

GOOD PRACTICE GUIDE:

Containment for Potent Compounds





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Preface

This Good Practice Guide started out as an English translation of *ISPE D/A/CH: Containment Handbuch (Edition 1)* with the goal of expanding the content to the global community. The resulting document includes extensive information and guidance on all aspects of containment for handling potent compounds in the pharmaceutical industry. The multinational team consisted of engineers, toxicologists, hygienists, and analysts from major pharmaceutical companies and suppliers. A collaboration of the ISPE Containment Community of Practice and the ISPE D/A/CH Affiliate Containment Community of Practice, these experts drew on their extensive experience to consolidate this multidiscipline knowledge into one document.

It is understood that there is no single technical solution applicable in all situations, for all companies, anywhere in the world. The intent of this Guide is to educate users by presenting the issues and background associated with controlling the uncontrolled transmission of potent compounds in the pharmaceutical industry, and the numerous technologies that may be applied when specifying new containment solutions or evaluating existing units.

Discussion of proprietary technologies is included to convey practical information to the readers. In no way does this Guide endorse or promote the use of these items.

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Table of Contents

1	Introduction	7
1.1	Background	7
1.2	Purpose and Objectives	7
1.3	Scope and Usage	8
1.4	Key Concepts	9
2	Fundamental Considerations	11
2.1	The Value Proposition	11
2.2	The Term: Containment	11
2.3	Primary and Secondary Containment	12
2.4	Occupational Exposure Limits and Hazard Categories	13
2.5	Limit Values for Containment Planning	15
2.6	Regulatory Requirements	16
2.7	Basic Concepts	17
3	Deciding the Containment Strategy	19
3.1	Definition of Containment Strategy	19
3.2	Determining the Exposure Potential	24
3.3	Other Considerations for Containment Strategies	29
4	Risk Assessment	31
4.1	Risks	31
4.2	Risk Management Process	31
4.3	Methods	33
4.4	Risk Assessments in the Manufacture of Potent Compounds	33
4.5	Handling Risk Assessment Outcomes	34
5	Consideration of GMP Aspects	35
5.1	Regulatory Links between Occupational Safety and GMP Aspects	35
5.2	Aspects to be Considered with regards to a Joint Risk Assessment: GMP and Occupational Health	39
5.3	Achievability of the Protection Goals	40
5.4	Occupational Hygiene Limit Values in the GMP Context	45
6	Lifecycle of Containment Solutions	49
6.1	Conception and Planning	49
6.2	Procurement	49
6.3	Factory Acceptance Tests, Site Acceptance Tests, and Commissioning	53
6.4	Routine Operation of Equipment	53
6.5	Decommissioning	58
7	Process Requirements	59
7.1	General Process Requirements	59
7.2	Production of APIs	67
7.3	Pharmaceutical Production – Solid Dosage Forms	94
7.4	Pharmaceutical Production – Dry Powder Inhalers	118
7.5	Continuous Manufacturing	119
8	Containment Systems – Primary Containment	121
8.1	Barrier Systems	122
8.2	Extract-Based Systems	128
8.3	Process Interfaces and Transfer Ports	143
8.4	Material Transfer by Pneumatic Conveying Systems	166
8.5	Sampling Systems	168

9	Containment Systems – Secondary Containment	173
9.1	Cleanroom Classifications	173
9.2	Cleanrooms.....	173
9.3	Spatial Concepts.....	174
9.4	Decontamination/Containment Systems (Cleaning Systems)	193
9.5	Ventilation	197
9.6	Services Media	197
10	Containment Systems – Air Cleaning/Filtration Technology	199
10.1	Mechanical Separation Systems.....	199
10.2	Air Filters.....	201
11	Occupational Hygiene	213
11.1	Introduction	213
11.2	Containment Performance Assessments.....	213
11.3	OH Sampling and Analytical Methods.....	221
12	Cleaning/Waste Treatment.....	225
12.1	Process Systems	225
12.2	Rooms (Secondary Containment).....	227
12.3	Air Locks	227
12.4	Cleaning Media	230
12.5	Contaminated Waste	234
12.6	After-Treatment of the Waste	234
12.7	Cleaning Limit Values (Occupational Safety and GMP).....	234
13	Administrative and Human Elements	235
13.1	Training	235
13.2	Unplanned Emission/Spillage Recovery Procedures.....	235
13.3	Safety Data Sheets	236
13.4	Personal Protective Equipment.....	237
13.5	Exposure Monitoring	238
14	Appendix 1 – Executing an Occupational Hygiene Air Sampling Plan.....	239
14.1	Survey Preparation	239
14.2	Employee Interface/Communication	239
14.3	Sampler Deployment	239
14.4	Field Data Collection	239
14.5	Process Information	240
14.6	Use of Exposure Controls	240
14.7	Product Use	240
14.8	Sampling Period.....	241
14.9	Quality Assurance	241
15	Appendix 2 – Collection and Submission of Occupational Hygiene Samples... 245	
15.1	Preparation for Sampling	245
15.2	Post-Sampling Preparations and Storage Pending Shipment and Analysis	245
15.3	Shipping Procedures.....	245
16	Appendix 3 – References	247
17	Appendix 4 – Glossary	251
17.1	Acronyms and Abbreviations	251
17.2	Definitions	254

1 Introduction

The potency of pharmaceuticals, including Active Pharmaceutical Ingredients (APIs) and drug products, has been increasing over the last few decades, presenting increasing risks in pharmaceutical manufacturing from handling and processing potent compounds. Protecting production workers (including cleaners, analytical, and other staff), patients, and the environment must be achieved during their manufacture. Various containment solutions and other preventive measures are deployed to reduce the risk to a tolerable level.

This *ISPE Good Practice Guide: Containment for Potent Compounds* describes the essential elements to consider when implementing containment technologies, and spans the lifecycle from planning, deployment and operation, to decommissioning.

1.1 Background

Containment encompasses all measures (including very simple ones) that limit the spread of substances or agents potentially leading to worker exposure. The planning, construction, commissioning, operation, and performance verification of containment facilities pose a great challenge for producers, engineers, safety professionals, operators, and suppliers. There are a number of regulations, laws, decrees, Health, Safety, and Environment (HSE) standards, Good Manufacturing Practices (GMP), and directives that typically must be met.

Containment protects the employee and environment from the adverse and/or pharmacologic effects of the product. This protection is achieved by preventing emissions from processing activities that lead directly or indirectly to worker exposure by one or more entry routes (inhalation, ingestion, skin absorption, etc.). Further protection benefits include preventing airborne powder deposition on the floor or other surfaces, which can lead to contamination in other products, or in the environment through, for example, subsequent release into wastewater systems. Additionally, containment measures have the potential to protect the product from the employee (inadvertently contaminating the product).

Process containment or primary containment may reduce the requirements for secondary containment, high room air change rates (decreasing energy demand), and rigorous room entry procedures (reducing the need for scrubbing in, gowning, using respiratory Personal Protective Equipment (PPE)).

1.2 Purpose and Objectives

This Guide has been developed through the collaboration of experts from various disciplines and geographic regions. The aim is to reach a common understanding and interpretation of requirements on containment technologies to better meet worker and manufacturers' needs, reduce production costs, and support product quality.

Containment involves many different disciplines, concepts, and technologies to protect the product, people, facility, and environment. This knowledge base is widely dispersed. One of the objectives of this Guide is to consolidate this knowledge into one document that describes and discusses the methodologies, processes, and technologies commonly used in the pharmaceutical industry.

To create awareness and encourage the effective use of containment equipment, this Guide aims to educate pharmaceutical industry engineers, occupational hygienists, managers, and executives regarding:

1. The evolving types of containment equipment and facilities, their rapidly improving performance, and the innovative methodologies being developed to enable effective performance

2. Driving these technologies into use by clearly demonstrating their value in terms of employee health, financial benefits, product quality, patient safety, productivity, energy savings, and simplified regulatory compliance

Additionally, this Guide has been developed to assist pharmaceutical companies in applying appropriate and proportionate containment measures that provide benefits such as:

- Develop a common understanding of the issues associated with effective containment design, selection, and operation
- Promote a risk-based approach to ensure the containment solution mitigates the risk to personnel and product while avoiding over-engineering
- Diminish the dependency and necessity for PPE and over-gowning, thus improving ergonomics, reducing time needed for gowning and degowning, and mitigating user exposure to associated potent chemical contamination
- Increase productivity, yield, and product conformity (i.e., higher quality)
- Decrease the risk for contamination
- Decrease the need for excessive ventilation (room air changes), resulting in lower energy costs while positively affecting climate change
- Decrease the risk to the environment by the loss of API (an important emerging issue with antimicrobial resistance, hormones, and API toxicity to aquatic organisms)
- Increase productivity by reducing production downtime via shortened changeover times, quicker transfer of product between unit operations (via vacuum transfer for example), decreased time spent gowning, degowning, and scrubbing in.
- Decrease the risk for quality issues related to particulate matter or other contamination, degradation, and loss of asepsis

1.3 Scope and Usage

This Guide applies to the planning, constructing, commissioning, operating, and conducting performance verification of new containment units, as well as for upgrading, modifying, or decommissioning existing units. It covers pharmaceutical installations that produce solid, semisolid, and liquid dosage forms, sterile or non-sterile, API, clinical samples, along with laboratories.

This Guide can also aid in assessing the compliance of existing containment facilities with current industry regulations and trends. It assists in the selection of state-of-the-art technologies. Discussion of proprietary technologies is included to convey practical information to the readers. In no way does this Guide endorse or promote the use of these items.

Explanations on PPE, explosion protection, biosafety and aseptic containment are out of scope for this Guide, as are vapors, aerosols, and flammable contents. While mentioned in this Guide for completeness, the requirements for these topics are found elsewhere in the appropriate regulations and guidance documents.

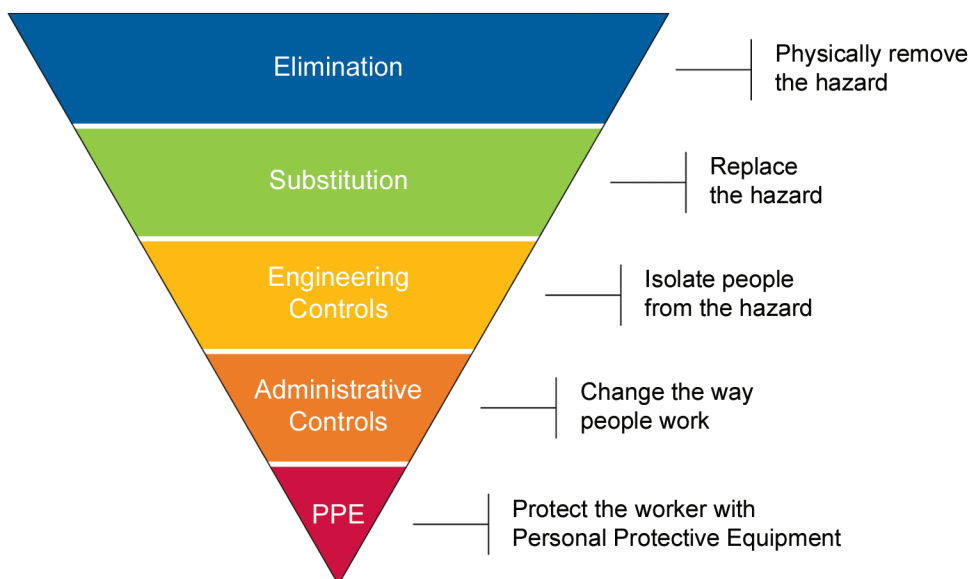
This Guide is neither a technical standard nor a regulation. It is not intended to replace existing legislation or regulations that apply to facilities of this type.

1.4 Key Concepts

1.4.1 Hierarchy of Control

This Guide follows the Hierarchy of Controls approach (see Figure 1.1), which is a commonly accepted principle to control HSE risks. Note that in parts of Europe, China, and Japan, these controls are legally mandated.

Figure 1.1: Hierarchy of Controls (Adapted from NIOSH [1])



Containment best practice starts with:

1. Elimination of the hazardous or process step completely. Though the potent compound in most cases cannot be eliminated due to process registration, the control of the hazard may be enhanced, if possible, by reducing the quantities handled at a given time or changing its physical form to a less or non-dusty solid or a liquid solution.

Where this cannot be achieved, the following approaches (in order of preference) should be put in place:

2. Substitution with a less hazardous substance
3. Implementation of engineering controls (containment of the process step)
4. Implementation of administrative controls (training in best technique or limiting time of exposure by job rotation or other means)

In the event that the first three of the aforementioned, preferred methods are not feasible, then personal protection equipment must be used. Examples of PPE include respirators, air hoods, safety glasses, and impervious gloves and garments.

Note: PPE should be used as a last safety measure, that is, not as primary protection for preventing exposure.

1.4.2 Key Terms

This section introduces key terms as they are used in the context of this Guide.

Potent Compound is an ingredient that has an effect on human beings or other organisms at a very low level of exposure. In this Guide, potent compound is used for substances that may be highly hazardous or toxic to exposed workers.

Industrial/Occupational Hygiene – The use of the term *industrial* or *occupational* is a regional distinction. This Guide uses Occupational Hygiene.

Anticipated Performance of a Containment System:

High Containment Systems typically are based on barriers with highly controlled access for introducing/removing materials. The outside exposure to workers or environment will be very low and allows handling of high potent compounds.

Low Containment Systems are typically systems with limited access but allows certain open handling.

Note: Open extract-based systems such as local extracting systems do not typically provide effective containment performance with high or medium-risk activities.

Level of Barrier Containment:

Full Barrier System – fully contained, such as a high-performance isolator

Partial Barrier System – occasionally opened or has partial barriers, for example, Restricted Access Barrier Systems (RABs) and fume hoods

Open Barrier System – open extract-based systems with uncontrolled access, in most cases not effective for dust control for medium or low Occupational Exposure Limits (OEL) values

2 Fundamental Considerations

2.1 The Value Proposition

Thinking of containment as a risk-based approach leading to *containment only when needed* has evolved to the belief that containment benefits much more than simply worker safety. The potential benefits of contained systems are also of significant interest to patient safety, regulators, shareholders, and the environment. Contained systems may not only eliminate the need for PPE, but may also reduce excessive sophisticated (time consuming) procedures for gowning, extensive room cleaning between batches and campaigns, and high levels of general and local exhaust ventilation leading to high energy costs or labor-intensive steps such as manual transfers between process steps.

This Guide is a tool to select new or assess existing containment solutions. This Guide also seeks to demonstrate that the benefits are substantial to overall productivity, quality, and patient protection, in addition to mitigating potential worker over-exposures. That being said, there may be operations where the disadvantages of containment outweigh the benefit. An analysis of the pros and cons should be conducted when there is a question.

2.2 The Term: Containment

The term “containment” in this Guide is the limitation of the spread of a substance or an agent by the application of engineering-based controls. Containment should be considered as an engineering control, that is, control at the source of emission or close to it. Engineering controls are also called collective protection measures as everyone in the work area benefits from them, contrary to PPE, which only protects those persons who wear it.

Containment comprises all measures (including very simple ones) that limit the spread of substances or agents. Containment is always relative, that is, containment does not always simply refer to a so-called closed system. In practice, the question is not, “Is containment necessary?” or “Is there containment?” but, “How much containment is necessary?” or “What level of containment is in place?”. The decision to invest in containment should be based on the protection level needed for personnel and/or product.

The containment solution should be based on the evaluation of the potency, toxicity, and biological activity of the material handled, and other factors such as the amount and volatility of the material and the duration of exposure. Many other risk factors may affect the exposure risk in particular cases; these are considered in more detail later in the Guide. Processes in which potent substances are handled may require more sophisticated containment. Containment should also consider GMP aspects regarding contamination, as a containment system is a powerful tool to support the reduction of contamination by airborne and mechanical transfer.

There is no such thing as a completely closed unit. The improvements in analytics make it possible to detect substances in ever smaller amounts; traces may be detected even outside of units for which extremely high containment efforts have been made. One of the drivers for these analytical refinements is that new medicines are becoming increasingly target specific and are thus more effective at ever-decreasing doses. They are not only potent for the patient, but also for the operator involved in their manufacture. Small residues may become critical for the patients as well as for the worker and can require special precautions in manufacturing areas in which other products may also be manufactured. In such multi-product facilities, besides occupational health aspects, GMP aspects related to contamination need to be considered.

In planning containment for equipment, the complete flow of both personnel and material must be considered. Protective measures must be planned not only for production processes, but also for peripheral and ancillary processes. Ancillary processes include cleaning, maintenance and repair of equipment and exhaust air filter installations, and the disposal of cleaning materials. Particular attention should be paid to the disposal of waste (see Chapter 12). Also, likely failure modes need to be taken into account.

2.3 Primary and Secondary Containment

Primary containment refers to those measures that reduce the spread of a substance from the actual production equipment. (See Chapter 8.) Secondary containment refers to the measures that reduce the spread of the substance that escaped primary containment. If a process step can be eliminated or replaced with a safer alternative, that should be given priority. (See Chapter 9.)

Examples of primary containment measures are:

- Ventilated balance enclosures, or other ventilated enclosures
- Isolators used for weighing APIs
- Continuous liner systems, e.g., for discharging dryers
- Housings for tablet presses and attached devices such as metal detectors, In-Process Control (IPC) samplers, dedusting units

Examples of secondary containment measures are:

- Cleanrooms
- Air lock systems and pressure gradients between corridors and the production room
- Adhesive floor mats to reduce inadvertent transfer of material via footwear

When designing and planning installations, it is important that the primary and secondary containment systems are aligned. If the primary containment is robustly effective, it may be possible to achieve savings on secondary containment. The focus should always be on the optimization of the primary containment, as this offers the best protection for workers, and minimizes airborne and mechanical spread of the substances being handled.

Recognition of this principle determines the planning of the installation. Installation should be planned from the inside out. First, equipment should be selected that provides suitable containment for the intended range of products. Next, the design of the secondary containment needs to be determined. Material that is effectively contained by the primary containment devices/system cannot spread further and cause a remote issue. That is particularly relevant for potent products where problematic emissions of material from the equipment may not be visually detectable.

Finally, based on the secondary containment of the production rooms, the layout of the facility, the space requirements for it, and then the structure of the building can be elaborated.

These fundamental design principles are sometimes difficult to realize, in particular when equipment is to be installed in an existing structure limiting the design layout.

2.4 Occupational Exposure Limits and Hazard Categories

Determining the necessary level of containment should begin with the hazard assessment. The containment solution required to control the exposure of workers is directly related to the hazards of the chemical substances handled and the exposure potential of the operations performed (volume, dustiness, level of energy, etc.). Occupational toxicologists perform hazard assessments that result in OELs, DNELs, etc.). These OELs represent nominally safe airborne concentrations of chemical substances for workers. OELs allow engineers to determine a containment solution that limits worker exposure appropriately. Similar toxicological assessment to determine the hazard can also deliver Permitted Daily Exposures (PDEs) or Acceptable Daily Exposures (ADEs)¹. They are used to determine GMP-relevant cleaning limits in shared facilities.

Health-Based Exposure Limit (HBEL) is an umbrella term for the various limits of this type (e.g., OELs, PDEs). They have become significantly more important since the EMA established new requirements for cleaning multipurpose systems [2]. The cleaning limits must be substance-specific and toxicologically and scientifically derived. These requirements are in Chapters 3.6 and 5 as well as in Annex 15 of the EU GMP guidelines [3]. On 1 July 2018, PIC/S (Pharmaceutical Inspection Cooperation Scheme) adopted the new Chapters 3 and 5 of the EMA GMP Guideline word for word as Part I of the “Guide to good manufacturing practice for Medicinal Products” [4]. On the same date, the EMA “Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities” [2] was also adopted by PIC/S [5].

The EU Guideline [2] calls this toxicologically derived limit value a health based exposure limit (or PDE). The term ADE is used synonymously (see also the *ISPE Baseline® Guide: Volume 7 – Risk-Based Manufacture of Pharmaceutical Products (ISPE Baseline Guide: Risk-MaPP (Second Edition))* [6]).

The PDE is based on the scientific interpretation of all data available on the relevant substance (e.g., clinical, preclinical data, comparison with related molecules). The PDE is defined as the dose at which no negative effects occur even in the most sensitive population group and with lifelong administration. Since the bioavailability of a substance can vary for the different routes of uptake (inhalation, oral, parenteral, and dermal administration), PDEs are defined for all relevant routes of uptake. PDEs are used to calculate OELs as well as the cleaning limit values for product contact surfaces in multipurpose systems. Depending on the route of administration of the next drug to be produced on the equipment, the corresponding PDE raw data (oral, parenteral, etc.) is used in the calculation.

This Guide focuses in particular on compliance with OELs by means of containment. The standards of the EMA [2] for the derivation of scientifically based health-based exposure limits are congruent with the toxicological principles that have been used in occupational toxicology for the derivation of OELs for decades.

Similar limit value derivation also applies in other chemical legislation around the world, for example, by the different REACH legislation² in Europe [7], Korea [8], and China [9]. Here, as with OELs and PDEs, derived no-effect concentrations are established for different exposure scenarios.

By definition, PDEs apply to lifelong exposure. OEL values are set for the inhalation route and for 8 hours per day. They also refer to chronic exposure (5 days per week, a whole working-life span). Where there is a risk of unwanted effects from exposure peaks, Short-Term Exposure Limits (STELs) are defined. Often, the reference period for such STELs is 15 minutes.

Even if OELs and PDEs are derived according to the same principles (and often in one operation), a clear distinction must be made. OELs determine the level of containment required to provide worker exposure control. PDEs are used to calculate cleaning limit values for surfaces that come into contact with products in multipurpose systems (e.g., Maximum Allowable Carryover (MACO); Maximum Safe Carryover (MSC)).

¹ The terms PDE and ADE are used synonymously [2]. See also *ISPE Baseline Guide: Risk-MaPP (Second Edition)* [6]).

² REACH stands for Registration, Evaluation, Authorisation and Restriction of Chemicals.

OEL is used here as a generic term for all workplace limits. Companies, occupational health authorities, or professional associations may have proprietary names for their OELs.

The derivation of the PDE and OEL, takes place in several steps:

- Purely qualitative determination of the critical effect of the substance.
- The maximum daily dose is determined at which the critical effect will not occur.

The PDE or OEL can almost never be read directly from the available data. It must be derived by interpretation of the available information and the use of adjustment factors.

- When assessing pharmaceuticals, the important data to consider are:
 - Clinical data from the use of the drug in humans
 - Preclinical data, e.g., animal test data, *in vitro* activity data
 - Data from better studied related molecules

The EMA guideline [2] explains how health based exposure limits should be determined. (This is also discussed in Chapter 5 of this Good Practice Guide).

Guidance for setting PDEs/ADEs can be found in:

- EMA: Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities [2]
- PIC/S: Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities [5]
- ASTM E3219 Standard Guide for Derivation of Health-Based Exposure Limits (HBELs) [10]
- *ISPE Baseline Guide: Risk-MaPP (Second Edition)* [6]

It is common practice to also derive OELs from these GMP limit values (PDEs, ADEs).

As, by definition, OELs are set for the inhalation route of exposure, it is customary to always set a PDE for the inhalation route, even if the inhalation route has no GMP relevance. In practice, PDEs are often found without specification of the route of exposure to which they apply. In these cases, the simplified formula "OEL = PDE divided by 10 m³" can lead to incorrect OELs, for example, when the PDE was calculated for the oral route of absorption, but the substance is poorly absorbed orally (but significantly better absorbed when inhaled). Similarly, OELs may be too low if they are derived from parenteral PDEs and uptake by inhalation is known to be lower.

Note: The derivation of an OEL from a PDE without a bioavailability assessment is discouraged.

Another aspect might be that OELs are set for healthy workers, but PDEs are for the most vulnerable in the general population. Therefore, in some cases, higher daily exposures can be allowed for workers than for patients. Some toxicologists work with a default factor that sets the OEL higher than it would result from direct derivation from the inhalation PDE. Others do not make this correction, because justifiable correction factors are usually so small that they are irrelevant in practice, but can give rise to discussions. For certain substances such as teratogens, no correction is allowed, because the most sensitive subpopulation is part of the working population.

The calculation is normally performed first for the exposure pathway for which the best data is available. The PDEs for the other exposure routes and the OEL are then derived from this.

If there are not enough data on a substance to assign an “exact” OEL to it, categorization systems are used that assign the substance to a health hazard category (from little to extremely active). These categories are also referred to as classes or bands. Occupational Exposure Band (OEB) is the most frequently used term. See Section 2.6.

2.5 Limit Values for Containment Planning

Containment systems are generally planned based on OELs. OELs are usually expressed as 8-hour Time-Weighted Averages (8-hour TWA).

If a substance has an OEL of, for example, $100 \mu\text{g}/\text{m}^3$, then a person may also be exposed to concentrations of higher than $100 \mu\text{g}/\text{m}^3$ for a limited time. The prerequisite is that these times of higher exposure are compensated in the same shift by time periods of lower exposure, so that an 8-hour mean value of $100 \mu\text{g}/\text{m}^3$ is not exceeded. With regard to the exposure peaks, care must be taken to ensure that these peaks do not have any undesirable health effects, such as irritating effects.

In principle, it would be acceptable for a person to work 4 hours on equipment where the OEL is exceeded by a factor of 2 if it can be guaranteed that this person will have no other exposures to the same or similar substances in the same shift. This requires organizational measures and leads to limitations in the deployment of the staff. In addition, practice shows that the need for such organizational restrictions is not always taken into account or well documented and soon forgotten. This may lead to a risk of overexposure resulting from the cumulative doses from different activities that the person carries out during the same shift.

Modern systems, especially multipurpose systems, are planned in such a way that they do not depend on organizational measures for the protection of their staff. Work-task assignments can then be made in a completely flexible manner.

To ensure that it is not possible – or at least very improbable – to exceed the OEL during normal operations, many companies have defined Design Exposure Limits (DEL).

The DEL is derived from the OEL of the “most potent” substance or product in the portfolio of a particular piece of equipment. The DEL is defined as the maximum safe exposure level averaged over the duration of each unit operation and not as an 8-hour average unless the operation happens to last 8 hours. A DEL is always equal to or lower than the OEL.

An example of a DEL system:

- DEL period of reference: The duration of the unit operation (e. g., 8 hours for a packing machine, 10 minutes for a powder transfer process)
- Differentiation between short and long unit operations:
 - Long: duration more than 2 hours
 - Short: duration less than 2 hours
 - > DEL for long unit operations: 50% of the OEL (average over the duration of the unit operation; often less than 8 hours, but can be up to 8 hours)
 - > DEL for short unit operations: 100% of the OEL (average over the duration of the unit operation, not over 2 hours)

2.6 Regulatory Requirements

Regulations covering the GMP aspects of containment include:

- EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guidelines (particularly Chapters 3 and 5, and Annex 15) [3]
- EMA: Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities [2]
- PIC/S: Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities [5]
- US: FDA 21CFR211 Current Good Manufacturing Practice for Finished Pharmaceuticals [11]

The basic requirements for worker protection for the EU are laid down in the framework directive 89/391/ EEC [12]. It states that the employer has a duty to protect employees from health hazards at the workplace. To do this, the employer must carry out and document the corresponding risk analysis.

Similar laws also apply in Switzerland [13], the UK [14], the US [15], Canada [16], most of Latin America, and some parts of Asia. These regulations reflect good Occupational Hygiene (OH) practice. The UN International Labour Organization (ILO) [17] has also included these principles in its recommendations and guidelines (e.g., “Guidelines on occupational safety and health management systems” [18]), which have been ratified by many countries, even if they do not explicitly have such provisions in their regulations. The same rules can also be found in all relevant textbooks on health protection at work.

Regulations and laws stipulate that workers must primarily be protected by technical measures (also known as collective protective measures) and that PPE can only be used as the primary protection against overexposure if no feasible technical measures exist.

In principle, the risk from hazards at the workplace can be described using the following formula:

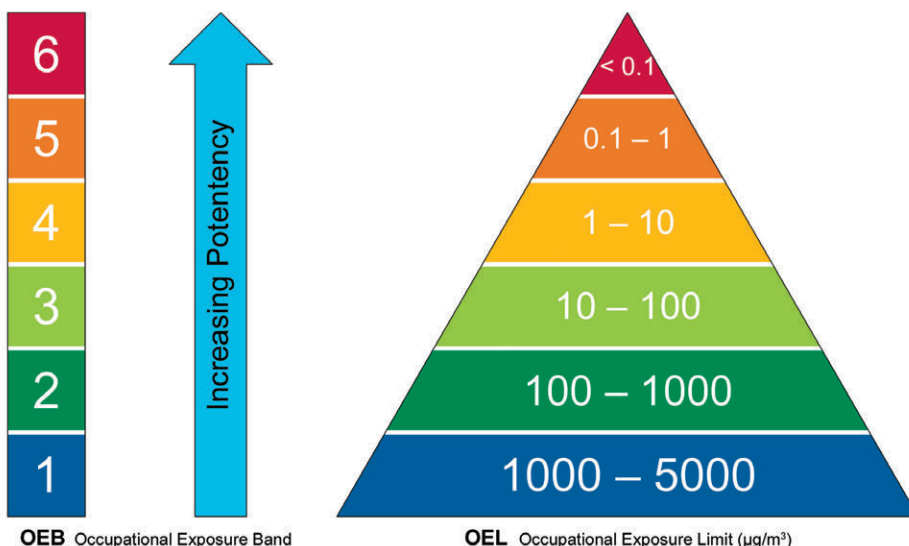
$$\text{Risk} = \text{Hazard} \times \text{Exposure}$$

This means that a risk can only be defined if information on both factors, hazard (in this case: the toxicological-pharmacological properties of the materials) and exposure (in this case: the level of exposure to these materials), is available. The result of the toxicological-pharmacological properties/the occupational toxicological evaluations, the hazard element, is the OEL. OELs are typically derived in the same scientific assessment process along with PDEs/ADEs. See Section 1.4.

OELs also exist in official lists and from recognized expert groups, such as TLVs (ACGIH, USA [19]), MAKs (DFG, Germany/Suva, Switzerland [20]), AGWs (AGS, TRGS 900, Germany [21]), VME (INRS, France [22]), and PELs (OSHA, USA [15]), but these are not discussed here as they are usually set for commonly used industrial chemicals.

If the data is insufficient to set a refined OEL for a substance, it may be placed into a health hazard category, ranging from low potency to high potency for the substance. An example is shown in Figure 2.1. These categories are also referred to as classes or bands. The most frequently used term is Occupational Exposure Band (OEB). These categorization systems are not harmonized and mostly comprise 4 to 6 categories, whereby the least potent substances are assigned to Category 1 and those with the highest potency are assigned the highest category number. If a substance is “only” categorized without having its own OEL, the conservative (“high-potent”) end of the category is generally used as the de facto limit value and thus, as the driver for the level of containment.

Figure 2.1: Compound Classification



2.7 Basic Concepts

2.7.1 Building Concept

Whether one is dealing with a new or existing building, there should be a conceptual description in which all the regulatory requirements (GMP, HSE, etc.) are described. This chapter does not discuss building regulations, regulations for the prevention of fire and explosion, earthquake protection, or similar. Here, the requirements are only considered from the worker exposure point of view.

Special building concepts may be required where specific identified substance classes are not permitted to be manufactured in shared facilities and must, as a result, be manufactured in dedicated facilities. This requirement for dedication may not only be applicable for production rooms and the corresponding air locks, but also for utilities and media such as liquids, gases, and ventilation systems. For more information, see *ISPE Baseline Guide: Risk-MaPP (Second Edition)* [6].

The substance classes that may not be produced in the same facilities used for the production of other APIs include:

- Highly potent allergens such as beta-lactams, e.g., penicillin or cephalosporins
- Radiopharmaceuticals
- Material of an infectious nature unless validated inactivation and/or cleaning procedures are established and maintained
- Ectoparasiticides, e.g., substances for the treatment of lice

For all other products, a risk analysis must be carried out to show whether a multipurpose operation of the facilities concerned is permissible, and that the building concept can fulfill all requirements.

GMP guidelines published in the US [11] and Europe [3] generally agree that multipurpose operation of facilities is not permitted if:

- The risk cannot be adequately controlled by operational or technical measures (e.g., sufficient cleaning is not possible)

- Scientific data from the toxicological evaluation does not support a controllable risk (e.g., allergenic potential from highly sensitizing materials such as beta-lactams), i.e., it is impossible to define a scientifically well-founded PDE/ADE
- The relevant residue limits determined from the toxicological evaluation cannot be detected by validated analytical methods (i.e., there is no analytical method sensitive enough to show that cleaning has been sufficient)

Once the decisions have been made concerning which substances or products are to be manufactured in which areas and which containment requirements result from the various substance data, the planning for the actual production areas may begin.

The entire facility, including processing rooms, must be depicted in a site plan. This should include layouts, air quality classification drawings (ISO 8/Controlled Not Classified (CNC)/Not Classified (NC) area, etc.), HVAC pressure diagrams, HVAC distribution diagrams/PIDs, personnel and equipment movement diagrams, gowning locations and standards, room finish details, etc.

2.7.2 Administrative/Organizational Controls

Labor laws in most countries stipulate that technical measures are to have precedence over administrative controls. Technical measures are also considered to be more reliable than administrative controls.

While important, administrative controls mainly support the efficacy of technical protective measures and prescribe actions to be taken in the event of a technical failure. Typical examples of this are the limitation of exposure periods by task rotation, repair and maintenance plans, Standard Operating Procedures (SOPs), and signs indicating mandatory or forbidden behavior. Further discussion is found in Chapter 13.

Operators must be periodically trained on all organizational measures with attendance and details of training sessions documented. See Chapter 13.

2.7.3 Flow of Personnel (Operator Movement)

The flow of personnel, materials and equipment must be clearly regulated. This can be documented in various plans such as the layout plan, the site plan, the building plan, or the floor plan.

Depending on the classification, cleanrooms must be accessed via appropriate air lock systems with a controlled separation of zones. Putting on PPE and removing it again often takes place in the air lock, as does decontamination and storage. Short paths should be aimed for. Detailed information on technical design is described in Chapter 9.

2.7.4 Flow of Material

The flow of material can be described as the chain of process transportation, provisioning, processing or manufacturing, testing, and storage, or also the sequence of the individual process steps from the raw material to the finished product. Depending on the spatial arrangement, it is possible to differentiate between the horizontal and vertical flow of material and even a mixture of both.

The flow of material must be clearly regulated and depicted in appropriate material flow plans that should be part of a change control system (see also Chapter 9). In general personnel flow and material flow should be segregated.

The introduction and removal of materials should be carried out via appropriate material air locks. Externally soiled containers must be cleaned in the air locks in order to avoid contamination with other materials, and also to prevent unprotected workers from coming into contact with the substance.

3 Deciding the Containment Strategy

3.1 Definition of Containment Strategy

Following the standard Hierarchy of Control approach, unless elimination or substitution of potent compounds can be achieved, an engineered containment approach should be applied. The definition of the containment approach and the selection of appropriate primary engineered containment systems and supporting secondary containment and facility design approaches then need to be developed. This process incorporates an assessment to define the scope and severity of risks involved in all activities associated with the facility, including all relevant significant factors that may affect the mitigation selection process. The containment requirements are defined by a full understanding of the processes, materials, and other factors affecting the risk to worker, products, environment, etc., followed by a risk assessment approach to define whether, and if so what, additional controls might be required. Once completed, the assessments and the supporting decisions can be incorporated into a containment strategy document detailing the controls (primary/secondary/facility/administrative/PPE) proposed to mitigate the risks to tolerable levels.

There are multiple benefits provided by the production of the containment strategy at the start of the system design process:

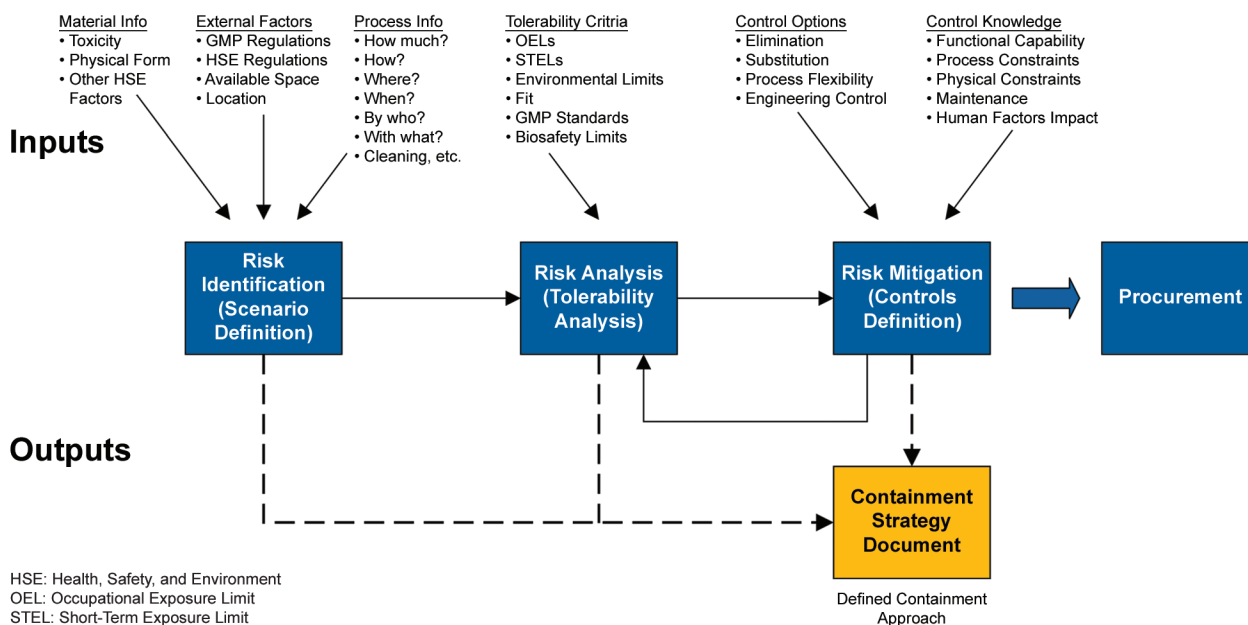
- A common understanding of the risks associated with activities and materials is established early in the project, with a clear definition of how they will be managed and controlled.
- A standardized coherent approach is defined to apply to similar risks subsequently identified, avoiding a case-by-case approach which may result in wide range of different technical approaches being applied across a facility which may be difficult to maintain and justify to users and regulators.
- Following project completion and performance testing of the installed systems, the containment strategy provides a model definition of risks and effective controls applicable to a particular application, e.g., laboratories, tablet manufacturing etc., which can be used as a starting point for similar future installations.

Ideally a single general control piece of equipment should be applied to mitigate potential exposures, with alternative approaches applied only where a suitable practical solution in line with the general principle and/or industry standards is not available. The containment strategy should be agreed at the concept/planning stage, initially at a high level with the option to develop to a more detailed level as design progresses. The Hierarchy of Controls (elimination/substitution/engineering controls/administrative controls/PPE and Respiratory Protection Equipment (RPE)) should be applied from the start to ensure that effective exposure control is in place. For example, a “high-containment” facility based on the use of closed processes or engineered containment (isolators, etc.) to control emissions should only rely on the use of PPE for rare occurrences (e.g., emergency spill recovery) or where effective practical primary and secondary containment is not possible.

At a more detailed level, the preparation of a matrix appended to the containment strategy document listing all identified potential emission risks relevant to the specific installations and activities with associated controls and justifications can be useful to record the decision made, and the assessed risk and basis of the system selection.

The purpose of the Containment Strategy document is to define the “What” (exposure risk), the “How” (how it is to be controlled), and the “Why” (the background to deciding on the control approach).

The definition of containment requirements and identifying “best fit” containment or other exposure controls is a logical process requiring the input of appropriate information or knowledge at appropriate stages as shown in Figure 3.1.

Figure 3.1: Defining Containment Requirements Process Flowsheet

3.1.1 Risk Identification

The inherent risk of a process is a function of inherent material toxicity and other scenario-specific factors which affect the likelihood of emission/transmission/exposure. The main factors normally considered as affecting the latter include, but are not limited to:

- The process to be carried out
- Duration of emission and associated potential exposure(s)
- Details of the process equipment ("openness," energy input, material quantity present)
- The relative location of the potentially exposed individual to the emission source
- The capability of the operator and compliance with best practices and SOPs
- The material form ("dustiness")

Knowledge of these and other relevant factors can be used to develop an understanding of the inherent uncontrolled risk to potentially exposed individuals in the workplace, other products, or the environment. In particular cases, other factors may become important, for example, the impact of relative humidity on material dustiness, or the presence of solid materials which sublime to form vapors at ambient temperatures hence rendering standard particulate filtration ineffective. Knowledge of material properties and process detail is critical to understanding whether such typically unusual factors may be relevant.

Other HSE information such as flammability, explosivity or environmental impact may also affect risks and subsequent control definition. All materials (including raw materials, intermediates, final product, cleaning and decontamination agents) should be considered, as should all processes including charging, processing, discharge, cleaning, maintenance (planned and unplanned) and emergency conditions such as spillage/unplanned loss of containment.

In addition to the process/material risks, the GMP and HSE regulatory requirements for segregation and control should also be reviewed as these may mandate or otherwise drive an equipment and/or facility design toward specific control approaches, for example, the use of RABs and positive pressurization of exposed product work areas with high quality air for aseptic processing.

Other constraints such as available space in the facility and location specific issues such as local supplier support, and user experience with containment and high hazard chemical handling should also be noted as these may have a bearing on containment system selection.

3.1.2 Risk Assessment

The assessment of the risks of injury, adulteration, or environmental impact in particular cases is critical to ensure effective control protocols are in place to meet statutory or otherwise necessary standards. There are many available methods of assessing risk and the user needs to use experience to apply an appropriate model. It is essential however that the method used considers those factors identified in the risk identification stage that will have a major impact on the risk of exposure, adulteration, etc., and avoids a simplistic hazard-based approach where the risk and associated controls are defined solely by the hazard rating of the material of concern.

The risks identified in the assessment stage need to be checked against identified tolerability criteria to determine whether further controls are required, and the degree of control needed. These may be statutory limits (typically for worker exposure to common industrial chemicals and for environmental emissions), internal company-derived values such as API OELs or PDEs, or other best practice values for specific material classes that might be applicable. Assuming that elimination/substitution are not viable and further controls are required, then an assessment of control options and their impact on the risk assessment needs to be completed.

3.1.3 Risk Mitigation

Assuming risk assessment has shown a requirement for additional controls to meet tolerability requirements, the options for controls need to be reviewed and their effectiveness incorporated into the risk assessment to determine whether they can sufficiently mitigate exposure to achieve the desired performance, or whether additional or enhanced controls will be required. In addition to containment performance, the “fit” with the process, ergonomic, facility, regulatory and location requirements must be included in the assessment, for example, a process that requires manual charging of 200 kg of solid into a reactor will be difficult to carry out manually via a glove port-based isolator, and automation of the charging process might be a better option. Similarly, the selection of a specific complex automated split valve system in a location with no local supplier spares support may require additional thinking on internal maintenance and spares holding approaches. Internal company operational requirements, such as the use of specific docking technologies for containers to be transferred between sites or production units, should also not be forgotten.

The impact of GMP and other parallel HSE design requirements (e.g., area classification, biosafety, ergonomics etc.) may also affect control solution selection, and compromises may be necessary to specify a coherent approach that meets the requirements of HSE, GMP, and other relevant considerations.

This is necessarily an iterative process, relying on knowledge of the containment options, their capabilities, their constraints and other factors such as complexity, space, and utility requirements. These are discussed for specific control system types in more detail in Chapter 5.

Once this step is complete, the general approach to controlling emissions is defined, including supporting utility, cleaning, and PPE requirements. These should be recorded in the Containment Strategy document, and design can proceed toward detail design and procurement.

3.1.4 Methodologies for Assessing Risks and Defining Containment Strategy

There are many available methods for carrying out risk assessments and the following sections consider several general approaches.

3.1.4.1 Use of Existing Quantitative Data

The optimum method of risk assessment is the comparison with available quantitative breathing zone data supplemented with surface measurement data derived from similar, if not identical, situations. In addition to enabling reliance on data associated with an effective system from a previous similar application, it has the benefit of including the impact of all factors relevant to the assessed scenario, including those which might be otherwise individually considered insignificant. There are typically two sources: internal and external (for example, reported performance data in literature or at conferences). Internally sourced data from within the company tends to be more detailed including all raw data and supporting observations while the latter may only include summary and statistically averaged data, though more detail may be available from the authors on request.

The problem with the use of such approaches is the typically very limited quantity of data generally available, and identifying and quantifying the impact of differences between the quantified data case and the case being risk assessed. Issues are typically with differences in material dustiness, human factors, equipment type/scale/detail, and activity scale/duration/frequency. Care and relevant expertise need to be applied to interpret and extrapolate data effectively but it can be very useful in many cases.

A subset of the external source of quantitative data is the containment supplier's data. This is often prepared in line with the *ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment*³ [23] methodologies, which allows some degree of understanding of system capabilities and can aid in the effective mitigation design selection.

3.1.4.2 Exposure Models

The second commonly used approach is to use published models that take a number of factors into consideration, which typically have a major impact on the exposure risk.

The modeling approach typically uses a combination of word models for individual key risk factors or simple quantified ranges scoring approach to define an Exposure Potential (EP), which can then be cross referenced on a table with the potency of the material of concern to give a risk ranking with an associated recommended generic primary containment strategy, for example, extract systems, barrier isolation, etc. These are usually relatively easy to use and can give a quick high-level view of the containment required. Individual major Pharma companies have also developed similar internal model approaches, to get the EP.

Such models are typically based on unpublished company-specific data that may have been extrapolated to cover multiple alternative scenarios which may appear superficially similar, but which in reality can differ very significantly. As a result, while the models can propose suitable containment approaches in a proportion of cases, in the remainder they may be completely inappropriate, and either propose either an excessive or potentially inadequate exposure control approach resulting in excessive cost and difficulty in process integration and operation, or excessive risk of operator injury. It should also be noted that other considerations, such as GMP and maintenance of aseptic conditions, may drive alternative approaches that will vary from the proposed model output. As a result, it is essential that the user reviews the output of such models with containment system specialists and/or experienced colleagues to ensure that the proposed technical approaches suggested by the model are coherent and appropriate before confirming the containment strategy approach to be applied. In all cases, the performance of the installed solution must be measured following installation using appropriate airborne and surface sampling techniques identified elsewhere in this guide.

Qualitative modeling systems are designed to be easy to use and can give a rapid answer. However, there may be concerns as to the basis, relevance, quality, quantity, and robustness of the information supporting the model, which is not always clearly stated and which is uncertain. Tools may be designed for use with a specific scale of operation and may not scale effectively to, for example, laboratory operations where the very small quantities of material handled and the use of standard control systems such as fume cupboards/hoods are not effectively considered in the model.

³ The *ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment* [23] is often referred to as the SMEPAC Guide.

Some publicly available modeling approaches give outputs including quantified ranges of exposure potentially giving an illusion of precision that may not be warranted by the supporting data. Especially with models using only two or three risk factors such as dustiness and quantity handled, there is a risk that the model does not include another key factor that has a critical impact on exposure in a particular exposure case, for example, frequency of use, user capabilities, energy input, etc. Additionally, factors such as ambient temperature and relative humidity in the workplace can have very significant impact on material dustiness and hence airborne dust exposure in particular materials. [24] Finally, some cases can be difficult to define, for example, is the relevant quantity for sampling the sample size (grams) or the sampled batch size (kgs or more)? As a result, it is recommended that care is taken with the reliance on such models and that decisions taken on their application are supported as far as possible with coherent and comprehensive quantitative data where this is available.

The following model has been used to advise the selection of containment strategies for the safe handling of potent materials within facilities, subject to the support of specialist oversight and confirmation. The model essentially includes two steps:

1. Assign an EP for a specific exposure risk source based on three major factors affecting the scale of exposure
2. Cross-references the EP above against a nominal potency based on the material OEL or OEB classification to give a Primary Containment Solution (PCS) band to be applied. A description of the generic primary and secondary containment approaches that are applicable to each PCS band are included.

A similar approach is applied to secondary containment selection for cleaning and migration based on a parallel set of risk factors to identify a Migration Potential (MP) again cross referenced with a material potency band to give a Secondary Containment System (SCS) band with associated generic description of what each SCS band represents technically.

The model proposes four generic strategy levels, and the following methodology helps to advise which might be applicable in the case assessed. The details of the different generic strategies proposed in the model for primary and secondary containment systems are listed in Tables 3.1 and 3.2.

Table 3.1: Primary Containment Strategy (PCS)

Primary Containment Strategy (PCS)	PCS 1	PCS 2	PCS 3	PCS 4	PCS 5
# of Physical Barriers*	0	0	1	2	No operator present
General			No Open Handling of Solids or Liquids		
Description of Generic Approach	Effective Room Ventilation (min 6–8 AC/h)	Extract-based Systems	Barrier-based Containment	Enhanced Barrier-based Containment	Automated or Robotic Processes within Barrier-based Containment
* Number represents the nominal number of physical barriers between the exposure source and the worker.					

Table 3.2: Secondary Containment Strategy (SCS)

Secondary Containment Strategy (SCS)	SCS 1	SCS 2	SCS 3	SCS 4
Number of Barriers to Surroundings	0	1	1/2	2
Operations Scale		Separate Room	Separate Room Maintained under Negative Pressure with or without Air Lock Access	Separate Room with Pressure Controlled Air Locks Separate Material and Personnel Access
Laboratory	Standard Laboratory Layout	Separate Laboratory or Room	Separate Laboratory Maintained under Negative Pressure	Separate Laboratory with Access Air Locks Maintained under Pressure Differential Control

3.2 Determining the Exposure Potential

The EP in any specific case is determined by many factors associated with the specific materials present, the work environment, human factors, and activities associated with the exposure risk. It is important that the system to be considered and associated control limits are defined, as well as all stages of a process, as occasionally seemingly low-risk activities actually present a relatively high exposure risk requiring containment. The model considers several factors that are commonly key to determining the risk of exposure in many cases, allowing the identification of an appropriate EP band (EP 1-EP 4) relating to the relative risk of exposure. The following parameters considered to generate EP are:

1. "Spread Potential" (also known as "dustiness" for solids) based on physical and chemical properties of the substance such as:
 - Particle size
 - Electrostatic charging propensity
 - Boiling Point (BP) versus gas vapor
 - Vapor pressure versus gas vapor
 - Viscosity
2. Process/Activity details
 - Amount of material processed or handled
 - Relative position of the exposed individual to the source
 - Duration of the process steps
 - Frequency of the process steps
 - Presence of pure substance, a blend/mixture, or solution, e.g., percent API
 - Liquid semisolid or solid

- Particle size > 100 µm is not inhalable (although may present a risk of oral or eye exposure through hand contact with contaminated surfaces)

3.2.1 Spread Potential

The spread potential reflects the likelihood of the material to remain present in significant concentrations in the air. This largely depends on the physical properties of the substance, whether it is a gas, a liquid, or a solid. In the case of liquids, the BP and the vapor pressure are of particular interest, and in for solids, the particle size and electrostatic chargeability. Depending on this, the spread potential is classified as minimal, low, medium or high, based either on specific parameter values (e.g., vapor pressure) or word models describing the form of the material (as for solid “dustiness”). Note that some nominally “wet” materials such as centrifuged solids can be dusty if effective solid/liquid separation is achieved, and the residual liquid content in the solid is correspondingly low. Treat all potent materials with nominal OELs less than 10 µg/m³ as “high” spread potential regardless of physical solid form. The spread potential descriptions and classifications are included in Table 3.3.

Table 3.3: Spread Potential Related to Potential Exposure (Primary Containment)

Spread Potential			
Minimal	Low	Medium	High
	Low Volatility NBP > 250°C	Volatile NBP > 120°C	Highly Volatile NBP < 120°C
	Granules without fine dust OEL > 10 µg/m ³	Moderately dusty, low fine dust content OEL > 10 µg/m ³	Very dusty, electrostatically charging fine dust OEL < 10 µg/m ³
Low Concentration in Aqueous Solution	In Solution/Suspension (Solid in Liquid)	Dilution Active Substance/ Excipient (Solid in Solid)	Pure Potent Material

The other factors considered by the model to determine the EP are the quantities handled and the duration of the corresponding process step.

Length of Time

When it comes to the duration of the process step, a distinction is only made as to whether the operation lasts shorter or longer than 15 minutes. This reflects the period the operator will be present and hence at risk of exposure.

It can make sense to divide the process into separate operations with individual assessments, especially if other factors vary between these, but care needs to be taken to account for multiple sequential “short” operations that will essentially come together as a “long” near-continuous exposure for the operator involved.

Quantity

The quantity handled incorporates several potential factors impacting exposure including the amount that can become airborne, the human factors associated with handling, and the typical energy input into the material associated with processing/handling. For the model, a distinction is made as to whether “smallest” quantities (< 10 mg), “small” gram quantities (< 500 g), “medium” quantities in kilogram range (0.5–200 kg) or “large” quantities (> 200 kg) are present and being processed/handled.

Table 3.4 allows determination of the EP band from cross referencing the spread potential value with the quantity band for either a “short” or “long” time period.

Table 3.4: Exposure Potential (Primary Containment)

Quantity	Spread Potential			Length of Time
	Low	Medium	High	
Smallest (< 10 mg)	EP 0	EP 1	EP 1	Short < 15 min
	EP 0	EP 1	EP 1	Long > 15 min
Small (< 500 g)	EP 1	EP 1	EP 2	Short < 15 min
	EP 1	EP 2	EP 3	Long > 15 min
Medium (0.5–200 kg)	EP 1	EP 2	EP 3	Short < 15 min
	EP 2	EP 3	EP 4	Long > 15 min
Large (> 200 kg)	EP 2	EP 3	EP 4	Short < 15 min
	EP 3	EP 4	EP 4	Long > 15 min

The derived EP band is then cross referenced with the nominal OEB range for the potent material of concern to determine the appropriate PCS (shown in Table 3.5).

Table 3.5: Primary Containment Strategy

OEB Range	Exposure Potential (EP)				
	0	1	2	3	4
OEB-6 (< 100 ng/m ³)	PCS 2	PCS 3	PCS 4	PCS 4/5	PCS 4/5
OEB-5 (0.1–1 µg/m ³)	PCS 2	PCS 2	PCS 3	PCS 4	PCS 4/5
OEB-4 (1–10 µg/m ³)	PCS 1	PCS 2	PCS 2	PCS 3	PCS 4
OEB-3 (10–100 µg/m ³)	PCS 1	PCS 2	PCS 2	PCS 2	PCS 3
OEB-2 (0.1–1 mg/m ³)	PCS 1	PCS 1	PCS 1	PCS 2	PCS 2
OEB-1 (> 1 mg/m ³)	PCS 1	PCS 1	PCS 1	PCS 2	PCS 2

3.2.2 Secondary Containment Strategy

The secondary containment specified here relates to the protection of workers remote from the source in the event of primary containment failure. This is generally not needed if primary containment is effective and the API does not present an acute hazard. In addition, in many cases, the requirements derived from GMP standards or the relevant contamination risk assessments may also be higher resulting in a stricter primary and secondary containment strategy. As with primary containment, it is critical that all relevant considerations including GMP, the environment, and worker health are included in the selection of secondary systems.

The methodology applied in the model is similar to that used for primary containment strategy in that a MP is derived from consideration of relevant factors, and then cross referenced against the material potency class to determine the generic secondary containment approach.

3.2.3 Migration Potential

The MP depends on two factors: the Secondary Containment Spread Potential (SSP) and the quantity. The SSP relates to the likelihood of the spread of residual material following cleaning and decontamination. As with primary containment this is largely dependent on the physical properties of the potent compound (gas, liquid, solid). For liquids, important factors include the BP, the vapor pressure, and the possibility of aerosol formation due to the process conditions. The order of solvent BP relates to cleaning where high BP solvents, e.g., sticky oils, can be difficult to remove and so have poor cleanability, and so present an enhanced exposure risk. In the case of solids, the particle size and the electrostatic chargeability are important, again determining a degree of material “dustiness.”

It should be noted that potent materials with a nominal OEL of 10 µg/m³ are considered as having a “high” SSP regardless of form based on the experience of the team that developed the model. Depending on the description and potency, the SSP is classified as “minimal,” “low,” “medium,” or “high.” See Table 3.6.

Table 3.6: Spread Potential Related to Potential Carryover and Cleanability (Secondary Containment)

Secondary Spread Potential (SSP)			
Minimal	Low	Medium	High
	Highly Volatile, BP < 120°C	Volatile, BP > 120°C	Low Volatile, BP > 250°C
	Granules without fine dust and OEL > 10 µg /m ³	Moderately dusty, low fine dust content and OEL > 10 µg/m ³	Very dusty, electrostatically charged and fine dusts all materials with OEL < 10 µg/m ³
Aqueous Solutions and Low Concentration	In Solution/Suspension (Solid in Liquid)	Dilution Active Substance/ Excipient (Solid in Solid)	Solid/Pure Potent Substance

To determine the carryover potential, it is necessary to know the quantities handled. As for primary containment, a distinction is made as to whether gram quantities, kilogram quantities, or tons are handled. If these two variables, the spread potential and the quantity handled, are known, the MP can be determined. See Table 3.7.

Table 3.7: Carryover Potential (Secondary Containment)

Amount	Secondary Spread Potential (SSP)			
	Minimal	Low	Medium	High
Smallest (< 10 mg)	MP 0	MP 0	MP 1	MP 1
Small (10 mg–500 g)	MP 0	MP 1	MP 2	MP 3
Medium (0.5–200 kg)	MP 1	MP 2	MP 3	MP 4
Large (> 200 kg)	MP 2	MP 3	MP 4	MP 4

The secondary containment strategy can now be determined with the MP and the OEB class (shown in Table 3.8). The prerequisite for this is a functioning primary containment.

Table 3.8: Secondary Containment Strategy

OEB Range	Migration Potential (MP)				
	MP 0	MP 1	MP 2	MP 3	MP 4
OEB-6 < 100 ng/m ³	SCS 1	SCS 2	SCS 3	SCS 4	SCS 4
OEB-5 0.1–1 µg/m ³	SCS 1	SCS 1	SCS 2	SCS 3	SCS 4
OEB-4 1–10 µg/m ³	SCS 1	SCS 1	SCS 2	SCS 3	SCS 4
OEB-3 10–100 µg/m ³	SCS 1	SCS 1	SCS 1	SCS 2	SCS 3
OEB-2 0.1–1 mg/m ³	SCS 1	SCS 1	SCS 1	SCS 1	SCS 1
OEB-1 > 1 mg/m ³	SCS 1	SCS 1	SCS 1	SCS 1	SCS 1

3.2.4 Containment System Effectiveness

While the methods above are useful to determine a high-level strategic approach to mitigation of potential exposures, at some point more detailed assessment based on specific systems may be required, for example, a model might define the requirement for a barrier isolator system, but will not advise whether it should be flexible or rigid, or whether transfers should be via Bag-In/Bag-Out(BIBO) air lock, rapid transit port, or split butterfly valve. Details of the typical applications and the benefits and concerns of individual equipment systems are noted in Chapter 8, but a similar risk assessment approach to detailed primary equipment selection including detailed process and human factor requirements can be carried out during the later design processes to develop the integrated containment equipment design. The decisions made and the supporting considerations can either be incorporated into the containment strategy or the system User Requirement Specifications (URS) as desired to record the “what” and “why” behind specific equipment selection.

The containment performance of individual containment systems is typically based on available quantified exposure measurement data, either based on standardized-type tests such as described in *ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment* [23] or from data from commissioning or in-use testing. Similar comments as those noted above for the use of quantified data for containment strategy definition apply and care should be taken in applying the data for materials and operating approaches very different from those the quantified data is derived from. As such, quoted performance values (i.e., system “x” achieves containment level “y”) should not be considered as guarantees or even limits of performance in a particular application; performance can be significantly better or worse depending on specific factors that apply in specific cases.

Extrapolation of data between reported cases and the conditions under consideration is important, for example, most surrogate testing of powder containment systems use micronized lactose or similar “dusty” materials. It would be reasonable to expect a significantly better containment performance if the actual material to be handled was a wet granular solid or similar “low-dustiness” material. Care should also be taken where systems may be made up of multiple components with different capabilities; arguably such an integrated system (for example, a barrier isolator with multiple charge/discharge systems) is only as effective as its weakest element. Similarly, consider the ease of use of a system, especially where significant manual interaction is required, such as a bag-out tie and cut. Difficulties in operation of such systems due to poor layout or other physical constraints can significantly impair containment performance to well below reported levels achieved in optimal installations.

3.3 Other Considerations for Containment Strategies

3.3.1 Administrative Controls

The aims of administrative controls are to minimize the exposure risks of workers to potent compounds through the clear identification of the presence of potent compounds, the provision of effective working procedures to minimize the risk of exposure, and access to suitable equipment in appropriate locations to allow the procedures to be carried out.

Details of commonly applied administrative control approaches are included in Chapter 13. The approaches applied should be noted in the containment strategy document as critical to maintaining effective containment of emissions.

3.3.2 Personal Protective Equipment

While good exposure control practice and the Hierarchy of Control puts the use of PPE at the bottom of the list of preferred exposure risk management approaches, there are times when it is necessary to use it in the workplace, either to support primary containment system operation (e.g., wearing of gloves in LEV cabinets), as a back-up where containment system effectiveness is as yet unproven, or for unplanned excursions from normal activities (e.g., emergency online maintenance requiring contained systems to be opened, or for spillage recovery). For the purposes of the containment strategy, it is critical to:

- Define conditions where the use of PPE should be applied and what type of system (e.g., supplied air suit, disposable mask etc.) will be used.
- Define who will be wearing it and ensure that appropriate training, fit testing, etc., is provided.
- Define where it will be stored so that it is readily available for use, particularly for emergency or abnormal spillage situations.
- Identify supporting utility or facility systems required to enable the relevant PPE use, for example, supplied breathing air systems, battery storage and recharge locations, single-use systems storage.

All the above should be noted in the containment strategy document to ensure that the requirements this raises are appropriately considered and included in the scope of the facility design, user training, and PPE logistics.

A discussion of PPE systems is included in Chapter 13.

4 Risk Assessment

Risk is a function of hazard and exposure, and assessing risk is fundamentally important for the safe manufacturing of potent compounds. The procedures used for assessing risk are, at least initially, largely independent of the specific topic of containment in the pharmaceutical industry. People make daily decisions based on risk assessments, yet often are unaware of their assessment.

In the manufacture of pharmaceuticals, it is important to realize that there is no such thing as “zero risk.” However, when determining risk, the challenge lies in the ability to determine or define the “acceptable risk” for a given system based on risk severity and likelihood of occurrence.

Depending on the kinds of risks to be evaluated, it is possible to differentiate, for example, between quality risk assessments (as carried out using ICH Q9 [25]), process risk assessments, or health risk assessments. In all cases, all possible hazards should be considered within a particular topic to determine the resulting risks.

4.1 Risks

Risk is the “*likelihood of an identified harmful consequence as a function of exposure to a hazard*” [6], which can be expressed as:

Risk = Hazard × Probability (Likelihood of Occurrence)

As the hazard is a fundamental property of the material (API, product, etc.) it cannot be reduced or removed, the risk is, therefore, determined by the probability/likelihood of occurrence of an exposure to the operator, the environment, or cross-contamination with other pharmaceutical products. Even diluting the API (e.g., in preparing the formulation) does not change the hazard; it only changes the probability of occurrence.

Therefore, the only component that can be influenced is the probability/likelihood of occurrence, or when considering hazards from contamination by potent compounds, the duration and degree of exposure.

To assess and mitigate risks in pharmaceutical manufacturing, multiple risk assessments are conducted in three areas:

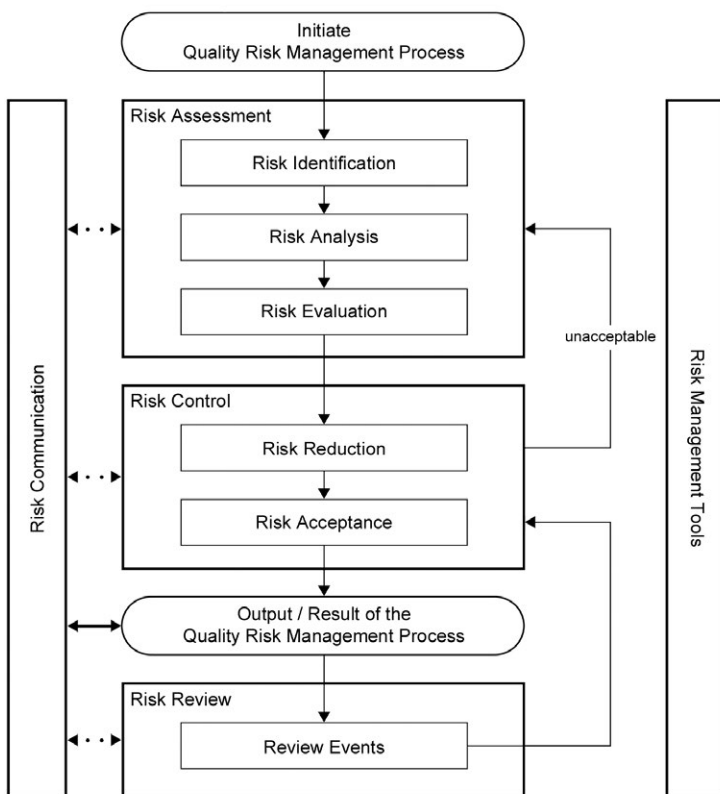
- Health risks for people and the impact to the environment
- Quality risk
- Process hazards

The data assessed includes historical data, theoretical analyses, and other relevant information, as well as input from involved functions.

4.2 Risk Management Process

The process presented here (from *ISPE Baseline Guide: Risk-MaPP (Second Edition)* [6]) provides the typical way to perform a risk assessment. This approach considers the optimization of resources (i.e., focusing on the processes defined as critical) and the systematic and consistent implementation of a risk management system with risk analysis as its central element. This is described in ICH Q9 [25] and shown in Figure 4.1.

Figure 4.1: Risk Management Process [25]



While the focus of the regulatory authorities is on protection of the patient, which defines the basis for ICH Q9 [25]. This is shown in the *ISPE Baseline Guide: Risk-MaPP (Second Edition)* [6], which provides a scientific, risk-based approach based on ICH Q9 for managing the risk of cross-contamination to maintain an appropriate balance between product quality and operator safety. However, the generic risk management approach detailed in ICH Q9 can be used for any process, including the assessment of worker exposure to potent compounds.

The first step of the risk management process is to determine the possible risks. For the purposes of this guide, this includes all activities or occurrences that might give rise to a potential exposure to chemicals (potent or otherwise) in the work environment.

The next step is the Risk Analysis, which examines the causes and consequences of the identified risks more closely, e.g., using methods described in Chapter 3. Once this step has been completed, it is followed by the Risk Evaluation. In this step, the factors of probability of occurrence and degree of severity of the identified risk are evaluated including how likely it is that an error occurs and remains undetected until injury is caused, and how significant this injury would be.

Next, measures are defined to minimize the evaluated risk and determine whether or not the residual risk is tolerable against defined standards.

The process ends with a review of events, which may lead to further risk assessments.

4.3 Methods

There are a variety of methods available from both practice and the literature that can be used to carry out risk assessments. The most well-known, commonly applied, and accepted methods include:

- Bowtie Analysis
- Failure Mode and Effect Analysis (FMEA)
- Hazard Analysis (HAZAN)
- Hazard Analysis and Critical Control Point (HACCP)
- Hazard Identification (HAZID)
- Hazard and Operability Study (HAZOP)
- Layer of Protection Analysis (LOPA)
- Process Hazard Review (PHR)
- Safety Integrity Level (SIL) Analysis
- What if/Checklist

These tools do not yield answers as to whether a hazardous situation is or is not acceptable. They offer tools for identifying cases of hazard exposure and resulting critical factors. The data obtained along with what is known about the performance of a system (or systems) can be used to determine whether a situation will be tolerable and/or acceptable using a particular containment approach.

4.4 Risk Assessments in the Manufacture of Potent Compounds

Performing thorough risk assessments for the handling of potent compounds help ensure employee exposure protection and control emissions to the environment.

The level of protection required is prescribed by the workplace OELs for each potent compound. The control of the cross-contamination risk might be accomplished together with the aforementioned aspects, but the GMP aspects are not part of the focus of this Guide.

Factors to be considered in the risk assessment include:

- Type and duration of the release of the product (including during process activities, cleaning, maintenance, system failure etc.).
- Nature of the products, such as pharmacological potency or toxicity, physical characteristics, the flow of materials and personnel
- Scale of the process, e.g., laboratory, pilot, manufacturing (quantity of material handled)
- Human activities during the manufacturing process
- Equipment design and location relative to potentially exposed individuals

- Safety factors, thresholds
- Product and operator protection

Finally, there must be an evaluation of whether all planned measures to minimize risk are sufficient or acceptable, or if improvements to the concept or action plan are needed. A risk analysis may be carried out at any time, but as a minimum should be part of the planning phase. For new capital projects, a risk analysis should be initiated during the early stages of design, and updated as detailed design develops. Special attention should be paid to the qualifications of the risk assessment team members in terms of expertise and availability, as risk assessments can be extensive and significantly impact a project's scope.

4.5 Handling Risk Assessment Outcomes

Risk assessment outcomes, findings, and associated actions should be effectively communicated to all personnel impacted by the risk assessment, for example, process operators, cleaning and maintenance staff as well as HSE and operational management. Risk assessments can generate a significant number of actions, all of which need to be effectively managed in keeping with the principles of good project management. Additionally, the evidence associated with an action's closure must be documented. If the action is rejected by the approval authority, the reasons why it has been rejected, and what further action is required to permit closure, must be noted. A review of the risk assessment may be required after closure of all action items to ensure that the final design results in a level of acceptable risk.

5 Consideration of GMP Aspects

In pharmaceutical manufacturing areas, product protection and occupational safety are of great importance. It is therefore important to reconcile the different perspectives. Risk analyses play a crucial role in both areas.

Toxicological data serves as the basis for cleaning and exposure limit values when working with active substances. Exposure measurements such as air measurements in production rooms and results of wipe tests on surfaces can be used demonstrate that cross-contamination via airborne and mechanical routes is under control. [26]

This chapter takes a closer look at common and sometimes divergent regulatory and organizational aspects of GMP and occupational health and safety. Some of these aspects are previously addressed at a high level in Chapter 2.

5.1 Regulatory Links between Occupational Safety and GMP Aspects

The necessity, scope and quality of containment in the manufacture of API and pharmaceuticals are important issues not solely determined by OH and safety aspects. Aspects of GMP must also be taken into account. The focus of GMP is on patient safety, which should be guaranteed by product quality. This is ensured in part by controlling material migration within a facility so that the risk of contamination and cross-contamination of any kind (particulate, microbiological, chemical) is minimized by structural, organizational, engineering, and operational measures.

Regardless of the product, the focus of GMP is on avoiding the risk of contamination, either introduced from external or process-related sources. Particularly when manufacturing sterile products under aseptic conditions, the focus is very much on avoiding microbial contamination without neglecting the issues of cross-contamination or occupational safety.

Microbiological contamination plays a decisive role in determining the requirements for containment for manufacturing sterile products. Annex 1 of the EMA GMP guidelines [27] specifically requires the use of containment for such activities. (See also Chapter 2 in this Good Practice Guide.) The specification of containment systems to ensure aseptic conditions and sterility is not discussed further here.

The requirements of the GMP regulations for the specification of containment systems in preventing non-microbial cross-contamination are less well-defined than for aseptic processing. This chapter considers and compares occupational safety and GMP aspects.

To address all concerns associated with occupational safety as well as those of protection from microbial contamination, effective primary containment is always part of the solution. A great advantage of using primary containment is that the risk of significant contamination of the rest of the facility is greatly reduced.

Not only is the risk of airborne cross-contamination reduced, but also the risk of contamination via the indirect mechanical route, for example, by transfer from contact with contaminated surfaces, personnel or mobile equipment (see also Chapter 5.21 EMA GMP Guidelines) [26]. However, this does not mean that the whole issue of contamination is resolved. The highest risk, in addition to mix-ups, continues to be contamination from contaminated surfaces with direct product contact. The containment device constitutes an additional barrier that may occasionally create additional complicated cleaning. However, this aspect can generally be overcome by careful design including features such as integration with Clean in Place (CIP) or Wash in Place (WIP) systems, isolators that can be opened to allow for easy access for final cleaning, and valve systems that can be dismantled, etc.

The different aspects of occupational safety on one hand and GMP (cross-contamination) on the other are compared in Table 5.1.

Table 5.1: Comparison of Aspects of Occupational Safety and GMP

	Occupational Safety	GMP
Target Group	Production Workers	Patient
Primary protection goal	Protect workers from exposure (Protection of the environment from escaping substances)	Protect product from contamination (Protection of the drug from contamination from the environment)
Type of exposure or form of taking a drug	Of the employee: • Inhalation • Dermal • Oral¹	The patient ² depending on the dosage form: • Oral • Parenteral • Inhalation • Dermal
Length of exposure to the substance/contaminant	Repeated/continuous during work/production	Upon intake of the drug
Assumptions about exposure duration	Entire working life, every working day, 8-hour shift	Lifetime treatment with the drug
Substance limit/pollution	Concentration in the room air (OEL, proportional to the PDE _{inhalative})	Amount of contaminant in a maximum daily dose of the drug (PDE _{RA} ²)
1. With poor hygiene and hand-to-mouth contact 2. Relevant are the Route of Administration (RA) and the maximum daily dose of the drug containing the impurity		

The regulatory requirements are best illustrated using internationally recognized regulations. ICH [28] has adopted various guidelines, many of which have been adopted directly or indirectly by other countries in their own regulations.

ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients [29] states that:

“appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials...”

ICH Q7 also cites the need for dedicated facilities for *“highly sensitizing materials.”* Further:

“Dedicated production areas should also be considered when material of...high pharmacological activity or toxicity is involved...unless validated inactivation and/or cleaning procedures are established and maintained.”

Quality-related risk management is described in general terms in ICH Q9 Quality Risk Management [25]. Both ICH guidelines are shown in Part II or as an annex in the EU GMP guidelines [3].

The requirements for cleanrooms and room classes are comprehensively described in ISO 14644 [30], which is also referenced in Annex 1 of the EU GMP guidelines (Manufacture of Sterile Medicinal Products) [27].

For the manufacture of multiple products in the same facility, the *ISPE Baseline Guide: Risk-MaPP (Second Edition)* [6] provides a scientific risk-based approach to ensure product quality issues (avoiding cross-contamination) are properly addressed. The approach is based on ICH Q9 Quality Risk Management [25].

For production in, or export to, the US, the FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice [31] needs to be followed.

The *ISPE Baseline® Guide: Volume 2 – Oral Solid Dosage Forms (Third Edition)* [32] and the *ISPE Baseline® Guide: Volume 3 – Sterile Product Manufacturing Facilities (Third Edition)* [33] provide detailed recommendations for manufacturing technologies used to manufacture Oral Solid Dosage (OSD) forms and sterile products respectively.

In Europe, the regulatory requirements relating to GMP and cross-contamination are essentially laid down in EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guidelines Part 1 for drug products and Part 2 for active ingredients (drug substances) [3]. Chapter 3 (buildings, systems and equipment and their potential for reducing cross-contamination [34]) and Chapter 5 (production [26]), as well as Annex 15 Qualification and Validation [35] for aseptic production, are important for the containment discussion in the case of pharmaceuticals, in addition to Appendix 1 [27].

Part 2 is relevant for the production of active ingredients with defined requirements for a documented assessment based on risk to harm human health. In Part I, the design of the building, systems, and equipment and their potential for reducing cross-contamination are specified in Chapter 3. Chapter 5 deals with the subject of production, with sub-chapter 5.21 showing various technical and organizational measures that can be used to reduce the risk of cross-contamination. Annex 15 discusses setting health-based exposure limits and their use in defining cleaning limits for product contact surfaces required not only for the production of drug products but also in the manufacture of active ingredients.

The manufacturer must conduct documented risk assessments based on scientific or toxicological data. They serve to carry out, evaluate, and carefully balance GMP considerations as well as workplace safety.

The US 21 CFR 211.42 [36] states:

“There shall be separate or defined areas or such other control systems for the firm’s operations as are necessary to prevent contamination...” for all classes of compounds.

Depending on the design, primary containment offers the possibility of limiting contamination to a small defined space with high effectiveness (ideally the interior of process equipment that comes into contact with the substance), thereby separating workers from the product and preventing uncontrolled migration of contaminating materials. In this way, both the GMP and the occupational safety goals are often achieved. During the design process, opportunities for closed processing should be evaluated. Closed processing and effective primary containment are the best way to protect both the product and personnel.

Two examples of the results of this consideration for pressure gradients in an isolator are given in Table 5.2. In one case, the aspects of occupational safety predominate and, in the other case, the aspects of product safety. In the latter case, thanks to the high degree of effective barrier containment that an isolator offers between the interior and exterior if effective well-engineered interfaces are selected, the use of a positive pressure within the isolator may be acceptable from a worker protection perspective depending on the risk assessment that considers the potency of the material of concern.

Table 5.2: Simplified Isolator Examples from a Joint Risk Assessment

Examples of the results of the joint risk assessment (in one example, aspects of occupational safety predominate, on the other hand GMP)	Occupational Safety Prevails	Product Safety Prevails
	Working with a non-sterile highly active substance in an isolator.	Working with a sterile substance in an isolator.
	To protect the environment, this substance is best handled in the isolator under negative pressure.	To ensure sterility, the isolator should be operated under positive pressure.

However, cases are not always so clear cut. Solutions that take both aspects into account to ensure the protection of the employee and the patient must be worked out together. In sterile production, the protection of the patient is critical, and the isolator is almost always operated at positive pressure to prevent contaminant ingress and to maintain sterile conditions. See Section 8.1.1. Additional design features may be needed however to prevent the escape of highly toxic substances. These design features need to be evaluated in the risk assessment and validated to demonstrate the achievement of the required containment.

It is common industry practice that the toxicologists and other experts involved establish PDEs/ADEs and OELs using the same principles and within the same work process. PDEs are set for those routes of exposure that are relevant to cleaning product contact surfaces in shared facilities. For example, for the cleaning of a tablet press, the oral PDE is the basis for establishing cleaning limits. By definition, OELs are set for the inhalation route. If the same toxicological groundwork for PDEs is to be used for setting OELs, systematically, a PDE must also be set for the inhalation route of exposure even though this route may be irrelevant from a GMP cleaning perspective.

When deriving limit values, all existing relevant data must be used. Such data may be clinical and preclinical data. For data-poor substances, using the Threshold of Toxicological Concern (TTC) or data from similar molecules that have been better investigated may be chosen. Data sets for the different molecules of interest vary greatly; therefore, the details of the approach for setting these health-based exposure limits vary from compound to compound. This work should be done by an experienced expert.

Experts can find guidance on setting these limit values in documents such as:

- EMA: Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities [2]
- PIC/S: Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities⁴ [5]
- *ISPE Baseline Guide: Risk-MaPP (Second Edition)* [6]
- ASTM Standard E-3219 [10]

All guidance documents propose similar approaches. In the GMP domain, the most broadly recognized guidelines are those of the EMA and of PIC/S.

Where the necessary data is available, the first step is to qualitatively determine the lead effect of the substance, that is, the first unwanted effect that will appear if the dose of a substance is incrementally increased. The second step is to determine the maximum daily dose at which this effect will not appear in the most sensitive subpopulation, even if exposure is lifelong. Ideally, clinical and preclinical data are available as starting points for one or for several limit value calculations.

Depending on the available database, adjustments may be made to ensure that:

- The limit is protective for humans (in EMA/PIC/S [2, 5], adjustment factor F1)
- The limit is protective for the most sensitive subpopulation (F2)
- The limit is protective for lifelong exposure (F3)
- The limit is protective even if the effect of the substance is particularly severe (F4)
- No unwanted effects will be seen at the dose expressed by the limit (F5)

If appropriate, the expert also considers pharmacokinetic data reflecting accumulation and bioavailability via those routes of exposure that are of interest.

⁴ These EMA and PIC/S guidelines are identical.

If the dataset on a compound allows, the following formula for setting a PDE is often used. It is based on EMA and PIC/S guidelines [2, 5]:

$$\text{PDE} = \frac{\text{NOAEL} \times \text{weight adjustment}}{\text{F1} * \text{F2} * \text{F3} * \text{F4} * \text{F5}}$$

While some experts may use slightly different adjustment factors (particularly F2) for workers (OEL setting) and patients (PDE setting), there must be a reasonable correlation between OELs and PDEs. This correlation should be sound and transparent as it might be questioned during regulatory inspections and other audits such as those carried out along the supply chain, e.g., via the Pharmaceutical Supply Chain Initiative (PSCI) [37].

5.2 Aspects to be Considered with regards to a Joint Risk Assessment: GMP and Occupational Health

Based on the regulatory requirements cited in Section 5.1, documented risk assessments using scientific and toxicological data must be prepared by the manufacturer.

In order to answer the question of whether a joint or a separate risk assessment for occupational health and safety and GMP should be carried out, it is first necessary to clarify what is required. There can be different scenarios:

- GMP and occupational safety (e.g., toxic product in dedicated or multipurpose system)
- No GMP but occupational health and safety (e.g., treatment of toxic waste)
- GMP but less complex occupational safety measures (e.g., production of substances with relatively low potency)

Ultimately, every risk assessment should evaluate the manufacturing equipment and process, including the interfaces, with regard to their function and protective mechanisms. Then a decision must be made as to whether they are suitable from the point of view of occupational safety for manufacturing a specific product or not. The question is whether, in routine operation, the existing containment is sufficient to protect the employee from overexposure without PPE. The process to answer this can be divided into the following categories:

- Process specific
- Product specific
- Quality specific
- Occupational health and safety specific

During risk identification, for example, using a fishbone diagram, the risks to consider can be identified in order to allocate them to occupational safety and/or GMP.

A risk assessment should always be carried out by a team. Suggestions for the composition of the teams for a risk assessment can be seen in Table 5.3.

Table 5.3: Team Composition Occupational Health and Safety and GMP

Occupational Health and Safety	GMP
Project Manager	Project Manager
Production/Manufacturing Area	Production/Manufacturing Area
Occupational Hygiene	Quality Control
Additional experts, e.g., from engineering, safety, toxicology, maintenance and repair, quality assurance, cleaning validation	Additional experts, e.g., from engineering, safety, toxicology, maintenance and repair, quality assurance, cleaning validation

As Table 5.3 shows, the composition of the teams is very similar. It therefore makes sense to consider the aspects of GMP and occupational safety using a combined team. The advantage is improved flow of information, allowing more information to be taken into account using different perspectives and experiences.

Whether the risk assessment is then created as a joint document or separate documents depends on regional requirements and operational structures. Separation into two documents is easily possible if the risks are clearly marked as GMP and/or occupational safety during identification and assessment.

The recommendation is to conduct a joint risk assessment and to document it separately depending on the situation.

5.3 Achievability of the Protection Goals

Containment systems are used to actively protect employees during the manufacture of a drug. Depending on the design and application, containment systems can have an impact on the manufacturing process. For example, from a GMP point of view, there can be additional interventions in the process that are relevant, such as increased cleaning effort due to additional containment systems, or an increased risk of cross-contamination if the shared product contact surface is increased by the containment systems. Especially with a required PDE in the low microgram or nanogram range, it makes sense to consider the OH and GMP requirements (with regard to containment) together in order to control both risks. As a rule, however, the joint consideration will show that both OH and GMP benefit from adequate containment.

For equipment processing a highly potent product with a low PDE value, good cleanability is only achieved with a good hygienic system design (hygienic design). Connectors, seals, closure systems, filter ports, and the various containment systems used in product transfer are critical as these have locations that are difficult to clean or where it is difficult to demonstrate adequate cleaning. Filter changes and possible contamination must be considered in detail both from a GMP point of view and to protect employees. Hygienic measurements are advantageous as support for the corresponding risk analyses.

For isolators and closed containment equipment, the physical barrier helps ensure that exposure can be contained in a much smaller and defined space. The space to be cleaned after the process step may therefore be considered as limited to the isolator or the closed containment equipment itself. Isolator and closed equipment cleaning is much easier to accomplish than cleaning the entire production area (room including floor, walls, exterior of equipment, etc.). Such cleaning would be required in the case of open product handling. Isolators or closed containment equipment in negative pressure operation protect employees and the environment from contamination.

Product residues adhering to surfaces that do not come into contact with the product can theoretically be carried away by mechanical action or by airflow and lead to contamination. Although this risk is very small, surfaces that do not come into contact with the product may still need to be cleaned.

Possible GMP risks requiring assessment:

- Additional surfaces, gloves, and seals on isolators or contained transfer systems, such as Rapid Transfer Ports (RTPs) or split butterfly valve systems, can lead to product contamination on surfaces and should be replaced upon product change or be subject to cleaning validation. (Note that in general, many small parts are exchanged or used for one specific product only (product dedicated)). Gloves are almost always exchanged because cleaning usually cannot be validated.
- Filter change and thus possible recontamination in the subsequent product
- Foreign particles in the product due to damaged surfaces or seals
- Components in the manufacturing process that are difficult to access are also more difficult to clean
- Change in external conditions such as temperature, humidity, airflow
- Changes in the cleaning process

Containment systems usually consist of different components and processes, which together lead to effective employee protection.

Example Containment Systems and Points to Consider:

- Negative pressure in isolator
 - Intake of contaminated outside air and contamination of the product in the isolator
 - Intake air filtration according to required specifications
 - Inlet air intake from an environment with the required air quality
 - Installation of the isolator in an environment with required air quality
 - Leak test before processing the product in the isolator
- Isolator housing as a barrier between the highly active substance and the environment
 - Additional surfaces and more difficult cleaning
 - Cross-contamination by previously manufactured product and microbiological contamination
 - Hygienic design: optimal design of the surfaces for cleaning, e.g., rounded corners and good accessibility (Figure 5.1)
 - WIP/CIP of the inside of the isolator
 - Automated cleaning process and cleaning validation
 - Decontamination of the inside of the isolator using hydrogen peroxide (H₂O₂)
 - High surface quality without damage, e.g., scratches

- Gloves
 - Intake of contaminated outside air and contamination of the product in the isolator in the event of a leak
 - Inadequate design of glove seal at shoulder ring can result in hidden product deposits
 - Product migration into the material of the gloves
 - Leak test of gloves and glove seats before processing the product in the isolator
 - GMP compliant glove seal on the shoulder rings to prevent product buildup on the glove seals
 - Product-dedicated gloves or new gloves for each campaign
- Sealing of the glass panes
 - Intake of contaminated outside air and contamination of the product in the isolator in the event of a leak
 - Inadequate design of the seal of the glass pane and as a result product deposits in hard-to-reach places which can be released the glass panes are opened
 - Use of low-dead space pneumatic seals
 - Continuous monitoring of the seal for possible pressure loss
 - Opening of the isolator after CIP/WIP cleaning (e.g., at the end of a campaign), carrying out a visual inspection of all critical points and, if necessary, conducting additional manual cleaning
 - Ideally with a hinged or removable front panel
- Endless liner
 - Intake of contaminated outside air and contamination of the product in the isolator in the event of a leak
 - Leak test before processing the product in the isolator
 - Replacement of the liner when changing products
 - Integrity verification and guarantee of the endless liner by the manufacturer
 - Foil closure systems (crimps or welding)
- RTP
 - Intake of contaminated outside air and contamination of the product in the isolator in the event of a leaky connection
 - Leak test before processing the product in the isolator
 - Maintain and regularly replace seals
 - Support device on the outside of the insulator for larger RTP kegs (often necessary to protect the seal)

- Dedusting filter systems
 - Possible recontamination when changing the filter due to transfer of particles from the contaminated filter to the new filter
 - Testing for function and fit
 - Only install new filters after the contaminated filter has been removed and the filter seat cleaned

Example of a technical solution to avoid contamination on the gloves and on the sealing of the glass pane:

The glove shoulder rings are secured by an additional mechanical seal of the glove sleeve. (See the example in Figure 5.1.) This prevents product dust from being deposited on the glove attachment. A hygienically designed pneumatic seal connects the glass pane to the isolator housing.

Figure 5.1: Isolator

Used with permission from SKAN AG, <https://skan.com/de/home>.



Using Split Butterfly Valves for GMP and Worker Protection – Points to Consider:

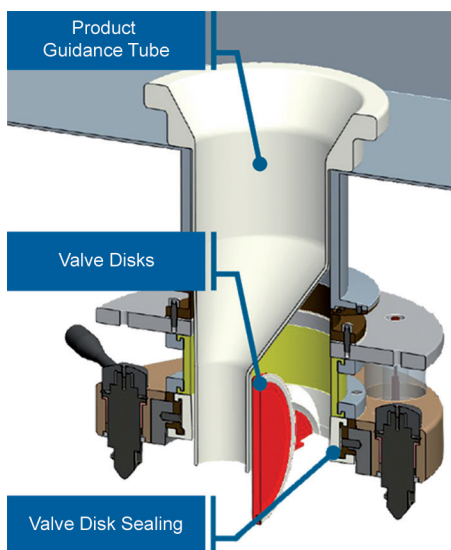
- Valve seals
 - Product deposits on the valves faces that are exposed when the valves are undocked (separation of active and passive valve) and not wiped off manually after each undocking action.
 - Incorrect installation of the seals
 - Cracked/damaged seals (due to age, solvent exposure, material abrasion etc.)
 - Reduce product contact with valve and risk of deposits by means of a funnel (see Figure 5.2)
 - “Flushing” the space between the valve halves with air or solvent prior to complete undocking
 - Regular inspection, maintenance, and replacement of seals
- Valve surface
 - Mechanical wear and tear on the surface during use and cleaning

- Reduce product contact with valve and risk of deposits by means of a funnel
- “Flushing” the space between the valve halves with air or solvent prior to complete undocking
- Regular inspection, maintenance, and replacement of seals

Figure 5.2 is an example technical solution that helps prevent contamination of the seal and valve disk. The funnel is inserted once the split butterfly valve has been opened, reducing contact between the substance and the valve and its seal. This measure results in less exposed material when the valve is closed and undocked, thereby improving containment and reducing the risk of significant material migration potentially leading to a significant risk of worker exposure or product cross-contamination.

Figure 5.2: Funnel to Protect the Seal and Valve Disks from Product Deposits

Used with permission from SKAN AG, <https://skan.com/de/home>.

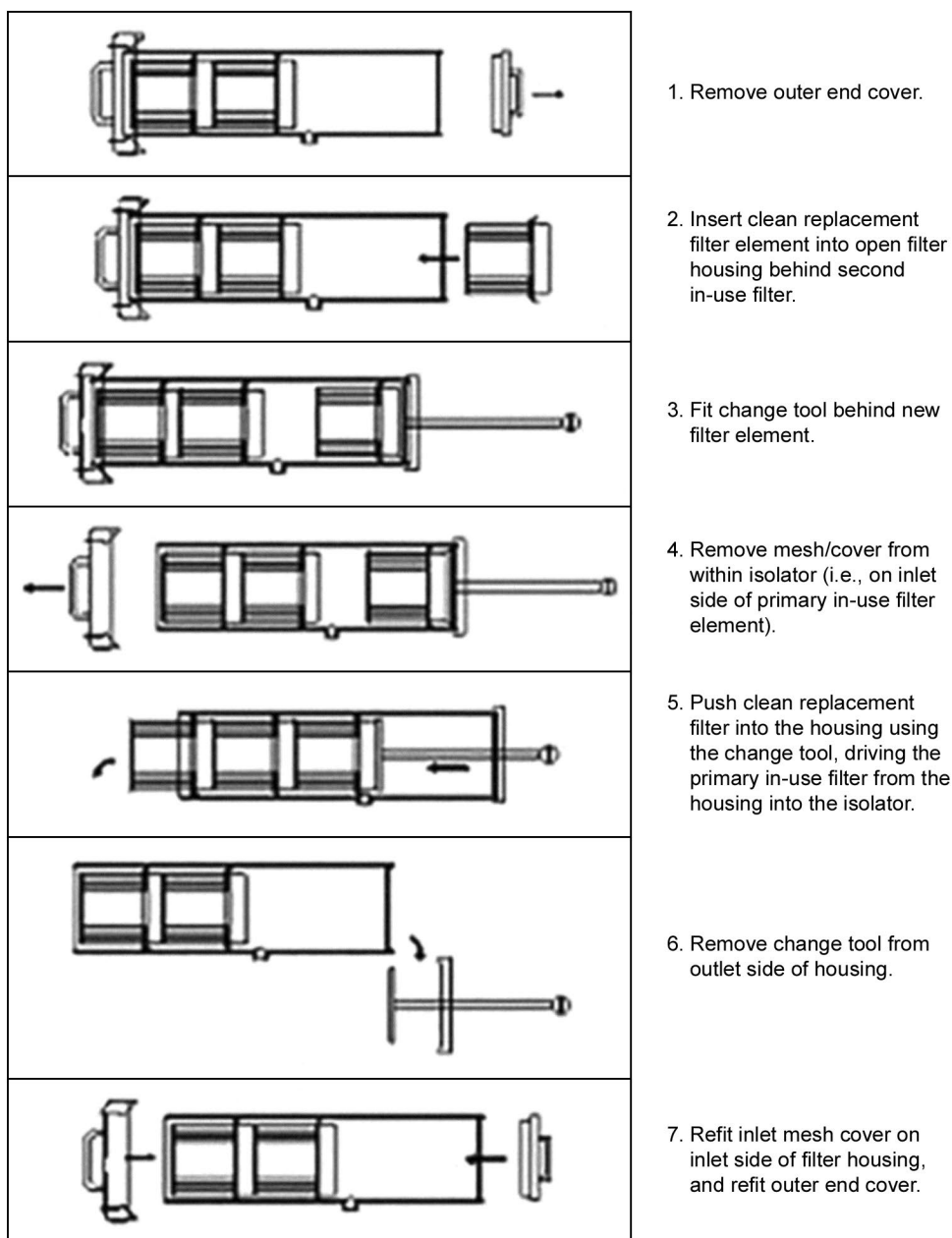


- Seal of the filter seat
 - Filter seat not checked properly and product deposits on critical surfaces that are difficult to clean during product changeover
 - Filter technologies with high-containment docking adapter to avoid product deposits in critical areas
- Filter change
 - When changing the filter, product particles from the contaminated filter can become detached and contaminate the new filter
 - Avoiding a filter change where the new filter can come into contact with the contaminated filter, e.g., push-push systems

Push-push (see Figure 5.3) and bag-out safe-change filters are the standard solution for non-sterile applications to prevent cross-contamination.

Figure 5.3: Push-Push Filter

Used with permission from SKAN AG, <https://skan.com/de/home>.



5.4 Occupational Hygiene Limit Values in the GMP Context

Avoiding cross-contamination is an important aspect of GMP. Risks of such cross-contamination must be determined by appropriate risk analyses, for example, according to ICH Q9 [25]. This results in the necessary risk management measures, such as:

- Organizational measures to avoid mix-up
- Facility or equipment dedication or cleaning validation in multipurpose plants to minimize carryover through contaminated shared product contact surfaces

- Segregation of facilities and rooms through structural or organizational measures (e.g., through doors, antechambers, air locks, separate room ventilation systems or HVAC systems equipped with terminal High Efficiency Particulate Air (HEPA) filters in the room, HEPA filters in filter systems, pressure gradients, or sink or bubbles between rooms, obligatory change of clothes). Primary process containment is the most effective measure to reduce or prevent product carryover via the airborne route or mechanical transfer and segregation, in addition to secondary containment, is the best alternative.

Organizational measures to avoid mix-ups and cleaning validation are well established, but segregation measures are more controversial. In the past, the discussion primarily revolved around secondary containment measures, that is, how to prevent material released in the production area from being carried outside.

Only recently have GMP guidelines explicitly taken into account the fact that the risk of mechanical or airborne cross-contamination is not only influenced by the secondary containment, but also, or even more strongly, by the quality of the primary containment. If the product remains in the equipment, it does not leak out and cannot be carried elsewhere by air or mechanical transfer. In the context of avoiding cross-contamination by air and by mechanical transfer, primary and secondary containment must therefore be considered together. If a plant has a primary containment that meets the requirements, the secondary containment measures can be relaxed under certain circumstances. If the equipment in a facility is relatively poorly contained by primary and process systems, the secondary containment may not reliably prevent remote transmission, leading to potential cross-contamination.

This is reflected in Chapter 5.21 of the EMA GMP Guideline [26], in which a total of 23 technical and organizational measures are listed that a company can use as evidence that it has its cross-contamination risks under control, including:

Paragraph 5.21 Organizational Measures

“(i) Dedicating the whole manufacturing facility or a self contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness”

“(iv) Depending on the contamination risk, verification of cleaning of non product contact surfaces and monitoring of air within the manufacturing area and/or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer.”

This means nothing more than a review of the primary containment and reflects the knowledge that personal protection through technical measures also benefits GMP.

As part of their workplace exposure assessments, many companies have carried out air measurements in the production rooms and the adjacent surroundings. Some have also performed wipe tests during the same measurement campaigns [23].

In principle, it should be possible to use the data that was originally collected for reasons of OH in a GMP context. Although of secondary importance from the point of view of industrial hygiene, Good Laboratory Practice (GLP)-compliant analysis may be required. When interpreting measurement results, the following questions are examples of discussions that may arise:

- What does it mean for the risk of cross-contamination of Product A, which is manufactured in Room A, if an air concentration of Product B in the neighboring Room B (OEL 50 µg/m³) of 10 µg/m³ is measured?
- What does it mean, expressed as a cross-contamination risk for the following product in the same room, if there is still 1 µg/cm² of the previously produced product (OEL 50 µg/m³) on the walls and floors?
- What does it mean if in the “clean corridor” 0.5 µg/m³ of a product is measured, which has migrated there from an adjacent production room?

The measured contaminations must be correlated to the corresponding PDEs, i.e., the more critical a substance, the lower its PDE and the lower the tolerance for contamination of air and surfaces, even if they are not in contact with the product. It is difficult to put this logical approach into practice quantitatively, that is, to set GMP-tolerable limit values for the air or for surfaces that do not come into contact with the product. The connection between such contamination and a specific risk for the product is difficult to quantify.

Furthermore, a product is at greater risk the longer it is exposed to a potentially contaminated environment during the manufacturing process. The risk of contamination by air or mechanical transfer is reduced when the product is in closed equipment and nothing can enter from the environment. Here, too, good primary containment brings great GMP advantages.

Various factors must be taken into account when considering risks and interpreting the measurement results, for example:

- Potency of the contaminant (expressed as PDE)
- Maximum therapeutic daily dose of the cross-contamination recipient
- Length of time during which the recipient is exposed to cross-contamination from the atmosphere of the production room
- For assessing airborne cross-contamination: filtration systems and pressure gradients
- Ask whether, in the case of accidental contamination, it would be distributed in a whole batch and thus diluted, or whether everything would end up in one or a few individual doses of the recipient product
- Extent to which contaminants could detach from non-product contact surfaces and get into the next product

The applicable GMP regulations require active ingredients and medicinal products to be manufactured with the same quality at all times, under the same conditions – batch by batch, daily dose by daily dose. Deviations are only accepted within narrow limits.

It is different in OH. Incidents happen and one is prepared to deal with them. A plastic bag can tear, a vacuum transfer line can become clogged and may have to be dismantled, or an intervention in the manufacturing process becomes necessary. If one could measure in such situations, the exposure values would be much higher than under routine conditions. Wipe tests are pointless for visible contamination after an accident. Ad hoc air measurements are not possible in the event of an accident, as they have to be carefully prepared and cannot be organized from one minute to the next. Wipe tests are usually only useful after appropriate cleaning in the event of an accident.

In the case of accidents, not only do unusually high exposures occur, but they can hardly be quantified.

To address such “outlier” data from a GMP perspective, these questions may be asked:

- Is the entire production now “Out of Specification” because the exposure data could not be met?
- Do products that were produced in the room next door when the incident occurred have to be destroyed because the normal conditions were not maintained?
- Which sampling cassettes should be used for the air measurements? The sampling cassettes commonly used in OH measure particle-selectively, i.e., they measure the particle fractions as they would be inhaled by humans. However, this is not relevant in the GMP context.
- Where exactly should be measured?

- Are dry or wet wipe tests expected?
- What validation criteria are expected for analytical methods and how sensitive must they be?
- What are the requirements for the analytical laboratory?

All of these are examples of questions that need to be answered if wipe samples are to be taken from non-product contact surfaces or if air measurements are to be carried out in the production rooms and adjacent areas in order to then use the results as GMP data.

Risks to the patient from cross-contamination by air or mechanical transfer are low. Suggestions for cleaning limit values for surfaces that do not come into contact with the product, e.g., inside isolators or freeze dryers, have been published. A purely visual inspection is usually not sufficient if highly active substances have been produced.

These references may be helpful: PDA Paper "Isolator Surfaces and Contamination Risk to Personnel and Patient, November 6/2017" [38], PDA Journal "Preventing Cross Contamination during Lyophilization: GMP and Occupational Cleaning Requirements for Nonproduct and Indirect product contact parts" [39].

In the PDA publications, toxicologists and containment experts from the GMP environment and from occupational safety have proposed acceptance values for residual surface contamination derived from PDEs and OELs. In the case of highly active substances, i.e., those with very low limit values, it is sometimes analytically very laborious to prove that the proposed very conservative limit values are actually complied with.

It would be useful to know how badly the drug, be it the contents of a vial or a tablet, could become contaminated by air. Unfortunately, the available data does not generally allow an objective and quantitative assessment in a specific situation of how much contamination can be brought into a product by contaminated gloves or moving parts. Therefore, unrealistic worst-case assumptions are usually used ("all molecules on the floor and walls go into the product").

In the case of highly active substances, visual cleanliness is usually not enough to show that no critical surface contamination has built up inside the isolator. Therefore, swab tests (wiping tests) are often carried out after cleaning. The risk of exposure for the worker after cleaning can arise primarily from hand contact. The palm of a hand typically measures approximately 1 dm². Therefore, swabs are taken from an area of this size of 1 dm² ("palm of the hand concept").

In addition, however, the contamination outside the containment device should also be considered in the risk analysis. If work is carried out in isolators, substance release is usually very limited, but the containment is often not an isolator and worker protection must also be ensured.

Keeping air contamination at levels below the OEL and keeping non-product contact surfaces clean almost always ensures that no GMP issues arise due to airborne or mechanical transfer. The corresponding data can be helpful in discussions on this topic.

When it comes to occupational safety, a frequently used model assumes that a trained employee in the area in which increased contamination is expected will absorb via skin contact no more than the amount of product that is deposited on 1 dm². In an area where no contamination is expected, for example, in the "clean corridor," one assumes 10 unprotected hand contacts/working day might occur as a worst case. Here, the benchmark for safe surface contamination may be 1/10 of a PDE on 1 dm².