How to set up a Project for Handling High Potent Products under Isolator

Case Study

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The following article is a case study. We focus on the definition of different phases of a high potent product handling project under isolator. The processes to be carried out in the isolator environment will be the weighing of products, with exposure limits of 0,01 µg/m^3. During the project, we will analyse the different phases that will allow us to adequately assess the risks and select the appropriate mitigation mechanisms.

KEYWORDS: Isolation, Containment, Drug production, Handling High Potent Products

El siguiente artículo es un caso de estudio. Nos enfocamos en la definición de las diferentes fases de un proyecto de manejo de productos de alta potencia bajo aislador. Los procesos a realizar en el ambiente del aislador serán el pesaje de productos, con límites de exposición de 0,01 µg/m^3. Durante el proyecto analizaremos las diferentes fases que nos permitirán evaluar adecuadamente los riesgos y seleccionar los mecanismos de mitigación adecuados

PALABRAS CLAVE: Aislamiento, Contención, Producción de fármacos, Manejo de productos de alta potencia

INTRODUCTION

Containment in the use and handling of high potent products has several aspects that must be analysed before tackling a project with this type of product. Containment is not absolute. The different levels of containment that can be obtained will depend on the system and technical solutions that we apply. The different levels of containment that can be obtained will depend on the system and technical solutions applied. The evaluation and verification of the containment level must be in accordance with the analysis and detection capacity.

The development of new and more active pharmaceuticals ingredients and with lower therapeutic doses, it forces extreme containment measures and ultimately also forces the use of increasingly sophisticated analytical detection techniques.

A drug production project with a highly potent active ingredient requires a detailed study, from concept to validation. In this article we want to focus on the field of primary containment that we can achieve with a suitable design of the process under isolator. In particular, we will analyse a product weighing process.

PROJECT PHASES

It is important to carry out the analysis of the project in phases and to do it in an orderly manner to analyse all the steps of the process, particularly in this case a process of weighing a high potent product.

1. User Requirements Analysis.
   a. Product(s) to be weighed.
   b. Characterisation of the products.
   c. Batch sizes to be weighed.
   d. Number of batches per shift.
   e. Product reception containers.
2. Risk Assessment.
3. Containment Strategy.
4. Conceptual design of containment equipment.
5. Detailed Design of the containment equipment.

» Another important point is to determine the toxicity of the product to be handled. In many cases, a detailed characterisation of a product is not available

6. Mock-Up of the proposed solution.
   a. Ergonomics test.
   b. Material transfer tests.
   c. Mock-up validation.
7. Equipment construction.
8. FAT testing.
9. Full Equipment Qualification.
10. Containment Validation (SMEPAC) [3].

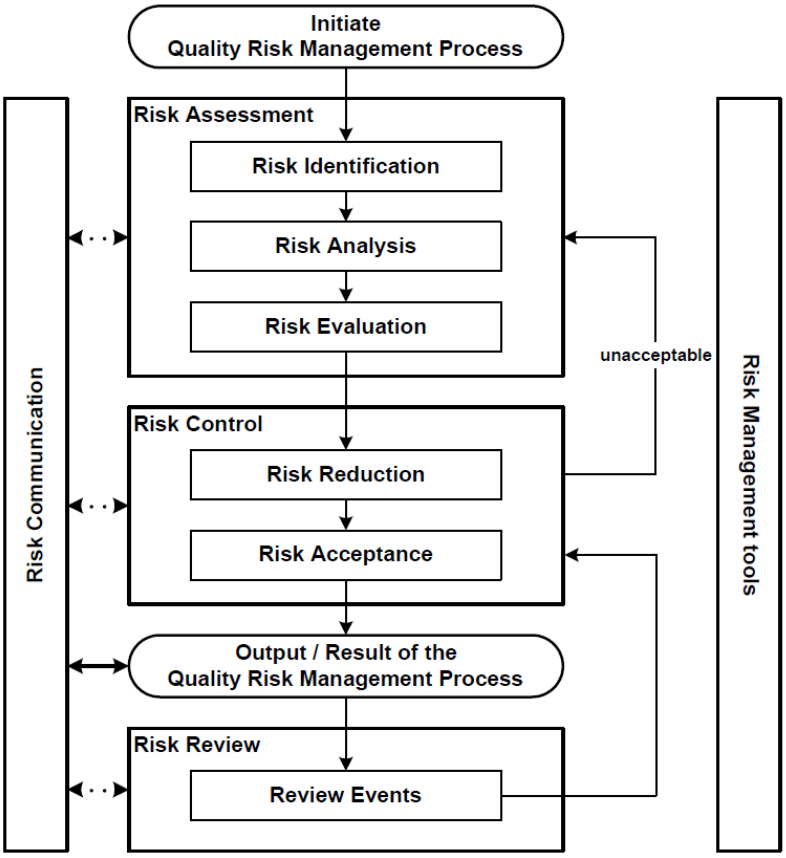
CASE STUDY

1. User Requirements Analysis

In this article we study a weighing case with the following starting data:

- API, characterised as OEL=0.01µg/m^3 and a containment level characterized OEB<0.01µg/m^3.
- Product in powder form. It's

FIGURE 1. Typical Risk Management Process [1]



uniform and powdery fine solid, is a non-crystalline and light powder that is suspended generating clouds.

- Source Container: Drum different dimensions.
- Weighing batches from 0.1 to 7 kg.
- Closed containment system for safe transfer to formulation reactor.

2. Risk Assessment

Before initiating a risk analysis of this nature, it will be necessary to establish a basis for proper management (Figure 1).

From the human resources point of view, it is necessary to name a person in charge, and to create a multidisciplinary team to analyse and approach the assessment from all perspectives:

In this case the project team would be formed by :

- Responsible:
  - Laboratory Engineering Manager.
- Other Resources:
  - Laboratory Production Manager.
  - Laboratory Weighing Area Operator
  - Laboratory HSE Manager.
  - Advisor: Containment Expert and Isolator Manufacturer
  - Raw Material Supplier.

Detailed product characterisation

Another important point is to determine the toxicity of the product to be handled. In many cases, a detailed characterisation of a product is not available. In addition to the fact that there is no universal and unique system for categorising exposure control bands, pharmaceutical companies often define themselves the values based on their knowledge of the product itself, therapeutic compounds, work environment, equipment, controls, and other factors [7,8].

A common example might be Occupational Exposure Band (OEB 1) (>1000 µg/m^3), OEB 2 (10 to 1000 µg/m^3), OEB 3A (1 to 10 µg/m^3), OEB 3B (0.01 to 1 µg/m^3), OEB 4 (<0.01 µg/m^3) [6].

These categories are set based on a detailed toxicological evaluation of all possible adverse effects. The final determination of the product category does not depend on a single factor, such as the therapeutic dose. The categorization and the OEL must be carried out by an expert occupational toxicologist that will determine the level of containment necessary for a safe work with the product.

- Planning. Detailed planning is important, and adequate knowledge of the personnel involved and their availability is also important.
- Contents of the risk analysis:
  - Starting data.
  - Analysis, e.g., following FMEA (Failure Mode Effects Analysis) (Figure 2).
  - Conclusions document.
- Communication of RISKS:
  - Information Distribution Group.
  - Communication with Regulatory Authorities.
- Review and monitoring of process risks.

FMEA Analysis (Failure Mode Effects Analysis) (Table 1 and 2)

3. Containment strategy

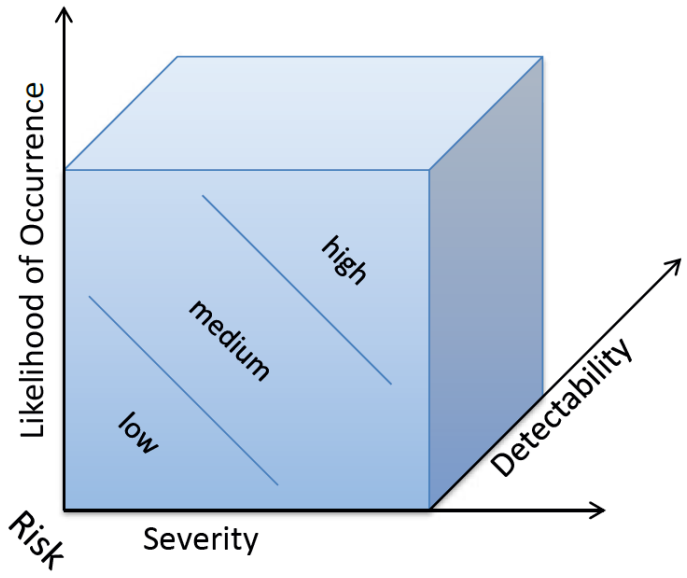
The risk assessment concludes that the containment level of the primary barrier is such that it can only be achieved using an isolator.

In this phase, the laboratory must draft the URS document, with as much definition as possible. It is intended that this document should include the most important aspects of the isolator from the end-user's perspective.

Many of these aspects are covered in the following conceptual and detailed design points.

4.Conceptual design of the containment equipment

FIGURE 2. FMEA method [4]



Risk Priority Number = Likelihood of Occurrence x Detectability x Severity

From a conceptual design point of view, we propose an isolator with the following characteristics (Figure 3):

- Containment isolator, with Air Lock for material transfer, with two gloves for handling loads, and main chamber with 4 gloves, with integrated weighing scale.
- Chamber and Air Lock with internal ISO 8 classification, turbulent flow, and door with inflatable seals.
- Filtration system through H-14 Push-Push filters, and double H-14 Push-Push extraction filters. No air recirculation.
- The isolator must be airtight class 3 according to ISO 14644-7.
- The isolator chamber must be welded, seamless, rounded, self-draining, and easy to clean. The internal roughness Ra<0.6.
- A weighing system must be integrated, with a weighing scale suitable for the batch size and with the scale display easily accessible by the operator inside the isolator itself preferably.
- Manual cleaning with spray gun in the air lock and spray balls and spray gun in the main chamber.
- Control system with HMI, allowing monitoring of the equipment and processes, with an integrated

CHART 1.

RESULTS OF THE RISK ASSESSMENT

RISK IDENTIFICATION		RISK ANALYSIS	RISK EVALUATION		TOTAL	RISK CONTROL STRATEGY		
PRODUCT & PROCESS PERSPECTIVE								
PRODUCT CHARACTERIZATION	POTENTIAL RISK	DETECTABILITY	SEVERITY	PROBABILITY	RISK PRIORITY NUMBER	RISK REDUCTION METHOD	FINAL RISK	COMMENTS
Product Toxicity OEL OEL <0,01µg/m3.	Exposure during sampling/weighting	3	3	3	27	Use Isolator	Accepted	Exposure <0,01µg/m3
Number Batch per day - Value 2	Total Exposure Risk Time, per day.	2	2	2	8	Use Isolator	Accepted	
Batch Size - Value 0,5 to 7 kg	Bigger batch, bigger risk.	2	2	2	8	Use Isolator	Accepted	
Product Pulverulence	Product remaining floating in the air	3	3	3	27	Use Isolator	Accepted	
Explosive Index - ATEX , Ignition Sensibility <0,2	Risk of explosion.	1	3	1	3	No ATEX clasification neccesary.	Accepted	Ignition Sensibility <0,2
PRIMARY BARRIER: MATERIAL TRANSFER PERSPECTIVE								
RAW MATERIAL PACKAGING	POTENTIAL RISK	DETECTABILITY	SEVERITY	PROBABILITY	RISK PRIORITY NUMBER	RISK REDUCTION METHOD		COMMENTS
Drums	Product loses during opening and close the containner. Diferent drum sizes.	2	3	2	12	Drum Docking System compatible with diferent drums sizes.	Accepted	Raw material supplyer have to provide doble and continues bag inside.
Cans with threaded cap.	Product loses during opening and close the containner	2	3	2	12	Use Air Lock chamber big enought, and open the cans inside the isolator.	Accepted	Only valid for small containers.
Bottles, cans to transfer the product to production.	Product loses during opening and close the containner	3	3	2	18	Split Buterfly Valve or Single use foil transfer System with special connections.	Accepted	Usefull for transfer the product to production.
PRIMARY BARRIER: HUMAN RESOURCES PERSPECTIVE								
REGULAR PRODUCTION	POTENTIAL RISK	DETECTABILITY	SEVERITY	PROBABILITY	RISK PRIORITY NUMBER	RISK REDUCTION METHOD		COMMENTS
Normal Operation	Mistakes due to lack of trainning.	3	3	3	27	Training in HAPI sampling and weighing, GMP, Containment. Use of Mix Reality Technology.	Accepted	
Docking Systems and RTP	Mistakes due to lack of trainning in transfer systems.	3	3	2	18	Trainning to use transfer systems, docking systems and RTP connectors.	Accepted	
Primary barrier use.	Mistakes due to lack of training in primary barriers and Containment requirements.	3	3	2	18	Training to use Isolators.	Accepted	
PPE use.	PPE selection, clothes, gloves, mask, cap. Risk during gowning and degowning during the entrance and exit from containment area.	2	3	2	12	Trainning about PPE in containment evironment.	Accepted	
Exposure during the Degowning process.	After an incident where an operator has been exposed to an abnormally large amount of product. Risk during degowning.	3	3	2	18	Mist shower before degowning. Emergency management training.	Accepted	
PRIMARY BARRIER: CLEANING AND MAINTENANCE PERSPECTIVE								
MAINTENANCE	POTENTIAL RISK	DETECTABILITY	SEVERITY	PROBABILITY	RISK PRIORITY NUMBER	RISK REDUCTION METHOD		COMMENTS
Open Isolator	Exposure of maintenance staff	3	3	3	27	Emergency management training, and containment training.	Accepted	
Filter Change	Exposure to the powders in the filters.	3	3	2	18	Use BI/BO filters.	Accepted	
Isolator Ventilation System Monitoring	Lose tightness and containment, for any technical reason.	2	3	2	12	Monitoring: pressure inside isolator, inflatable gasket status. Periodically HEPA filters integrity test.	Accepted	Including an Alarm management system.
CLEANING PROCESS	POTENTIAL RISK	DETECTABILITY	SEVERITY	PROBABILITY	RISK PRIORITY NUMBER	RISK REDUCTION METHOD		COMMENTS
Regular Cleaning	Exposure of staff. Cross contamination.	3	3	3	27	Primary Barrier Cleanability, roundes corners, drainability. Cleaning Validation.	Accepted	
WIP & Spray Balls	Insuficient cleaning posibilities, manual process.	3	3	3	27	Wet cleaning, manual and semiautomatic cleaning process with spray balls. Cleaning Validation.	Accepted	
Waste Material	Exposure during waste removal.	3	3	2	18	Safe waste material transfer. Cotinues liner or disposable betabag with RTP.	Accepted	
Waste Water	Product loses through drain point, after WIP.	3	3	3	27	Connect drain point to a controled drain network.	Accepted	

LITEK PHARMA - Containment Risk Assessment

CHART 2.

INTERPRETATION OF THE RPN

RISK PRIORITY NUMBER (RPN)	PRIORITIES FOR ACTION AND DEDICATION OF RESOURCES
19 < RPN < 27 : HIGH RISK	Priority and immediate action
	Maximum dedication of resources and information
9 < RPN < 18: MODERATE RISK	Secondary action, through an action plan
	Less dedication of resources and information
1 < RPN < 8: LOW RISK	Deferred action or not required
	Minimum dedication of resources and information

electronic data recording system validatable according to GAMP5.

- Integral alarm management system for the isolator.
- Integration with the laboratory's MES system.

Material inlet/outlet ports:

- **Inlet:**
  - Air Lock for infeed of materials and tools of sufficient size. Two gloves to allow for debagging tasks.
  - DRUM elevator, prepared for different sizes, and sealed with inflatable gaskets during operation.
- **Outlet:**
  - Split Valve Port, to metal bag or bottle.
  - Waste Port, to continuous liner, with inflatable gasket seal port port or RTP.

At this stage, the FDS (Functional Design Specification) document must be drafted, which covers the functional aspects of the isolator design.

5. Detailed design of the containment equipment

Regarding the detailed design, we distinguish 5 main sections. Mechanical Construction, Material Transfer System, Cleaning System, Control System, Ventilation and Filtration System.

a. Mechanical Construction

The main chamber and the air lock chamber are made of 3 mm stainless steel AISI 316L sheet, with the rest of the auxiliary construction elements of stainless steel AISI 304 (Figure 4).

The surface finish of stainless steel is less than Ra<0.6 µm inside and Ra<1.2 µm outside.

Isolator and air lock chambers are designed to be hermetic and leak test compliant with ISO Class 3 classification 14644-7.

Isolator Chambers designs are cGMP compliant and will be fully welded. The interior surfaces are constructed

FIGURE 3. Basic design, air lock and main chamber

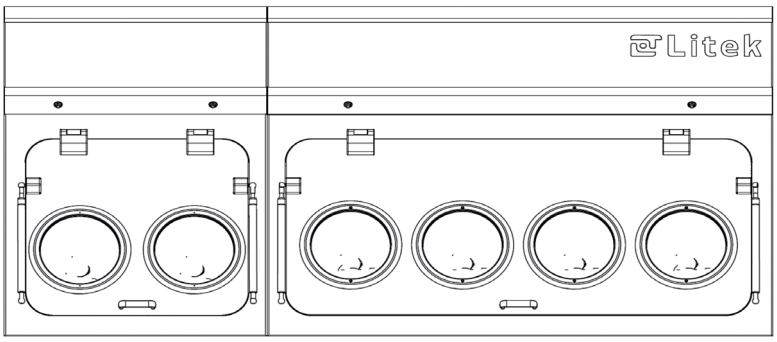


FIGURE 4. 3D modelling of the proposed solution

FIGURE 5. Drum loading at the base of the isolator

with rounded corners that provide smooth interior surfaces and surfaces that prevent cracking.

• The doors of the isolator are made of tempered glass, with inflarable gaskets seals.

b. Material Transfer Systems

Inlet:

Air Lock for entry of materials and utensils of sufficient size. Two gloves to enable debagging tasks.

Drum elevator, prepared for different sizes, and sealed with inflatable gaskets during operation (Figure 5).

Outlet:

Split butterfly Valve Port, to plastic bag or metal bottle (Figure 6).

Waste Port, a continuous liner, with inflatable seal port or RTP.

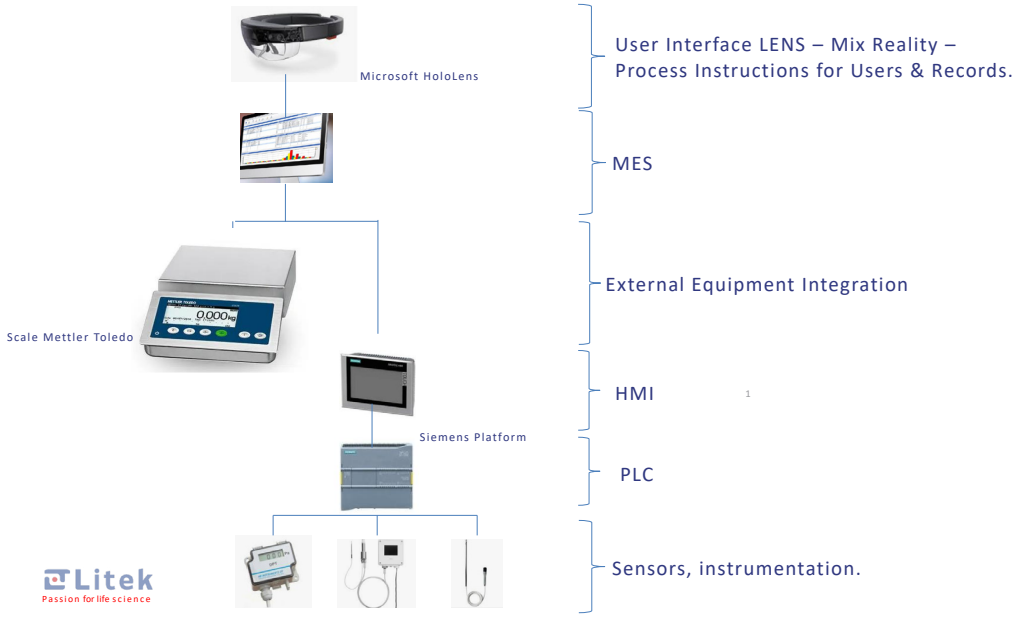
c. Cleaning System

Manual cleaning with spray gun in the air lock and spray balls and spray gun in the main chamber. In the airlock normally only has to be performed the debagging or unpacking of the product container. The primary bag shouldn't be open in the airlock.

» If there is no previous experience in the project team, it is important to have the support and advice of experienced specialists and manufacturers of isolators

FIGURE 6. Outfeed product through split butterfly valve

FIGURE 7. Control System Architecture



» Projects involving the handling of high potent products are recommended to be studied and evaluated following some of the reference guides [1,2,3,4,6], and the current GMP regulations

In the main chamber the product will be handled by operator, and the cleaning of this chamber will require a detailed study. Spray balls, connected to CIP circuit will allow the cleaning of most of the product dispersed along isolator.

d. Control system

The control system is based on an Industrial PLC connected to sensors and detectors level of the isolator for its correct operation. This software has an electronic register according to GAMP 5 (Figure 7).

This control system can be integrated with the laboratory's MES system.

An interface solution based on mixed reality technology is integrated, in which the operator using the isolator will have real-time access to all the information necessary for its correct use. For example, he has real-time access to the standard operating procedures, so that he can review each step of the process through the mixed reality system and avoid errors during the process.

In the same way, the operator himself, through the mixed reality system, will be able to inform the system of the progress of the process, in such a way that there is total traceability and electronic registration of each step.

e. Ventilation and Filtration System

The ventilation and filtration system consists of a compact ventilation module with separate supply and exhaust EC fans. The classification obtained inside the chamber is ISO 8 according to ISO14644.

In the Air Lock and in the isolator chamber the ventilation configuration are similar, with the same functionalities. HEPA H-14 filtration is foreseen in the supply air and a double HEPA H-14 filter in the extraction of both the Air Lock and the main chamber.

The filters are of the PUSH-PUSH type so they can be changed from inside the isolator, allowing a safe filter change.

6. Mock-up of the proposed solution

The manufacture of a mock-up of the isolator in disposable material (wood or cardboard) on a scale of 1:1 is highly recommended for the ergonomic study of the isolator. In this way the user can evaluate the functionality of the isolator for the specific processes defined and it can be modified and finally approved after the construction of the definitive model in stainless steel.

CONCLUSION

Projects involving the handling of high potent products are recommended to be studied and evaluated following some of the reference guides [1,2,3,4,6], and the current GMP regulations. It is necessary to form a multidisciplinary team to tackle the project with the highest level of knowledge and to carry out a detailed risk assessment. If there is no previous experience in the project team, it is important to have the support and advice of experienced specialists and manufacturers of isolators who will help to ensure that the result is functional and meets the operational requirements.

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