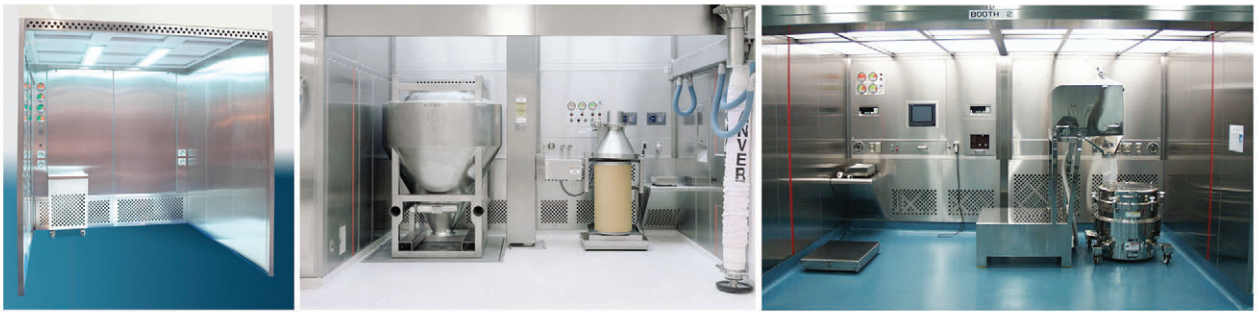
In order to eliminate/limit the spreading of the product during dispensing, the use of isolator technology, down flow or cross flow booths may be used depending on the OEL classification and amount of volatile material handled.

Down flow booths are an alternative approach to containment. This device surrounds a process with unidirectional low velocity air that is forced downward to prevent dust from entering the operator breathing zone. While in operation, the booth air is constantly recirculated through its high efficiency air filters. This concept can prevent exposures, but does not prevent product spills to the floor of the area; also, it is more effective around smaller objects like a drum rather than larger objects that shield the dust source like a super-sack. For further information, see Chapter 5 of this Guide.

Down flow booths can influence smaller weigh scales with their downward airflow making it difficult to stabilize the scale readings. Often, pre-manufactured booths are preferred over stick built systems because of the advanced modeling/testing by original equipment manufacturers within their factories (see Figure 8.5).

Both isolator and room pressure differentials play an important role in preventing the migration of the potent powders towards the surrounding areas.

Figure 8.5: Typical Down Flow Booths
Used with permission from Extract Technology, extract-technology.com



8.4.4 Formulation

Formulation areas can be closed transfer or open operations where powders are transferred into totes, drums, or blending equipment. For open transfer during formulation, the same controls used during dispensing can be effective for control of powders. In all cases, be vigilant in using room air pressure differentials to prevent migration of potent powders to surrounding areas.

8.4.5 Blending

Blending areas can be closed transfer or open short exposure operations. For open transfer during charging or emptying of the bender local extract hoods/ducts should be properly located to capture fugitive emissions. Other techniques to ensure particles are captured are proper room air patterns and mass flow to direct particles down to low level extract points. A typical IBC blending unit shown in Figure 8.6.

Figure 8.6: Typical IBC Blending Unit
Used with permission from Matcon, http://www.matconibc.com/

8.4.6 Washing Area

Wash areas during operation are sources of high humidity with the multiple cleaning operations possible in one area. Operations vary from open washing of vessels and parts to closed parts washers, as shown in Figure 8.7. Open operations offer the most challenge for HVAC designers as humidity must be removed as close to the source as possible. The ductwork design should also include pitching the vapor extraction duct towards the room to allow condensation to drain and not accumulate in the duct or ceiling void. Special duct materials of construction include the use of aluminum and stainless steel to eliminate rust which forms over time on galvanized sheet metal exposed to high humidity or water.

Ultra-sonic baths are typically fitted with a local vapor extraction around the back of the baths to remove humidity and minimize the operator exposure to cleaning chemicals and water vapor.

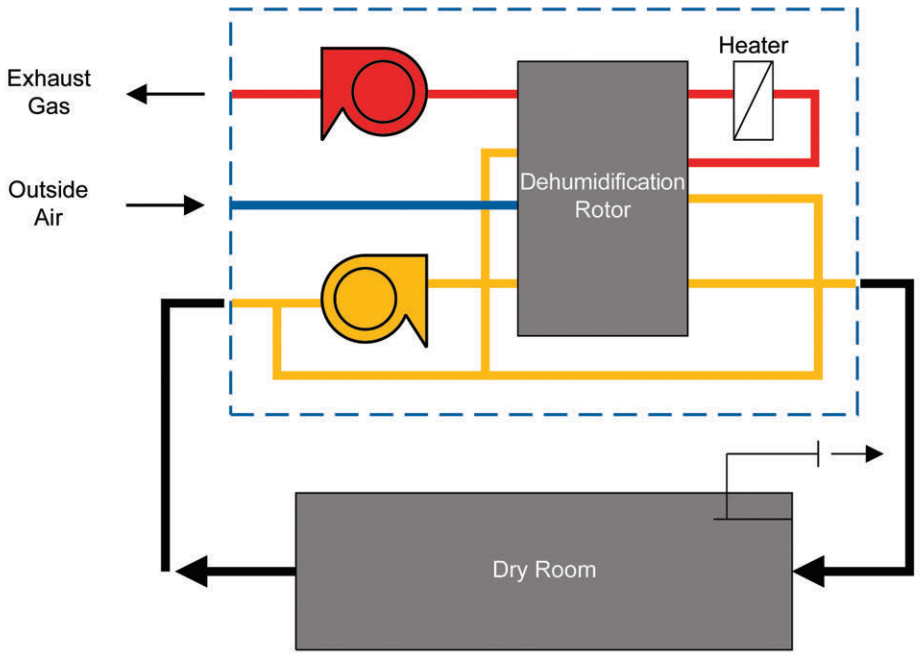
For the closed parts washer below, the designer may consider providing an area of down flow of filtered air at the exit of cleaned parts to help support drying and prevent contamination of cleaned parts.

Figure 8.7: Typical IBC Washer
Used with permission from Matcon, http://www.matconibc.com/

8.4.7 *Drying Rooms*

Clean parts from the wash area need to dry. A drying room on the clean side of the washing area is used to decrease the drying cycle time of parts. The washed parts are exposed to clean dry air. Drying rooms are typically operated between 30°C to 50°C (90°F to 120°F). Dedicated recirculating systems are recommended for this application. Figure 8.8 shows a typical configuration for a dry room HVAC system.

Figure 8.8: Typical Dry Room HVAC Configuration
Used with permission from Taikisha Ltd., http://www.taikisha-group.com/



8.4.8 Drying Units

The final step in chemical synthesis is drying the product (or intermediates). Drying is done by evaporating solvents from solids. Solvents are then condensed for reuse or disposal. The pharmaceutical industry uses several different types of dryers, including tray dryers, rotary dryers, drum or tumble dryers, and pressure filter dryers. Powder emissions during the discharge of the dryer typically represent the highest HVAC risk. LEV, containment, down flow booths, or closed connections, as well as proper room airflow patterns and pressurization, are recommended to control dust emissions.

8.4.9 Tablet Printing

Room temperature and RH may affect printing success. Normal drying environments are generally 18°C to 24°C (65°F to 75°F), and 30% to 65% RH may be required. Another factor impacting dry time is air movement within an area. Direct exposure to heating, air conditioning, and ventilation ducts will accelerate drying of the ink, and may cause premature loss of critical solvents.

8.4.10 Milling

Milling and micronization operations utilize high energy to reduce the size of product powders. This combination of energy and small particle size tends to increase the risk of product dust emissions in these rooms. Containment is an essential element of size reduction processes to control the risk of cross-contamination and operator exposure. One method for the containment of such fine powder during milling, is the use of an isolator or exhausted enclosure to ensure all fugitive material remains contained.

8.4.11 Compaction

Roller compactors are very prevalent in the pharmaceutical industry to increase the bulk density of the material for the final product. The feeder into the top of the roller compactor is typically fitted with local exhaust if the charging area is open to the environment. As with the milling equipment, isolators or enclosures are also used to contain roller compactors with the ever-increasing potency of process material (APIs, etc.).

8.4.12 High and Low Shear Granulation

Low shear wet granulation processes use very simple mixing equipment. High shear wet granulation processes use equipment that mixes the powder and liquid at a very fast rate. Fluid bed granulation is a multiple-step wet granulation process performed in the same vessel to preheat, granulate, and dry the powders. It is used because it allows close control of the granulation process.

The charging of powders typically requires LEV, down flow, or an exhausted enclosure to control emissions. The final granulation is typically less likely to become airborne due to the large particle size and moisture content.

8.4.13 Coating Machines

Automatic coaters are used for all kinds of coatings, both inert and active. These units require internal airflow and are normally equipped with a supply air handler and dust collector. Explosion proof design is required for alcohol containing coatings. The room surrounding the coater may be the source of supply air in smaller coaters, where room conditions should be appropriate for the intended use. The use of solvent based coatings may require LEV and possibly once through air supply to prevent the buildup of solvent vapors. The compressed state of raw tablets typically does not require dust control on charging of tablets into a coater; however, dust control may be required in the case of highly potent compounds.

8.4.14 Compression Machines

Compression machines require a dust collection connection on top of the machine to remove particles generated during feeding and compression of the tablets. These connections are expected to carry more than just fugitive dust and are typically connected to a dust collector. Care should be taken in locating the dust collector connection without interfering with the chutes transferring material from the floor above or the hoist positioning the IBC above the equipment. Local exhaust will be required if the charging area is open. In addition, for highly potent compounds, the tablet discharge may require some LEV as well.

8.4.15 Encapsulation Machines

Encapsulation machines require a dust collection connection on top of machine to remove particles generated during feeding and compression of the tablets. These connections are expected to carry more than just fugitive dust and are typically connected to a dust collector. Care should be taken in locating the dust collector connection without interfering with the chutes transferring material from the floor above or the hoist positioning the IBC above the equipment. Local exhaust will be required if the charging area is open. In addition, for highly potent compounds, the tablet discharge may require some LEV as well.

A capsule deduster is normally connected to the outlet of the encapsulation unit to remove residual product from the outside of the capsule. A dust collection connection may be required at the top of the deduster.

8.4.16 Extrusion

The feeder into the top of the extruder is typically fitted with local exhaust if the charging area is open to the environment. As with milling equipment above, isolators and enclosures are also used to contain extruders with the ever-increasing potency of process material (APIs etc.).

8.4.17 Primary Packaging

Most packaging processes can typically be divided into four main steps: primary, secondary, tertiary packaging and palletizing.

During the primary packaging process, the product is filled into the primary container and closed. The environment in the primary packaging area should be equivalent to that provided during manufacturing. The primary packaging enclosure may be a local enclosure or a dedicated room. In the case of dedicated rooms, access to the primary packaging room should be through pressure managed airlocks. In all cases, primary packaging air pressurization should be managed to minimize contamination and operator exposure.

Primary packaging is usually segregated from secondary packaging for any given packaging line. The conveyor line opening in the division between primary and secondary packaging, offers additional pressurization challenges to the designer. It is desirable to have positive airflow through this conveyor opening to prevent product contamination. An exhausted or air supplied enclosure can help control contamination and manage potent compounds.

8.4.18 Secondary and Tertiary Packaging and Palletizing

Secondary packaging starts directly after the product is isolated from the environment and ends where the patient or commercial specific package is complete. In the tertiary packaging step the product is prepared for logistics and distribution. The palletizing action concludes the packaging process.

Packaging lines are typically noisy and as a result are specified with enclosures around their motors. These motor enclosures may require venting to remove heat.

8.5 Room Design

In a facility where multiple products are exposed, a primary/secondary system using a central outside air conditioning unit with dedicated secondary recirculating air handling systems with individual duct systems may be more practical and cost effective than filtering return air to a central unit or the use of once-through air. The requirements for filtration of supply air depend upon the desired level of protection (see Chapter 6 of this Guide). As a minimum, the supply air should be filtered to meet ASHRAE Standard 62.1 [73].

8.5.1 Level 1 Protection Area

Product does not need specific filtration requirements. Air filtration should be provided to protect the coils within the AHU, the occupants, and to facilitate housekeeping. A minimum of Minimum Efficiency Reporting Value (MERV) of 6 or 7 is suggested, with MERV 11 final stage filtration recommended. See EN 779 [42] and EN 1822 [43] for EU equivalents. Higher filtration may be required to accommodate natural airborne materials such as pollen, coal dust, or quarry dust.

8.5.2 Level 2 and Level 3 Protection Areas

A minimum of MERV 13 is suggested with MERV 14/15 recommended. If air is being recirculated to the HVAC system, in a multi-product plant a 99.97% or H-13 (EN 1822 [43]) HEPA filter in either the supply or return air duct system will normally provide adequate protection against cross contamination between exposed low potency products and materials. A single HEPA filter should provide between 5 and 6log reduction in airborne cross-contaminant mass.

If the HEPA filter is critical to deterring cross contamination, or if a failure of the primary HEPA filter would jeopardize product integrity, a backup HEPA filter should be considered. A double HEPA filter installation (one on supply, one on return or both in series in supply) should provide between 10 and 11 log reduction in airborne cross-contaminant mass. Even with one HEPA failed to only 90% efficiency, mass reduction should be over 7 log.

If the HEPA filter is critical to deterring cross contamination, it must be checked periodically (per regulation). It should be noted that HEPA filtration is not considered adequate to suppress vapors or hazardous gases. If HEPA filters are utilized in the supply air system, periodic testing is recommended to confirm proper installation and performance. Testing of total filter efficiency is recommended and scan testing of the entire face of the filter, while acceptable, is not generally required.

8.6 Monitoring and Control

Regular monitoring of critical points should record and indicate when critical parameters exceed operational limits. Instrumentation should be provided to monitor cGMP critical room parameters and alarms. It is recommended to monitor, record, and/or alarm with instrumentation, which is not part of the HVAC control system. Alert limits can indicate when a monitored parameter is beginning to drift out of control, prior to an action alarm. It is also considered good practice to monitor the performance of equipment, such as fans and coils and control components via a non-cGMP validated BAS.

Instruments for critical room parameters should be part of the qualification, ongoing validation, and change control program. Qualification plans should address sensors, alarms, and recording systems for critical parameters.

Control devices have an accuracy range which can affect the design tolerance. Care should be taken to ensure that sensors and monitors fall within the level of operating tolerance required for the space. Sensors, transmitters, indicators, records, and alarms, etc., used for monitoring critical parameters should be periodically calibrated to National Institute of Standards and Technology (NIST) standards [x]. The location of controls and sensors should be carefully considered to allow access for regular maintenance and calibration.

Building Management Systems (BMS) and EMS are used to control HVAC and utility generation within OSD and other GMP manufacturing facilities. Not included in this Section are how BMS systems integrate with access control, security, fire alarm, Closed Circuit Television (CCTV), and process automation and MES.

8.6.1 Alarm and Event Reporting

Alarms will warn of pending, actual, and continued deviations from process limits and improve safety. Events provide indication that a process step or condition has been achieved as well as operator interventions. Alarm annunciation and reporting may take several forms depending on the purpose and priority of alarms (e.g., screen alarms, email, pagers, printouts, etc.). For further information, see ANSI/ISA-18.2-2009 Standard [87].

8.7 Implementation

This section outlines configurations and other implementation choices and their impact on OSD forms manufacturing facilities.

8.7.1 Single versus Multi-Product

Understanding the current and future non-sterile manufacturing operation is critical to the design of the HVAC system. Where systems serve dedicated single product manufacturing suites, the risk of cross contamination is greatly reduced. Where products are in a dry form and exposed to room air without barriers or capture, they can become airborne and migrate by air, personnel or common transport devices to other product areas. Multi-product suites may also include multi-purpose rooms where process operations will vary from product to product.

An effective means of segregation is a separate air system for each product manufacturing operation. In this system design, directional airflow and pressurization schemes must still consider the different process operations to avoid cross-contamination of product at different stages in the manufacturing process and to contain dust generated by each operation. For systems serving multiple product manufacturing rooms, non-recirculating systems or once through systems can reduce risk of cross-contamination. However, filtration is also an effective means of reducing cross-contamination where once through systems are not required for ventilation. In most systems, the amount of outside air should be based on ventilation requirements driven by operators, process, type, and quantity of compounds or chemical exposure, makeup air for equipment of local exhaust ventilation, or pressurization in lieu of perceived risk mitigation.

HVAC systems serving manufacturing areas serving multi-product manufacturing areas should also be provided with means to prevent cross-contamination of different products through common ductwork. System designs should consider cross-contamination potential under normal operation and failure scenarios. Non-recirculating system designs do not completely remove the risk of cross contamination as certain failure conditions could result in reversal of airflow between room exhaust inlets.

8.7.2 Potent and Toxic Material System Considerations

Facilities that handle potent or toxic materials such as cytotoxic, mutagenic, and highly sensitizing, genotoxic or teratogenic materials require additional containment provisions to protect the personnel as well as the environment, and product from exposure and cross contamination.

If at all possible, primary containment should be provided at the unit operation level. However, some equipment is not capable of this containment philosophy. In these cases, a local exhaust ventilation design that effectively contains these materials is critical.

Since the room will provide secondary containment, airlocks with differential pressures cascading from outside the suite through the airlock are recommended to provide additional physical barriers and secondary containment of product. Due to increased PPE requirements, atypical temperature and humidity requirements may be in order. A

thorough understanding of the standard operating procedures for personnel, material, and waste flow is required. Containment of airborne transfer of particulate is paramount in pressurization schemes for all rooms in the suite including gowning and de-gowning spaces.

Filters are recommended in exhaust systems serving these products, to protect maintenance personnel and the environment. If filters are changed from outside the room, safe change (Bag-In/Bag-Out (BI/BO)) enclosures are strongly recommended. Due to the concentration of fugitive emissions onto the filter face over continuous exposure, BI/BO should be evaluated for all exhaust filters serving these areas. This includes dust collection systems serving spaces handling these compounds.

Terminal HEPA filters at the room level on the supply and exhaust air systems will protect the ductwork systems serving these rooms from hazardous dust. Once through systems are also common in this application due to the increased risk associated with recirculation; however, they are not required.

8.7.3 Flammable Vapor Issues

Solvent based manufacturing may present a hazard to the building and occupants. Building and Zoning Codes, NFPA, and insurer's requirements may affect HVAC system configuration, components, and size.

Airflow rates in areas where solvent vapors are present should be based on dilution requirements to maintain the OSHA Permissible Exposure Limit [88], ACGIH® Threshold Limit Value (TLV), applicable building codes or as required to maintain 25% of the Lower Explosive Limit (LEL) during normal operations. As a minimum, mechanical ventilation should ensure one Cubic Feet per Minute (CFM) of exhaust per square foot (approximately 18 m3/hr/m2) as required by NFPA 30 [89] and ASHRAE standards [69].

Often, when dilution ventilation is used to control flammable vapors, the TLV for the material drives the dilution air volume, not the LEL.

Recirculation of flammable vapors, as well as hybrid mixtures (the mixture of flammable vapors below the LEL with dust) is often allowed by code (with appropriate LEL detection) but is not recommended. Areas where flammable materials are stored or dispensed should usually be served by once through air systems. Local exhaust ventilation is recommended at points of flammable material exposure.

Consideration of increased ventilation during a spill (purge mode) is recommended. Depending on the value of the product in these rooms, HVAC systems may be oversized to handle this emergency situation but this is atypical.

Building electrical hazard classification and effective system and equipment grounding should be applied to HVAC components and instrumentation in accordance with national and local codes and standards.

Refer to local fire codes for additional monitoring, instrumentation, and system design provisions.

Positive ventilation of airlocks may be required to meet code expectations for separation of electrical classifications. Consult with the electrical engineer to verify.

8.7.4 Combustible Dusts Considerations

Combustible dusts are defined by NFPA 68 [29] as a finely divided solid, 420 µm or less in diameter that presents a fire or explosion hazard when ignited. Many OSD operations have dust that has the potential of being combustible. Combustible dust, when combined with oxygen and an ignition source, has the potential to deflagrate. In the US, OSHA has issued a National Emphasis Program (NEP) for combustible dust due to the number of dust fires and explosions. In addition to a housekeeping review, the program focuses on prevention of dust cloud deflagrations and explosions. In order to assess the risk potential for the likelihood of a dust explosion occurring, the following steps should be completed:

- Characterize the fire and explosion properties of the dust
- Determine the likelihood that a dust cloud with the properties and conditions to propagate a flame may form
- Determine whether adequate sources of ignition exist
- Identify the types and tasks of operations involved
- Review the frequency and duration of the tasks

Since dust collection systems in OSD manufacturing facilities have the potential for deflagration as sufficient fuel (dust at collector), oxygen, and ignition (potential electrostatic discharge), or other sources of ignition are all present at the collector. Therefore, it is critical that the duct conveying velocity is such to prevent dust from accumulating within the ductwork, a path to ground for electrostatic energy is provided via grounding straps, proper deflagration venting or suppression systems are provided at the dust collector, isolation is provided at the dust collector to prevent flame propagation back into the facility. For these reasons dust collectors. For further information, see NFPA 68 [29], 69 [30], 92 [90], and 654 [28].

8.7.5 Room Distribution and Containment Strategies

Room distribution should be arranged to minimize dust and to protect the operators, and product by flushing the operator and process zones with a clean supply air from the ceiling and return or exhaust airflow should be installed low in the room away from the operators and equipment. The primary containment of dust should be at the source (equipment). Local exhaust ventilation and isolation technology can reduce HVAC requirements significantly over general room ventilation strategies and improve product and process quality, but may place operating and cleaning burdens on the facility user. Containment of dust is paramount as the OEL of the compounds utilized decreases.

Non-aspirating supply air devices are recommended as induction type supply diffusers by design induce room air due to the coanda effect of these types of air outlets. Perforated screen type diffusers, such as unidirectional flow diffusers and terminal HEPA diffusers, offer non-aspirating flow.

Room return or exhaust registers need to be placed to prevent water from being drawn through them during cleaning or wash down periods and should be constructed of materials that tolerate frequent moisture and cleaning. Return or exhaust ductwork should be sized to allow dust particles to remain in the vertical ductwork that can be cleaned to avoid cross contamination by conveying dust beyond the local environment. Removable cores are recommended for return/exhaust grilles to allow cleaning of vertical ductwork in the vicinity of the low return grilles.

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. Supply diffusers, registers, and grilles should be selected to provide the required airflow characteristics noted above. Devices should be selected to minimize both sound transmission and noise generation, due to the airflow through the ductwork or from the air-handling equipment.

8.7.6 Energy Conservation and Life Cycle Costs

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 life cycle cost. Life cycle costs typically are an order of magnitude greater than the initial capital cost. Many HVAC system designs are overly risk adverse resulting in excessive life cycle costs. In addition, the impact of these systems to the carbon footprint of the Facility Owner can be reduced without increasing the risk to protect and personnel protection. Risks and benefit factors to be considered in a life cycle cost analysis include:

- Local exhaust ventilation and isolation technology to reduce room airflow requirements
- Utilization of recirculating systems with means to prevent cross-contamination in lieu of once-through systems.

- Maximizing the design, alert and alarm temperature, and relative humidity ranges to what is required for the product and personnel comfort.

- Intelligent building automation system algorithms that provide dynamic airflow conditions to meet the required room environment based on the current conditions. For example, supply air dew point control and reset, static pressure reset, chilled water optimization, boiler plant optimization, etc.

- Combined Heating and Power (CHP) is often attractive, especially where there are incentive programs available due to the relatively typical year round heating requirements of OSD manufacturing facilities.

- Condensing boilers for hot water reheat systems that utilize low temperature hot water and can leverage heat recovery of low grade heat from air compressors, etc.

- Heat recovery methods should be considered for improved energy efficiency for once-through systems. Appropriate heat recovery methods for OSD forms manufacturing facilities include installation of heat pipes, run around loops and plate heat exchangers. Careful consideration should be made when selecting these systems to determine if the added cost of the heat recovery system (materials, maintenance, and increase in fan energy due to the added pressure drop through the heat recovery device) is offset by the energy recovered. Maintenance of these systems may be a problem if exhaust is conveying hazardous materials.

- Filter life cycle cost analysis and optimization considering the material and labor cost of each type of filter and change out strategies.

- Consideration of a facility's life expectancy and future flexibility for usage and expansion should be considered. HVAC system components sized for future needs but operating at reduced capacity may be incapable of providing adequate temperature or humidity control at reduced load.

9 Electrical

9.1 Introduction

From the electrical perspective, issues that should be addressed in an OSD forms manufacturing facility include:

- Cleanability of exposed electrical equipment
- Flush lighting should be used wherever possible
- Conduits and raceways should be hidden (not exposed) in production areas

The cleanability of exposed electrical equipment is the primary concern for electrical systems in an OSD forms manufacturing facility, although the degree may differ based upon the level of protection required.

Electrical power distribution systems are not considered critical systems and are not subject to regulatory oversight and validation requirements, as they do not directly affect the quality of OSD pharmaceutical product. The equipment which produces and controls the pharmaceutical processes, and provides clean and controlled environments for the manufacturing areas for OSD pharmaceutical drugs, requires a source of electric power and an electrical power distribution system that are reliable and maintainable.

A properly designed electrical distribution system should provide reliable electricity to OSD pharmaceutical equipment. This Guide provides design and maintenance criteria to assist in the proper design of an electrical system that is intended to provide a reliable electrical service.

9.2 Power Distribution Overview

9.2.1 General

The electrical power circuits for OSD pharmaceutical equipment should adequately deliver electrical power at the equipment's utilization voltage. The equipment utilization voltage should be specified based on the typical electrical power where the OSD pharmaceutical facility is located. It will normally be low voltage, 480/277Volt or 120/208Volt 3 Phase 60HZ in the US, 230/400Volt 3 Phase 50 Hz in Europe. Other countries will have different voltages and frequencies. Larger loads, typically above 200HP in the US or 500kW in Europe, may be serviced with higher voltages.

When a power distribution system is properly designed, its integral over current and overload protection equipment should provide selectivity. Selectivity is defined as:

> *"A general term describing the interrelated performance of relays and breakers, and other protective devices; complete selectivity being obtained when a minimum amount of equipment is removed from service for isolation of a fault or other abnormality."* [91]

When complete selectivity exists, only the faulted or overloaded portion of an electrical distribution system will be disconnected, allowing the remaining portions of the electrical system to continue to operate properly. The term selectivity also can refer to a system's ability to transfer to an alternate power source when power is lost from the normal source.

For critical instruments, controllers, and systems, an Uninterruptible Power Supply (UPS) may be required under economic aspects.

9.2.1.1 *Normal Power Sources*

Normal electrical power is the electricity that is normally available at the process and environmental equipment within an OSD pharmaceutical facility. It is delivered to the equipment through the facility's normal electrical power distribution system. Normal power is the source that is relied on to provide electrical energy. In most cases, it is the local utility. The electrical service is the equipment that connects the utility to the facility electrical distribution system.

9.2.1.2 *Emergency Power Sources*

Emergency electrical power should be provided, where required, to meet statutes and to reduce economic loss caused by an interruption in normal service.

The power distribution system circuits that carry emergency power for life and fire safety systems should be reliable. Understanding the emergency power requirements for all equipment loads, and providing a reliable emergency source and distribution system for each, is an important step in the design of electrical power systems for an OSD forms manufacturing facility.

Multiple sources of power, such as an alternative utility source and an onsite engine generator set source, can collectively provide normal power to the OSD forms manufacturing facility when connected to its radial distribution system. When evaluating onsite generation, consideration should be given to whether the generator will ever need to be on line at the same time as utility power. If this is the case, synchronization equipment will be needed. The engine portion of the generator can be diesel, natural gas, propane, or gasoline. Onsite fuel supplies, typically diesel or propane, may be required when the engine generator set is used for legally required emergency loads.

Environmental regulations (e.g., water pollution control) may impact the choice of fuel and/or engine set selection.

9.2.1.3 *Reliability*

Reliable electrical power systems deliver continuous electricity to the loads at their utilization voltage. When designing an electrical power distribution system for an OSD forms manufacturing facility, each load should be evaluated to determine its relative need for reliable power, as compared to other loads within the facility. The fewer electrical circuits and electrical components between the power sources and the load, the more reliable the power system is for the load. This can be determined by reviewing the One Line Diagram.

Accurate drawings can be helpful in evaluating electrical distribution reliability and providing cost effective maintenance of a system.

Other considerations that should be evaluated when designing a reliable power distribution system for a particular load include:

- Providing alternative and emergency sources of power
- Primary and secondary selectivity within the power distribution system
- Proper application and settings of ground fault protection
- Elimination of the potential for circulating currents within the grounding system

9.3 Electrical Equipment Located in Hazardous Areas

Hazardous areas, in relation to electrical installations, are defined as locations where potentially explosive/flammable atmospheres may exist, e.g., locations where the following are present, processed, handled, and/or stored:

- Flammable gases

- Liquids
- Mists
- Combustible dusts/fibers/particles

A Hazardous Area Classification identifies locations where potentially explosive/flammable atmospheres may exist. This analysis considers the:

- Methods of containment
- Ventilation to the area
- Properties of the flammable/combustible materials
- Methods of handling, storing, and transportation

The Hazardous Area Classification groups the locations into Divisions or Zones depending upon the level of hazard.

Levels of hazard may be defined by various fire codes, directives, and standards, e.g.:

- NFPA 70: National Electrical Code® (NEC®) [31]
- EU ATEX Directive 99/92/EC (also known as ATEX 137) [27]
- IEC 60079-10 [92]

In the US, two Hazardous Area Classifications systems may be used to define the levels of hazard:

1. NFPA 70: National Electrical Code® (NEC®) Article 500 which defines Divisions [31]
2. NFPA 70: National Electrical Code® (NEC®) Article 505 which defines Zones [31]

Other regions have adopted the Hazardous Area Classification system defined in IEC 60079-10 [92], which defines Zones.

An initial Hazardous Area Classification should be performed early in the design phase to allow the specification of long lead equipment and to facilitate design changes before the design is fixed. A further formal Hazardous Area Classification is usually required. Consideration should be given to locating equipment outside of defined Hazardous Areas, if feasible, due to the additional cost/complications of suitably rated equipment. Criteria should be established before executing the work for new and renovated facility projects. See Figure 9.1 which depicts a flowchart of the decision making process.

Electrical equipment should be suitable for the defined Hazardous Area in which it will be installed, in accordance with the relevant codes/standards. Defined Hazardous Areas have a Zone/Division, Class (US) and Group information. Suitable rated equipment should follow defined protection concepts, such as explosion proof, intrinsically safe, increased safety. Consideration should be given to the selection of protection concepts during the design phase and should be based on life cycle cost and operational impact. Low energy circuits that are frequently used for instrumentation may use intrinsically safe circuits.

Electrical equipment should be installed appropriately in accordance with the relevant codes/standards and may need to be inspected before it is put into service.

Figure 9.1: Area Classification Process Flowchart Example

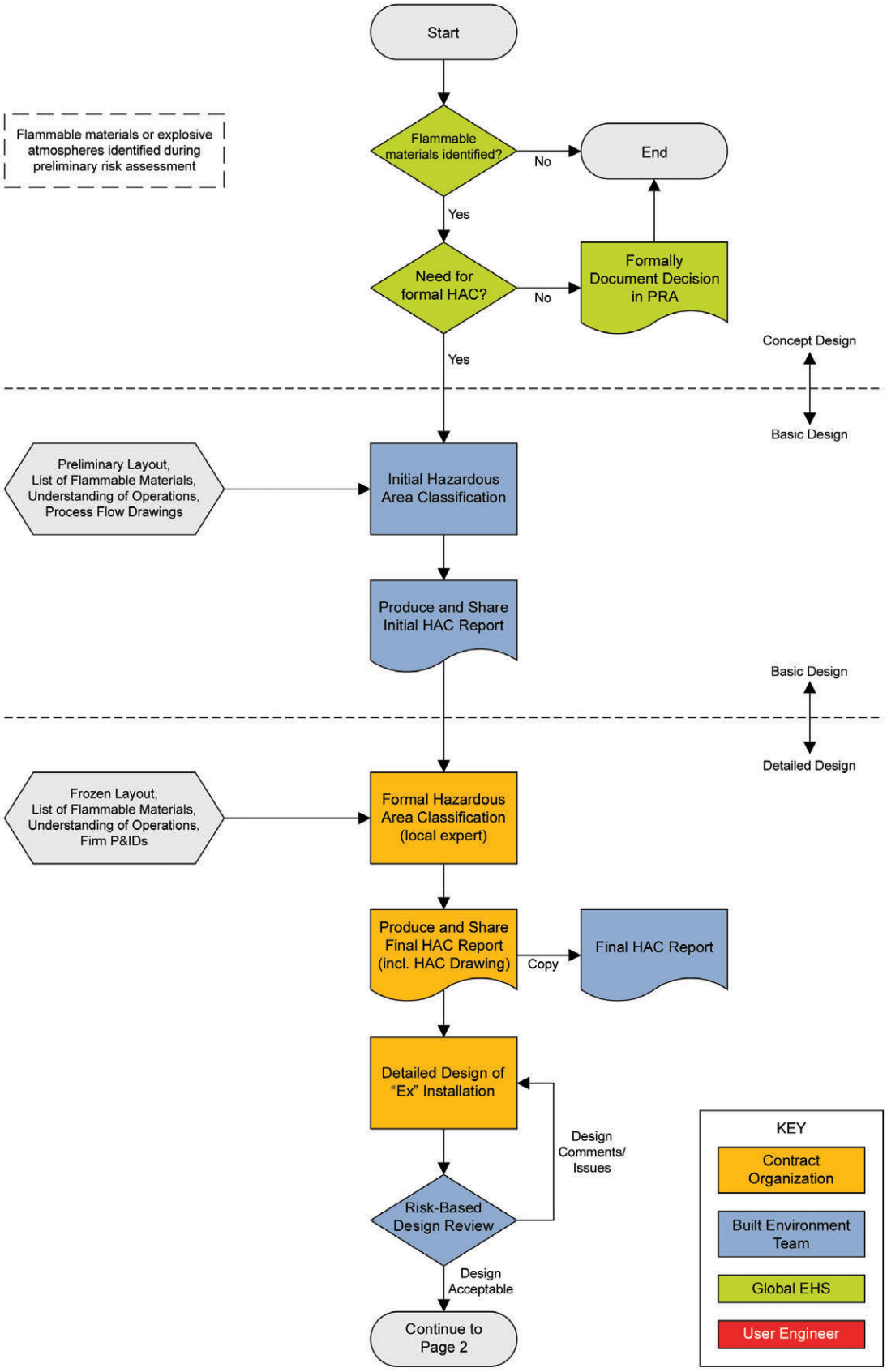
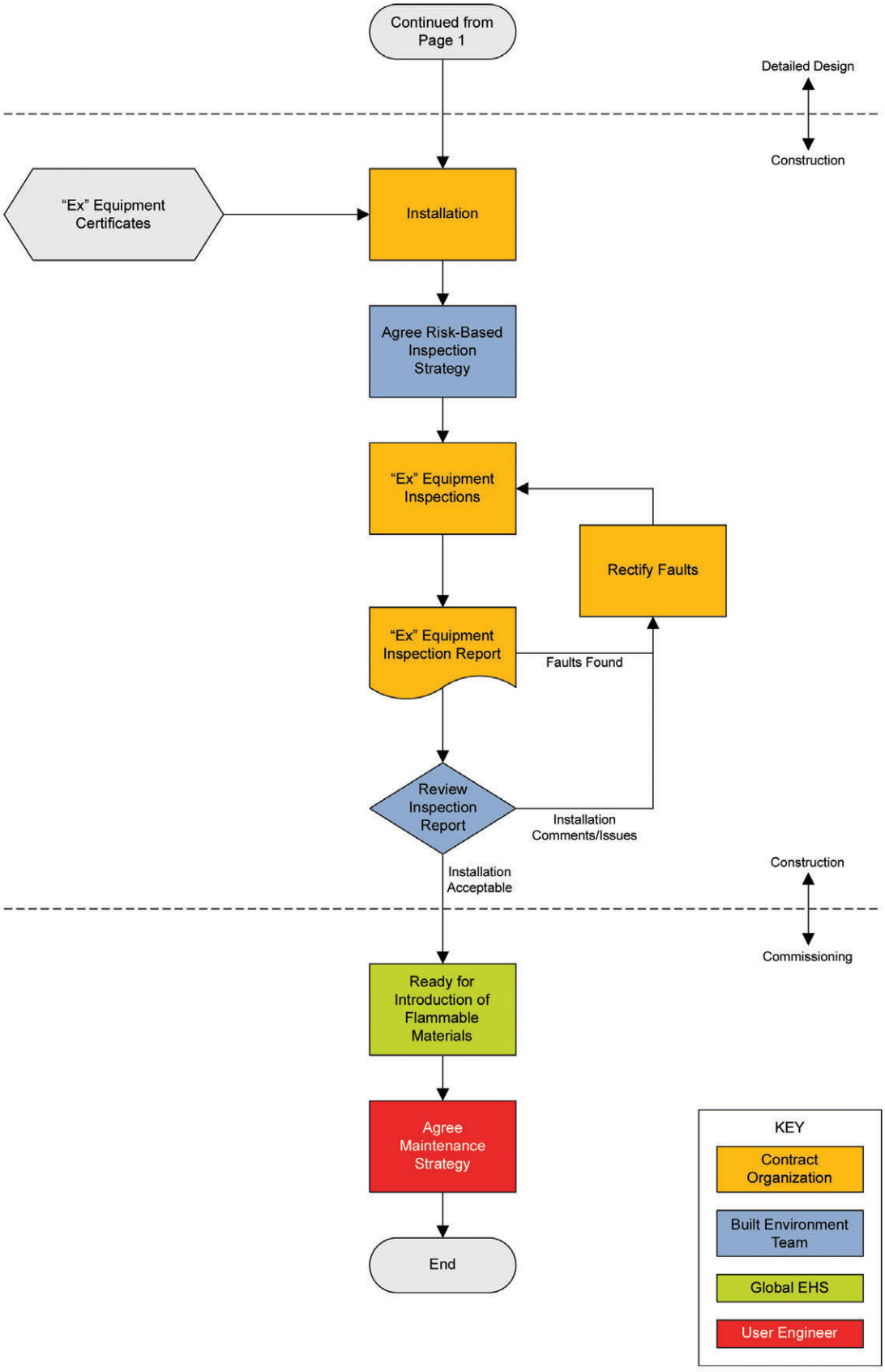


Figure 9.1: Area Classification Process Flowchart Example (continued)



9.4 Identification and Labeling

Electrical components should have a permanent and durable identification tag that corresponds exactly with the components designation on the One Line Diagram.

Electrical circuits must be labeled and/or color coded in accordance with the local wiring code/standards.

Electrical outlets should have a permanent and durable identification tag designating their power, overcurrent and disconnecting device, and their location (panel board or switchboard).

Electric motors, or their local disconnecting means and/or controller, should have a permanent and durable identification tag designating their power overcurrent and disconnecting device and their location (panel board, switchboard, or motor control center).

9.5 Lighting

The lighting design should consider the quality of the light (e.g., lighting levels, glare, color rendering) required to support an activity within a given space, and the total lifetime cost, including energy consumed and maintenance costs. Long life lighting technologies (such as LED luminaires) can reduce energy consumption and reduce the need for maintenance activity within clean environments. Design consideration should be given to safe maintenance access (such as changing of lamps) and GMP risk for maintenance activities (such as risk of fluorescent tube breakage). For a more detailed discussion of lighting requirements based on the chemistry of drug substances, see ICH Q7 [93].

9.6 Wiring Methods

9.6.1 Equipment

Conductors and their raceways should comply with all local and national codes where the OSD forms manufacturing facility is constructed and designed, based on the guidelines (described in Section 9.9. In the US, conductors should have the capacity to carry 125% of their continuous load and should be protected by both overcurrent (short circuit) and overload protection. In Europe, conductors should be designed to stand overload and short circuit according to the protectors used.

Low voltage circuit breakers, which include Molded Case Circuit Breakers (MCCB) and Low Voltage Power Circuit Breakers (LVPCB) are equipped with either bimetallic or electronic trip devices that in the case of MCCBs may or may not be adjustable. Instantaneous circuit breakers, also known as motor circuit protectors, can be used only for motor branch circuit protection when an integral part of a motor controller with overload protection.

9.6.2 Surge Protection

This type of protection should be provided at the secondary of each substation transformer and again at downstream distribution panels that service sensitive equipment.

9.6.3 Equipment

For systems where communications cables link components together, surge suppression should be considered for these cables.

Motors may have solid state overload protection with ground fault and single phase protection or conventional bimetallic overloads. The current setting of the overload device should be based on the applicable electrical code, such as the NEC® in the US [31]. It can be higher for motors having a 1.15 service factor and can have longer time delays when required for starting. Class 20 overloads have a longer time delay than Class 10 overloads and Class 30 overloads, typically used for high inertia motors, has a longer time delay than Class 20 overloads. In Europe, low voltage motors are standardized and have different temperature classes, which should be accounted for in the layout of the electrical supply.

9.6.4 Considerations

Electrical codes may require ground fault protection on low voltage systems that have high available short circuit fault currents because of the damage caused by ground faults. Ground fault protection devices may not coordinate with load side circuit breakers or fuses. This makes complete selectivity impossible and the selection of a circuit protection device will affect the selection of ground fault devices.

9.7 Motors and Drives

9.7.1 Motors

The use of high efficiency motors will only be beneficial when the load on the motor is 60% or more of its nameplate. High efficiency motors tend to become more appealing due to increasing energy prices.

The motor housing should be selected based on knowledge of the environment in which it will be placed, e.g., hose down location and corrosive location.

If a motor is to be used with a variable frequency drive, it should be specified when purchasing the motor. These motors will tolerate the elevated voltage levels that may be seen at the motor terminals due to standing waves from reflection of energy at the motor terminals. These motors also will tolerate the harmonic distortion that can be present.

9.7.2 Variable Frequency Drives

Variable frequency drives should be used only where the application requires the speed to vary in response to a process condition. If the motor will run at fixed speed, it is not cost effective to use a variable frequency drive. Consideration should be given to the distance between the motor and the drive when using a VFD. The drive output can cause standing waves to form on the motor feeder, due to impedance mismatches at the terminations. The level of voltage can be high, depending on the distance between motor and drive.

9.7.3 Motor/Drive Package

The total process situation should be examined when considering a variable speed application. A cost analysis should be performed to assure the application warrants the additional expenditure on motor and drive.

9.8 Grounding

There are two types of electrical grounds:

1. System grounds: connect the neutral or common of a grounded power system to earth

2. Equipment grounds: include metal raceways and copper conductor that are bonded together at many points within a power distribution system and serve as a path for return ground fault currents

When designing the grounding means for portable equipment, cleanability should be considered in the selection of the method used to make the ground connection.

9.9 Preventive Maintenance

9.9.1 Considerations

Electrical circuits and components should be inspected on a periodic basis and should have an annual preventive maintenance procedure. In Europe, the periodic inspection is defined by local regulations and does not generally require annual activities. The use of thermal scans can help identify faults early.

A record and the cause of the tripping of circuit breakers should be maintained. In Europe, this is required for high power circuit breakers only.

9.9.2 Cleanability

All devices should be listed and installed in accordance with the requirements of the listing. Consideration should be given to the surface temperature, cleanability, and electrical classification of the device.

All devices used in Level 2 and Level 3 product protection areas should be able to withstand the pressure and temperature of any water streams used for wash down. For instance, this may require a glass lens in place of a plastic one.

Devices used in a Level 2 product protection area should be located so that dust that may accumulate on the fixture will not be able to fall into exposed product if it becomes dislodged from the device.

Devices used in a Level 3 product protection area should be designed and installed to prevent the accumulation of dust or other materials. For lighting applications, a recessed fixtures or surface fixture with a teardrop shape may be beneficial.

10 Control and Instrumentation

10.1 Introduction

This chapter considers Control and Instrumentation (C&I) Systems for OSD manufacturing facilities and focuses on:

- Those facility and environment controls which affect patient safety and product quality
- The major topics that drive decisions regarding the design and set-up of process control systems

This chapter aims to provide design guidance, which results in cost effective system designs, capable of being qualified.

Process control systems are used in nearly all facilities. Control platforms may be deemed to affect patient safety and product quality if they control, monitor or record a CPP, or directly affect a CQA. Instrumentation also may be considered critical if it comes into direct physical contact with the product.

The functions described in this chapter may be combined within a single system or be performed by several independent systems.

Different operational preferences and priorities can influence both a preferred solution. Relevant design criteria which should be considered include:

- Safety
- Reliability
- Maintenance

Process control systems encompass a wide variety of systems, e.g.:

- Programmable Logic Controllers (PLCs)
- Supervisory Control and Data Acquisition Systems (SCADAs)
- Distributed Control Systems (DCSs)
- Manufacturing Execution Systems (MESs)

For further information, see the *GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems* [94].

Validation strategies should be based on a defined risk-based approach. Testing strategies should be based on a predefined estimate of the level of risk, and provide traceability and information allowing critical parameters to be determined.

10.2 Process Instrumentation

The appropriate level of automation and information required for a process should be defined before instrument design is considered. The level of instrumentation should be determined by the type of process. Processes can vary from an entirely manual operation to a fully automated process based on a downloaded recipe. A fully automated system is likely to require more instrumentation than a manual operation.

The control system platform and signal technology should also be defined as these can influence the type of instrumentation selected (e.g., DeviceNet™) which is typically used with a PLC rather than a DCS. Where a specific instrument is not available in the chosen bus technology, a different instrument may need to be considered.

The level of qualification for an automated system should be specified. For further information on design and qualification of an automated system, see *GAMP® 5* [95].

10.2.1 Instrument Selection

They type of signal technology should be defined for instruments prior to selection. Instrument types include:

- Transmitters
- Valves, including:
  - on/off valves
  - control valves
- Scales
- VFDs

Accuracy and reproducibility of the instrument should match or exceed the requirements of the process to be controlled.

The level of competence of selected suppliers should be appropriately assessed. This assessment should be tailored depending on the type of supplier, and on the risk, complexity, and novelty of the Process Control System that is being assessed.

The area electrical classification can influence both the type and location of instrumentation; considerations include:

- The process operation (e.g., whether operators need to see a local indicator)
- The area electrical classification

Instrumentation should be suitable for the operation in the area electrical (and environmental) classification.

The proposed location of an instrument can also determine the selection of the instrument housing. If the location is an electrically classified area, the housing should meet NEC® [31] requirements for that classification. If the instrument is to be located in a “clean” environment, the cleanability of the instrument and its ability to handle frequent wash down should be considered. The housing should also be compatible with the cleaning agents that will be used in the room or area.

Instrumentation process connections and wetted surface finishes should meet the requirements of piping specifications. Fluid service contact materials of construction for instrumentation should be compatible with, and appropriate for, the system on which a unit is installed. Wetted parts of instruments in contact with product fluids should be either 316L Stainless Steel with a final finish that conforms to the applicable piping specification or a polymer such as USP Class VI PTFE or EPDM. O-rings, seals, etc., in contact with product fluids should be made of USP Class VI platinum-cured silicone or peroxide-cured Ethylene Propylene Diene Monomer (EPDM).

The pressure rating of the exposed element should exceed the maximum operating pressure of the system on which it is installed.

In sanitary applications, sensors should be of sanitary design with minimum dead legs and crevices. In-line sensors and control elements should be designed and installed such that an instrument completely drains when not in service.

10.2.2 Reliability

Reliability can be affected by the:

- Process environment
- Maintenance procedures

The precision and accuracy of measurement values provided by sensors should be considered. Duplicate sensors may be used for CPPs.

10.2.3 Design

Instrument design should consider the intended use of instrumentation in a process, along with calibration and maintenance requirements, e.g.:

- Instrumentation that will be removed regularly should be installed with a conduit union or other comparable fitting to facilitate removal
- Where operators need to see a local indicator, instrumentation should be located so that operators have an unobstructed view from normal operating positions

Gowning and de-gowning of maintenance personnel can add significant complications to routine calibration and maintenance requirements.

Where possible, transmitters should be mounted locally to a sensor to minimize the length of uncompensated signal cable. Mounting of transmitters should facilitate frequent operator access for calibration and maintenance. Sufficient cable length should be provided for sensors to allow for removal of devices to a common, floor level location for calibration purposes. Transmitters should be capable of withstanding process temperatures, either inherently or via the mounting configuration.

The amount of exposed conduit and wire should be limited in “clean” environments.

Piping should not be used to support instruments unless specifically indicated as such. The only exception to this is inline components. Hand rails should not be used to support instruments or equipment.

10.3 General Process Control Information

Process control systems control processes either directly or through operator intervention. Process control elements include:

- Collecting data from devices and operators
- Process monitoring
- Recording/archiving of data
- Data mining and analysis

Processes can be controlled either manually or automatically.; however, for OSD facilities 'manual control' generally refers to operators setting values. Automatic control can range from traditional P&ID control of set values to advanced process control involving SCADA and recipe control.

Control Platform

Unit procedures or skids within OSD forms manufacturing facilities usually have their own control platforms designed and configured by the supplier. Control platforms can include local instruments, PLCs, and operator interfaces. The control and data collection is limited to the local application.

SCADA Systems are usually used to capture data at a facility level. SCADA systems control local unit procedure PLCs and collect data from remote PLCs for retention to a common historian. Using SCADA systems, process control can be closely integrated at a batch level and recipe applications are more common.

A historian can provide full historical trending capabilities. The trending on a local controller is limited in memory where as a historian is designed to retain the process data to meet compliance requirements. The data can either remain on the server or be archived for long term storage.

Recipe Design

A phase is a group of shared actions performed to complete a specific task. The grouping of phases to complete a batch is called a recipe. A recipe may include product specific CPPs. An automated process is usually programmed by phases.

Recipe structures are usually based on the ISA S-88 Standard [96]. The ISA S-88 Standard prescribes that the manufacturing recipe should include the following structure:

- Recipe (also named procedure)
- Sequence of operations
- Operation
- Phase
- Equipment module 3
- Control module 4 (sensor, actuator level)

The role of this hierarchy is emphasized where several batch runs are likely to be operated simultaneously in an equivalent environment.

10.3.1 Critical Control Parameter

A critical control parameter is a parameter that is known to have a direct effect on product quality. The parameters should be controlled and process values captured and recorded. Critical control parameters should be provided with an identification tag and is documented on the P&IDs. An acceptable operating range and alarm limits should be set for each parameter, to notify operators when the acceptable process range tolerance is about to be exceeded, or if has been exceeded. Where a critical control parameter is phase specific, the acceptable operating conditions should be based only on that specific phase.

Alarms and Deviation Handling

Four common alarm settings are:

1. Low-low (i.e., process has exceeded the acceptable process range)
2. Low (i.e., parameter is approaching an out of range value)
3. High (i.e., parameter is approaching an out of range value)
4. High-high (i.e., process has exceeded the acceptable process range)

If the parameter has exceeded the acceptable process range, an exception may result in order to capture the abnormal processing.

Alarm types are either permanent or phase dependent:

- Permanent alarms are always active and do not depend upon the current recipe or phase under execution. These include status alarms, which are independent of batch critical parameters
- Phase dependent alarm triggers should be activated on phase start and then de-activated on phase completion. This includes process alarms, which are dependent on critical process variables

10.3.2 User Access Security

User access security and control of users is required in a pharmaceutical manufacturing facility. The security platform is usually based on roles and responsibilities. The authorization level of users (e.g., administrator, operator, maintenance, and read only access) can be used to define the actions and/or changes a person can make based on the defined level.

Specific user IDs are usually assigned to each operator. A unique user account enables the use of electronic signatures, etc., throughout an audit trail. User authentication can be integrated with domain or controlled locally.

10.4 General Environmental Control Information

The environment of the manufacturing facility should be controlled. Environment controls include humidity, pressure, and temperature, although other parameters may be necessary for a specific process or room occupancy. These would typically include:

- Airlock airflow control
- Airflow volume and direction
- Particle counters

- CO_2
- Leak detection

These parameters are usually set by the design criteria used for the specific operations performed in the specific space. They may, however, be adjusted by an operator with the appropriate access level.

The field devices controlling and monitoring these parameters or “points” can be trended for historical information, and alarm limits can be set up to indicate:

- Abnormal condition
- An alarm condition (either high or low)
- A pre-alarm condition (either high or low)

In a pharmaceutical operation, and based on accepted protocols, these point values should be monitored by a segregated or dedicated system set up for regulatory compliance. The values should be monitored by an approved incorruptible data historian.

The control of these devices or “points” is written into code (Proportional-Integral-Derivative (PID) loops) that is used by a BAS.

A typical BAS controls the mechanical equipment such as air handlers, boilers, chillers, Variable Air Volume (VAV) or constant volume airflow terminals, as well as laboratory equipment such as fume hoods and room pressurization schemes.

Additional equipment such as specific skid mounted apparatus can be controlled or monitored by a BAS with either hardwired or networked methods, such as BACnet™, Modbus®, OLE for Process Control (OPC), etc. Wireless technology is also used for connectivity of specific devices.

The BAS usually controls occupant comfort, can control critical environments to precise levels, and may be integrated into other disciplines such as Security and Life Safety systems.

Reports showing existing alarms, operator logs, trouble conditions, out of service devices, etc., are usually either automatically generated as determined by the administrator level operator, or can be manually downloaded by the operator.

10.5 Statistical Process Control

SPC is founded on data based models which are derived from historical data often capture during Design of Experiments (DOE) or analysis of actual data. These quantitative models provide continued process verification; i.e., if a process is currently under control, within specifications, or not in control. The source of variation may be found though analysis of the data versus the model. The data based model aids in building process understanding, which could be used to improve the process.

For further information, see the *ISPE PQLI® Guide: Part 4 – Process Performance and Product Quality Monitoring System* [97].

10.6 Process Analytical Technology

The FDA issued guidance in 2004 [98] which describes a framework for the implementation of innovative pharmaceutical development, manufacturing, and quality assurance. The guidance encourages the application of process controls, continuous improvement, and knowledge management tools along with the vision of a new approach to pharmaceutical manufacturing and regulatory efficiency. The FDA encourages the use of PAT tools for online control of CPPs. PAT tools are widely used to measure, understand, and improve the pharmaceutical processes.

10.6.1 Measurement and Control of Key Process Parameters using PAT

Automated systems can be used to monitor and control the process. Online monitoring methods such as NIR) analysis, can help to identify the endpoint of the granulation process. In roller compaction, ribbon density, and particle size, distribution measurements can be measured online and used for process control. In tableting, compression forces can be monitored online and tablets can be rejected based on atypical compression detection, rather than actual testing. Other critical properties can also be measured At-line, e.g., tablet weights, hardness and thickness.

PAT technologies can provide more thorough thumbprints of product quality than previously used indirect measurement, e.g., product temperature is used as an indication of product moisture during fluidized bed drying. Chemometric solutions can be used to evaluate multivariate batch data and models such as Partial Least Squares (PLS) or Principal Component Analysis (PCA), can be applied to characterize CQAs. The PCA model is used to define a quality fingerprint while the PLS model predicts things which cannot be measured directly.

10.6.2 PAT Analyzers

PAT Analyzers can be:

- In-line
- On-line
- At-line

Spectroscopic technologies include:

- Infrared
- NIR
- Raman
- UV-NIR
- Particle size analysis via Focused Beam Reflectance Measurement (FBRM)

In-line NIR spectroscopy technologies allow direct and accurate measurement of quality related material properties, such as product moisture and product API concentration. Integration of PAT analyzers in a control platform using a quality data management system can improve process control and product quality. This can lead to better understanding of the CQAs impacting the product quality and quality by design.

For further information, see the I*SPE PQLI® Guides: Part 2 – Product Realization using Quality by Design (QbD): Illustrative Example* [99] and *Part 4 – Process Performance and Product Quality Monitoring System* [97].

10.6.3 PAT Role in Continuous Processing

A key enabler for the development of continuous processing is a quality data management tool. A feedback and feed forward control scheme to ensure product is always being manufactured within the quality tolerance can be developed using the CQAs in Advanced Process Control (APC). A quality data management tool aligns the data with the resistance time or micro batch flow through the process. For example, a modification made during the drying step will have an effect on the dissolution testing and the delay before this change must be taken into consideration in the control design. In addition, the tool provides data mining which enhances the overall process knowledge.

10.7 Batch Record/Electronic Batch Record

A Batch Record is a list of manufacturing instructions for the drug production and operator entered fields to capture batch specifics, i.e., material lots consumed and produced. Batch Records are not unique to the OSD market.

OSD forms manufacturing facilities usually have a paper on glass system or MES to capture operator entered data. These solutions include electronic Batch Records, which are the complete batch production separated into unit procedures.

A paper batch record may allow more flexibility than an electronic system, e.g., completing items is a specific order or doing two steps in parallel. Process knowledge is needed when designing an electronic batch record in order to program operator efficiencies into the electronic system.

10.8 Manufacturing Execution Systems

Manufacturing Execution Systems (MESs) are regularly found in OSD forms manufacturing facilities to aid in the tracking and release of material between unit procedures. The scope of a MES can vary from a system used for Weigh and Dispense, equipment tracking, or material genealogy, to an integrated comprehensive electronic batch record system. MES interface with ERP systems to track raw material and finished goods inventory. MES are frequently based on a relational database.

10.8.1 Weigh and Dispense

Most MES installations start with a Weigh and Dispense application. The Bill of Material (BOM) is the formulation. The BOM line items are scaled, based on the production recipe size. The materials to be dispensed include active ingredients and excipients. The quantity of the API to be dispensed is dependent on its potency. The exact quantity is calculated and the associated excipient quantity is adjusted accordingly. Each weighed line item is configured with a tolerance. A Weigh and Dispense system can be integrated with an automated weighing application. The use of an integrated scale can ensure that a user weighs the required quantity of the material and removes the requirement for two signatures.

10.8.2 Material Genealogy

A MES can provide full material genealogy. When a material is consumed in a batch, the MES can ensure that it is the appropriate material for the batch, released and not expired. In addition, a MES can create a unique ID for each produced material lot. The materials can be tracked at either the material lot or container level. Container level tracking can allow for container specific release. The entire lot needs to have the same quality status for material lot tracking.

A MES can track raw material lots into Work in Process and production. This can allow for easy reporting of material consumption. A report can be created to show all final lots that include a specific raw material log or forward genealogy report. The reverse report, or backward genealogy report, takes the final lot and will report all raw material lots consumed.

10.8.3 Equipment Tracking

A MES can also track all equipment used in the production of a batch. The system can enforce cleaning and material contact rules. The equipment will have pre-use and post-use cleaning rules. These rules can be defined in the MES and enforced during performance cleaning.

10.8.4 Fully Integrated Electronic Batch Recipe

A fully integrated Electronic Batch Recipe can read and write CPPs to the Process Control System (PCS). Critical recipe parameters for the batch are written to the PCS at the start of the unit procedure. The electronic batch record will capture critical process values directly from the PCS and any critical alarms that need to be reviewed by quality. When an operator is required to manually enter a value or charge a raw material, a field will appear informing the operator the entry is required. The fully integrated batch recipe reduces the product release review cycle because all the data is in a centralized electronic report.

10.9 Commissioning and Validation

A comprehensive risk-based commissioning and validation process is required to ensure that computerized systems including IT infrastructure, PCSs, and process instrumentation that control and monitor OSD facilities and processes meet regulatory requirements and guidance (e.g., 21 CFR 211.68 [100] and 21 CFR Part 11 [101], EU GMP Volume 4 Annex 11 [102], PIC/S [103]). Formal agreements should also be developed for off-site or third party IT providers (e.g., Datacenter) that supply either direct or indirect IT services to the OSD facility or process. For networked IT or PCSs, which could be exposed to cyber security or malware threats (e.g., Conficker, Stuxnet), appropriate isolation and/or antivirus software should be installed on the IT infrastructure, network servers, and other associated PCSs which may have operating systems that are vulnerable to such risks. For further information on the development of the quality plan that governs the IT infrastructure and PCSs see *GAMP® 5* [95].

Commissioning and Validation life cycle phases include:

- Concept development
- Project planning and execution
- Operation/change management
- Periodic reviews
- Retirement of asset

Key requirements include:

- Validation testing should be based on the results of a risk assessment of the process control strategy.
- The design and architecture of PCSs are strongly influenced by critical aspects. CPPs should be identified prior to development of user and functional requirements.
- At a functional specification level, CPPs should be clearly identified, along with related tests which should provide evidence of a sufficient remediation of the risk. It is recommended to write the tests scripts simultaneously with performing the functional analysis.
- Functional analysis should identify the relevant CPPs for any object levels (i.e., recipe, phase, equipment module, control module) and the related tests to be carried out (including the measures to be taken in case a parameter goes out of range).

- Appropriate traceability should show that the requirements were met through validation testing and can be traced to configuration or design elements.

- For fully integrated electronic batch recipes, appropriate validation controls should be developed for customized or configured parameters. The validation controls should be managed in a similar fashion as the PCSs, by leveraging a life cycle approach.

- User access security controls should be tested appropriately and should include both positive and negative testing to verify that only authorized staff can obtain system access. Regular reviews of individuals with system access should be conducted to ensure that off-boarding processes are effective.

Supplier Management

A formal agreement should be established with either internal or external IT or process control providers. A formal assessment and/or audit program should be established to verify the effectiveness of a supplier's Quality Management System (QMS) and to ensure compliance to the formal agreement.

11 Other Considerations

11.1 Introduction and Non-cGMP Risk Considerations

This Chapter provides an overview of HSE and controlled substances considerations, which should be considered during a comprehensive risk assessment (see Chapter 3 of this Guide). Non-cGMP risks that should be considered are summarized and an overview of the basic technical and procedural approaches that may be used to mitigate these risks is provided. In addition to information provided in this Chapter, project teams should be aware of local requirements and facility policies.

This Chapter is intended for use as a guide to the types of non-cGMP information that should be gathered as part of an organization's risk assessment and mitigation process.

11.1.1 Categories of HSE Risk

HSE personnel should focus on preventing or mitigating categories of risk, including:

- Occupational exposure from chemicals or physical agents (see Section 11.2 and Chapter 5 of this Guide)
- Physical injury from process hazards (see Section 11.3)
- Physical injury and business interruption from fires, explosion, equipment overpressure (see Section 11.4)
- Unwanted environmental releases (see Section 11.5)
- Community response and emergency preparedness (see Section 11.6)

11.1.2 Controlled Substances Risk

The US Drug Enforcement Agency (DEA) (www.justice.gov/dea [104]), which has requirements surrounding scheduled narcotics and focuses on the potential for diversion of products, aims to provide:

- A successful mass balance through all handling steps, from raw material to finished product
- Physical security for the finished product

European equivalents of the DEA are the European Medicines Agency (EMA) [105] and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [106].

Containment technologies may assist in scheduled narcotic product security (see Section 11.7).

11.2 Strategies to Control Employee Exposure to Hazardous Materials

11.2.1 Introduction

Inherent risks resulting from exposure to hazardous substances should be minimized. Risk is a function of two factors:

1. Hazard
2. Exposure

Hazard depends on the toxicological or pharmacological properties of each substance.

The extent of contact by workers with active pharmaceutical compounds or other chemicals represents exposure. Exposure can be minimized using a hierarchy of controls (see Chapter 10) which uses an integrated approach of engineering control measures, administrative controls, and Personal Protective Equipment (PPE). For further information, see Chapter 5 of this Guide.

11.3 Preventing Physical Injury and Life Safety

This Section outlines how exposure to physical agents whose cumulative impact over time can lead to physical injuries. It also outlines the key life safety areas for a project team to address to prevent falls, etc.

11.3.1 Exposure Assessment for Physical Agents

Exposure to physical agents, which have a cumulative effect, can lead to chronic physical injuries or other health effects.

11.3.1.1 Noise

Hazard	Typical Equipment	Program Management
Partial or complete loss of hearing from workplace noise levels in excess of regulatory thresholds	• Sound enclosures • Compressed air mufflers • Exhaust silencers • Active noise suppression • Vibration dampening • Building acoustic design	• Hearing conservation • Hearing PPE and behavior management • Noise surveys • Audiometric testing • Routine training • Audits

11.3.1.2 Ionizing Radiation

Hazard	Typical Equipment	Program Management
Human tissue damage from exposure to ionizing radiation from radioactive process sensors or from processing of radio-pharmaceuticals Intake of radioactive particles into the body via inhalation, ingestion, dermal puncture, or absorption	Equipment designs that: • Maximize distance from radioactive source • Minimize exposure time • Shield radiation sources with appropriate materials • Contain radioactive particles with isolation technology or ventilation	Radiation Safety: • Written program with principles of radiation protection • Protective clothing and respiratory PPE • Exposure monitoring • Formal training • Signage and labeling • Radioactive material procurement and handling procedures • Contamination control surveys • Radioactive waste handling and disposal • Emergency procedures • Audits

11.3.1.3 Heat Stress

Hazard	Typical Equipment	Program Management
Heatstroke: life threatening, body heat up overwhelms normal thermoregulatory defenses Heat exhaustion: overheating of body due to exertion and high temperature environment	• HVAC to cool spaces to acceptable levels • Fans or other personal cooling devices if temperature > 35°C (95°F) (moving air > 35°C (95°F) adds heat to an operator) • Reduce heat emitted by equipment or building or both	• Heat monitoring • Personal cooling vests or vortex suites • Medical surveillance • Routine training • Audits

Heat stress is not usually a problem while working in cGMP areas that have acceptable climate control systems. Problems could potentially arise in warehouse loading docks, rooftops, and unconditioned mezzanines. ACGIH® [70] provides guidance on heat stress assessment and management.

11.3.1.4 Ergonomics

Hazard	Typical Equipment	Program Management
Back injuries and other muscular cumulative trauma injuries (hands, arms, etc.) when the job tasks are not in balance with the physical capabilities of the employees	• Lifting devices (e.g., scissor lifts) • Operator/machine interface design in accordance with ergonomic principles (e.g., keyboard orientation, reach into isolators, lifting patterns)	• Written program • Ergonomic SOPs, PPE, and behavior management • Ergonomic surveys • Routine training • Audits

11.3.2 Life Safety

Life safety addresses equipment and procedures to prevent physical injury from machinery, falls, and toxic conditions in confined spaces. It also addresses emergency response equipment and emergency egress requirements.

11.3.2.1 Machine Guarding

Hazard	Typical Equipment	Program Management
Physical injury to operator by machinery at point of operation, by power transmission device, or operating controls	• Physical barriers or machine guards • Interlocks and logic controls • Emergency shutdown • Check specific regulatory machine guarding requirements for the local geography	• SOPs and behavior management • Inspection and maintenance of guard equipment • Routine training • Audits

There are similar regulations to prevent physical injury in the US and Canada. In addition to national regulations, the EU Machine Guideline, 2006/42/EC [107] is considered important.

11.3.2.2 Lockout/Tagout (LOTO)

Hazard	Typical Equipment	Program Management
Physical injury to operator by release of equipment energy sources (electrical, pneumatic, hydraulic, gravity, etc.) during service or maintenance	• Mechanical devices (e.g., lockable valves, electrical disconnects, automatic shutdown switches, and logic) to positively isolate equipment from hazardous energy sources to achieve "zero energy state" • Check specific regulatory machine guarding requirements for the local geography	• LOTO SOPs and behavior management • Inspection and maintenance of guard equipment • Routine training • Audits

11.3.2.3 Fall Prevention/Protection

Hazard	Typical Equipment	Program Management
Physical injury to operator, due to falls during elevated work above floors or platforms; 1 m or 4 ft may be a regulatory threshold depending on location	• Passive fall protection • Guard rails on stairs, elevated locations, such as platforms or roofs, ladders • Safety nets • Safe walking surfaces with good traction • Minimizing trip hazards • Active fall protection • Fall arrest systems such as body harnesses, lanyards, and shock absorbers • Fall arrest suspension points adequate for considerable impact of a fall	• Fall protection and prevention SOPs and behavior management • Retrieval plans to anticipate arrested fall movement to prevent injury on another surface and to effect emergency recovery • Inspection and maintenance of equipment • Routine training • Audits

11.3.2.4 Confined Space Entry

Workplace spaces are considered "confined" because their configurations hinder the activities of personnel who enter, work in, and exit them. Confined spaces are locations that meet the following criteria:

- Large enough that they can be bodily entered
- Limited means of access and egress
- Not intended for continuous occupancy

Examples of confined spaces include:

- Storage tanks
- Process vessels
- Coaters
- Dryers
- Tumble blenders
- Covered mixers
- Air handlers
- Duct work

Less apparent confined spaces include manholes, vaults, pits, underground storage tanks and vaults, and trenches.

Hazard	Typical Equipment	Program Management
• Airborne gases, vapors, or dusts at life threatening concentrations • Oxygen deficient or oxygen enriched atmospheres • Potentially flammable or explosive atmospheres • Liquids or powdered material contents, that could engulf a person • Inwardly converging sides or a configuration that can trap a person • Electrical, mechanical, thermal, or fall hazards	• Minimize need for confined space entry in design, install sensors in confined spaces for external monitoring • CIP versus manual entry for cleaning • For air handlers, ducts, dust collectors, provide access doors for cleaning and external filter changing, such as BIBO designs	• Confined space entry written program describing confined spaces, requirements for entry permit, ventilation, safety monitoring during entry, emergency response, and removal procedures • Routine training • Audits

11.3.2.5 Asphyxiation (room air oxygen less than safe levels)

Hazard	Typical Equipment	Program Management
• Process gases other than oxygen, that reduce breathing air oxygen concentrations below safe levels • Examples include nitrogen gas for inerting or combustion products from heating processes	• Closed nitrogen system design with safeguards to prevent equipment pressurization • Operating area oxygen sensors, monitors, alarms, and shutoff devices	• Confined space entry as appropriate • Equipment hazard warning labels • Inspection and maintenance of alarms • Routine training • Audits

11.3.2.6 Life Safety for Emergencies

Hazard	Typical Equipment	Program Management
Spills of powder or liquid chemicals onto eyes or body	• Safety Showers (SSs) and Eye Wash Fountains (EWFs) within regulatory distances of likely spill locations, accessible with unobstructed path, and clearly marked	• SS/EWF program • Inspection and maintenance • Routine training • Audits
Initial response to fire or chemical spill	• Fire sprinklers, extinguishers, suppression systems as appropriate • Design to contain spills and spill control kits • First aid and other emergency responder equipment	• Coordination with site and community emergency responders • Inspection and maintenance • Routine training • Audits
Being trapped in a building during an emergency, such as a fire or chemical release	• Unobstructed way of exit travel from any point in the building with well-marked paths, functioning emergency exit doors, and clear path from exit door to assembly area set at a safe distance • Alarm systems (light or sound or both) which effectively cover entire facility	• Written program • Inspection and maintenance • Routine training • Audits
Being unable as an emergency responder to access the buildings and their utility systems	• Clear access roads and paths for emergency equipment • Clearly marked shutoffs for utility, piping, and electrical systems emergency alarm indicators in a central location	• Written emergency response program • Practice drills with site and community emergency responders • Routine training • Audits

11.4 Hazardous Operations

11.4.1 Hazards

The physical, chemical, or thermal properties of materials may present a risk of overexposure, thermal decomposition, fires or dust explosion, over-pressure or under-pressure. Consequences from inadequate safeguards can include injury or illness, equipment or facility damage, and releases to the environment, which can result in significant downtime and business interruption. This Section describes typical material hazards, outlines physical, chemical, and thermal properties that should be used to characterize hazards, and discusses mitigation strategies. It is recommended that a project team conduct a complete hazard and risk assessment early in the life of a project. The EU is covered by ATEX 95 [1] and ATEX 137 [27] regulations. National regulations also may apply.

11.4.2 Building Code and Insurance Implications

Building designs should meet local, state, or national code requirements and may be subjected to fire or over-pressure from hazardous operations. In addition to design requirements and safeguards associated with applicable regulations and fire and building codes, many insurance companies have additional requirements for maintaining "highly protected risk" facilities and reducing the risk of business interruption. For further information, see Chapter 6 of this Guide.

11.4.3 Performing a Process Hazard Analysis or Similar Risk Assessment

An initial step of hazard or risk assessment is to understand process operations, the energy input into each process step (e.g., mechanical or fluid/gas pressure), and the inherent hazards of the materials being processed. For example, most pharmaceutical compounds are solid organic chemicals, which have very small particle sizes for efficacy; this presents an increased risk for a dust explosion. Knowledge of the physical operations (e.g., milling/blending, fluid bed drying, granulation) associated with processing operations should be obtained. During a risk assessment, process flow diagrams, electrical classification drawings, piping and instrument diagrams, equipment drawings and specifications, and other key engineering documents should be used to assess the adequacy of safeguards. A systematic assessment tool, such as HAZOP, What-If, Process Hazard Analysis, or other recognized tools for identifying hazards and exposures, should be used in determining how to mitigate the identified risks. For further information, see Chapter 3 of this Guide.

11.4.4 Deflagration Hazards

Organic molecules, and some inorganic molecules, have the potential to burn very rapidly, generating large amounts of combustion gases in a small timeframe; the equipment in which this occurs can burst or rupture from this overpressure. A deflagration propagates the combustion zone at less than the speed of sound. A detonation propagates faster than the speed of sound and cannot be controlled. In the "Explosion Pentagon" all five conditions should exist simultaneously for a deflagration to occur:

1. Ignition source
2. Fuel
3. Oxygen or other oxidizer
4. Mixing
5. Confinement

The risk of static electricity issues is increased by a dry environment. The inherent flammability and combustibility hazards of materials should be accounted for during design to contain or suppress possible deflagrations in accordance with recognized guidelines, such as US NFPA Standards [26]. If there is a hybrid mixture of flammable vapors/gases and combustible dusts, this mixture often has a lower ignition temperature than the values for either the dust or the vapor. Safe practices for handling flammable liquids and gases should be established.

11.4.5 Dust and Liquid Physical, Chemical, and Explosive Properties for Defining Relative Hazard

Dust: any finely divided solid material, < 420 µm in diameter or passes through a 40 mesh screen

Particle Size Distribution (PSD): most organic dusts are combustible. Decreasing particle size typically increases the Deflagration Index or KSt

Bulk Density: density of a powder varies if PSD shifts – affects sizing calculations for any openings through which it should flow.

Pmax: maximum pressure (bars) developed in an un-vented test vessel. Along with the maximum rate of pressure rise, it is used to calculate K_{St}

K_{St} or Deflagration Index: for a dust cloud (bar-m/sec), used to rate the relative deflagration risk and hazard class for designing, explosion venting, or explosion protection systems. Most organic dusts and some metal dusts will have a K_{st}

Melting Point (MP): if heated to its MP, a powder can liquefy. If it cools below the MP, the solid mass might block drain or relief openings, or bind rotating equipment

Dust Deflagration Hazard Classes:

Hazard Class	K_{St}	Pmax
ST-1	< 200	10
ST-2	200 – 300	10
ST-3	> 300	12

Minimum Exposable Concentration (MEC): (g/m^3 or mass/volume) minimum concentration of the combustible dust cloud that will support a deflagration; also known as Lower Flammable Limit (LFL)

Limiting Oxidant Concentration (LOC): concentration of a gaseous oxidizer below which a deflagration cannot occur. Nitrogen typically used to reduce oxygen below LOC levels

Minimum Ignition Energy (MIE): (milliJoules or mJ) minimum amount energy release in a combustible mixture, which can cause flame propagation. Relative risk of static ignition hazard. < 25 mJ threshold of concern for static ignition sources

Resistivity and Relaxation Time: ability of solids to hold or dissipate a charge of static electricity (> 109 Ohm/m threshold of ability to hold a charge)

Thermal Stability (T Onset, dP/dT, impact/shock sensitivity, etc.): if your material is suspected of being a reactivity hazard, these properties provide some dimensions on the relative risk

Liquid Vapor Pressure: pressure exerted by a liquid. More volatile liquids have higher vapor pressures. It is a temperature dependent function. **Note:** that increasing vapor pressure increases the potential for deflagration.

Boiling Point (BP): temperature at which the vapor pressure of a liquid equals the surrounding atmospheric pressure. If liquid temperature is close to its boiling point, it may readily evaporate into large volumes of vapor that need to be vented from the equipment to prevent over-pressure

Flashpoint: minimum temperature at which a liquid evolves vapor in sufficient concentration to form an ignitable mixture at the surface of the liquid

NFPA 30 Liquid Deflagration Hazard Classes:

Hazard Class	Flash Pt	Boiling Pt
Flammable IA	< 23°C (73°F)	< 38°C (100°F)
Flammable IB	< 23°C (73°F)	≥ 38°C (100°F)
Flammable IC	≥ 23°C (73°F), < 38°C (100°F)	---
Combustible II	≥ 38°C (100°F), < 60°C (140°F)	---
Combustible IIIA	≥ 60°C (140°F), < 93°C (200°F)	---
Combustible IIIB	≥ 93°C (200°F)	---

Flammable Limits: minimum LFL and maximum/Upper Flammable Limit (UFL) concentrations in a gaseous oxidizer that will propagate a flame

Minimum Ignition Energy (MIE): (mJ) minimum amount energy release in a combustible mixture which can cause flame propagation. Relative risk of static ignition hazard. MIE most flammable liquids < 1 mJs

Conductivity: (picoSiemens/m or pS/m) ability to allow the flow of static electric charge (conductive liquid > 10^4 pS/m; semi-conductive > 10^2 pS/m, < 10^4 pS/m; non-conductive < 50 pS/m). There are conductivity additives for some non-conductive liquids if they are acceptable for your process quality requirements

11.4.6 Protective Design Features

This Section provides examples of risks and techniques used to mitigate combustible dust or flammable vapor deflagrations and emergency relief of boiling liquids caused by equipment fire exposure. Depending on the inherent risk of the material, application of one or more of these techniques may be necessary. In addition, safe handling SOPs should be established. Local codes and standards should be referred to for further guidance, such as NFPA documents (e.g., 30, 68, 69, 77, 91, 497, 499, and 654) [26], or similar ATEX regulations in the EU [1 and 27]. There also may be additional national regulations in EU countries.

Deflagration Hazards

Preventing Ignition

Static electricity and other sources of ignition should be controlled, using approaches such as:

- Equipment bonding and grounding
- Conductive flooring with personnel grounding
- Piping design to prevent static charge buildup
- Nitrogen inerting
- Reducing rate of charge generation
- Charge neutralization
- Liquid conductivity additives
- Electrical classification

Relieving Deflagration Overpressures

Reinforced equipment, rupture disks, and explosion panels should vent to a safe location. Highly hazardous compounds should not vent to the atmosphere.

Isolation

Isolation should prevent deflagration spread to equipment protected against deflagration overpressure, using approaches, such as:

- Chemical suppression systems
- Flame front isolation using mechanical equipment
- Flame front diversion
- Chemical isolation

Spark detectors may be used to initiate protective action in some of these approaches.

Emergency Relief Venting

Where there is a fire exposure to above ground tanks, emergency relief venting of boiling liquids should be used. Fire under equipment containing flammable or combustible liquids produces significant volumes of vapor. Reinforced equipment should be used to minimize the size of relief devices and equipment should vent to a safe location away from the fire zone.

Reactivity and Physical Hazards

This is a specialized field and recognized experts should assist in establishing a safe processing design.

11.4.7 Preventing Equipment Overpressure and Vacuum Collapse

Process and utility equipment can be subjected to high pressure or vacuum during normal operation. Table 11.2 summarizes some hazards that can cause equipment overpressure or underpressure in excess of safety ratings, along with typical mitigation strategies.

Table 11.1: Hazards and Mitigation Strategies for Process and Utility Equipment

Hazards	Mitigation
Overpressure: • Pressure sources transmitted through connected gas or liquid piping • Liquid thermal expansion Vacuum Collapse: • Connected vacuum source • Cooling of condensable vapors by internal or external means	• Reinforced equipment as per ASME or EU equivalent codes • Pressure relief devices: flow limiting orifices; pressure relief valves, rupture disks and membranes, and pressure vacuum vent valves, all discharged to a safe location • Vacuum relief devices: valve free vent lines, pressure vacuum vent valves, vacuum breakers

11.5 Environmental

11.5.1 Introduction and Permits

Environmental laws, regulations, and ordnances set the requirements for protecting the quality of air, surface water, and ground water.

Pharmaceutical manufacturing facilities are required to comply with environmental regulations, which apply to facility air emissions, wastewater discharges, and waste streams.

Preconstruction permits may be required from appropriate regulatory agencies prior to initiating construction activities, including site development and foundation work. Facilities are required to perform monitoring and recordkeeping in accordance with the requirements of any issued operating permits and regulations. There should be awareness of permitting process steps for the agencies with jurisdiction over the facility.

11.5.2 Environmental Issues Comparison

Industrial sources should address in risk assessments, and outlines typical risk mitigation strategies.

Table 11.2: Environmental Issues Comparison

Environmental Issues Comparison	Issues for Industrial Sources to Address	Typical Risk Mitigation
Air Emissions: public air quality should be maintained below national air concentration standards for pollutants, such as: • Particulate Matter (PM) • Carbon monoxide (CO) • Nitrogen oxides (NOx) • Ozone • Sulfur dioxide (SO_2) • Hazardous air pollutants	Controlling air emissions from process and utility systems operations, whether continuous, intermittent, or fugitive to meet regulatory requirements	Process vents or local exhaust ventilation systems to contain and collect pollutants at the sources for treatment by air pollution control devices, such as: • PM: fabric filters, wet scrubbers, mechanical collectors, HEPA filters • Hazardous solvents: thermal oxidation, gas absorbing scrubbers, adsorption • Combustion byproducts, such as NOx, SO_2, CO: selective catalytic reduction
Wastewater: the following waste water measurements should be maintained below the national standard prior to discharging for the facility: • pH • Biological oxygen demand • Chemical oxygen demand • Total suspended solids • Hazardous chemical pollutants	Controlling wastewater discharges from operating processes and cleaning operations to meet regulatory requirements	Wastewater control systems, such as: • Publicly owned treatment works or sewage treatment facilities within pretreatment standards if applicable • Onsite wastewater treatment systems, such as equalization and primary clarification, waste activated sludge, ozonation, ultraviolet light, pH neutralization, and possibly tertiary pollutant removal for discharge to streams, rivers, lakes, and other public waters
Groundwater: public aquifers should be maintained below national water concentrations to protect drinking water	Prevention of spills of hazardous chemicals into the ground	Groundwater control systems, such as double-walled piping, leak detection and containment systems for underground tanks, and an erosion and sedimentation control plan during construction
Storm Water: public surface waters should be maintained below national water concentration standards from runoff and snowmelt in contact with manufacturing and construction activities	Prevention of hazardous chemical contamination of rain runoff from buildings from process normal and emergency vents, spills, other sources	Storm water control systems, such as collection and containment systems for process and truck mat runoff with dikes, curbs, or retention basins. This can be avoided if the process is totally enclosed in building with no contact with rainwater
Solid and Hazardous Waste: the public should be protected from exposure to hazards from municipal, industrial, hazardous, infectious, medical, radioactive, and other regulated wastes	Minimization waste generation through process design and dispose of wastes as per regulations	Regulatory control of waste generation, storage, transportation, treatment, and disposal of hazardous wastes and other hazardous materials. Pharmaceutical facilities may store wastes on site only temporarily in accordance with regulations

11.5.3 Transportation of Hazardous Materials

Chemicals, APIs, and hazardous waste may be considered hazardous material when placed in a transportation network. Organizations may be required to develop hazardous material security plans for specified shipments, including many bulk shipments.

Projected hazardous material shipments should be reviewed against the hazardous material security plan requirements to determine to what extent the facility will be affected, as shipments may not be within the scope of the security plan.

As with hazardous waste, there can be significant fines and penalties for improper shipment of hazardous materials and waste, particularly if shipping personnel do not have the required training.

11.5.4 European Union Environmental Regulations

EU Environmental Regulations are similar to the regulations of the US and Canada. There may be additional national regulations in EU countries.

11.6 Community Response and Emergency Preparedness

Risks should be managed on site, and chemical releases or fires that could be harmful to local communities should be prevented. For predictable accidents, sites should establish emergency procedures, have appropriate emergency equipment, and train personnel in emergency procedures and equipment. A close working relationship with a community's first responders, such as the Fire Department, is considered beneficial so that they know what the hazards are and where they are located.

Many sites communicate plans to the local community as reassurance that the hazards on site are being managed. Most jurisdictions have laws or guidelines on Emergency Preparedness.

11.7 Controlled Substances

The US Drug Enforcement Agency (DEA) and other jurisdictions have requirements surrounding scheduled narcotics and focus on the potential for diversion of raw materials through finished product.

There are many requirements surrounding security that do not involve control of the powder within the process train itself. Containment of APIs that prevents the possibility of significant employee exposure via inhalation or dermal absorption, also improves the chances for successful mass balance, as losses are minimized during the processing steps. In addition, many containment technologies also act as a physical barrier to criminal diversion of the product, e.g., employee theft. An example of this would be a hydraulically activated split butterfly valve assembly from an IBC to the next piece of process equipment. If it takes process control equipment to mechanically open the IBC, the potential for theft of product is significantly reduced.

Attention should be paid to the fact that it is often necessary to place process material in a vault during off hours, including material in an IBC. IBCs and vault doors should be sized appropriately.

12 Appendix 1 – Cost Factors in OSD Manufacturing

12.1 Introduction

There are many considerations and constraints when determining the total cost of ownership of building or operating an OSD forms manufacturing facility. Location, licenses, regulations, work force, and market conditions are some of the factors that will influence capital investment opportunity and economical operations. In a constrained capital environment, it is important to prioritize strategic and baseline investments across the capital portfolio and place investment to satisfy revenue, compliance and business objectives. As commercial products are produced, it is essential to understand the cost of components for manufacturing. As we align project investment possibilities to strategy, how can we deliver new assets in a cost-effective manner and ensure OSD manufacturing objectives are met? This appendix provides topics for consideration when defining cost for capital investment opportunities and operations for OSD manufacturing.

12.2 Life Cycle Costing

Life Cycle Costing is applied across a broad range of business investment decisions and can be referred to as the Total Cost of Ownership or Life Cycle Cost:

- What cost is associated with maintaining the equipment?
- How long will we have this product on the market?
- When do the new regulations begin?
- What is the depreciation on the new facility investment?
- How fast can we manufacture and distribute product in that region?

When delivering capital investment projects or launching a new product the question is usually:

- How much will it cost?
- Why does it cost that much?

This Guide recommends the following guideline activities and deliverables when considering capital investments in OSD forms manufacturing facilities, to ensure a successful life cycle costing strategy.

When initiating a project, align with sponsors and customers on scope definition, key milestone dates and an order of magnitude estimate. SMEs will be required to review scope definition for considerations by categories that can align with cost components (architectural, process, utilities, etc.). A project initiation sheet or project charter can outline key considerations or concerns where cost may be a factor.

When planning a project and compiling the project deliverables for a capital proposal to request funding, it is important to have an accurate cost estimate. The estimate will include the all the cost factors for delivering a new asset. There may be other life cycle costing deliverables in planning such as Total Cost of Ownership Analysis, conceptual studies, technology options, facility and utility load matrix, all with cost ramifications.

In considering cost factors for a new asset, the project team and sponsors should agree on the basic deliverables and details appropriate for the project size and complexity. Deliverables include an OSD User Requirements Brief or an Approved Basis of Design document. Schedule and project execution plans along with project scope alignment to compliance requirements for quality, HSE, local code, and procurement. In planning, consider best practices and successful engineering solutions from similar projects. Upon funding and committing resources, establish Change Control for both project delivery and aligned with quality requirements.

While a project is in execution, the customer, project team of management, procurement, safety, quality and operations are working together to keep cost at or below established budget targets.

Deliverables to maintain cost control include Scope Change Management, Project Risk Analysis, a continued value management effort that should extend to suppliers of goods and services. Typically, the execution phase of a capital investment project includes the use of third party service providers to satisfy planning, design, construction, and verification objectives. These business partners may have the best information on options and methodologies when considering cost components for your OSD project or manufacturing delivery.

At the end of the capital investment for new assets, the operations phase of the project or product life cycle is entered. It is important to transfer knowledge and lessons learned in all aspects to satisfy good manufacturing practice, safety, and compliance. Some project teams may collect benchmark data and compare with early project estimates and cost change control to assess forecast accuracy and confirm final project cost expectations.

Life cycle costing is an integral to delivering effective and affordable OSD facilities. By applying tools and techniques, project investment capital can be aligned with operations, energy, safety, and compliance goals. Applying a Life Cycle Cost or Total Cost of Ownership process may provide better understanding in these areas:

- Facility options: purchase, expand, renovate, decommission, new versus renovation, modular versus traditional build, room finishes (floors, walls, ceiling, hardware, areas and space to satisfy people/equipment/product/material/waste flows
- Site development considerations: site work, site utility upgrades, local code requirements, temporary conditions
- Utility and energy alternatives: key utility requirements of water, electricity, gas, oil, coal, and waste streams. Process utilities such as high purity water, clean steam, specialty gases, and waste treatment
- Manufacturing technology platform options: process equipment, process utility, automation, containment, and isolation and separation technologies
- Automation options: automation philosophy, system impact assessments, instruments and controls, component impact assessments, redundant systems, HAZOP and safety requirements
- Facility operational requirements: Mechanical: HVAC classification requirements for unit operations and containment, operational considerations, AHUs and controls, local exhaust, dust collection, steam, water, plumbing, sprinkler, redundant systems. Electrical: lighting, devices, receptacles, fixtures, emergency power, uninterruptible power source, security and egress systems, distribution, code requirements
- Value management: value management is a continuous process that supports the goals of life cycle costing. As phases are repeatable and overlapping in the life cycle process, it is important to update and review scope definition, continue best practices and successful engineering solutions, conduct peer reviews and input by SMEs while ensuring good communication and knowledge transfer

- Cash Flow Forecasting: cash flow forecasting is a process that considers the key disciplines of scope management, estimating, schedule management, the capital procurement process, and project change control to provide current financial status of a project for awareness and risk mitigation. The management of scoping, estimating, scheduling, resourcing and communicating activities are considered to be going well if an accurate prediction can be made for:

    1. How much money will be needed?

    2. When will it be spent?

12.3 Cost Drivers

A diagram of facility costs for OSD forms manufacturing facilities may be a scatter diagram. OSD forms manufacturing costs are as varied as the size, type, and location of operations. There are pilot plants, clinical manufacturing facilities, warehousing, raw material or component manufacturing facilities, product development centers, and multi-purpose facilities that all have unique cost drivers for facilities and operations. The requirements for unit operations, HVAC, process systems, people/material/product/waste flows, and controlled versus unclassified spaces for these manufacturing platforms can be as varied as the products on the market.

There are many variables that may be compared to satisfy operational objectives. Perhaps the more impactful is the location of the manufacturing investment. The global market locations for OSD manufacturing is expanding into international regions and there can be major cost differences when investing in equipment, material, labor, logistics and energy for markets such as the US and Puerto Rico, Europe, Brazil, Japan, China, and India.

OSD forms manufacturing variables may also include many options for investment such as third party service providers, manufacturing partnerships, internal core solutions, and external enabling services. Facility cost considerations may include the availability of the workforce, compliance and local code requirements, process flexibility and utility capacity, and redundancy strategies.

There are three main categories that influence operational costs of OSD manufacturing include:

1. **Manufacturing Process and Process Equipment:** cost factors for assets include the initial cost of purchase, costs associated with installation, start-up, and verification. For the company's balance sheet, depreciation of production facilities, equipment, and other manufacturing fixed-assets must be accounted for. Depreciation cycles for new assets may range from 5 to 7 years for automation systems, 15 years for equipment assets, and 20 years for building and site assets.

2. **Raw Materials:** APIs and excipients are in demand on the global market with great ranges for availability and cost. The demand for raw materials continues to increase as our industry grows into new and emerging markets. The volatility in the raw materials markets can lead to dramatic shifts in the cost of raw materials and their associated components, typically a focal point for many OSD manufacturing CFOs. It is important for manufacturers to focus on their raw material management strategies to satisfy unit cost and consumer cost expectations.

3. **Manufacturing Life Cycle Time:** the product manufacturing cycle time can greatly influence the overall cost to producing an OSD product for market. Whether manufactured in one facility or as part of a global supply chain, the product process steps from receiving raw materials to distributing commercial product each contain a component of product unit cost. Manufacturing time includes among the most considerable cost factors, direct labor. From employees on the shop floor to the site leader, labor costs are typically among the greater cost factors when considering Return on Investment of your revenue stream. Occupancy costs, such as insurance, property taxes, and minimal life safety system utilities are other cost impacts related to the manufacturing life cycle and with impacts to the product annual income statement.

Key cost drivers in OSD forms facility design, construction and operations are typically captured in a good project cost estimate. Architectural, Process, Mechanical, Electrical, and Project Delivery cost estimates will include key cost drivers for the facility and operations life cycle.

A summary of the key cost drivers that affect the construction and operation of an OSD manufacturing facility is provided in Table 12.1.

Table 12.1: Summary of the Key Cost Drivers

		Base Option	
Cost Drivers		**First Cost ($/SF)**	**Operating Cost 20 Years ($/SF)**
Site Development			
Building Structure			
Building Envelope			
Interior Construction			
Mechanical –	HVAC		
	Plumbing		
Electrical –	Power		
	Lighting		
	Special Systems		
Process –	Equipment		
	Automation		
Energy and Utility Costs			
Maintenance Costs			
Cost of Alterations			
Present Worth			

12.4 Optimization of Processes for Reduction of Life Cycle Costs

The conditions for potential optimization of processes are typically identified early in the planning cycle of a capital investment project. Market demands and global compliance changes present challenges and opportunities to consider process upgrades. Strategies for design and installation, operations, and product life cycle will influence the ability to identify, manage, and control life cycle costs. Cost reduction possibilities are an important aspect of a good operational master plan. There may be hundreds of possible situations that may lead to optimized operations resulting in lower cost.

Below are a few scenario examples when considering cost factors for OSD manufacturing.

Scenario Examples for Reduction of Life Cycle Costs

- Reduction of energy costs with investment for energy recovery of process equipment

  One scenario is the Utilization of “Day Mode” and “Night Mode” for HVAC systems. As a cost reduction effort, “Night Mode” reduces air flow volume and maintains room pressure while the room is idle. “Day Mode” has a validated recovery time to the specific environment requirements While there is an initial cost for optimization, there is significant cost avoidance for on-going operations. The process is in compliance and energy costs are reduced by 25%.

- Increase the yields or provide engineering solutions to reduce product losses during manufacturing

  One scenario is an Automation of processes or sub-processes. Elimination of human error or increasing capacity with automated process steps that will reduce labor cost and creates cost avoidance with reduction in losses of raw materials. PAT can be used to measure, understand, and improve the solid dosage process.

- Reduction of cleaning and changeover times

  The use of automated or semi-automated cleaning processes typically results in a considerable reduction in operational costs. The use of continuous operations is growing as efficiencies contribute to lower costs and faster manufacturing time when compared to traditional batch processes

  Factors include:

  - Reduction in labor costs
  - Reduction in facility size, and cost avoidance with lower utility consumption
  - Reduction in disposal, waste, and “single use” costs
  - Increase in the production up-time and availability

There are certainly more ways to save on life cycle costs. The possibilities of process optimization are not always cost-driven. For example, automation may be required to satisfy product quality or worker’s safety objectives. A thorough understanding of both the product and the process technology are required for successful optimization.

A life cycle costing approach should consider a total investment over the life cycle of the product or manufacturing facility. Theoretically, applying this approach should result in a lower total cost of ownership. Table 12.2 presents a simplified illustration of a spreadsheet comparison of initial investment and life cycle operating costs. A life cycle cost analysis does not guarantee savings, but it will improve the ability to make informed decisions.

Table 12.2: Simplified Comparison of Base and Final Cost

		Base Option		LCC Final Option	
Cost Drivers		**First Cost ($/SF)**	**Operating Cost 20 Years ($/SF)**	**First Cost ($/SF)**	**Operating Cost 20 Years ($/SF)**
Site Development					
Building Structure					
Building Envelope					
Interior Construction					
Mechanical –	HVAC				
	Plumbing				
Electrical –	Power				
	Lighting				
	Special Systems				
Process –	Equipment				
	Automation				
Energy and Utility Costs					
Maintenance Costs					
Cost of Alterations					
Present Worth					

Benchmarks can be good predictors of project and operating cost. There are many publications dedicated to providing current unit costs and cost trends. Value engineering methodology should be utilized when considering improvements to facilities or materials in OSD forms manufacturing.

13 Appendix 2 – Example Risk Assessment for OSD Facility Upgrade

The following risk assessment is only one example of several possible ways to perform a risk assessment. It is only being supplied as an example of how to perform a risk assessment. Refer to the ISPE PQLI® Guide – Part 2 [99], for other examples of risk assessments.

Scenario: An existing facility is being considered for initial manufacturing of an important new OSD pharmaceutical product to support its introduction into major global markets. Although the design of a new facility is underway to support long term requirements, the new facility will not be completed and approved for use until well after the anticipated fast-track approval of the new product which is expected to meet an important unmet medical need. To ensure product quality and prevent cross-contamination, the existing facility will require major upgrades as part of an approved capital project.

Step 1: Determine GMP and non-GMP design, qualification, and maintenance considerations for ensuring project success (e.g., safety, product quality, cycle time, schedule)

GMP:

- The new product will be introduced into an existing dedicated manufacturing area requiring evaluation and potential upgrade of the existing HVAC system
- The new and existing product will require validation of the cleaning processes to prevent cross-contamination. In addition, determine cross-contamination limits as required
- The existing facility zoning will need to be evaluated for potential upgrade due to the anticipated rigorous regulatory audits to support approval of the new product

Non-GMP:

- The API is prone to dusting and highly active (PBECL-3) and will require engineering and/or procedural controls (see Step 3)
- Although the existing facility is capable of processing flammable solvents, a review of the existing electrical classifications will be required to ensure the new solvent can be safely accommodated
- Need to meet fast-track project schedule and budget targets

Step 2: Identify the potential GMP and non-GMP risks for the determined design, qualification and maintenance considerations (see Step 1)

GMP:

- Out of specification potency or other quality deficiency
- Contamination with other products manufactured in this facility
- Product contamination with other vectors (e.g., people, pests, etc.)

- Facility does not meet cGMPs expectations during Pre-Approval Inspection(s)

Non-GMP:

- Operator exposure to unacceptable levels of highly hazardous API (PBECL-3)

Note: appropriate methods need to be used to establish acceptable exposure limits for such PBECL-3 compounds

- Dust or solvent vapor explosions in existing process equipment
- Not meeting electrical classification requirements for new solvent
- Not meeting project schedule which delays availability of new medicine to patients
- Not meeting project budget

Step 3: Initiate identification of potential GMP and non-GMP failure scenarios based on risks/hazards identified in Step 2 and a detailed evaluation of the process

The manufacturing process includes the following sub-processes:

- Sub-division: Sub-divide highly hazardous (PBECL-3) API from a large container to a smaller charging canister that is equipped with a specially designed port that attaches to the granulator for contained charging (see Granulation). The API is also susceptible to dusting and consequently should be sub-divided and weighed in a down flow booth to meet acceptable operator exposure limits. Alternately, operators require full body covering PPE to ensure their safety. The excipient containers arrive pre-weighed from the vendor and are ready for charging, but require an identity verification using PAT (NIR technology). The API and excipient containers are then transferred to the granulation suite

- Granulation: The API and excipients arrive into the granulation suite through an airlock that ensures a pressure differential between adjacent lower class zones. The excipients can be manually charged to the granulator which was designed for dust and solvent explosion protection with a 12 bar maximum allowable pressure rating. Following closure of the granulator, the API will be charged through an alpha-beta port which can be easily retrofit to the granulator using one of its sight glasses. The solvent is then added to the closed granulator and the mixing is controlled to an endpoint that considers both granulation time and power draw. When complete, the granulated product is ejected through a closed drop chute into the fluid-bed dryer located in the floor below. Due to the lower API concentration and residual solvent in the granulated product, no special operator controls are required during cleaning other than awareness of residual solvents. Although a new solvent is being introduced by the new product, the facility is currently designed to handle similarly flammable solvents

- Fluid-Bed Drying: The fluid-bed dryer is currently rated for solvent and dust explosion prevention with a 12 bar maximum allowable pressure rating. The lower API concentration in the granulated product also significantly reduces operator exposure concerns. The fluid-bed drying process is controlled to an endpoint that considers both time and PAT (NIR technology). The dried granulated product is then packed into IBCs and sent to the compressing area. Similar to the granulation step, no special operator controls are required during cleaning other than awareness of residual solvents

- Compression: The IBC from granulation is connected to the compression machine. The compressing machines are modern and are equipped with automated thickness and weight control. Some additional controls during cleaning are required due to the presences of low levels of the highly hazardous API resulting from any broken tablets

- Coating: Some additional controls during cleaning are required due to the presences of low levels of the highly hazardous API resulting from any broken tablets. Finally, there are no flammable solvents used in this part of the process (water only).

Step 4: Finalize failure scenarios and assess their relative priority using severity, probability of occurrence, and ability to detect (see example below). For scenarios which exceed your acceptable level of risk (i.e., risk tolerance), apply risk mitigation/reduction and controls. Also consider development of contingency plans (as required).

Table 4.1: Example Risk Assessment for OSD Facility Upgrade to Accommodate New Product

Sub-Process	Activity, Potential Failure Scenario and Impact	Type of Risk	Severity	Probability	Ability to Detect	Priority of Risk[1]	Risk Mitigation/ Reduction and Controls	Contingency Plans
Sub-division	Incorrect API weighment which results in OOS assay	GMP	High	Low	Medium	Medium	• Training and calibration programs for scale • SOP that clearly describes process and includes second person check (per 21 CFR)	
	Cross-contamination via HVAC system	GMP	High	Medium	Medium	High	• Install HEPA filters in HVAC system • Swab/ inspect HVAC ducts after campaigns	Consider moving existing products to another facility
	Cross-contamination via equipment	GMP	High	Medium	Medium	High	• Ensure validated cleaning programs in place • Swab/inspect equipment after campaigns	
	Contamination of product by other vectors (e.g., pest)	GMP	High	Low	Medium	Medium	• Ensure pest control program in place • Include additional zoning (if possible • Add airlocks/ differential pressure (if possible)	Temporary use of PPE if booth has long-lead time

Table 4.1: Example Risk Assessment for OSD Facility Upgrade to Accommodate New Product (continued)

Sub-Process	Activity, Potential Failure Scenario and Impact	Type of Risk	Severity	Probability	Ability to Detect	Priority of Risk[1]	Risk Mitigation/ Reduction and Controls	Contingency Plans
Sub-division (continued)	Operator exposure to highly hazardous API	Safety	High	Medium	Medium	High	• Install contained weigh booth • Training program for API handling	Consider moving existing products to another facility
Granulation	API left in charge canister – low assay	GMP	High	Low	Medium	Medium	• Add vibrator to charge canister • Procedurally verify that canister is empty	
	New solvent requires electrical upgrades	Safety	High	Low	High	Low	Considered to be low risk since facility already handles solvents	
	Cross-contamination via equipment	GMP	High	Low	Medium	Medium	Ensure validated cleaning programs in place	
Fluid Bed Drying	New solvent requires electrical upgrades	Safety	High	Low	High	Low	Considered to be low risk since facility already handles solvents	
	Cross-contamination via equipment	GMP	High	Low	Medium	Medium	Ensure validated cleaning programs in place	
Compression	Cross-contamination via equipment	GMP	High	Low	Medium	Medium	Ensure validated cleaning programs in place	
Coating	Cross-contamination via equipment	GMP	High	Low	High	Low	Considered to be low risk as the API should be a very low levels at this stage in the process	
Prior Approval Inspection	Failure to pass Agency Inspection	GMP and Bus	High	Medium	High	Medium	• Ensure Quality Systems are in place • Perform rigorous internal auditing	

Note 1. See Table 14.2: Priority of Risk – Based on GAMP® Severity, Probability, and Detection Model

Table 14.2: Priority of Risk – Based on GAMP® Severity, Probability, and Detection Model

Severity	Probability	Ability to Detect	Priority of Risk
High	High	Low	High
High	High	Medium	High
High	High	High	Medium
High	Medium	Low	High
High	Medium	Medium	High
High	Medium	High	Medium
High	Low	Low	High
High	Low	Medium	Medium
High	Low	High	Low
Medium	High	Low	High
Medium	High	Medium	High
Medium	High	High	Medium
Medium	Medium	Low	High
Medium	Medium	Medium	Medium
Medium	Medium	High	Low
Medium	Low	Low	Medium
Medium	Low	Medium	Low
Medium	Low	High	Low
Low	High	Low	High
Low	High	Medium	Medium
Low	High	High	Low
Low	Medium	Low	Medium
Low	Medium	Medium	Low
Low	Medium	High	Low
Low	Low	Low	Medium
Low	Low	Medium	Low
Low	Low	High	Low

Step 5: Ensuring On-going Performance

To ensure on-going performance of this facility and process, the following activities are recommended for this facility:

- Perform Annual Product Review (e.g., review atypical events, change controls)
- Perform GMP audits by the Quality Assurance function
- Perform predictive monitoring and maintenance on process and safety equipment

Step 6: Continuous Improvement Philosophy

Use experience from the process to further reduce risks. Re-visit the risk assessment on a regular basis (e.g., every two years) or when major change request is being reviewed.

14 Appendix 3 – Containment and Isolation: Further Information

14.1 Introduction

Regulated companies should develop internal criteria that can be used to evaluate compounds based on readily available data from Manufacturers Safety Data Sheets (MSDSs), API manufacturers, etc. There is a continuum of toxicities, and a continuum of potential exposure levels and emission scenarios which are a function of multiple independent variables. The relationship of one to another in each specific process step or activity defines the emissions control requirement. Some rules of thumb or standard solutions exist for general processes and material toxicology ranges, but the User should assess the specific case at hand to ensure that the constraints of the justification for a "standard solution" are not breached.

A high-level criteria matrix is listed below as one example of an approach which groups together combinations of emission controls in increasing stringency. In such an approach, the top axis of the matrix is generally defined as a "band" or a range of OELs that would trigger a particular set of criteria. The left axis is often labeled with the unit operations that are employed by the company for manufacturing. Matrices developed by firms processing potent compounds can range from the simple table shown below to very detailed and measures covering several pages. A preferred approach is to develop a risk assessment more tailored to the compound and specific unit operations and facility in question. However, lacking that, the example below offers an expedited or first-pass approach for planning purposes.

Firms should develop an internal policy around the handling of compounds defining how it will assess OELs, and how they generally plan to control product emissions and isolation. This policy should generally address:

1. Toxicology assessment and product on-boarding or on-going review (OEL Development)
2. Facility Design and Engineering Controls
3. Surrogate Monitoring
4. Respiratory Protection Program

14.2 A Broad Overview of Containment Provisions

In general, the approach with highest assurance for manufacturing that is contained/isolated from other operations is via a separate and independent building with the appropriate architectural and mechanical features. In this model, all processes used for the manufacture of highly hazardous drugs would also use closed processes, closed transfer systems, and contained systems for the cleaning of equipment. Whether the above redundant approach (contained processes plus separate building) is actually warranted would, as with the other approaches mentioned, be indicated by the outcome of a risk assessment.

The same closed process approach should also be applied to an appropriate level for the following "common building" scenarios.

If a separate manufacturing building is decided against, and a containment module is instead provided in or adjacent to an existing area, then in general the next highest assurance approach is for it to be located in a dedicated area physically separated from the rest of the manufacturing facility. In this approach mechanical (HVAC) systems would remain isolated by serving the separate areas. Consideration would also be given to having the mechanical areas housing the HVAC (and other fan/filtration equipment) for the two areas being in separated and distinct areas as well, so migration between the two units would be more controllable during times of their maintenance and repair.

Architectural separation of the two areas which are “under one roof” would include internal traffic flow procedures, walls above ceilings to structural deck levels, and airlocked pressure differential controls (airlocks might also be called for in instances with different products being handled in any case). Personnel and material ingress and egress would have provisions (engineering, procedural, and/or administrative) for appropriate levels of decontamination to limit or eliminate compound migration.

Where a secondary airlock system is not possible, design guidelines can be applied to single operation modules (e.g., contained tableting room). Since multiple operations are required to manufacture a product, this approach will require multiple, separated, containment modules. Here, strong consideration for material movement in completely sealed containers through non-containment areas that connect the individual containment rooms would be indicated.

As in the previous tiers, personnel and equipment should enter and exit containment modules through airlocks or have data to support the reliable containment of the compound within the manufacturing area.

Provision of, and storage for, PPE for personnel should be considered in these areas in the event of an upset condition and as an added measure of protection.

Based on the risk assessment for an area, HVAC systems for these facilities should be considered with low wall returns, potentially as single-pass systems and have provisions for the removal/replacement of the filters in a contained manner such as a Bag-In/Bag-Out (BIBO) system. They should also be rigorously tested to ensure that a correct airflow is achieved that passes treated air passed the breathing zone of the operator and does not create turbulent air pockets that “re-entrain” emissions. Where recirculated HVAC air is preferred, due to high external relative humidity or the presence of humidity sensitive material on-plant, the air should be suitably and robustly filtered to prevent spreading contamination by the HVAC system or to create an increasing concentration of materials within the system.

Table 14.1 provides examples of how physical properties of materials handled and the energy input by the process can affect potential exposure. This assessment should be completed on a case-by-case basis by personnel knowledgeable in both the process and its containment possibilities.

Table 14.1: Material and Process Factors Affecting Emissions

Characteristic	Lower Risk	Higher Risk
Part A: Material Physical Characteristics Affecting Emissions		
Physical form	Wet	Dry
Particle size	Large	Small
Flowability	Predictable	Difficult to handle
Density	Heavy	Light
Structure	Crystalline	Non-crystalline
Electrostatic	No	Yes
Part B: Process Characteristics Affecting Exposure		
Process equipment	Closed design	Open design
Process energy input	No energy or velocity, low temperature	High speed mechanical motion, high temperature
Pressure differential	Low	High
Transfers between unit operations	None	Multiple
Operator training	Frequent and up to date	Rare
Operator skill or technique	None required	Highly dependent
Task type	Routine	Non-routine
Duration	Short	Long
Task frequency	One time	Multiple operation

Engineering controls include technical equipment approaches, ranging from ventilation options that shape airflows to move airborne contaminants away from an operator's breathing zone, to closed process design and total isolation of the process materials with physical barriers and specialized transfer devices. Careful evaluation and design is recommended for each situation. Approaches listed in Table 14.2 are shown in two groupings: Ventilation Controls and Closed Process Controls.

Table 14.2: Engineering Controls Options

Descriptions	Advantages	Disadvantages
Ventilation Controls		
General Exhaust Ventilation Supply and exhaust large volumes of conditioned air (typically > 10 air changes/hr) through the manufacturing suite to disperse emissions from spills and other releases (see Chapter 7)	• Easily disperses widespread emission sources, such as vapors or gases	• Generally not effective by itself for controlling emissions for higher hazard materials, typically used in conjunction with other engineering controls in OSD facilities • General air velocities too low to capture most particulate contaminants, dust settles • High cost for once through conditioned HVAC air
Local Exhaust Ventilation (LEV) Hoods or enclosures on process equipment that exhaust air around the emission sources and away from the operator's breathing zone and convey contaminants to air cleaning equipment (see Chapter 8 of this Guide)	• Capture emissions at their sources with well-designed hoods • Reduced room HVAC air volumes	• Limited effective reach to keep contaminants out of operator breathing zone • Operator technique dependent • Contaminants could be pulled into product if LEV applied incorrectly • Discard product collected by LEV • Air cleaning device may need explosion protection
Downflow Booths Small room or enclosure with low velocity (100 ft/min) downward airflow around workstation to push contaminants away from the operator's breathing zone	• Useful for manual operations for which a more contained approach is not feasible • Secondary layer of containment for some unit operations	• Emissions land on the floor, cleanup issue • Operator technique dependent • Electrical energy consumption to move large volumes of high quality conditioned air
Closed Process Controls		
Flexible Wall Isolators Flexible Intermediate Bulk Containers (FIBC) or disposable flexible film isolators with built-in gloves or transfer sleeves designed to surround a manual task or piece of equipment. **Note:** there are performance differences between FIBCs and flexible film isolators.	• Emissions fully contained • Custom designed and adaptable • Quicker availability from manufacturer than rigid isolators • More forgiving of ergonomic differences between individuals than rigid isolators • Developing internal cleanout procedures usually not necessary • FIBCs easy to fill and discharge • Reduced need for HVAC air volumes	• Results dependent upon good operator technique • Careful disposal techniques required to prevent contamination of operator or workspace • Disposable devices are an on-going operating expense

Table 14.2: Engineering Controls Options (continued)

Descriptions	Advantages	Disadvantages
Closed Process Controls (continued)		
Close Coupled Process All steps of the process are sealed with little chance of release to the suite. Examples include: automated dispensing, vertically stacked process, transfers with Intermediate Bulk Containers and Active/Passive containment valves, multiple unit operations in one housing, and pneumatic conveying	• Emission sources within the physical confines of the unit operation • No easy path for external contamination to enter the product • Can separate product part of equipment from technical part of the equipment to limit size of manufacturing space • Need for housekeeping is reduced • Reduced need for HVAC air volumes	• Higher capital cost for equipment • Process flexibility may be limited • Some unit operations cannot easily be CIP'd so some equipment entry is required for cleaning
Rigid Wall Isolators Specialized rigid enclosures built around equipment, often with a dedicated HEPA air filtration system. Manipulations of the process through built in gloves. Materials passed in and out through airlock-like chambers or other devices. Mockups in design phase confirm operability	• Emission sources within the physical confines of the unit operation • No easy path for external contamination to enter the product • Can separate product part of equipment from technical part of the equipment to limit size of manufacturing space • Need for housekeeping is reduced • Reduced need for HVAC air volumes	• Ergonomic limitations to accommodate different size people make process difficult to operate and should be resolved to be feasible • Higher capital cost for custom designed equipment • Process flexibility may be limited • Some unit operations cannot easily be CIP'd so some equipment entry is required for cleaning • Careful consideration for containment weak points such as shaft passages, sampling systems, etc.

Vacuum Cleaning Equipment

Cleanup methods can cause the release of contaminants to the environment around the equipment. Use of compressed air or high pressure water cleaning can spread contaminants over a wide area, making the cleanup process a high exposure job that takes a significant amount of time. Vacuum cleaning with its exhaust airflow patterns around a cleaning tool provides a limited amount of containment. Table 14.3 compares portable vacuum cleaners to central vacuum cleaning systems. An effective cleaning approach should establish a complete program of housekeeping areas, cleaning methods, and cleaning agents.

Table 14.3: Vacuum Cleaning Equipment Comparison

Vacuum Cleaning Equipment	Advantages	Disadvantages
Portable vacuum cleaners with HEPA filters (explosion preventive designs available as well as high potency rated units)	• Stored away until needed for a spill	• Finding unit and bringing to a spill • High exposures possible when emptying unit if not Bag-In/Bag-Out (BIBO) system • Keeping a number of units emptied and maintained
Central vacuum cleaners with local hoses and tubing network to remote dust collection	• Cleanup tools readily available • Continuous discharge of collected dust	• Higher energy consumption • Exposures when cleaning tubing network, particularly with highly hazardous materials

14.3 Proof of Performance

Proving that new containment equipment meets the user requirements is an important activity during Commissioning and Qualification. (See the *ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment* [54] for information on setting up and testing containment capability and surrogate testing.) It may be appropriate to develop a protocol that would apply to a unit operation and complete a surrogate testing protocol.

ASHRAE, AIHA, and ACGIH® contain procedures for establishing the baseline performance of LEV systems. In the US, there are two organizations, the Associated Air Balancing Council and the National Environmental Balancing Bureau, which certify testing and balancing firms, which are available to complete ventilation system commissioning. Consistent conveying velocity throughout the system is important for LEV performance. Testing firms should have demonstrable experience with LEV issues. EU Directive 2008/1/EC [108] provides a similar European procedure.

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16 Appendix 5 – Glossary

16.1 Acronyms and Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists (US)
ACH	Air Changes per hour
ADE	Allowable Daily Exposure
AGV	Automated Guided Vehicle
AHU	Air Handling Unit
AIHA	American Industrial Hygiene Association
API	Active Pharmaceutical Ingredient
ASHRAE	American Society of Heating, Refrigeration and Air-Conditioning Engineers (US)
ASME	American Society of Mechanical Engineers (US)
ASTM	American Society for Testing and Materials (US)
ATEX	ATmospheric EXplosible
BAS	Building Automation System
BFD	Block Flow Diagram
BIBO	Bag-In/Bag-Out
BPE	Bioprocessing Equipment
C&I	Control and Instrumentation
cGMP	current Good Manufacturing Practice
CIP	Clean In Place
COP	Clean Out of Place
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DEA	Drug Enforcement Agency (US)
DX	Direct Expansion
EMA	European Medicines Agency
EMS	Environmental Monitoring System
EU	European Union
FDA	Federal Drug Administration (US)
FIBC	Flexible Intermediate Bulk Container

FMEA	Failure Mode Effects Analysis
GEP	Good Engineering Practice
GMP	Good Manufacturing Practice
HAZOP	Hazard and Operability
HEPA	High Efficiency Particulate Air
HSE	Health, Safety, and Environment
HVAC	Heating, Ventilation, and Air Conditioning
IBC	Intermediate Bulk Container
ICH	International Council for Harmonization
ISO	International Standards Organization
IT	Information Technology
LED	Light Emitting Diode
LEV	Local Exhaust Ventilation
MERV	Minimum Efficiency Reporting Value
MES	Manufacturing Execution System
MHLW	Ministry of Health, Labour, and Welfare (Japan)
NEC®	National Electrical Code® (US)
NFPA	National Fire Protection Association (US)
NIR	Near Infrared
OEL	Occupational Exposure Level
OSD	Oral Solid Dosage
OSHA	Occupational Safety and Health Administration (US)
P&ID	Process/Piping and Instrumentation Diagram
PAT	Process Analytical Technology
PCS	Process Control System
PLC	Programmable Logic Controller
PPE	Personal Protective Equipment
QbD	Quality by Design
RH	Relative Humidity
RO	Reverse Osmosis
RPE	Respiratory Protective Equipment

SCADA	Supervisory Control and Data Acquisition
SME	Subject Matter Expert
SOP	Standard Operating Procedure
SS/EWF	Safety Showers and Eye Wash Fountains
URS	User Requirement Specification
USP	US Pharmacopoeia
UV	Ultraviolet
VFD	Variable Frequency Drive
VOC	Volatile Organic Compound
WHO	World Health Organization
WIP	Wash In Place

16.2 Definitions

Acceptable Risk

In quantitative terms, the level of potential cross-contamination is below the ADE (acceptable daily exposure) with a statistically relevant number of samples, covering all modes of cross-contamination, mix-up, retention, airborne and mechanical transfer. In qualitative terms the risk priority number (RPN) is within documented acceptance criteria or where the opinion of SME's is used in the assessment.

Action Level

A level at which manufacture should cease. It is typically set below the absolute limit to allow for data variability and is documented and monitored.

Allowable Daily Exposure (ADE) (US FDA)

The daily dose of a substance at which no adverse effects are anticipated for any route, even if an exposure occurs for a lifetime. Acceptable Daily Exposure as defined by FDA and Permitted Daily Exposure (PDE) referenced in ICH Q3A(R2) [52].

Airborne Concentration

The concentration of a molecule of interest in air over a period of time. Collected by IOM or Cassette filters, typically requires concentration determined by specified method, duration of sample and average airflow rate over the duration to calculate the concentration expressed as mcg m^3/duration in minutes this requires calculation. This is the primary route of exposure occupationally and is rarely a cause of cross-contamination.

Airlocks

A room or chamber with two interlocked doors designed to maintain the pressure differential between two areas served by the airlock. With the door open to an area the control pressure is lost.

Alarm Level

A level at which the item being monitored reaches a level deemed to trigger a review and correction without suspending manufacture, typically between 1/10 and 1/5 of the absolute limit of failure.

Active Pharmaceutical Ingredient (API)

Active drug substance and intermediates which exhibit hazard, as opposed to excipients which are generally recognized as non-hazardous. For cross-contamination, the API of one compound has to enter another product.

Detection

One of the three numeric values used in FMEA analysis, the others are Severity and Occurrence, used as a factor to indicate how easily and consistently the exposure can be identified and quantified. It ranges for > 99.9% detection by automated means to undetectable by current means.

Boundaries

Used to describe areas that are separated and, where controls exist, to maintain that separation. Examples are HVAC, Area Classifications, AHU Zones, Room, Suite, Block, Facility, Site, Gowning, Access, Personnel, Material, Equipment, and product boundaries. All designed to control mix-up, retention, airborne and mechanical transfer.

Compounds (or products)

Term used to cover a formulation of Active(s) and Excipients.

Control and Monitoring

A system in which automation modulates performance to meet demand are incorporated and where the output is recorded and alarmed, requiring Technical and Operational reaction, and where failure to remedy in a set time leads to a reportable incident.

Cross-Contamination (ISPE Baseline® Guide: Risk-MaPP [11])

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

Emission

A detectable concentration escaping its process or containment boundary with the potential to become an exposure. It is not an Exposure.

Exposure

An emission that has been ingested by any route into a worker or patient at a level to cause harm or exceed the limit (OEL) (ADE).

Failure Modes and Effects Analysis (FMEA)

A risk assessment tool in which Severity, Occurrence, and Detectability are scored and ranked, with the objective of prioritizing risk, typically into three categories:

1. Cease manufacture until remediated
2. Continue manufacture but remediate within a stated time frame
3. Remediation not required

Gowning

Specialized single use or machine washable (if shown to be effective) clothing, designed to protect the operator from exposure and the product from contamination and cross-contamination, ideally comprising a single piece coverall, gloves, headgear, bootees and safety glasses.

Hazard (ISO/IEC Guide 51 [106])

The potential source of harm for cross-contamination; the ADE/PDE sets the degree of Hazard.

Health based Limit

A limit where no adverse effects are expected and are determined using toxicological and pharmacological data (i.e., ADE).

High Risk

In quantitative terms, the level of potential cross-contamination is above the ADE with a statistically relevant number of samples. In qualitative terms, the risk priority number (RPN) is unacceptable if it is at or exceeds Action level set by the company and takes all routes of cross-contamination into consideration.

Low Risk

In a qualitative risk assessment, it is when there is little or no perceived risk so that there is no need for remediation. The low risk RPN has to be determined, documented and justified.

Heating, Ventilation, and Air Conditioning (HVAC)

System providing the required air quality, quantity and pressure gradients to be protective of the product and operators. It is a key factor in establishing and maintaining boundaries.

Isolators

Rigid or flexible, devices which are capable of containing the product and where any emission is below the Alert level of concentration. It is normally either passively aspirated or connected to a ventilation system that is negative for non-sterile use and is positive for a sterile process. The performance should be routinely monitored for containment.

Maximum Daily Dose (MDD)

The total dose that is documented in the NDA or Abbreviated New Drug Application (ANDA) as the limit for daily consumption, it may not be realistic for the dosage being manufactured. MDD is expressed in weight of active/day for solids and weight of active per unit volume for liquids where the MDD is expressed in volume (e.g., 5 mg/ml MDD = 20 ml so there would be 100 mg in a MDD).

Realistically, in most cases the maximum number of tablets in a day is about 16, (there are exceptions) the best way to determine the MMD is to look at the manufactures recommendations to physicians or refer to a reputable source for recommended MDD. MMD's are used to determine how many MDD's are in a batch so that the limit of cross-contamination can be set.

Mechanical Transfer

It is the transfer of the Hazard on hands, feet, gowning, equipment, and packaging to another place where it can become an exposure to the occupational and patient populations. It is of particular significance at single dosage.

Medium Risk

A compound for which the ADE is expected to be below the alert level at all times, but which is determined from data to be close to the ADE alert level with a statistically relevant number of samples. In qualitative terms, the Risk Priority Number (RPN) number has to be determined, documented and justified.

Mix-Up

The manipulation of people, materials, and equipment documentation in such a way that a product is contaminated by an item from another product. The risk is that the contaminated product will be mislabeled as a result of the error. Normally captured by redundant assessment, however it is very difficult to detect.

Occupational Safety

The safety of the worker and prevention of exposure to the Hazard.

Occurrence

A rating factor used in risk analysis/assessment tools to indicate how often the exposure takes place considering plausible pathways. Occurrence is determined by data not perception.

Occupational Exposure Limit (OEL)

A health based air borne concentration which under exposure levels should be controlled for occupational safety.

Placebo

It is a substance that has no therapeutic effect, used to aid detection of cross-contamination.

Plant Garb

Uniform worn in the facility which is not directly in contact with Product. It protects both the operator and the product from contamination and prevents the mechanical transfer into the home on street clothing.

Patient Exposure

Exposure to a prescribed to cross-contamination of the prescribed drug by other drug substance taking into account the route of administration. Exposure occurs if the amount present in the daily dose exceeds the ADE or other health based limit.

Patient Safety

Protection of the patient from exposure.

Plausible Pathway

The route a cross-contaminating compound would have to take in order to contaminate another product in sufficient quantity to be above the ADE or health based limit.

Pressure Differential

The difference in pressure between two points typically across a filter or between a process room and a corridor to show the pressure gradient is being maintained.

Pressure Gradient

The designed pressure differential between rooms and corridors, and protective of the product and the worker. Needs constant monitoring and the ability to react to varying ambient pressure and changes in the usage of secondary supplies and exhausts. The use of flow rate monitoring leads to failures in maintain the desired gradient. (e.g., vacuum to a press which can be off or on and which will change the pressure differential unless the system modulates to compensate.

Restricted Access Barrier (RAB)

Is an enclosure around an aseptic process which is open at the bottom, so that any aerosol generated becomes an emission, but where intervention is via gloves.

Retention (ISPE Baseline® Guide: Risk-MaPP [11])

Carryover of material on product contact surfaces from one product to another in the same equipment used in a sequential or campaign manner; the residue or accumulated product on product contact surfaces.

Risk (ISO/IEC Guide 51 [109])

The combination of the probability of occurrence of harm and the severity of that harm.

Risk Products

The product deemed to have the greatest potential for cross-contamination. The risk may be different due to the scale of operation, the equipment used, and spatial and temporal separation. A risk product can also be vulnerable product.

Routes of Exposure

The route by which an Emission can become an Exposure, this differs between occupational and Patient populations.

Routine Performance Monitoring

A risk-based plan should be prepared for routine performance monitoring to show that a qualified system continues to perform as designed.

Safe Levels

For product quality, safe levels are any exposures at or below the ADE. For occupational health, safe levels are any exposures at or below the OEL. These levels are defined as not exceeding and therefore at a level that allows a statistically relevant and defensible statement of at or below the ADE or OEL.

A patient taking a therapeutic drug has an expectation that the benefits outweigh the harm the drug can cause. In the case of cross-contamination, there is no expectation of benefit from another substance in the product so there can be no tolerance for harm. By demonstrating that any exposure is significantly below the limit set by a qualified toxicologist using peer reviewed methodology, acceptable levels of risk can be determined. Specific Quality Risk Management Plans (QRMP) show how the facility, HVAC, gowning, procedures, flow routes and closed processing are all used to demonstrate a robust and redundant management of the risk of cross-contamination.

Safe Threshold Value

The amount of carryover of a residual compound (API, cleaning agent, degradant etc.) into the next product manufactured that can be taken by a patient over a lifetime without an appreciable health risk. The safe threshold value is calculated from the Acceptable Daily Exposure.

Severity (ICH Q9 [3])

A measure of the possible consequences of a hazard.

Shared Surface Area

The product contact surface area shared by the risk and vulnerable product. If the utilization of equipment is full monitored and controlled it is possible to assign equipment in such a way that the shared surface area is reduced, or particularly large surface area equipment may be dedicated.

Spatial Separation

Processes separated by at least two normally closed doors, with a pressure gradient protective of the separation, and by walls that are from floor to soffit. Be aware of contiguous interstitial spaces typically walls only extending to the ceiling that can and do provide a plausible pathway.

Surrogate

A substance used in lieu of the actual hazard, normally chosen as a worst case in terms of emission potential and because it does not pose an occupational risk.

Temporal Separation

Processes in the same areas separated by time and a full clean. Airborne concentrations dissipate over time. However, sedimentation onto surfaces and the dislodgement of material caught in occluded areas can cause cross-contamination.

Toxicologist

A suitably credentialed individual who assesses the hazard of a compound or reviews such assessment.

Vulnerable Product

A product determined by review to be vulnerable to cross-contamination; can also be a risk product.

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