

ALLAN W. ADER
J. JUSTIN MASON
JOHN P. FARRIS

Important elements in evaluating contract manufacturing organizations in the handling of "potent" active pharmaceutical ingredients and products

ABSTRACT

It is a universal truth that research, development manufacture and formulation of potent active pharmaceutical ingredients (APIs) and products requires both "hardware" (facilities, equipment and engineering controls) and "software" (programs, practices and procedures) to adequately protect personnel and the environment. When employing third party contracting organizations, there is a need to evaluate safe processing with the same rigor as other aspects of drug development, such as quality assurance. Elements needed by the third party contract manufacturing organization involve the recognition of the degree of hazard of the API or product, risk assessment and evaluation through industrial (or occupational) hygiene assessment of potential exposure to workers in the chemical plant, pharmaceutical plant or laboratory environment, and the application of appropriate and verified containment and control measures to maintain exposures below acceptable levels. Specific elements should include categorizing (or "banding") the API based on inherent potency and toxicity, linking the category to safe handling practices and control strategies, developing Occupational Exposure Limits (OELs) and suitable industrial hygiene analytical methods, implementing engineering controls to meet the OEL with emphasis on containment at the source of emissions and verifying the degree of containment and control through industrial hygiene quantitative assessment. Drug innovators should evaluate and assess (either with internal staff or through an independent expert) whether these elements are in place as part of their overall process of qualifying third party contract manufacturing or R&D organizations. The consequences of not managing this aspect well can include potential for delay in speed to market, lost revenue for the drug innovator (and third party manufacturer), damage to the business relationship, decreased workforce confidence and potential liability.

INTRODUCTION – A DIALOGUE WITH A DRUG INNOVATOR

A recent conversation with the Project Team Leader at a drug innovator company again pointed out to us the issues that face Project Teams and CMC (chemistry, manufacturing and control) teams within biotechnology and pharmaceutical companies developing active pharmaceutical ingredients (APIs) and products. Many of these companies have new and innovative drugs that are either "potent", "cytotoxic" or "-genic" (carcinogenic, mutagenic, a developmental toxicant or a reproductive toxicant). For a variety of reasons (lack of manufacturing capability and/or capacity, facilities or for other business reasons) the innovator organization often needs to use third party organizations to research, develop or manufacture their potent active pharmaceutical ingredient or product. It is a vested interest for the innovator that operations at the third party manufacturer are done in a safe manner to allow the innovator to bring the product to market without delay due to occupational exposure or environmental contamination issues and not least, to limit liability. "The HVAC system was sophisticated and looked great", the Project Team Leader said. He added, "The contract manufacturer was doing renovations in the suites that sounded like they knew what they were doing". Although the Team Leader was well-versed in the chemistry, clinical efficacy, pharmacological mechanism of action, quality assurance and product formulation issues of his company's drug, he did not have the skills to make a judgment as to whether the third parties being evaluated were "pretenders" (not able to really do the work) or "contenders" (capable and knowledgeable) in what we call "potent compound safety". The inability of the Project Team Leader to evaluate the contractor's capability in this area resulted in an inadequate selection process and forced the company to 'guess' that the placement of their product would be safe and not lead to incidents. The contractor selection process would have benefited greatly if the Project Team leader was capable of assessing an effective potent compound safety program. Effective potent compound safety involves the

"hardware" (facilities, equipment and containment) and "software" (programs, procedures and management) necessary to safely manufacture and process potent APIs.

WHAT IS A "POTENT" COMPOUND AND SHOULD THERE BE A CONCERN?

The history of "potent" compounds may have had its roots with the use of opioids of the 19th century and steroid hormones of the mid-20th century. Over time, however, several definitions have arisen in the industry, including the following:

1. A pharmacologically active ingredient or intermediate with biological activity at approximately 150 micrograms per kilogram of body weight or below in humans (therapeutic daily dose at or below 10 milligrams); or
2. An active pharmaceutical ingredient or intermediate with an Occupational Exposure Limit (OEL) at or below 10 micrograms per cubic meter of air as an 8-hour time-weighted average (TWA); or
3. A pharmacologically active ingredient or intermediate with high selectivity (i.e., ability to bind to specific receptors or inhibit specific enzymes) and/or with the potential to cause cancer, mutations, developmental effects or reproductive toxicity at low doses; or by default
4. A novel compound of unknown potency and toxicity.

Historically, in the recent past and currently, handling of "potent" compounds has been and is associated with occupational illness when appropriate engineering controls, work practices or personal protective equipment have not been properly applied. In the past two decades, the application of computer modelling, high throughput screening and a greater understanding of molecular biology and disease mechanisms has led to more targeted therapies that are given at lower and more effective doses. This has led to an increasing number of potent compounds entering pipelines and to an increasing need for companies to handle these compounds in a safe manner. Concurrent with these developments has been a growing emphasis on outsourcing of R&D and manufacturing of both APIs and finished products. The dependency of the drug innovator on the third party contractor to adequately understand the nature of the API and the technology of the manufacturing processes employed, makes each issue that arises, including potent compound safety, more acute. This is especially so in such a competitive business where "first to market" is paramount to the potential for product success.

WHAT IS "REALLY NEEDED" TO SAFELY MANUFACTURE A POTENT API OR PRODUCT?

Just like other support systems within pharmaceutical manufacturing, research and development, a systematic approach that involves management of all affected employees is required for a compound to be safely manufactured. A "contractor assessment" or qualification should include determining whether the following systematic elements are in place as part of a "potent compound safety" program.

1. Review of the Potential Hazards Associated with Pharmaceutical Drug Substances and Drug Products - Recognizing the Hazard

Prior to bringing a new compound in from a drug

innovator, the third party manufacturer should assess the toxicity and potency of the API and determine its category or band (1, 2). This assessment needs to be documented for each API handled and should be conducted by a professional trained or knowledgeable in occupational health, pharmacology, toxicology, medicine or a related field.

The representative of the drug innovator with a potent API may need to supply more than just the Safety Data Sheet for the compound for this assessment. The drug innovator should be asked by the contractor to supply the Clinical Investigator's Brochure, the pharmacological mechanism of action and the internal category or control band of the API, as well as information on the safety and environmental effects of the drug. It is in both parties interest that this information exchange takes place. The drug innovator may have to take responsibility to ensure that this information is provided. If this information is not requested by the third party contractor, this may indicate that the contractor does not fully understand the nature of the hazard of the drug substance or product or what needs to be evaluated to make this assessment.

2. "Tools" to Evaluate and Measure Exposure - Evaluation of the Hazard and Risks

To properly assess the hazard and associated risk, in addition to categorizing or placing the compound in a control band, Occupational Exposure Limits (OELs), "safe or acceptable" airborne limits based on existing data for occupational exposure to a compound and Acceptable Surface Limits (ASLs), "safe or acceptable" surface limits for occupational health purposes should be developed. These tools are usually not available in the early stages of product development.

Different tools for effective evaluation of risk should be used as new chemical (pharmaceutical) entities (NCEs) progress along their development timelines. As, by definition, little information is known about the toxicology of NCEs, categorizing or "banding" should be used and a more general approach to control taken. If even less information is known, for example in the case of late stage intermediates, a "default" band requiring conservative handling practices should be adopted. When sufficient toxicological information becomes available, a scientifically defensible Occupational Exposure Limits (OEL) should be developed using quantitative toxicological risk assessment. This typically occurs at Phase IIb or later in drug development, so the OEL will typically be applied when larger quantities are needed and where more specific process-related controls can be applied. Developing an OEL means that the working environment, based on subsequent specific testing for the presence of a material, can empirically demonstrate that the working environment is safe. An OEL should not be developed without the intention to monitor against it.

Concurrent with the establishment of an OEL for a compound, must be the development of an industrial hygiene (IH) sampling and analytical method to allow monitoring of the workplace to occur. This will require high sensitivity and suitably validated analytical techniques to be adopted. The workhorse for this sort of work is high performance liquid chromatography (HPLC) validated for air samples and increasingly for potent compounds more sophisticated method, such as enzyme-linked immunosorbent assays (ELISAs), radio-immunoassays (RIAs), or liquid chromatography with mass spectrometry (LC/MS) methods.

The third party contractor should work in partnership with the drug innovator to develop these tools for assessment

SafeBridge Recommended Facility and Process Exposure Controls

When we assess a facility either initial or as part of the SafeBridge Certification program, we look for the following in terms of containment and control of potent compounds.

- **Essentially no open handling of powder.** Open handling should be strictly limited to only very small quantities (100 mg) and engineered local exhaust ventilation (LEV) should be located at points of dust or vapour release. Engineered LEV means a specifically designed exhaust hood and duct system engineered to the American Conference of Governmental Industrial Hygienists (ACGIH) standards or equivalent.
- **Closed material handling and transfers.** This may be achieved through barrier isolators but can also be achieved through use of intermediate bulk containers (IBCs) equipped with split butterfly valves (SBVs) or equivalent if direct connections are not possible. Barrier isolators need to be equipped with rapid transfer ports (RTPs)
- **Combining of process steps to minimize transfer points** (e.g., integrated drying and filtration; integrated milling and blending).
- **Avoiding drying and transfer of dry isolated process intermediates** (in a chemical synthesis operation) through use of reslurry methods and use of wet filter cake wherever possible.
- **Avoiding process equipment and activities that generate high dust levels or are difficult to contain.** Eliminate unnecessary or redundant handling/processing/transfer tasks and substitute processes and activities that generate less dust or are well contained.
- **Designate areas are with appropriate notification and hazard warning** (e.g., post the identify the compound(s) in use and associated hazards).
- **Access restricted/limited to those with need.** Only persons with appropriate training should be permitted in the work area.
- **Segregated gowning and degowning areas provided with a room airlock or anteroom.** Procedures for gowning and degowning should be developed and a "one-way" personnel flow should be established.
- **Utilize misting water showers** prior to entering a degowning room if exiting a processing area having significant dust generation.
- **Make locker rooms and showers contiguous with processing/work areas.** During facility design of commercial areas, connect locker and personnel shower rooms with the processing area such that workers can exist the processing area through a decontamination and degowning area into the locker and shower room.
- **Closed and isolated work areas.** Air pressure relationships between processing rooms and surrounding areas should be maintained such that the processing room is always negative to the anteroom and/or outer corridor (exception – sterile fill/finish operations).
- **Containment systems maintained at a neutral or slightly negative pressure** to control emissions in the event of a power loss.
- **Equipment clean-in-place (CIP) systems are preferred.** Area and necessary equipment cleaning should be done using HEPA vacuums and wet methods. Care should be given to vacuum system parts (hoses, filters etc.) that contact potent powders, as they will become contaminated during operation. If wash-in-place systems or procedures are not possible for equipment parts, then parts should be bagged prior to removal for final cleaning. Small parts cleaning should be performed in a designated area equipped with a local exhaust hood (such as a back draft slot hood) behind sinks and sideboards.
- **Safe change filters (bag-in/bag-out) are used on isolation/containment equipment** and fixed vacuum and dust control systems whenever possible.

of personal exposures in manufacturing the API or drug product. This often overlooked aspect of the business relationship should be routine and include who should pay for such development, similar to other business aspects of the drug development process. The third party should consider the "business advantage" of having industrial hygiene data on processes and equipment used in their facilities in order to inform prospective clients that they can achieve the OEL (or lower) levels established for the API or drug product being considered.

3. Containment and Controls Appropriate for the Hazard – Risk Reduction

Containment and controls should be employed which

are designed to control exposures at the source of emissions. The concept that "the room is the containment" is not adequate for potent compounds. International laws in Europe, USA and farther afield direct that exposure control should be applied at the source where it can protect the many as opposed to protecting each individual separately. SafeBridge routinely sees too much reliance being placed on personal protective equipment (PPE), with equipment limitations, variable use and poor understanding all giving rise to unacceptable exposures. There are a wide range of technologies and techniques available for safely controlling potent compounds in the workplace including: Glove box or barrier isolator technology, powders weigh hoods (in laboratory and testing situations), vertical process trains, intermediate bulk containers, special valving (e.g., split butterfly valves), ventilated enclosures, local exhaust hoods, glove bags and transfers using "bag tricks". New techniques are coming to market, most notably in the last few years, flexible film applications ranging from continuous liners techniques to flexible film disposable reactors.

4. Standard Operating Procedures (SOPs) for Potent APIs or Products

In addition to the "hardware" and facility features described, standard procedures for handling APIs or products based on their category (or control band) that links the category with safe handling practices and control strategies are required. The drug innovator should

inquire as to whether there are written procedures for handling and disposal of pharmaceuticals in production and laboratory environments based on their occupational health category, e.g., potent compounds should be handled in enclosures or contained systems. Furthermore, elements in place should include written procedures for specific operations such as: weighing and dispensing, solution make-up, proper use of laboratory hoods, proper use of powders weigh hoods, the appropriate personal protective equipment to wear with certain categories of compounds and conditions, proper procedures during the addition of drug substance, cleaning etc. The library of SOPs should include procedures for:

- **Proper use of engineering controls and maintenance of engineering controls or systems.** Local exhaust ventilation systems should be tested at least annually for flow rate and static pressure. Vessel leak checks should be performed as appropriate.
- **Appropriate personal protective equipment (PPE) to be utilized in an appropriate manner** including airline or powered air purifying respirators with proper cartridges (unless an industrial hygiene monitoring indicates a lower level of protection is acceptable), specifically selected chemical protective clothing and gloves, eye protection and head protection.
- **A program of qualitative and quantitative industrial hygiene exposure assessment** to be in place including the use of surrogate monitoring techniques to estimate potential exposures to developmental materials for which no monitoring techniques and exposure limits have been established.
- **Appropriate product deactivation or decontamination procedures to be applied.**
- **Process hazard reviews to integrate appropriate environmental, health and safety activities into manufacturing and R&D operations** (for example, evaluating fire protection and risk management issues, containment and control technology options and waste disposal considerations).
- **Periodic testing and maintenance for engineering controls.**

5. Training Programs in Potent Compound Awareness

SOPs covering potent compound operations are of no use without training of employees in their use and enforcement of their use. Furthermore, the issues surrounding potent compound management are not intuitive to people, and it takes time and understanding to truly appreciate the risks. Hazardous levels of HPAs above the OEL can be present but cannot necessarily be perceived by any of the human senses or indeed specifically measured by any real time sensors. This makes potent compound management in some senses more challenging than the nuclear industry where at least radiological materials can be detected in real time. The drug innovator should provide sufficient information on the API or product to help third party health and safety personnel to communicate product handling practices and associated toxicology of the API.

6. A Determination of the Environmental Impact of the Drug Substance or Product and Associated Manufacturing Processes

The drug innovator and third party need to understand the impact to operations if the material gets into

wastewater. This can be achieved through the conduct of short-term and cost effective "screening" environmental fate (i.e., persistence) and effects tests to determine the proper disposal procedures for waste streams from pharmaceutical operations. Tests should include effects on aquatic organisms, ready biodegradability and on sludge.

ASSESSMENT

To assess these elements requires significant training and experience in occupational health and safety with specific expertise in the pharmaceutical and chemical industry. These skills would typically be available in big pharmaceutical companies but not necessarily in virtual pharmaceutical companies, biotechnology R&D organizations and medium-sized entities. An assessment prior to placing the API or product at the third party is recommended.

CONCLUSION

In the same way that GMP, product quality and manufacturing technology are qualified with third party organizations, the drug innovator should qualify third party R&D and manufacturing organizations to include the potent API management elements described above when outsourcing the development or manufacturing of a potent API or drug product. The consequences of getting this aspect wrong can include over exposures to workers resulting in adverse health effects, worker concern over potential effects resulting work stoppages, interrupting of clinical supplies during critical trials, environmental contamination and impact to facility and/or local wastewater treatment facilities. Including this assessment as part of the process in selecting a third party contractor will help speed products to market by avoiding delays in the drug development process and limit liability due to potential occupational health, safety, and environmental concerns.

REFERENCES

1. Naumann, B. D. *et al*, Performance-Based Exposure Control Limits for Pharmaceutical Active Ingredients, *American Industrial Hygiene Journal*, 57:33-42, 1996.
2. Ader, A.W., Farris, J.P. and Ku, R.H., Occupational Health Categorization and Compound Handling Practice Systems – Roots, Application and Futures, *Chemical Health & Safety*, American Chemical Society, July/August 2005.

ALLAN W. ADER^{1*}, J. JUSTIN MASON²,
JOHN P. FARRIS¹

*Corresponding author

1. SafeBridge Consultants, Inc.
Mountain View, CA
2. SafeBridge Europe, Ltd
UK