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Technologies Featured:

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SPECIAL THANKS TO:

Hidden Scale-Up Hazards


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HAZARDS AND POTENT COMPOUNDS PRIMER

Technicians deal with hazards on a daily basis, and so it would make sense that the earlier in the development process that hazards can be considered, the better. Certainly, during scale-up, your project team will need to consider: Will I need to explore different material handling techniques because of the increased scaled-up volume of the API? If a successful Phase II or III project uses hazardous or flammable solvents, what are the operational risks associated with scaling the batch volume up to 100 or 1000 times?

POTENT COMPOUNDS: THE BASICS

In pharmaceutical manufacturing, we deal with compounds that elicit a reaction. In most cases, those reactions gain a positive outcome for the patients for whom they are prescribed, but for the workers inside the manufacturing facility where they are processed, it may be a totally different and hazardous story.

Potent Compounds are pharmacologically active ingredients that can cause a reaction in very small quantities- microgram or nanogram. Toxic effects are typically described in terms of the duration of the exposure in one of two ways:

Acutely Toxic means:

-Short Term Exposure: Single exposure or multiple exposures in a short timeframe

Chronically Toxic means:

-Longer Term Exposure: Repeated exposure over a longer period of time

Several industry terms are used to define exposure risks to workers. A few commonly used terms include:

PEL - Permissible Exposure Limit (OSHA)

TLV - Threshold Limit Value (ACGIH)

ECL - Exposure Control Limits

STEL - Short Term Exposure Limits

The pharmaceutical industry has settled on the term Occupational Exposure Limit (OEL) to designate exposure risks. OEL is defined as the maximum airborne concentration of a contaminant to which nearly all workers may be repeatedly exposed day after day without adverse effects, and normally expressed as a time-weighted average over an 8 hour day.

OELs are determined by toxicologists and should not be estimated by the layperson. Note that such calculations are referring only to airborne exposure, rather than exposure to the skin or eyes. OEL is calculated based on the following formula:

OEL = NOEL(mg/kg/day) x BW(kg)

V (m^3/day) x AF x SF x ⟨

NOEL = No Observable Effect Level - Humans

BW = Body Weight 50 - 70 kg

V = Volume Air Inhaled 10 m^3

AF = Accumulation Factor

SF = Safety Factors, up to 10^4

⟨ = Absorption Factor

Isolation Technologies

- 10 to less than 1 microgram/m^3
- Engineered solution with great deal of thinking through the process
- Figure out how to get items in/out plus cleaning scenarios
- Cost $$-$$$$

Positives: Excellent containment

Negative: Costs vary widely

Local Exhaust Ventilation (LEV)

- Technique driven performance/SOP
- 50 to 100 micrograms/m^3
- Potentially remove actives
- Supplement other containment devices
- Cost $

NEGATIVES:

- Highly dependent on the operator position
- Highly dependent on the extraction device position.
- Large surges will go outside the designated 'safe' zone.

POSITIVES:

Manufacturing flexibility, with a lower capital expense

BANDING SYSTEMS: HOW TO CATEGORIZE POTENT COMPOUNDS

From an engineering perspective we are challenged with how to provide solutions to mitigate the risks imposed by the handling and processing of potent compounds. To address this challenge many companies have developed banding systems. The banding systems compartmentalize exposure risks such that a given set of design parameters and procedures can assure safety for products having an OEL within the designed range. It is important to understand the definition of a specific banding system, as there is not an industry standard followed by all companies. For example, one company's given band may cover a range of OEL's down to 10 µg/m^3 while another company's band with the same designation only extends down to 20 µg/m^3. This has a significant impact on production capabilities and therefore should be clarified from the onset of a project. This cautionary note is very relevant to contract manufacturing organizations, which service a large portfolio of pharmaceutical partners.

Once containment ranges have been determined, engineering can more easily determine what type of equipment and facility to design. For example, compounds with OEL values greater than

1000 µg/m³ (see below), are basically considered nuisance dust - not harmful, not irritating and with low pharmacological activity. As OEL value decrease and approach 1 µg/m³ and below this is when compounds are considered highly potent as they exhibit extreme toxicity and potency, which will require much greater levels of control.

Air Flow Technology (AFT)

- Technique driven performance
- *10 (probably better at < 20) to 100 microgram/m3
- Potentially remove actives
- Barrier added to increase performance
- Cost $$

Positives: Good cost: performance ratios
Negatives: Difficult to truly reach 10 micrograms/m3 levels

CONTAINMENT TECHNOLOGIES REVIEW

One of the outcomes of banding is that containment should be achieved through the use of Engineering Control Measures, not just procedures and personnel protective equipment. Exposure control banding sets the framework to select technologies and procedures to be applied with a predictable and repeatable outcome. What technologies can be employed to bring these potent compounds under control in your manufacturing process?

Before deciding on containment strategies, it is important to review the type of physical activity planned for each production step. For example, a milling step, which is a high energy operation with the potential to generate significant levels of dust, would certainly require a different containment approach than a low energy sampling activity. It is important to understand that the performance of any chosen technology is a function of the process with which it is integrated.

CONTAINMENT TECHNOLOGIES AND ANTICIPATED PERFORMANCE METRICS

The following is intended to provide a high level overview of the basic containment technologies in common use within the pharmaceutical industry. In general, containment technologies fall into one of two types: one that leverages airflow and the other which provides a physical barrier to isolate.

Local Exhaust Ventilation (LEV)

The objective of Local Exhaust Ventilation (LEV) is to extract particles before they make it into the general processing area or into an operator's breathing zone. This is critical not only for the operators, but in situations where there is multi-product processing or batch segregation, the LEV technology can help to ensure control over cross contamination. Within the performance range of this technology, this might be appropriate for Bin Charging, Hopper Charging type activities.

One caution worth mentioning is that there is often a temptation to over-design the removal device but be cautious, because if the system works too well you could be removing ingredients and impacting the formulation assay.

Air Flow Technology [AFT]

Air flow technologies are based on a similar principle to LEV. The idea is to sweep air away from operators breathing zone and away from the emission source by utilizing uni-directional air.

Isolation Technology

Designed to mitigate the most hazardous situations, Isolation Technology provides a physical barrier between the emission source and the operator/environment. There are two basic approaches when considering system containment. The first and most commonly used is the applied isolator scenario in which an isolator is "bolted-on" to the system to be contained. The other approach is to select a system that has been engineered to be contained from the outset. One of the biggest challenges faced with any isolated system is how to introduce and remove items from the system. This requires an in-depth analysis to identify all routine and foreseen processing steps and interventions to assure that the system has a means to accommodate these requirements while still maintaining containment. In addition, consideration must be paid to how cleaning and maintenance will be accommodated.

SCALE-UP VERSUS SCALE-OUT: A CONCEPT WORTH EXPLORING

There are many reasons to consider scale-out versus scale-up when moving from pilot plant to manufacturing.

Scale-Up is traditionally used to achieve a batch size as defined by a manufacturing company as large enough to meet the anticipated market demands.

Scale-Out is the use of multiple smaller and more flexible batches to achieve commercialization - using sizes traditionally aligned with 'pilot scale' and still meet the quantities necessary to meet market demand.

One definition of the "scale-out" concept combines a hybrid scale-out and 'batch unit' approach, and attempts to limit some of the business hazards as well as the more tangible hazardous and potent materials discussed throughout this article. Certain aspects of containment, fire and explosion, handled carefully in a pilot plant, become a greater challenge when moving into manufacturing.

Clearly, scale-up of a successful pilot scale Phase II or III product involves more than just concerns about potent compound safety. Marketing, sales, engineering, manufacturing, finance, procurement & supply chain make the question "how much product will be needed?" a complex one, as Phases II and III come to a close.

The organization should carefully review the scale of the proposed operation. Bigger may not be better, especially when it comes to potent and hazardous materials in many of solid dosage form applications.

CONCLUSION

The world of potent compound hazards boils down to a simple fundamental - do everything you can to understand the compounds your process is dealing with, in the lab, at the pilot stage and in commercial manufacturing. Understand material data sheets, flammability, and combustibility.

In addition:

- Limit quantities when possible to below exempt amounts by scaling out instead of up
- Checking all the codes and regulations
- Do a hazard evaluation in the earliest stages of the process and then repeat it, challenging it at each stage of the design process
- Look at different mediation solutions - not just one, put them on paper, get two options, challenge it, do the pro-con analysis.
- Challenge your engineering team and your engineering firm.
- Select and implement procedures and the chosen technologies
- Do a performance verification
- Monitor as often and as thoroughly as the risks indicate
- Re-evaluate and adjust to changes