Handling of Highly Potent Pharmaceutical Compounds: Effective strategies for Contract Manufacturing Organizations

**KEYWORDS:** high potency, containment, control banding, OEL, pharmaceutical

**Abstract**
Manufacturing highly potent pharmaceutical products can be challenging and must be done in a contained manner in order to ensure the protection of employees handling these materials. An example of a control banding method for pharmaceuticals that is used to categorize employee hazard is presented. A summary of the key components of an effective potent compound containment strategy is also discussed. This strategy is based on a “containment at the source” philosophy with engineering controls being the primary method of control. Also of consideration are secondary control methods (e.g., air flow, administrative control, work practices, etc.) and Personal Protection Equipment needs.

**WHAT IS A HIGHLY POTENT COMPOUND?**
To date, there is not a universally accepted or regulatory-defined position as to what exactly is a highly potent compound. However, the pharmaceutical industry generally suggests that a potent compound may include an active pharmaceutical ingredient (API) with a therapeutic dose ≤10 mg; with an Occupational Exposure Limit (OEL) ≤10 μg/m³ as an eight-hour time-weighted average (8-hr TWA); with carcinogenicity, mutagenicity, teratogenicity, or reproductive toxicant potential at low doses; or, by default, a novel compound with unknown potency/toxicity (1).

**CONTROL BANDING AND OELS**
With these general guides in place, one can begin to differentiate between low potent and high potent compounds. It is recommended to have a specific OEL value for every API. For details regarding the calculation of an OEL, the reader is referred to previous publications (2-7). In the absence of a specific OEL value, it is still possible to group an API into a low potent or high potent category using a categorization banding system. In essence, control bands are estimates of where a qualified toxicologist feels the real OEL would reside based on existing toxicological data and professional judgment. There is no one universal categorization control banding system; as pharmaceutical companies have each developed their own company-specific system, due to differing factors such as types of therapeutic compounds, work environments, equipment, controls, and other factors (8, 9). Typically, categorization banding systems are divided into 4 or 5 groups (10-12).

Many pharmaceutical companies use a control banding system that includes bands that span one (or two) order(s) of magnitude, for example Occupational Exposure Band 1 (OEB 1) (>1000 μg/m³), OEB 2 (10 to 1000 μg/m³), OEB 3A (1 to 10 μg/m³), OEB 3B (0.01 to 1 μg/m³), OEB 4 (<0.01 μg/m³) as presented in Figure 1. Each toxicity category has a corresponding range of OELs. Table 1 provides details on the factors considered in determining the appropriate control band for a given API. These categories are determined based on a thorough toxicological assessment of all potential adverse effects. The final determination of the toxicity category is not dependent on one factor, such as the therapeutic dose, as the whole toxicity profile is reviewed when finalizing the category. Control bands allow agents of similar toxicity or risks to be grouped together. Each group is then matched with specific engineering controls handling practices, procedures, Personal Protective Equipment (PPE) requirements, and other factors. There are benefits and limits to the concept of a categorization banding system, which have been reviewed in other publications, as this system was developed with the intent that it would be used as guide by...
to accomplish total enclosure would include isolators and glove boxes. There are some limitations with their use which would include limited employee interaction with the process, ergonomic considerations, cleaning challenges, potential impact on the validation for a process, preventative maintenance and cost. However when practical, these tools are effective.

Local exhaust ventilation (LEV) can be a good tool for removing potential airborne dust from the process area if situated close to the source of dust generation. The disadvantage of these hoods is that they are dependent on correct positioning, proper air balancing and operator technique to be effective, and very high dust levels will limit their usefulness.

In the laboratory and for pharmacy operations, Powders Weighing Hoods (PWH) are specifically designed to keep airborne dusts away from employees during small volume open powder handling activities (e.g. dispensing, grinding, crushing, sieving, tap density, Karl Fischer, etc.). The laminar air flow draws the powder towards the back of the hood which has a plenum to capture particles and is then sent through a HEPA (High Efficiency Particulate Air) filter, where it is filtered and exhausted. In general, while also technique dependent, PWHs are an efficient and cost effective option to control airborne dusts of potent compounds. Laboratory fume hoods are effective tools for removing solvent vapours and work on the same laminar air-flow principle as the PWH. Some limited powder handling can be conducted inside of a fume hood, but it should be cautioned that these devices
Engineering Controls

Secondary Controls

POWERS:
- No open handling
- PWH, laminar flow hood, or isolator for dispensing
- Contained handling (e.g., closed process train, glovebox, isolator) OR equivalent "soft containment" (e.g., glove bags, bag procedures)
- Mechanical air flow away from operator, downflow booths, or LEV may be used if verified with IH monitoring
- Where containment is not feasible (e.g., breaking connections, cleaning, troubleshooting, etc.), LEV may be used for short duration
- Well in place system for equipment cleaning.

TRANSFER/DISCHARGE:
- Closed material transfer (e.g., split butterfly valves or rapid transfer ports, aerosol valve system) OR equivalent "soft" transfer containment techniques (e.g., continuous liner system, flexible enclosures)

SOLUTIONS:
- Fume hood, LEV or PWH required for procedures involving generation of liquid aerosols/mists (e.g. spraying, mixing, pumping)

FINISHED PRODUCT:
- Containment and/or LEV for drug process inspection
- Sampling to be conducted using PWH, containment of closed enclosures system

POWERS:
- No air recirculation in production suites if required engineering controls are not in place
- If required engineering controls are chosen, air recirculation permitted with use of double HEPA filtration
- Air changes to meet local building codes and as appropriate for comfort. Air flow distribution should minimize air currents in the room.

FINISHED PRODUCT:
- Reconstructed air permitted
- Good housekeeping
- Pressure differences as per GMP controls

Table 2. Example of a control strategy for handling a potent pharmaceutical with an OEL in the range of 1-10 μg/m³.

<table>
<thead>
<tr>
<th>Engineering Controls</th>
<th>Secondary Controls</th>
<th>PPE</th>
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<tbody>
<tr>
<td>POwers:</td>
<td>Secondary Controls</td>
<td>PPE</td>
<td>Additional Controls</td>
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<tr>
<td>No open handling</td>
<td></td>
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<td>Highly trained staff</td>
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<tr>
<td>PWH, laminar flow hood, or isolator for dispensing</td>
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<td>Restricted access as per GMP controls</td>
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<tr>
<td>Contained handling (e.g., closed process train, glovebox, isolator) OR equivalent &quot;soft containment&quot; (e.g., glove bags, bag procedures)</td>
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<td>Category area posted</td>
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<tr>
<td>Mechanical air flow away from operator, downflow booths, or LEV may be used if verified with IH monitoring</td>
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<td>Air monitoring (where feasible)</td>
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<tr>
<td>Where containment is not feasible (e.g., breaking connections, cleaning, troubleshooting, etc.), LEV may be used for short duration</td>
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<td>Medical surveillance</td>
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<td>Well in place system for equipment cleaning</td>
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<td>Procedures for cleaning, decontamination, preventive maintenance, waste disposal, and spills</td>
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<tr>
<td>TRANSFER/DISCHARGE:</td>
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<td>Paperwork kept in unvented glovebox or isolator to avoid contamination, OR equivalent measures to eliminate contamination of paperwork</td>
</tr>
<tr>
<td>Closed material transfer (e.g., split butterfly valves or rapid transfer ports, aerosol valve system) OR equivalent &quot;soft&quot; transfer containment techniques (e.g., continuous liner system, flexible enclosures)</td>
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<td>Controls must be implemented to ensure exposures to solids are maintained well below established OELs</td>
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<tr>
<td>SOLUTIONS:</td>
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<td>A monitoring system and alarm visual and/or audible are required to alert operators to the proper operation or failure of the air pressurization system</td>
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<tr>
<td>Containment and/or LEV for drug process inspection</td>
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<td>Exposure monitoring to confirm exposures below the OEL is required</td>
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<tr>
<td>Sampling to be conducted using PWH, containment of closed enclosures system</td>
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<td>Preventative maintenance program and testing schedule must be implemented to test and maintain LEV systems</td>
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Table 2. Example of a control strategy for handling a potent pharmaceutical with an OEL in the range of 1-10 μg/m³.
Good housekeeping is an essential part in maintaining a safe working environment. For example, vacuuming any visible dust on a regular basis during processing will decrease the amount of dust available to become airborne. Where feasible, tools should be dedicated to high potency areas and should be decontaminated prior to leaving the high potency area. Equipment moving in and out of the high potency area should be wiped down prior to exiting a production suite and/or area.

To reduce the release of a substance from the manufacturing suite, proper ventilation is required. Ventilation designed in the correct way will create a negative air flow that will keep air moving from the front of the room to the back, thus reducing the chance for the substance to escape into the hallway. Typically, 20 air changes/hr are recommended in suites where highly potent compounds are handled. Re-circulation of air between suites is not recommended for highly potent compounds, however re-circulation within the suite may be acceptable if the air is double HEPA filtered (on entering and once exiting the suite).

Conducting industrial hygiene air monitoring for the specific API is the best way to confirm that OEL values are being met (with the goal of achieving 50 percent of the OEL as the "action limit"). Materials have different properties that can affect their potential to become airborne (how sticky the material is, the percent of API, how it mixes/interacts with the excipients) and therefore to confirm containment, data for the specific API needs to be collected. Alternatively, air sampling can be conducted using a surrogate to provide an estimate to the level of containment that can be achieved. Design and acceptance criteria should be considered that compares to the category bands. Air monitoring in general is accomplished by setting up air sampling pumps equipped with filter cassettes (based on a validated Industrial Hygiene method) to capture the dust particles of the active ingredient. Personal samples are placed within the breathing zone of an operator and are used to compare to OEL values determining whether the process has been successfully contained. Task specific monitoring is recommended, especially for processes that may have gaps in containment to identify areas to improve. It is also recommended to not average the results over an 8-hour period, and instead use the data averaged over the length of the task measured. In pharmaceutical operations, as processes scale up, an Operator could be expected to handle a product more often or complete a specific task multiple times a day; the data should be reflective of these changing scenarios. This is to ensure that the employee is not overexposed should they conduct the same task more than once in a work shift. Area samples can be used to help identify weak points of containment on a piece of equipment. It is important to measure air concentrations in non-processing areas [e.g. hallways, gowning/de-gowning rooms, etc.] to gauge the level of protection of employees not directly involved with processing and to determine the effectiveness of the controls inside the room. Industrial Hygiene air monitoring techniques, sampling plans and design/acceptance criteria could be a topic of its own article.

Occupational health teams (consisting of physician, nurse, and safety professional) who are trained in occupational health, play an important role in communicating potential health effects to employees. Medical surveillance is a program designed to monitor the health of employees working with potent compounds and identify any potential problems or concerns early. For individuals that work daily with highly potent compounds, an intensive program should be established that typically involves a written health questionnaire every three months, compound specific testing (e.g. blood test specific to the API) every six months (or more frequently if required) and a full annual examination. However, these timelines are up to the discretion of the occupational physician. Less intensive programs may be set up for employees who do not work as frequently with potent compounds or who only handle lower risk production materials (i.e. finished products).

Paperwork is often required inside processing suites. Ideally, paperwork should be protected (e.g. sealed plastic sleeves) from contamination however this is not always practical as Technologists or Operators need to sign off on documents near their work station which requires them to handle the pages. Decontamination can also be used to reduce dust levels on the paper but this can be difficult if numerous pages need to be cleaned. Document ports are sometimes used that are designed to allow employees to record information through the use of gloves that are only accessible from inside the suite. Clean documents are then removed from the other side of the port. Another technique is to record information inside of an isolator and seal the paper in a plastic sleeve prior to removal. Glove bags can also be used inside the processing room for protection of paperwork. More innovative ways would include scanning or faxing documents from the processing suite or even more sophisticated methods of digitally recording information and downloading to a computer.

Personal Protective Equipment (PPE)

PPE functions as an effective backup to engineering and secondary control strategies, however it should not be relied upon as a primary defence. The most significant route of exposure is through inhalation (13). There are various types and models of respiratory protection available and it is important that the respirator matches the task. Common tools for protecting against dust exposures are filtering face-piece respirators (also known as dust/mist masks), half-mask air purifying respirators, and PAPR units. Dust/mist respirators and half-mask respirators will typically provide a respiratory protection factor from 5-10 times (14). That is, they provide 5-10 times greater protection to the employee than if no respiratory protection was used. PAPR units function by blowing filtered air through a hood that is placed over the employees head. The air passes from the back of the hood across the face and down out of the bottom to provide a constant flow of HEPA filtered air across the breathing zone of the employee. “Double-bibbed” hoods should be used when working with high potency products. Double-bibbed hoods allow the inner layer of the bib to be tucked into the disposable coveralls and the outer layer to allow the air to pass out. PAPR units provide a significantly higher level of respiratory protection than the previously mentioned respirators. For example, the US Occupational Health and Safety Administration (OSHA) indicate an Assigned Protection Factor (APF) of 1000 for full face-piece PAPRs (14). Disposable coveralls are a standard tool when handling potent compounds. They are an effective way to protect employees during high risk processes. Various brands of disposable coveralls are available so it is important that the brand selected is appropriate for the task. Other essential PPE would include eye protection, gloves, sleeve covers, and appropriate footwear.
CONCLUSION

Various methods for containing highly potent pharmaceuticals during manufacturing are available, however it is essential that an approach that works for your organization is utilized that still ensures the protection of employees (i.e. meeting OEL requirements). The key elements of an effective containment strategy discussed in this document should be part of this assessment. It is recommended that a risk based approach be used that is directly linked to air monitoring results as this will assist in identifying and prioritizing weak containment areas. Although this document focuses predominantly on employee safety aspects of handling potent compounds, this “containment at the source” philosophy will be equally valuable for product protection since it greatly reduces the chances of cross-contamination issues occurring with other products.

REFERENCES AND NOTES

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