Containing Potent Pharmaceutical Powders – A Strategy Guide

A Quadro Engineering White Paper

Mina Ibrahim, P.Eng., MBA
Product Manager, Solids – Quadro Engineering
IDEX Material Processing Technologies Inc.

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Contents

Introduction

With the rise in popularity of High Potency Active Pharmaceutical Ingredients (HPAPIs) there has come increased interest in the containment and safe manufacture of such compounds. As drugs become more potent, they become increasingly dangerous to the health of plant personnel and manufacturers face significant challenges in ensuring the protection of their workers. This paper will present the strategies employed to properly contain *pharmaceutical solid powders* of various potency levels. Focus will be on containment methods used to protect employees who have to enter the local manufacturing room. A containment strategy selection procedure will also be presented. Comprehensive discussion of the different strategies outlined in this paper can be found in the book *Containment Systems – A Design Guide* by Hirst, Brocklebank, and Ryder, which covers in more detail the methods of containing toxic powders and liquids.

There are two main goals in the containment of pharmaceutical drugs: The first being the protection of workers who are coming into proximity with the product and the second being the avoidance of product contamination. This second goal includes protecting the drug from environmental factors (such as dust, excess moisture, airborne pathogens, etc) and from contact with other drugs that may be manufactured in the same facility. As can be seen in Figure 1, an appropriate containment strategy protects the external environment (everything outside the containment barrier) from the drug and the drug from the external environment.

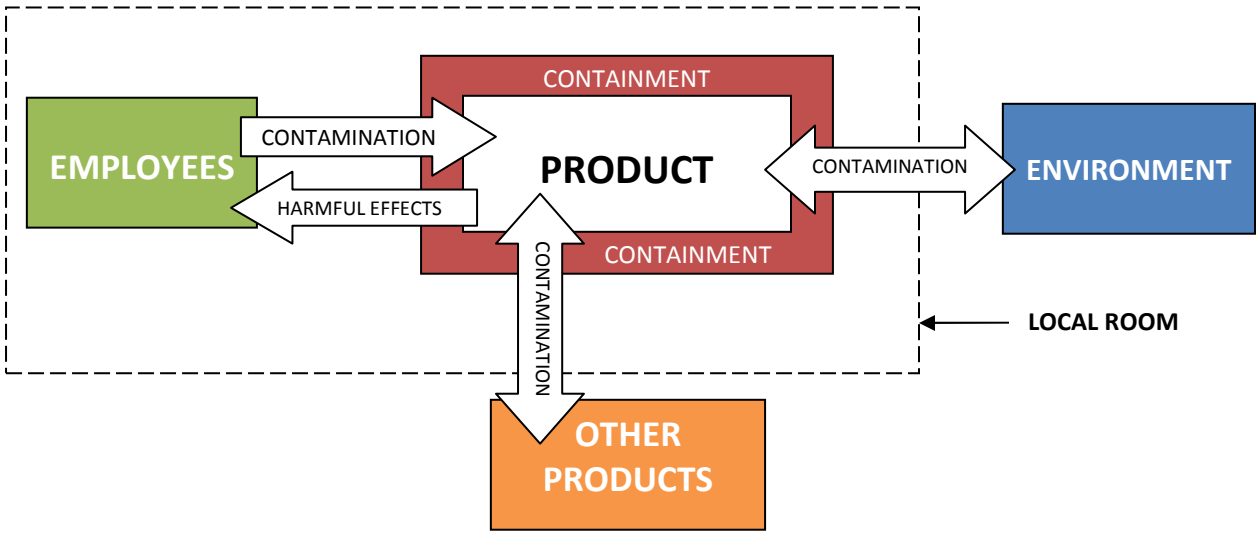

Figure 1: The Product and the External Environment

Formulating appropriate containment strategies requires studying the properties of the specific drug being manufactured and its effects on human beings. Various parameters such as OEL, OEB, STEL, and EP provide quickly identifiable ranges of danger for a specific drug, and help to identify what methods would be required to safely contain it. How these various parameters are used to arrive at a single containment strategy is outlined in Figure 2.

Identifying a Drug's Danger Level

Occupational Exposure Limits (OELs)

OELs are the most common method used to define product-specific exposure limits in the pharmaceutical industry. They are calculated by pharmaceutical companies for each new drug that is developed. An OEL is a measurement of mass of product in a given volume of air over a certain amount of exposure time; typically given as micrograms/cubic meter (µg/m^3) over an eight-hour Time Weighted Average (TWA). This indicates the acceptable amount of a drug that a worker may be exposed to during an eight-hour day for their complete life without risk to their health.

No Observable Effect Level (NOEL)

OELs are determined using the No Observable Effect Level (NOEL), which is calculated through clinical testing by administering a daily dosage in milligrams/kg of bodyweight to individuals, which is increased every day until the individual exhibits an adverse reaction. That NOEL is then multiplied by the average bodyweight of a human being and then divided by the volume of air that an average human breathes in eight hours to arrive at the OEL.

Operational Exposure Bands (OEBs)

Although not 100% adopted in the pharmaceutical industry, Operational Exposure Bands (also known as Hazard Groups) are common and classify OELs into six common ranges or bands, referred to either numerically (1 through 6) or alphabetically (A through F). For simplicity, this paper will refer to OEBs only numerically. These bands are listed for solid powders in Table 1 (1).

Table 1: Occupational Exposure Bands (OEBs) and Corresponding OELs for Solid Powders

Occupational Exposure Band	Occupational Exposure Limit
OEB 1 (or A)	10,000µg/m^3 – 1,000 µg/m^3
OEB 2 (or B)	1,000µg/m^3 – 100 µg/m^3
OEB 3 (or C)	100µg/m^3 – 10 µg/m^3
OEB 4 (or D)	10µg/m^3 – 1 µg/m^3
OEB 5 (or E)	1µg/m^3 – 0.01 µg/m^3
OEB 6 (or F)	<0.01 µg/m^3

Short Term Exposure Limit (STEL)

STELs are often provided for particular tasks that are routinely performed by a worker such as 15 minutes of milling. STELs are determined through the use of air samplers during the task and signify what level of exposure the worker will be subjected to during that task in µg/m^3. The STEL is used to calculate the TWA exposure level which is compared to the OEL of the product to ensure that the latter is not exceeded. That is done using the following three factors:

1. Number of tasks conducted during an eight hour shift
2. Length of time of each task
3. Concentration of API

For example: A worker must conduct three milling operations over an eight hour shift that take 15 minutes each to complete. Each milling operation has an STEL of 1 µg/m^3. This is conducted on a drug that contains 10% API.

This STEL of 1 µg/m^3 then translates to an exposure of 1 µg/m^3 x 3 tasks x (0.25 hr/8 hrs) x 10% = 0.0094 µg/m^3 TWA of eight hours. If the OEL of this drug is 0.01 µg/m^3 then the OEL is not exceeded and the shift schedule for milling this particular drug is acceptable. If, for instance, the OEL of the drug is 0.016 µg/m^3, the worker can be permitted to perform two more milling operations on the drug during his/her shift without exceeding the OEL (the worker's exposure would be 0.00156 µg/m^3 for five milling operations).

Containment Strategy Formation

Exposure Potential (EP)

The establishment of a proper containment strategy utilizes a substance's Exposure Potential (EP) which is based on three factors: Dustiness, Duration of Task, and Quantity Handled (1).

Dustiness

- Low: Non-friable solids, pellets, little or no observable dust during task
- Medium: Granular or crystalline solids, dust is observed but quick to settle
- High: Fine, light powder, able to form dust cloud that can remain suspended for several minutes

Duration of Task

- Short: Task duration of less than 30 minutes
- Long: Task duration of 30 minutes or longer

Quantity Handled

- Small: Lab scale/pilot plant – 1 gm to 10 kg
- Medium: Production scale – 10 to 100 kg
- Large: Large-production scale – over 100 kg

The EP for solid powders is determined using the three factors as shown in Table 2 (1).

Table 2: Exposure Potential for Solid Powders

Quantity Handled	Dustiness			Duration of Task
	Low	Medium	High	
Small	EP 1	EP 1	EP 2	Short
	EP 1	EP 2	EP 3	Long
Medium	EP 1	EP 2	EP 3	Short
	EP 2	EP 3	EP 4	Long
Large	EP 2	EP 3	EP 3	Short
	EP 3	EP 4	EP 4	Long

Containment Strategies & Equipment – Putting It All Together

The substance's **Exposure Potential** and its **Occupational Exposure Band** are used to finally arrive at an appropriate containment strategy, as shown in Table 3. Table 4 lists and provides a description of the strategies. The containment strategy procedure outlined in this paper is recapped visually in Figure 2.

Table 3: Containment Strategy Matrix for Solid Powders (1)

	EP 1	EP 2	EP 3	EP 4
OEB 1 $10{,}000\mu g/m^3 - 1{,}000\ \mu g/m^3$	**1**	**1**	**1**	**2**
OEB 2 $1{,}000\mu g/m^3 - 100\ \mu g/m^3$	**1**	**2**	**2**	**3**
OEB 3 $100\mu g/m^3 - 10\ \mu g/m^3$	**2**	**3**	**3**	**4**
OEB 4 $10\mu g/m^3 - 1\ \mu g/m^3$	**3**	**3**	**4**	**4**
OEB 5 $1\mu g/m^3 - 0.01\ \mu g/m^3$	**4**	**4**	**4**	**4**
OEB 6 $<0.01\ \mu g/m^3$	**5**	**5**	**5**	**5**

Table 4: Containment Strategies (1)

Strategy 1: Controlled General Ventilation	Only general ventilation of process area required.
Strategy 2: Local Exhaust Ventilation	LEV System is used to contain and remove contaminants from workers' breathable air. Achieved through point exhaust ventilation or unidirectional airflow booth.
Strategy 3: Open Handling within Isolator	Transfer or handling of material occurs in an isolator. Workers manipulate material through glove ports. Alternatively, high-integrity couplings such as split butterfly valves may be used for transfer of material between closed containers without the use of an isolator.
Strategy 4: Closed Handling within Isolator	High-integrity coupling must be used within an isolator, with manipulation of the closed containers to be performed through the isolator's glove ports. Open transfer not permitted inside the isolator.
Strategy 5: Robotic Handling	Used when risk of glove port breach is unacceptable due to extreme hazard of material.

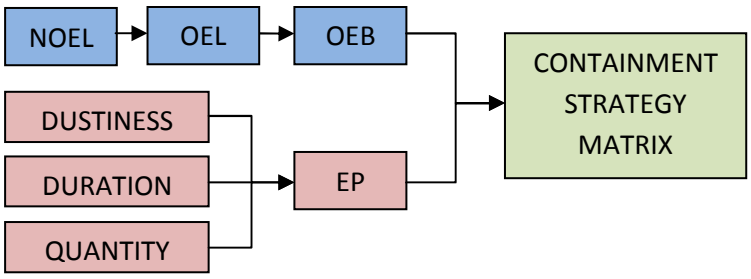

Figure 2: Procedure of Arriving at Containment Strategy

High-Potency Active Pharmaceutical Ingredients (HPAPIs)

The global pharmaceutical industry has seen a surge in the popularity of High Potency Active Pharmaceutical Ingredients (HPAPIs) over the past 10-15 years, with oncology drugs leading the HPAPI sector. Oncology is the fastest growing therapeutic segment in the pharmaceutical industry with over 860 new cancer drugs and vaccines awaiting approval by the Food and Drug Administration (FDA). Oncology drugs accounted for $48 billion in industry revenues in 2008 (2). The HPAPI market in general is forecast to grow 8.4% CAGR from 2009 to 2015 (3).

This tremendous growth in potent drugs can be attributed to HPAPIs' increased effectiveness and the fact that lowering dose and increasing potency can reduce the risk of side-effects from a drug. The increase in pharmaceutical drug potency has resulted in APIs that can be administered at doses of less than 1 mg (4).

An HPAPI is defined as being any of the following (2):

1. An API or intermediate with an OEL at or below 10 µg/m^3 eight-hour TWA (equivalent to OEB 4 or higher, see Table 1).
2. An API or intermediate with biological activity at or below approximately 150 µg/kg of body weight (equivalent to a therapeutic daily dose at or below 10 mg).
3. An API or intermediate with high selectivity (which is the ability to bind to specific receptors or inhibit specific enzymes) and/or have the potential to cause cancer, mutations, developmental effects, or reproductive toxicity at low doses.
4. A novel compound of unknown potency and toxicity.

HPAPI's can be small-molecule, biologic, or a hybrid. They include cytotoxic chemotherapy drugs, certain synthetic prostaglandins, monoclonal antibodies, certain hormones and opiates, and various other potent compounds (2).

Equipment Selection for Containment Applications

Solid powder processing equipment that is to be used in containment applications must be flexible in design and adaptable to external containment equipment such as gloveboxes. Appropriate processing equipment must also be designed with containment in mind; having high quality sealing and dust containment features. Equipment should be selected only from reputable manufacturers with a strong record of success in developing and building equipment for high containment applications.

Quadro® Comil® U5 – "Through-The-Wall" Design incorporated into a Glove Box Isolator

Mina Ibrahim is Solids Equipment Product Manager at Quadro Engineering, a division of IDEX Material Processing Technologies Inc. He holds a Bachelor's degree in Mechanical Engineering and an MBA in Strategic Marketing from McMaster University (Hamilton, Ontario). He is licensed as a Professional Engineer in the Province of Ontario.

About Quadro Engineering & IDEX Material Processing Technologies Inc.

Quadro Engineering, located in Waterloo, Canada, manufactures and markets an innovative line of size reduction mills, mixers, emulsifiers, powder dispersion units, shear pumps, high shear wet mills, security screeners and vacuum conveyors for the Food, Pharmaceutical, Cosmetic/Personal Care and Fine Chemical industries. Services include custom equipment engineering, process testing in Quadro's R&D Test Center, a complete Parts & Service Program, and a Rental Program featuring a wide range of Quadro equipment. Quadro Engineering is a division of IDEX Material Processing Technologies Inc., headquartered in Lake Forest, IL., USA. IDEX MPT Inc. is also the parent company of the Fitzpatrick Company and Microfluidics. IDEX MPT Group is always ready to meet the needs of its customers in more than 80 countries around the world.

Quadro equipment can be custom designed to meet any process environment including appropriate options for containment. Quadro has vast experience in providing processing equipment meeting containment levels as stringent as 1 µg/m^3. Quadro also offers a Fine Grind mill specifically designed for dust-tight fine milling of potent APIs. For more information regarding Quadro products, please visit www.quadro.com.

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