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/m$^3$ 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; however, 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/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$^3$) 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. Typically, LEVs need to be combined with additional control measures to maximize their containment potential (e.g. LEV around a connection between an intermediate bulk container (IBC) and blender). For high potent compounds local exhaust should be used in areas where containment is the weakest, such as during troubleshooting, at connection points, during cleaning and at locations where employees interface with equipment.

In the laboratory and for pharmacy operations, Powders Weighing Hoods (PWH) are specifically designed to keep airborne dust away from employees during small volume open powder handling activities (e.g. dispensing, grinding, crushing, sieving, tap density, Karl Fischer, etc.). The laminar airflow 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 dependant, 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
are not designed for powders. The potential exists that dust particles may be “kicked” back towards the employee, thus contributing to their exposure due to the turbulent airflow of the hood, and are therefore considered to have limited effectiveness when handling high potent compounds.

Closed material transfers are required for potent compounds. The most effective way to transfer an API is under a closed system, ideally utilizing a gravity-feed system or direct connection. Sealed valve systems (i.e. high containment split butterfly valves) and the use of IBCs are good tools to accomplish this. Although limited by operator technique, bag containment technology has improved considerably and can be an effective tool for handling highly potent compounds, particularly on smaller scale bench-top equipment. Bag rings and long drum liners should be used if discharging into bags or drums. Bag procedures require effective implementation of the “crimp and cut” technique to achieve good containment performance. Vacuum transfer techniques work well, however caution should be exercised to ensure that blended powders do not separate in the process and that appropriate measures (e.g. grounding) to control static electricity are in place to prevent potential explosions. Hand scooping of potent APIs is not recommended and must only be done with the use of a PWH, glove box or barrier/isolator. Where feasible, it is recommended to eliminate unnecessary/redundant handling, processing and transfers of product. In these cases, processes/activities that generate less dust or are well contained should be used in their place. An increasing industry trend is to move a product or an API into a slurry or solution early in the process. A slurry, solution or suspension can be much easier to handle and considerably reduce the risk of airborne dust being generated.

Secondary Control Measures

One technique to reduce airborne dust travelling outside of the processing suite is to ensure that the room has negative air pressure as compared to the adjacent corridor or work area. Buffer rooms are used as a barrier between high potent drug processing areas and public areas (i.e. hallways). Typically, air locks are incorporated in this zone to maintain the proper pressure differential to reduce the chance of the API escaping from the process area. It is recommended that air locks be set up so that the second airlock door cannot be opened until the first one is securely closed. Gowning rooms are designated areas for the employee to equip themselves with the appropriate PPE that is specific to the health risk associated with the API being handled. The gowning room typically opens through an airlock directly into the potent compound processing area. A specific decontamination/exit procedure should be established for employees leaving the process area. Specifically, any visible dust is first vacuumed from the PPE. Second, the employee passes through a misting shower and into a dedicated de-gowning room. The misting shower covers the employee’s PPE with a fine moisture layer that keeps dust particles from becoming airborne, thus contributing to their exposure due to the turbulent airflow of the hood, and are therefore considered to have limited effectiveness when handling high potent compounds.

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

**POWERS:**
- No open handling
- PWH, laminar flow hood, or isolator for dispensing
- Contained handling (e.g. closed process train, glovebox, bag procedures)
- Mechanical airflow 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.

**SECONDARY CONTROLS:**
- Containment and/or LEV for drug product inspection
- Sampling to be conducted using PWH, containment of closed bag system

**PPE:**
- Double-id PAPR with HEPA cartridges
- Sleeve covers (or other wrist protection)
- Double gloves
- Safety shoes
- Bottles (e.g. Tyvek®)
- Disposable overgowns (e.g. Tyvek®)
- Standard work uniform outside processing area

**ADDITIONAL CONTROLS:**
- Highly trained personnel
- Restricted access as per S/GC controls
- Category specimen
- Air monitoring (where feasible)
- Medical surveillance
- Procedures for cleaning, decontamination, preventive maintenance, waste disposal, and spills
- Paperwork kept in unventilated glovebox or isolator to avoid contamination
- OR equivalent measures to eliminate contamination of paperwork
- Controls must be implemented to ensure exposure to workers are maintained well below established OELs
- A monitoring system and alarm visual and/or audible are required to alert operators to the proper operation or failure of the air pressure system
- Exposure monitoring to confirm exposures below the OEL is required
- Preventative maintenance program and testing schedule must be implemented to test and maintain LEV systems.

**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 (once 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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