



VOLUME 2

Oral Solid Dosage Forms

Third Edition



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VOLUME 2

Oral Solid Dosage Forms

Third Edition

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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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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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 changeover¹
- 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 “<u>What</u> 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 “<u>What</u> 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 “<u>Where</u> 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 “<u>Where</u> 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 “<u>How Big</u> 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 “<u>How Big</u> 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 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 to 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 design.

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 depreciable 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 increasingly 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 contamination.

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 cleaning 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 m³ 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/m³. Typical tablet poured densities lie in the range 700 to 900 kg/m³.

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/m³. 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/m ³ < 10,000 µg/m ³	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
	Down Flow Booth	< 10,000 µg/m ³ > 20 µg/m ³	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
	Isolator	< 20 µg/m ³	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/m ³ < 10,000 µg/m ³	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
	Down Flow Booth	< 10,000 µg/m ³ > 20 µg/m ³	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
	Isolator	< 20 µg/m ³	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/m ³ to < 1 µg/m ³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
	Drums with Transfer Systems	< 10,000 µg/m ³ to < 1 µg/m ³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
	Bulk Bag and Docking Stations	< 10,000 µg/m ³ to < 1 µg/m ³ (see Note)	NEMA4/4X, IP66, or local equivalent	CL-2 Div II ATEX Zone 2
Blending	Post Hoist/Column IBC	< 10,000 µg/m ³ to < 1 µg/m ³ (see Note)	NEMA4/4X, IP66, or local equivalent	Not Applicable
	V Blend	< 10,000 µg/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (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/m ³ to < 1 µg/m ³ (see Note)	NEMA4/4X, IP66, or local equivalent	
	Fluidized Tangential	< 10,000 µg/m ³ to < 1 µg/m ³ (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/m³. 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/m³, 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/m³, 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