Handling Hidden SCALE-UP HAZARDS

Eliminating the tangible processing hazards and providing alternatives to the hidden business hazards of scale-up

By Sam Halaby, IPS; Russ Somma, PhD, SommaTech; and Mike Vileikis, IPS

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?

This article takes a look at the basics of potent compounds, fire and explosion hazard prevention and the associated business risks of scale-up with regards to potent compound considerations. This article will explore strategies for handling potent compounds in both the development and commercial manufacturing stages. Covered are the Basics, with definitions and explanations for the novice, but there are also some suggestions for eliminating extra risks during scale-up and also a summary of the current technology available for containment. There are options for leveraging pilot plant development knowledge to facilitate rapid commercialization and strategies for mitigating the risks associated with scale-up.

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

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

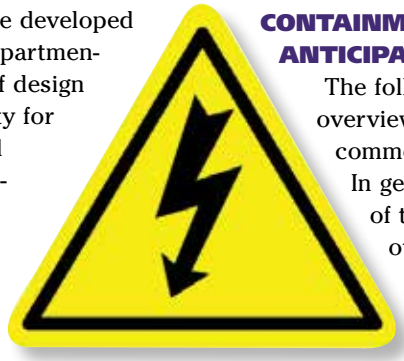
From an engineering perspective we are challenged with how to provide solutions to mitigate the risks imposed by the handling and processing of potent compounds. To address this challenge many companies have developed banding systems. The banding systems compartmentalize exposure risks such that a given 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/m^3 (see below), are basically considered nuisance dust - not harmful, not irritating and with low pharmacological activity. As OEL value decrease and approach 1 µg/m^3 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.

ENGINEERING CONTROL MEASURES: 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.

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/m^3 levels

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.

FIRE AND EXPLOSIVE HAZARDS

Where there are powders, potent or not, fire and explosion design considerations are always at the forefront of good, safe engineering design. An article about hazards would not be complete without some definitions, see below. You need to address fire and explosion mitigation during design and then again during operations and if there are any changes in the process, it must be addressed again.

Flammable and Combustible Liquids

Deflagration:

Propagation of a combustion zone at a velocity less than the speed of sound in the unreacted medium. Speeds typically far below 100 m/s, and relatively modest overpressures, below 0.5 bar.

Detonation

Propagation of a combustion zone at a velocity greater than the speed of sound in the unreacted medium. Speeds up to 2000 m/s, and substantial overpressures up to 20 bar.

Explosion

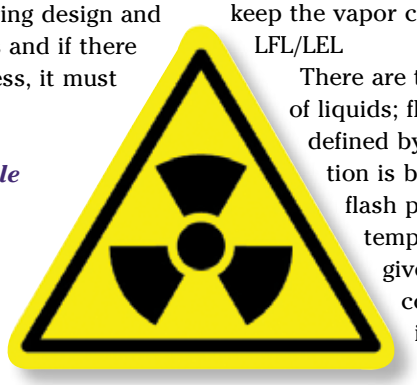
The bursting or rupture of an enclosure or container due to the development of internal pressure from a deflagration or detonation.

Three elements are necessary to start a fire. If you can eliminate just one of these through engineering, this breaks the Fire Triangle:

- Fuel
- Oxygen
- Energy

Flammable Range

It is important to understand that vapors and gases will only burn if their concentration in air is within a specific range. This range falls between what is called the Lower Flammable Limit (LFL) or Lower Explosive Limit (LEL) and the Upper Flammable Limit (UFL) or Upper Explosive Limit (UEL). If the concentration levels are below the LFL/LEL the condition is considered too lean to burn or explode and above the UFL/UEL too rich to burn or explode. It is recommended to keep the vapor concentration below 25-50% LFL/LEL



There are two different major classes of liquids; flammable and combustible defined by the NFPA. This classification is based on the compounds flash point; which is the minimum temperature at which a liquid gives off vapor in sufficient concentrations to form an ignitable mixture with air near the surface of the liquid. Combustible and Flammable liquids are defined by the NFPA as follows:

- Combustible Liquid – Flash point above 100°F/37.8°C
- Flammable Liquid – Flash point below 100°F/37.8°C

COMBUSTIBLE DUST

NFPA 654 defines a combustible dust as a particulate solid that present a fire or deflagration hazard when suspended in air or some other oxidizing medium over a range of concentrations, regardless of particle size or shape.

Combustible dust hazards will not be covered in great detail here, but there are certain terms that one should become familiar with when learning the language of combustible dust.

MIE: Minimum Ignition Energy
MIT: Minimum Ignition Temperature
Pmax: Maximum Explosion Pressure
LOC: Limiting Oxygen Concentration
Kst: Explosion Severity Index

FIRE AND EXPLOSION MITIGATION

During design, thought needs to be given both to controlling the liquid/gas/vapor dust source, controlling the sources of ignition and also limiting the potential for a second, more catastrophic explosion, caused by the airborne dust jettisoned into the workspace from the initial blast. Some areas to consider:

Source Control [Liquid/Gas/Vapor/Dust]

- Minimize escape. Use Capture Technology (filtration, condensation etc)
- Limit Quantities when possible, to below exempt amounts
- Use cleanable surfaces that minimize accumulation.

With dust explosions, the initial blast can cause surface dust to go airborne, increasing the potential for a second explosion. Often, the second explosion is more catastrophic than the intial explosion, so make certain that your SOPs include regular surface wipe-down.

- Regularly inspect open and hidden areas
- Use cleaning methods that don't generate dust

- Develop and implement SOPs

Ignition Sources

- Separate heated surfaces and heating systems from fuel sources.
- Ensure that your electrical equipment, material handling equipment and wiring is up to code
- Control smoking, static electricity, open flames and sparks but even more important check your portable equipment, fork trucks and lifts make sure they are designed for this type of hazard and class of the room. Ensure that these are restricted in coming from other areas of the plant if they are not properly designed.

Damage Control

Think about separating areas, or even segregating potentially hazardous areas of the process. Then, if you do have a loss there should be less potential to expand the loss to adjacent areas, because you have considered the following:

- Separation (distance) and segregation (isolation)
- Deflagration building venting and equipment venting
- Environmental dilution and inerting
- Spark detection and extinguishing explosion protection

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.

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

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.

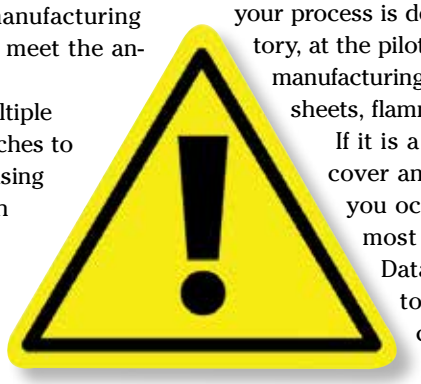
The organization should carefully review the scale of the proposed operation. Bigger may not be better, especially when it comes to potent and hazardous materials in many of solid dosage form applications.

Advantages of Scale-Out Include:

- Risk Reduction by avoiding a change in scale during process introduction.
- Potential Smaller Capital Investment in facility and equipment
- Market Demand can be met by increasing the number of smaller batch units
- Handle potent compounds and solvents in smaller, easier to control batches

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 laboratory, at the pilot stage and in commercial manufacturing. Understand material data sheets, flammability, and combustibility. If it is a new chemical entity, uncover any work done that can show you occupational risk, because most often, the Material Safety Data Sheet (MSDS) is not going to be available for the API compounds that have been discussed in this article. Look for any toxicology data as this will show some of the occupational risk



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

ABOUT THE AUTHORS

Russ Somma, PhD – President, SommaTech Consulting. Dr. Somma has more than 30 years of experience in the areas of production troubleshooting, dosage form development, manufacturing scale up, technology transfer and expertise in manufacturing clinical and commercial scale for a variety of OSD novel formulations and therapeutic groups. He possesses proven skills in business analysis and short- and long-term product development and commercialization strategies.

Mike Vileikis – Manager, Process Technology, IPS. Mike has over ten years of process, critical utility, and process instrumentation experience in the design of OSD (potent, non-potent and nutraceutical) R&D and manufacturing facilities. His experience ranges through the entire project life cycle from preliminary conceptual design through construction assistance.

Sam Halaby – Director, Process Technology, IPS. Sam has over seventeen years of experience in programming, designing, and qualifying technically complex biopharmaceutical manufacturing facilities ranging from clinical to full-scale production plants. His particular focus is in cGMP manufacturing design, including process technology evaluation, capacity analysis, cGMP environmental classification and operational analysis.