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Safety Comes First

Evaluating Hazards and Control Exposure to APIs

Ensuring Safety – The safe manufacture of potent active pharmaceutical ingredients (APIs) and products containing these APIs requires both hardware and software to adequately protect personnel and the environment.

Whether manufacturing in company facilities or outsourcing production to third party contract manufacturing organizations (CMOs), the technical capability, with associated quality program, to meet clinical or commercial requirements is not the only aspect which needs to be evaluated. There is a need to ensure, with the same rigor, that these operations are capable of safely handling potent APIs. Elements needed by the drug innovator and CMO involve the recognition of the degree of hazard of the API, evaluation through industrial hygiene assessment of potential exposure to workers in the pharmaceutical plant and laboratory support areas and the application of appropriate and verified containment and control measures to maintain exposures below acceptable limits are all critical.

A trend has emerged in pharmaceutical development to create compounds which are closely related to their endogenous human, animal or botanical counterparts. The structures of these new compounds have been altered to increase their potency and duration of action in the body. The result is the potential for worker exposure to highly active, longer-

lasting drugs. Therapeutic doses for new drugs tend to be in the low milligram or even microgram range. At the same time, a new paradigm of increased outsourcing of services is being developed by many companies, both in manufacturing and in R&D. This may be due to specific toxicity or potency issues surrounding the products being developed, cost, capacity, scheduling constraints of a manufacturing facility or specific limitations in the technology required to make the product.

These trends have created various challenges to drug innovators that use CMOs. Areas of concern include quality assurance, meeting timelines, cost control, product stewardship, third-party liability, business interruption, risk management and a general loss of operational control. It is in the interest of 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 delays caused by occupational exposure or environmental contamination issues. In assessing and verifying a CMOs ability to safely handle products containing potent, toxic or novel compounds, a systematic approach to potent compound safety must be applied which includes hardware (facility features, modern equipment and airborne emission engineering controls) and software (programs, practices and procedures).

Systematic Approach to Potent Compound Safety

1. Review and Document Potential Health and Safety Hazards

Prior to agreeing to manufacture a new compound for a drug innovator, a CMO should have the capability to assess the toxicity and potency of the API and to develop an occupational exposure limit (OEL) or determine its occupational health category (OHC) or band. This assessment needs to be documented for each API being handled and should be conducted by a trained professional who is knowledgeable in occupational health, pharmacology, toxicology, occupational medicine or a related field. A proper assessment usually requires more than just the material safety data sheet for the compound. The innovator should be asked by the CMO to supply the clinical investigator's brochure, the pharmacological mechanism of action and the basis for any internal categorization already done on the API, as well as other information on the physical hazards and environmental effects of the drug. It is in both party's interest that this information exchange takes place. It is as much the responsibility of the drug innovator to ensure that this information is provided as it is the responsibility of the CMO to request it. If a CMO does not request such information, it may be an indication that they do not fully understand the importance of evaluating the hazards of these products.

2. Determine Acceptable OELs

To properly assess the hazard and associated risk of handling potent APIs, OELs should be developed in order to establish safe workplace air concentrations and to enable the quantitative evaluation of exposure potential to workers. OELs represent an acceptable level of airborne exposure to nearly all workers for an eight-hour day, 40-hour work week, for a working lifetime. Although they are generally developed to protect the healthy worker, sometimes OELs are developed to protect certain sensitive subgroups, e.g. women of child-bearing age or asthmatics. An OEL should not be developed if there is no intention to monitor against it as there is no way of knowing if exposures are acceptable in advance of potential health effects. Therefore, concurrent with the establishment of an OEL, it is necessary to develop an industrial hygiene sampling and analytical method.

Sufficient data for the development of OELs and analytical methods are usually not available in the early stages of product development of new chemical entities. Therefore, categorizing or banding of these substances should be performed and a more generic approach to control taken. If very limited or no data is available, a default band or category requiring conservative handling practices should be adopted.

3. Applying Containment and Controls

Containment and controls should be employed that are designed to control exposures at the source of emissions. Use of personal protective equipment (PPE) as the primary means of worker protection is generally an unacceptable solution. There are a wide range of technologies and techniques available for safely controlling potent compound airborne emissions in the workplace. New technologies have been developed in the last few years, most notably flexible film applications ranging from continuous liners to disposable glove bags.

4. Institute a Program of Standard Operating Procedures

Written procedures for the handling and disposal of pharmaceuticals in production and laboratory environments based on their occupational health category should be established in facilities handling potent compounds. The library of standard operating procedures (SOPs) should include procedures for:

- Proper use and maintenance of engineering controls or systems;
- Proper use of PPE;
- Qualitative and quantitative industrial hygiene exposure assessments;
- Appropriate product cleaning, degradation or decontamination procedures;
- Process hazard reviews;
- Periodic testing and maintenance for engineering controls.

5. Conduct Training Programs

SOPs covering potent compound operations are of no use without proper training of employees and enforcement of appropriate behaviors by management. Differences in worker practices are the primary sources of variability in worker exposures. Awareness of proper techniques and of the hazards of materials handled should lead to more uniform, and hopefully lower, worker exposures. The drug innovator should provide sufficient information on the API to help the CMO health and safety personnel to establish product handling practices that are commensurate with the degree of hazard.

6. Determine the Potential Environmental Impact

Both the drug innovator and the CMO must understand the environmental impact of the API and associated manufacturing processes. This can be achieved by conducting short-term and cost effective screening tests for environmental fate and effects. The results are used to determine proper disposal procedures for waste streams from pharmaceutical operations. Tests should evaluate both biodegradability and effects on aquatic organisms and sludge.

Advantages of a Comprehensive Program

If a successful comprehensive program is implemented and the appropriate information is communicated between the drug innovator and the contractor, the likelihood of safely handling the material increases. The contractor will understand the nature and hazards of the product and have the knowledge and capability to handle it safely and take appropriate control measures. As a result, the product is delivered on-time, on-budget and according to specifications. Additionally employee incidents, exposures or accidents, environmental impairment and liability or regulatory issues will be limited. This will improve the company's business advantages by preventing occupational illnesses, enhancing speed to market, and reducing reliance on personal protective equipment.

OHC and Handling Practice System

The core element in the above mentioned programs is the implementation of an OHC and handling practice system. Too often these programs are applied incorrectly. Therefore, the following should be understood:

This system is not a substitute for the development of scientifically valid OELs and sensitive industrial hygiene sampling and analytical methods. Rather, it is designed to give guidance, based on experience, on safe handling until a meaningful, quantitative task-oriented industrial hygiene exposure assessment can be conducted.

If insufficient toxicity and potency data preclude the categorization of a novel compound using this system, the novel compound should be handled as a default OHC 3 material.

Categorization should be done by a qualified professional who understands the relative importance of each toxicity or potency criterion. All the criteria in a given OHC are not intended to apply to a given compound and the OHC should not necessarily be selected by the most conservative endpoint.

Compound characteristics and toxicity/potency criteria should be reviewed regularly as new information is developed and workplace experience is gained. Handling practices should be modified as appropriate based on new information.

In the same way that technical manufacturing capability, current good manufacturing practices (cGMPs), and quality systems are important, drug innovators should implement the potent compound safety management elements described above. This should occur regardless of whether the drug is made at the innovator's own facility, or whether the work is outsourced. Incorrect application of this systematic approach can lead to overexposures to workers, resulting in adverse health effects, worker concern over potential effects, work stoppages, interruption of clinical supplies during critical trials and environmental contamination impacting facility and/or local wastewater treatment facilities. Including this approach as part of the process of internal review and selecting a CMO will help speed products to market, avoiding delays in the drug development process and limiting liability due to potential occupational health, safety and environmental concerns.

► Contact:
Robert G. Sussman
Safebridge Consultants, Inc.
New York, NY, USA
Tel.: +1 212 727 0717
Fax: +1 646 304 2700
robert.sussman@safebridge.com
www.safebridge.com