RISK-BASED CONTAINMENT STRATEGY

A Case Study for a Synthetic Molecule API Facility

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Containment systems are essential in pharmaceutical manufacturing, ensuring product quality and protecting worker safety. They prevent cross-contamination, reduce occupational exposure to potent compounds, and support compliance with global Good Manufacturing Practice (GMP) standards. As manufacturing evolves, robust and adaptable containment strategies are increasingly vital for maintaining safety, efficiency, and regulatory alignment [1]. This article presents a case study demonstrating the design and verification of containment systems in a large-scale facility, highlighting best practices and industry relevance.

Containment systems play a vital role in pharmaceutical manufacturing, serving multiple functions across product quality, worker safety, and regulatory compliance. From a regulatory standpoint, containment is essential for meeting the stringent standards set by GMP guidelines. These standards, often harmonized globally through organizations such as the Pharmaceutical Inspection Co-operation Scheme (PIC/S), ensure robust process control and product quality assurance [2–8].

However, potent compounds are typically regulated within the broader framework of occupational health and safety regulations applicable to hazardous substances, rather than compound-specific regulations. Furthermore, the term *"potent compound"* lacks a standardized definition across the industry, with interpretations varying among different organizations, regulatory bodies, and regions. This variability in terminology and regulatory approaches presents additional challenges for global pharmaceutical manufacturing operations [9–15].

The implementation of appropriate containment systems in pharmaceutical manufacturing is often driven by multiple business and ethical considerations. Although regulatory compliance provides a baseline framework, the primary motivations often include protecting worker health, optimizing operational efficiency, ensuring effective capital investment with competitive running costs, building worker confidence, and maintaining company reputation. These factors collectively contribute to a sustainable manufacturing environment that balances safety, quality, and economic considerations.

Different countries and regions typically apply similar general health and safety regulatory frameworks to pharmaceutical manufacturing, rather than diverse regulations or regulations specific to active pharmaceutical ingredients (APIs). These general health and safety frameworks, when properly implemented, have proven to be fit-for-purpose for ensuring worker safety in API manufacturing environments.

Containment solutions can range from fixed engineering controls, such as isolators, to more adaptable options like flexible containment systems. Flexible containment refers to modular, often disposable barriers made of specialized materials that can be customized to fit various equipment and processes. These systems offer the advantage of being easily reconfigured to meet evolving regulatory requirements or changes in manufacturing processes.

This approach to containment, combining both robust and adaptable solutions, requires a thorough understanding of the regulatory landscape in all markets where a company operates or intends to sell its products.

The design and implementation of containment systems require comprehensive consideration of manufacturing process characteristics, the properties of handled substances, and applicable regulatory standards. By utilizing state-of-the-art technologies and design methods to realize effective and efficient containment solutions, we can significantly contribute to improving quality and safety in pharmaceutical manufacturing. Thus, containment systems are indispensable elements in ensuring the integrity of pharmaceutical manufacturing processes, and their importance is expected to increase further in the future.

This article discusses the design and verification process of containment systems and presents a case study based on this process, implemented through a multimillion-dollar investment project. The case study demonstrates how these principles were

put into practice in a real-world, large-scale pharmaceutical manufacturing facility development.

It is worth noting that in 2022, ISPE published the *ISPE Good Practice Guide: Containment for Potent Compounds* [16]. This Guide aims to achieve a common understanding and interpretation of containment technology requirements to better meet the needs of workers and manufacturers, reduce production costs, and support product quality. The Guide encompasses various fields, concepts, and techniques for protecting products, people, facilities, and the environment. One of its primary objectives is to consolidate the widely dispersed knowledge base by describing and discussing methodologies, processes, and technologies commonly used in the pharmaceutical industry.

Although the approach presented in this article was developed and implemented before the publication of the *ISPE Good Practice Guide: Containment for Potent Compounds*, it is important to emphasize that the fundamental principles of our design and verification processes align closely with those outlined in the Guide. This alignment underscores the robustness and industry relevance of our approach, demonstrating that it reflects best practices in containment system design and verification for pharmaceutical manufacturing.

CONTAINMENT SYSTEM DESIGN AND VERIFICATION

Although the quality risk management approach outlined in ICH Q9 [17] provides an excellent framework for ensuring product quality under GMP, it must be complemented by specific occupational health and safety considerations. In practice, these two sets of obligation—product quality and worker safety—may sometimes present conflicting priorities. For example, fully enclosed systems that minimize contamination risks might limit operator access and visibility, potentially creating safety hazards during maintenance operations. Conversely, open access designs that prioritize worker interaction may increase cross-contamination risks.

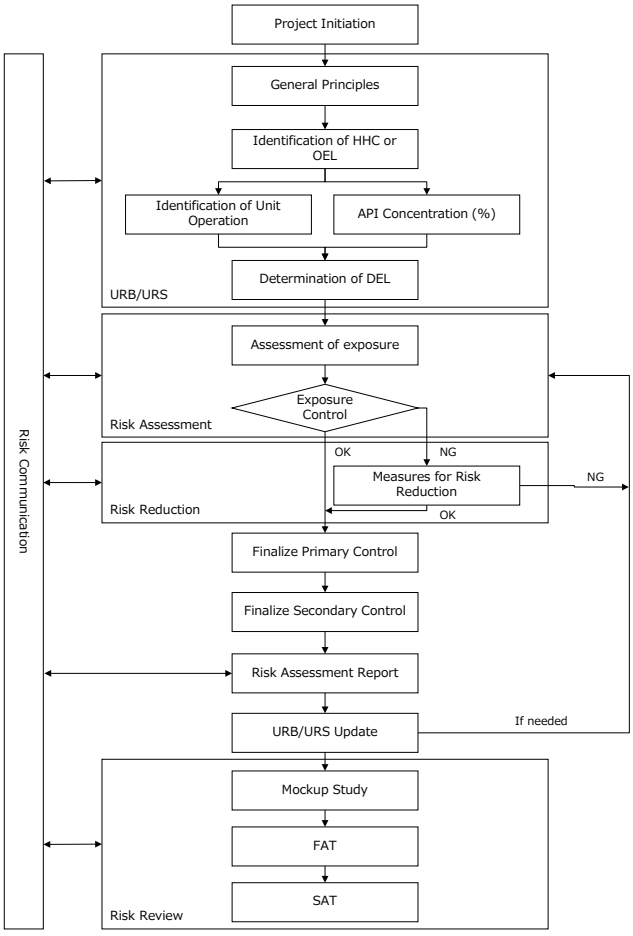
The design and verification process for containment systems must therefore balance both obligations through an integrated approach that addresses both aspects:

- Risk assessment (considering both product quality and worker safety)
- Risk control (implementing measures that satisfy both requirements)
- Risk review (evaluating performance against both quality and safety criteria)

This balanced approach ensures that containment systems meet both GMP requirements and occupational health and safety standards.

These steps enable a systematic approach to the design and verification of containment systems (see Figure 1). The following describes the containment system design and verification process based on the quality risk management approach shown in ICH Q9. This process can be applied from the initial design phase and used repeatedly until the completion of facility construction.

Figure 1: Example approach for containment system design and verification.



Note: This figure represents one possible approach to containment system design and verification. The process should be iterative, particularly during the risk assessment and risk control phases.

Abbreviations

HHC : Health Hazard Category
OEL : Occupational Exposure Limit
DEL : Design Exposure Limit
URB : User Requirement Brief
URS : User Requirement Specification
FAT : Factory Acceptance Test
SAT : Site Acceptance Test

Risk Assessment

Risk assessment is one of the most important steps in the design and verification process of containment systems. In this step, information about hazards is first collected. This includes evaluation categories of handled chemicals, occupational exposure bands (OEBs), unit operation, API content, and other relevant factors.

OEBs are a system of grouping chemicals with similar toxicity profiles. Each OEB corresponds to a range of occupational exposure limits (OELs). The use of OEBs allows for appropriate containment measures to be determined even when specific OELs for individual substances are not available. Although OEBs provide a practical framework for categorizing compounds and selecting appropriate

containment strategies, they are not the only approach. The fundamental goal remains controlling and/or containing exposure below the compound-specific OEL when available, as this directly addresses the actual hazard level of the substance.

The OEB-based approach can be used as an indicator of the hazard level of chemicals, typically classified on a scale from 1 to 5, with some systems extending up to six categories (various evaluation categories have been adopted by pharmaceutical companies in the past, and these classification scales continue to evolve in industry practice). However, the stringency of the required containment is not solely dependent on this category. Instead, it is determined by the overall risk, which is a function of both the hazard (as indicated by the category) and the potential for exposure, aligning with the ISPE guideline where risk equals hazard times exposure. It is worth noting that alternative approaches, such as hazard banding systems and direct risk assessment methods, are also available for containment strategy development.

Though higher categories generally indicate greater hazards, the actual containment requirements must consider both the hazard level and the likelihood of exposure. This means that even for high-category substances, if the exposure potential is very low, the required containment measures might be less stringent than for a lower-category substance with high exposure potential.

The OEL indicates the permissible concentration in the work environment where no adverse health effects are expected for almost all workers when exposed to a chemical for 8 hours a day or 40 hours a week over a working lifetime. The OEL is a crucial factor in describing the hazard component of the risk equation. It represents the maximum airborne concentration of a substance to which workers can be exposed without adverse health effects. As such, the OEL quantifies the inherent toxicity or potency of a chemical.

Next, the possibility of exposure is evaluated. This is a process of assessing the potential for worker exposure considering the properties and quantity of chemicals and the level of engineering controls. Chemical properties are classified into categories such as liquid, wet powder, powder, and fine powder, with each characteristic requiring appropriate containment measures.. Common examples of engineering controls that may be implemented include:

- Local exhaust ventilation (LEV)
- Draft chambers, fume hoods, safety cabinets, weighing hoods, walk-in drafts, ventilated workbenches
- Glove boxes, isolators, and other closed containment systems
- Isolators adopting more advanced containment technologies

It should be noted that these represent typical examples rather than prescriptive requirements. Organizations may implement alternative measures based on their specific risk assessments, operational requirements, and facility constraints. The selection of appropriate engineering controls should be guided by a risk-based approach that considers the specific characteristics of the processes, materials, and organizational context rather than following a rigid standardized framework.

This information is used to evaluate whether exposure can be adequately controlled. This evaluation should be conducted by qualified personnel with expertise in pharmaceutical containment and industrial hygiene, such as industrial hygienists and containment engineers. The evaluation must be based on scientific data, including quantitative exposure monitoring, published literature, standardized testing protocols, and verified vendor performance data. Obtaining robust data can be challenging outside large pharmaceutical companies; industry collaborations and standardized testing approaches may help address this limitation.

The evaluation results are categorized into "high possibility of exposure," "possibility of exposure under special circumstances," "low possibility of exposure," etc., with all decisions documented with clear scientific rationales. The results of the risk assessment are summarized in a containment system design risk assessment report and reviewed by stakeholders. This risk communication is an important process to connect with decision-makers and confirm the direction of the design.

Risk Control

If exposure control is deemed inadequate as a result of the risk assessment, risk reduction measures are considered. The priority of risk reduction follows the internationally recognized hierarchy of controls:

1. Elimination: Elimination of components, processes, transportation, etc. with hazards
2. Substitution: Substitution of raw materials, processes, equipment, transportation
3. Engineering controls: Implementation of engineering measures such as containment systems, isolation, and ventilation
4. Administrative controls: Implementation of work procedures, training, and operational practices
5. Personal protective equipment (PPE): Use of respiratory protection, protective clothing, gloves, etc.

This hierarchy represents a fundamental occupational health and safety principle that prioritizes control measures from most to least effective, with elimination being the most effective approach and PPE being the least effective.

These measures are considered and the best feasible method is selected. However, it is important to recognize that in pharmaceutical API manufacturing, the active ingredient itself is the hazardous material and typically cannot be eliminated or substituted, as its chemical structure is essential for therapeutic efficacy. Therefore, for APIs, engineering controls become the primary control strategy, with administrative procedures and PPE working in concert to deliver an integrated protection system.

It should be noted that even with robust engineering controls in place, PPE might still be required in situations where the risk of short-term exposure is too high, such as during maintenance operations, sampling activities, or in case of potential equipment failures. For example, when handling highly active APIs, more advanced engineering controls such as containment systems

and isolation technology are introduced, work procedures are optimized, and appropriate PPE is specified. The effectiveness of this integrated approach should be empirically demonstrated through industrial hygiene monitoring to verify that worker exposure remains below acceptable limits.

In considering risk reduction measures, it is important to evaluate technical feasibility while ensuring that safety is never compromised. Although economic considerations are inevitably part of facility design decisions, they should never take precedence over worker safety or regulatory compliance. All containment solutions must be fit-for-purpose with defensible scientific and legal rationales.

Appropriate investment in effective containment systems can be viewed as both meeting ethical responsibilities and supporting sound business practices. Organizations should consider that inadequate protection may lead to various indirect costs, potentially including regulatory concerns, legal considerations, health-related expenses, operational interruptions, and damage to company reputation. Thoughtful investment in proper containment, while requiring initial resources, can provide benefits through comprehensive risk management and operational stability.

Risk Review

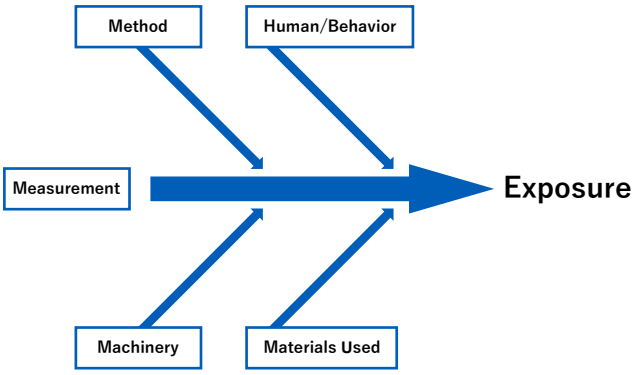
To verify the performance of the designed containment system, a containment performance assessment is conducted. This verification process might start as early as the factory acceptance test (FAT), though it is important to recognize that FAT operating conditions are not fully representative of the real process. The verification continues through the site acceptance test (SAT) stages following a sequential testing approach, with the SAT providing a more realistic operational environment. FAT and SAT may be included or omitted based on project-specific risk assessments, but complete verification should always ensure testing under conditions that accurately represent actual production environments.

First, exposure measurements are conducted using nontoxic placebo materials (e.g., lactose, naproxen sodium) to verify containment system performance without risk to personnel. Only after successful placebo testing demonstrates that the containment system meets the required performance specifications are exposure measurements with the actual potent compound conducted under carefully controlled conditions to confirm real-world containment effectiveness. The measurement results are compared with the containment performance target (CPT) to determine if the risk is acceptable. Finally, the status of the system is "in operation."

Containment performance is assessed using appropriate analytical detection methods such as high-performance liquid chromatography (HPLC) or gravimetric analysis. Measurements are conducted at least three times to ensure statistical reliability. The measurement results from both testing phases (placebo and actual potent compounds) are summarized in a containment performance assessment report and submitted to relevant departments.

The evaluation of measurement results is conducted from the following perspectives, in alignment with the systematic approach recommended in the *ISPE Good Practice Guide: SMEPAC - Standardized Methodology for the Evaluation of Pharmaceutical Airborne Particle Emissions from Containment Systems (Third Edition)* [18]: impact of machinery, method, human/behavior, and materials used (see Figure 2).

Figure 2: Root cause analysis in the *ISPE SMEPAC Good Practice Guide* [18].



These factors are comprehensively considered to ensure the reliability of the measurement results, following industry-standard protocols. If the measurement results do not meet the design exposure limit, the cause is identified and necessary improvement measures are taken, consistent with the troubleshooting methodology outlined in the *ISPE SMEPAC Good Practice Guide [18]*.

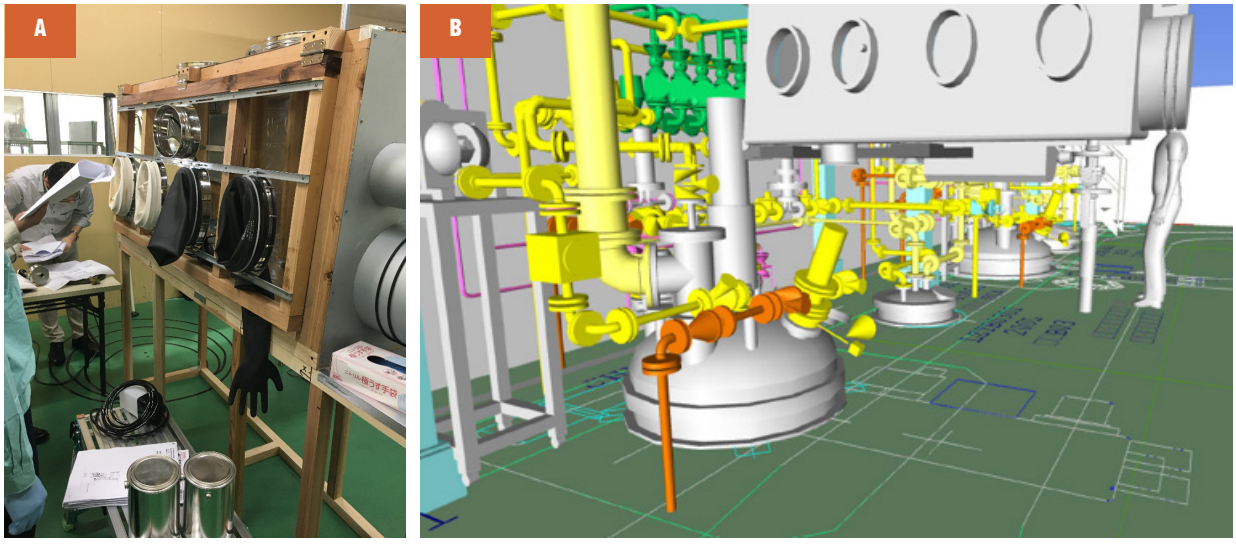
COMPREHENSIVE DESIGN AND OPTIMIZATION OF CONTAINMENT SYSTEMS

This section explores the critical aspects of containment system design and optimization in pharmaceutical manufacturing. It covers the selection of appropriate containment performance based on chemical hazards, the use of flexible containment solutions, and the implementation of secondary safety measures. The importance of design verification through mockups is discussed, along with the need for continuous improvement to enhance system robustness and efficiency. By addressing these key areas, manufacturers can develop containment systems that effectively balance safety, regulatory compliance, and operational efficiency in drug production processes.

PERFORMANCE OF CONTAINMENT SYSTEMS

The performance of containment systems needs to be appropriately selected based on a comprehensive risk assessment that considers both the hazard level (indicated by the OEL of the handled chemicals) and the potential for exposure, as per the ISPE Guideline where risk equals hazard times exposure [19]. This approach ensures that the stringency of the containment system is determined not only by the hazard but also by the exposure potential. Although higher evaluation categories may generally indicate a need for higher

Figure 3: Mockup for A) isolator and B) 3D modeling.



containment performance, the actual requirements depend on the overall risk assessment. For instance, a category 2 substance with high exposure potential might require more stringent containment than a category 3 substance with very low exposure potential. As examples of containment solutions:

- For lower-risk scenarios (lower hazard and/or lower exposure potential): ventilation-based controls of demonstrated control performance or draft chambers may be sufficient.
- For higher-risk scenarios (higher hazard and/or higher exposure potential): isolators or more advanced containment systems may be necessary.

However, these are general guidelines. The specific choice of equipment should be based on a thorough risk assessment considering both hazard and exposure factors. It is important to recognize that industry standards, including ISPE guidelines, have limitations and the field of containment engineering is relatively data sparse. When consulting experts or vendors, their recommendations should be critically evaluated against scientific principles. Decision-makers should seek evidence of successful implementations and performance verification rather than relying solely on theoretical claims.

Utilization of Flexible Containment

In recent years, the use of flexible containment has been increasing from the perspective of cost-effectiveness and flexibility. Flexible containment can be suitable for temporary use or small-scale production and has the advantage of easy installation and removal. However, other solutions—such as rigid containment systems, integrated isolators, and custom-engineered approaches—may be more appropriate depending on specific process requirements, material characteristics, scale of operation, and frequency of use. The selection of containment technology should be based on a comprehensive risk assessment of the specific manufacturing context.

However, careful consideration is needed for its adoption due to disadvantages such as susceptibility to damage during operation and limitations in negative pressure control. The decision to adopt flexible containment is made based on a comprehensive evaluation of factors such as frequency of use, nature of operations, and handled substances and quantities. In particular, the use of flexible containment is not recommended for potent compounds or large-scale production. Its use requires careful consideration when working with organic solvents, equipment with internal pressure fluctuations, or gases.

Design Verification Through Mockups

In the design stage of containment systems, it is sometimes recommended to conduct operability confirmation using mockups, depending on the complexity of the process and the level of containment required. This approach, when appropriate, allows for verification of the validity of design specifications in conditions close to the actual work environment. However, the necessity for mockup testing should be determined through risk assessment, considering factors such as process complexity, novelty of the containment solution, and potential consequences of design inadequacies.

In mockups, the design specifications are validated for all anticipated work tasks, including not only regular manufacturing operations but also cleaning and maintenance work (see Figure 3). The assessment results are summarized in a containment system design mockup report, and design improvements are made as

necessary. It should be noted that these mockup assessments provide valuable insights but may not fully represent all real-world operational scenarios.

Secondary Containment

Secondary containment is designed to prevent the contamination of areas outside of the production rooms where potent compounds are being handled. Even when appropriate primary exposure control is achieved, these secondary measures should be taken in preparation for incidents, depending on the risk assessment. Examples of secondary protection measures include:

- Room pressure differentials to direct airflow
- Installation of airlocks between areas of different classification or containment levels
- Installation of high-efficiency particulate air (HEPA) filters in room supply and exhaust lines
- Installation of controlled environments for PPE removal
- Provision of respiratory protection options including powered air-purifying respirators (PAPRs) and installation of air supply ports for airline suits when required

These secondary measures are important safety precautions to protect workers and the environment in case of emergencies. These measures are essential, especially in facilities handling potent compounds.

Industrial Hygiene Monitoring

Though surrogate testing during commissioning is essential for initial verification of containment systems, industrial and occupational hygiene monitoring provides critical empirical validation of engineering controls during actual operations. A comprehensive industrial hygiene monitoring strategy should include:

- Baseline monitoring: Conducted before routine operations to establish reference exposure levels
- Periodic monitoring: Regular sampling to verify continued effectiveness of containment systems during routine operations with actual APIs
- Task-based monitoring: Focused sampling during high-risk operations to identify potential exposure scenarios
- Individual and area sampling: Combination of breathing zone and static sampling to comprehensively assess worker exposure and containment effectiveness

Results from industrial hygiene monitoring should be compared against established OELs to ensure worker protection and validate that engineering controls are performing as designed under real production conditions. This ongoing empirical testing complements the surrogate testing performed during commissioning and provides real-world data on containment performance throughout the facility lifecycle. When monitoring results indicate potential issues, a systematic approach similar to the root cause analysis shown previously should be implemented to identify and address exposure concerns.

Continuous Improvement

The design and verification of containment systems is not a one-time process; it requires continuous improvement. Based on initial measurement results, monitoring and incorporation of new knowledge are conducted to aim for the realization of a more robust containment system.

It is also important to review and update existing containment systems in response to technological advancements and changes in regulatory requirements. Through such continuous improvement activities, it becomes possible to realize safer and more efficient pharmaceutical manufacturing processes.

API MANUFACTURING FACILITY IMPLEMENTATION CASE STUDY

The case study discussed here is the design and verification process of containment systems in a small and mid-size molecule API manufacturing facility, named FJ2. FJ2 is a facility that handles small and mid-size molecular compounds with high pharmacological activity and that incorporates advanced environmental, health, and safety technologies. The main equipment in FJ2 includes devices for processes such as weighing, reaction, filtration, extraction, crystallization, drying, and milling. This facility required a stringent containment level of below 0.05 mcg/m^3.

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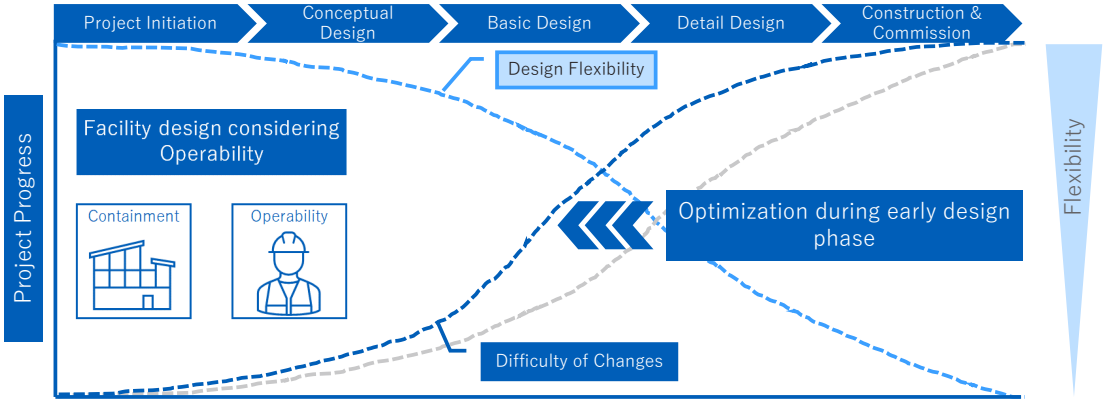
Figure 4: Design flexibility decreases through various stages.



Curve 1: "Design Flexibility" (high at project start, decreasing over time)
Curve 2: "Cost and Difficulty of Changes" (low at project start, increasing over time

The design and verification of containment systems is not a one-time process—it requires continuous improvement. In the case of FJ2, based on initial measurement results, work procedures were reviewed and equipment was fine-tuned to further improve performance.

Risk Assessment

In the risk assessment stage, information was collected about hazards, exposure possibilities were evaluated, and exposure control were considered. In this process, existing knowledge and experience, as well as the latest technical information, were utilized to refine the design policy.

Risk Control

In the risk control stage, engineering controls were prioritized as the primary risk-mitigation strategy for API containment. Although the traditional hierarchy of controls includes elimination and substitution as theoretical options, these are typically not feasible approaches in pharmaceutical manufacturing, where the APIs themselves are the target products. Elimination and substitution strategies are primarily relevant during early development phases (e.g., candidate selection, synthetic route design) and have minimal applicability during facility design and operation phases for an established API.

Therefore, focus was placed on implementing effective containment systems that ensure worker protection while maintaining operational efficiency. Particularly important was optimizing the design for both operability and containment performance, with worker safety as the paramount concern that must never be compromised. Although cost-effectiveness is a legitimate consideration in selecting among equally effective containment options, economic factors should always remain secondary to safety and compliance requirements.

Excessive focus on containment can impair operability, whereas prioritizing operability can potentially decrease containment performance. The key point in design was to balance both functions without sacrificing either aspect. This process of risk assessment and risk control was initiated from the early design stage and repeated as the amount of information increased throughout the design process. It is important to note that the earlier in the design process these assessments and controls are implemented, the more flexibility there is for making changes. As the design progresses to later stages, it becomes increasingly difficult and costly to make significant modifications.

In the early design phases, there is greater flexibility to explore various options and make substantial changes to the design based on risk assessments. However, as the design becomes more detailed and finalized in later stages, the ability to make major changes becomes limited. This underscores the importance of thorough risk assessment and control measures early in the design process. Figure 4 provides a visual representation of this concept, illustrating how design flexibility to make containment design changes decreases significantly as a project progresses through its

Table 1: Result of containment performance assessment for movable isolator.

*:Under LOD (Limit of Detection)

Sampling Point	N=1 (mcg/m³)	N=2 (mcg/m³)	N=3 (mcg/m³)	Cleaning (mcg/m³)
① in front of panel	<0.0004*	<0.0004*	<0.0004*	0.0015
② in front of port door	<0.0004*	<0.0004*	<0.0004*	0.0025
③ around port	<0.0004*	<0.0004*	<0.0004*	<0.0003*
④ connection point	<0.0004*	<0.0004*	<0.0004*	0.0019
⑤ operator	<0.0004*	<0.0004*	<0.0004*	0.013
⑥ background	<0.0004*	<0.0004*	<0.0004*	<0.0003*
⑦ background	<0.0004*	<0.0004*	<0.0004*	<0.0003*

lifecycle, whereas the cost and difficulty of implementing changes increases dramatically. Early risk assessment, mitigation and containment strategy development are therefore critical, as they allow for cost-effective design optimization when changes can be implemented with minimal impact.

Risk Review

Following the risk assessment and risk control stages, the containment system design was implemented. After implementation, as part of the ongoing risk management process, a containment performance assessment was conducted to verify that the constructed system met the design requirements. This verification testing was carried out during the FAT and SAT stages, which occur in the implementation phase of the project life cycle. The results of these tests were then incorporated into the risk review process to confirm that the identified risks were adequately controlled.

In the containment performance assessment, the amount of powder leakage from the equipment was measured by simulating actual operations. Measurement points were appropriately selected from the perspectives of worker protection, equipment capability evaluation, and cross-contamination evaluation [21]. The measurement results were compared with the set CPT to determine if the risk was acceptable. (A specific example of measurement results is shown in Table 1.)

These measurements were conducted following the *ISPE SMEPAC Good Practice Guide* methodology, which is an industry-standard approach for evaluating containment performance. Figure 5 shows the team running the test. It is important to note that although these results demonstrate excellent containment performance, they represent a single test event conducted in triplicate under specific controlled conditions.

The data presented should be interpreted with appropriate context. In real-world manufacturing environments, performance may vary due to factors, such as:

- Differences between surrogate materials and actual APIs
- Variations in operator technique and experience
- Changes in environmental conditions
- Equipment aging and maintenance status
- Process variations and scale differences

From these measurement results, it was confirmed that the designed containment system met the required performance under test conditions. However, ongoing monitoring during actual operations with APIs is essential to verify continued performance. A comprehensive containment strategy should include periodic verification testing, routine environmental monitoring, and operator exposure assessment to ensure sustained protection throughout the system's operational life.

Furthermore, similar measurements were conducted on equipment handling powders such as weighing, reaction, drying, and milling, confirming that they met the required performance under test conditions.

CONTINUOUS IMPROVEMENT

The design and verification of containment systems is not a one-time process—it requires continuous improvement. In the case of FJ2, based on initial measurement results, work procedures were reviewed and equipment was fine-tuned to further improve performance. As illustrated in the root cause analysis diagram (see Figure 2), multiple factors can contribute to exposure, including machinery, method, materials, and human factors (human/behavior). Though engineering controls are essential, human factors often play a critical role in containment effectiveness [18].

By applying this framework to our root cause analysis, we identified that operator adherence to standard operating procedures was a critical factor in achieving optimal containment performance (see Figure 2). This finding led to targeted improvements in training and procedural documentation, resulting in significant

Figure 5: Containment performance assessment.



performance enhancement with measurements below detection limits (<0.0006 mcg/m³) at all sampling points after implementation.

The lessons learned from this case study highlight several key recommendations for practitioners. First, a comprehensive root cause analysis should be conducted that considers all potential contributing factors rather than focusing solely on engineering controls. Second, implement regular competency assessments for operators handling potent compounds to ensure consistent application of containment procedures. These practical measures, when implemented alongside robust engineering controls, create a more resilient containment strategy that can better withstand the variability inherent in manufacturing operations.

The Importance of Documentation

Documentation plays a crucial role in the design, implementation, and continuous improvement of containment systems. In the FJ2 project, all activities are meticulously documented and finalized through stakeholder confirmation, reflecting a deep understanding of the importance of information consolidation and shared awareness among all parties involved.

Comprehensive documentation is essential throughout all project stages, from risk assessment and reduction to performance verification and continuous improvement. These documents serve as a valuable record of design decisions, performance measurements, and improvement activities, providing a complete picture of the project's evolution.

Notably, these documents are transferred to the manufacturing department after the completion of the construction, ensuring that the knowledge and decisions made during the design phase seamlessly transition into the operational phase. This continuity significantly contributes to the long-term efficient operation and safety of the facility.

Beyond the project phase, this comprehensive documentation also serves as the foundation and recording platform for ongoing repeat monitoring by operational staff. The established baseline performance data, testing methodologies, and acceptance criteria documented during commissioning become the reference points against which operational staff can compare subsequent monitoring results. This enables the demonstration of continued exposure control compliance throughout the system's operational life.

The ability to track performance trends over time, identify deviations from established baselines, and document corrective actions is a critical element in ensuring continued effective performance of installed containment systems. Without this robust documentation framework, it would be impossible to verify that containment systems continue to provide the required level of protection as equipment ages and processes evolve. Furthermore, thorough documentation is indispensable from a regulatory compliance perspective. Well-documented information serves as crucial evidence during audits and inspections, demonstrating the organization's transparency and accountability.

It is important to acknowledge the inherent uncertainty and reliance on systems that characterize containment work in pharmaceutical manufacturing. Despite meticulous planning, comprehensive documentation, and advanced facilities, the world remains uncertain and often nonintuitive. The pharmaceutical industry, regardless of technological sophistication, must continuously address the challenges of containment. Proactive

Table 2: Main deliverables in FJ2 related to containment.

Design Stage	Main Deliverables
Conceptual Design	• URB • Containment Facility Design Risk Assessment Report
Basic Design, Detailed Design, and FAT	• URS • Equipment List • Layout • Specifications • Piping and Instrumentation Diagram (P&ID) • Design Mockup Report/Operability Confirmation Report • Assembly Drawing • Factory Acceptance Test Protocol • Factory Acceptance Test Report • Factory Acceptance Summary • Containment Facility Design Risk Assessment Report (Revised)
Commissioning & Qualification	• Final Operability Confirmation Plan • Final Operability Confirmation Report • Containment Performance Assessment Plan • Containment Performance Assessment Report • Containment Performance Assessment Summary • Containment Facility Design Risk Assessment Report (Revised) • Piping and Instrumentation Diagram (P&ID) (Revised)

Table 3: Key items in URB related to containment.

Key Item	Summary
Containment Policy	• Specify the principles for ensuring worker safety based on company policy
Evaluation Category or IOEL of Chemicals to be Handled	• Clearly state the evaluation category or IOEL of chemicals to be handled in the equipment
Planned Equipment	• Summarize the planned equipment in a list • Specify any special containment functions if applicable
Process Details	• Describe anticipated process contents, properties of chemicals to be handled, and handling quantities • Clearly state API content and concentration of handled substances • Include equipment cleaning and maintenance operations
Containment Performance Target (CPT)	• Specify the required CPT for each equipment • State that compliance with CPT will be a condition for acceptance
Secondary Measures	• Include requirements for HVAC, changing rooms, showers, and airline systems • Airlocks between areas of different classification/containment levels
Auxiliary Facilities	• Specify waste treatment methods and necessary auxiliary facilities
Commissioning & Qualification	• Indicate whether mockups will be conducted and containment performance assessment will be performed during FAT • Specify that containment performance assessment during SAT are mandatory
Issues for Consideration	• If there are any special issues that require consideration during the design and verification process, specify them

monitoring systems are essential, as they can identify potential issues before they manifest as health concerns among personnel. Early detection through comprehensive monitoring protocols provides opportunities for intervention that protect workers' health and maintain operational integrity.

This recognition of uncertainty should not discourage rigorous containment efforts but rather emphasize the need for humility, vigilance, and continuous learning. Documentation systems must be designed not only to demonstrate compliance but also to capture near-misses, anomalies, and early warning signs that might

The FJ2 project demonstrates how a systematic approach can address these challenges while highlighting that safety is not an absolute state but rather a continuous journey requiring constant vigilance. Through transparent communication about residual risks and rigorous verification processes, the industry can work toward safer pharmaceutical manufacturing while acknowledging the complex nature of safety assurance in this field.

otherwise go unnoticed. Health surveillance programs for workers handling potent compounds should be robust and proactive, serving as an additional layer of protection beyond engineering controls.

The emphasis on documentation in the FJ2 project underscores its importance in preserving knowledge, facilitating continuous improvement, ensuring regulatory compliance, and ultimately enhancing the safety and efficiency of pharmaceutical manufacturing processes. By acknowledging the limitations of even the most sophisticated containment systems and maintaining vigilance through comprehensive documentation practices, this approach sets a best practice standard for future project management in the industry. Main deliverables and the user requirements brief in FJ2 are shown in Table 2. Key items in URB related to containment are shown in Table 3.

CONCLUSION

The design and verification of containment systems should be systematically implemented based on a risk-based approach. Although this approach aims for high levels of safety, it is important to acknowledge that work with potent compounds inherently involves high risks and significant uncertainties.

Obtaining reliable exposure data to demonstrate safety and support liability management remains challenging even with advanced technologies. This necessitates a conservative containment design with multiple protection layers and continuous industrial hygiene monitoring.

The FJ2 project demonstrates how a systematic approach can address these challenges while highlighting that safety is not an absolute state but rather a continuous journey requiring constant vigilance. Through transparent communication about residual risks and rigorous verification processes, the industry can work toward safer pharmaceutical manufacturing while acknowledging the complex nature of safety assurance in this field.

As a result of these efforts, the FJ2 project won the Innovation category at the 2023 ISPE Facility of the Year Awards. The judges highly praised the project for "focusing on process and employee safety throughout the project design and adopting innovative methods to achieve these goals" [23].

This case study demonstrates the importance of a risk-based approach and continuous improvement in the design and verification of containment systems for high-potency pharmaceutical manufacturing. By applying these principles in future pharmaceutical manufacturing facility designs, organizations will be able to construct safer and more efficient production systems.

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