

Manufacturing highly potent drugs: reducing the risks

An increasing number of brands contain highly potent active ingredients. That's good news for patients: they bring the magic bullet a step closer. However, manufacturing highly potent active ingredients potentially poses occupational risk for workers. John Farris, president and managing principal, SafeBridge Consultants, discusses the key elements and issues surrounding the manufacturing of highly potent active ingredients issue with *Pharmaceutical Visions* consulting editor Mark Greener

Since Paul Ehrlich raised the idea of the magic bullet some 100 years ago, pharmacologists have been engaged in a constant struggle to maximise therapeutic benefit while minimising risk, at least for patients. As a result, drugs have become increasingly potent, especially as molecular biologists uncover even more specific isoforms of target enzymes and an ever growing number of receptor subtypes. That's good news for patients – taking a lower dose of a more potent drug may limit the risk of side-effects compared to conventional therapy.

On the other hand, the growing number of potent drugs poses problems for manufacturing. As a result, there's been something of a re-evaluation over recent years of the ways in which the occupational risks of manufacturing are evaluated and managed. And when you consider just how potent some modern medicines are, a 're-evaluation' might be too late. For example, some agents are active at doses below 1 milligram. The occupational exposure

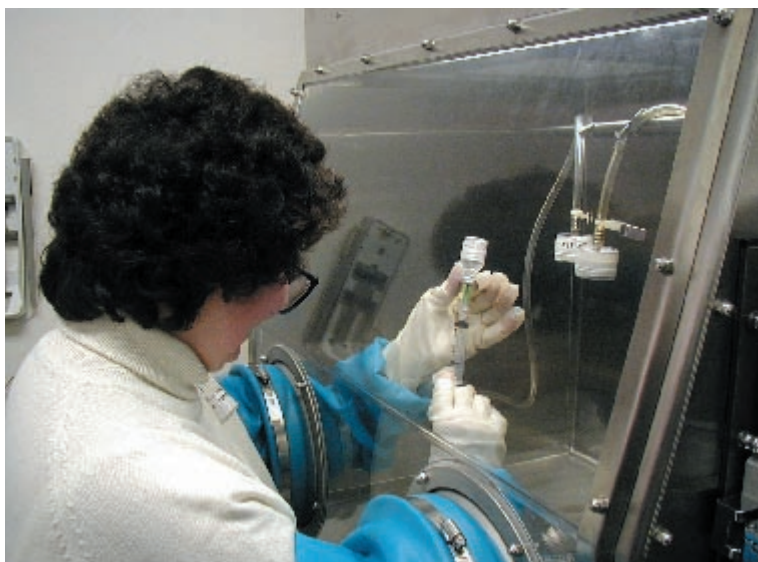
limit (OEL) for some drugs may be just 1µg per m³ as an eight-hour time-weighted average or less. Other drugs that bind to specific receptors or specific enzymes can cause cancer, mutations, developmental effects or reproductive toxicity, even at the low concentrations that would arise with conventional manufacturing processes. Hence, considering the risks of manufacturing needs to be part of the planning process before the drug is made.

CONSIDERABLE RISK TO WORKERS

In other words, a drug that offers considerable benefits for patients can pose considerable risks for workers. 'As the pharmacological specificity and selectivity of pharmaceutical products increases, so does the occupational risk,' says John Farris, president and managing principal, SafeBridge Consultants, Inc, who specialise in assessing the risks as well as providing containment and control solutions to safely manufacture potent compounds. 'It is important to distinguish a drug with a characteristic that poses a high

occupational risk from its characteristic therapeutic effect and benefit. For example, a drug that increases the acceptance of a transplanted organ is given to patients in high doses. However, occupational exposure to the drug may cause birth defects in the offspring of women who may come into contact with it. Drugs are designed to have targeted effects in patients. The goal of employers developing and manufacturing these products should be to have no health effects in their employees or contract workers.'

A growing number of pharmaceuticals contain highly potent active ingredients including hormones, cytotoxic drugs, prostaglandins, retinoids, some antibiotics and some narcotic substances. Currently, around 5-10% of products on the market contain highly potent active ingredients. However, data collected by SafeBridge Consultants, Inc of Mountain View, California, USA – a unique collaboration of occupational and environmental toxicologists, industrial hygienists, chemists, and safety and environ-



Industrial hygiene air monitoring performed on an operator doing drug reconstitution (a pharmacy operation) in an isolator. Note air monitors on the shoulder of the operator and inside the isolator

mental professionals providing environmental health and safety services – suggest that the proportion of highly potent active ingredients is higher, based on OELs.

One of the definitions of a high potency active ingredient or intermediate is an OEL at or below 10 micrograms per cubic meter of air as an eight-hour time weighted average. (The others are, firstly, a pharmacologically active ingredient or intermediate with biological activity at approximately 15 micrograms per kilogram of body weight or below in humans. This is approximately equivalent to a therapeutic dose at or below 1 milligram. Secondly, a highly selective pharmacologically active ingredient or intermediate that binds to specific receptors or enzymes and/or could cause cancer, mutations, developmental effects or reproductive toxicity at low doses. And, finally, novel compounds of unknown potency and toxicity.) SafeBridge estimates that approximately 40 to 45% of the OELs that have been set by the pharmaceutical industry are at 10 micrograms per cubic meter of air or less.

CORE ELEMENTS

As drugs are being moved into manufacturing more rapidly and with less exposure data, another risk assessment approach – occupational health

control categories or bands have been implemented in R&D and clinical manufacturing settings. Exposure control bands or categories are based on the ingredient's toxicology and pharmacology and descriptions of safe work environments. The five performance-based exposure control limit (PB-ECL) categories range from conventional handling practices for low potency (Category 1) materials, through 'no open handling' of potent or toxic (Category 3) ingredients, to closed processes using robotics (Category 5) (Naumann et al 1996).

Against this background, Farris comments that there are several core elements in high-potency manufacturing systems. These are detailed in the sidebar, but in essence the elements are:

- Developing a systematic approach to handle potent drugs safely.
- Developing standard operating procedures.
- Developing a training programme.
- Developing tools to evaluate and measure exposure.
- Designing and developing containment and controls.
- Developing systems to verify effectiveness.
- Determining and assessing the environmental impact of the active substance and associated manufacturing processes.

In particular, scaling production from laboratory levels to industrial quantities presents a challenge. 'Scale is a tricky question,' Farris admits. 'I have investigated more incidents of occupational disease in pharmaceutical R&D laboratories than in commercial manufacturing over the course of 21 years in the industry. More controls are usually in place and procedures more strictly defined in large-scale manufacturing, for example cGMP. However, one of the gaps to close is in the kilo/pilot plant scale of active pharmaceutical ingredient synthesis and in the formulation development/clinical scale of drug product manufacturing.'

Such dynamics, Farris believes, mean that contract companies are set to become even more important in the manufacturing of high-potency active ingredients. 'There are several reasons to outsource manufacturing, including capacity and scheduling constraints, technology limitations, cost and the toxicity and potency of the material,' he says. 'Provided companies that bring high-potency products to market have confidence in the manufacturing contractors, and big pharma companies continue to focus resources ever more on research and marketing, then contract companies will become more important in this area. Small biopharmaceutical companies are not likely to ever develop commercial potent compound manufacturing capabilities. Big pharmaceutical companies have more options and may choose to leave the potent compound manufacturing competency in-house.'

Clearly, companies need confidence in their high-potency manufacturing system. This applies as much to the outsourced manufacturing sector as to a company's internal clients – their workers – and non-governmental organisations concerned about the environmental impact. As a result, SafeBridge developed a programme it describes as 'unique' to evaluate and certify that an organisation is competent to safely

handle potent drugs. The programme consists of a pre-assessment review of client-submitted information, an on-site visit, evaluation against 60 detailed criteria, and a summary report that encompasses management, compound evaluation, containment and control and communication elements of potent compound safety.

'These criteria are used to determine if the client is an industry leader, meets current industry standards, needs improvement or does not have the systems, programmes or equipment in place in defined potent compound safety elements,' Farris says. 'SafeBridge performs the evaluation using board-certified toxicologists and occupational hygienists. The criteria were developed from years inside big pharma evaluating manufacturing facilities and working to prevent occupational health effects in workers. We are the external validation for the client company.'

It seems such validation will become more important over the next few years. Pharma may still be some way from the elusive magic bullet in most diseases. However one thing is certain: functional genomics in particular and molecular biology generally will lead to ever more potent agents. Patients will benefit from reduced risk of adverse events; the challenge may be to persuade internal and external stakeholders that there is no risk from the manufacture of highly potent active ingredients. ●

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REFERENCE

Naumann BD, Sargent EV, Starkman BS, et al Performance-based exposure control limits for pharmaceutical active ingredients *Am Ind Hyg Assoc J* 1996;57:33-42

CORE ELEMENTS IN HIGH POTENCY MANUFACTURING SYSTEM

Reviewing and evaluating the hazards

- Evaluate toxicological/clinical data against occupational health categories.
- Review physical/chemical properties, including explosivity and static electricity potential.
- Review process hazards to integrate appropriate environmental, health and safety activities into manufacturing operations – for example, evaluating fire protection and risk management issues, containment and control technology options, disposal considerations.

Standard operating procedures

- Develop written general procedures for handling and disposal of pharmaceuticals in a production and laboratory environment based on their occupational health category.
- Develop written procedures for specific operations such as: weighing, proper use of laboratory hoods, proper use of weigh hoods for powders, the appropriate personal protective equipment to wear with certain categories of compounds and conditions, proper procedures during the addition of drug substance, etc.

Training programmes

- Train employees in potent compound safety and product handling practices and toxicology.
- 'Train the Trainer'. Train the environmental health and safety or other staff on potent compound programme elements.
- Train supervisors and management on the business necessity of incorporating health and safety systems into product development and appropriate safety culture.

Evaluating and measuring exposure

- Develop occupational exposure limits (OELs), 'safe' limits based on existing data for occupational exposure to a compound.
- Develop industrial hygiene (IH) sampling and analytical methods for compounds (to allow monitoring of the workplace to occur).

Design and develop containment and controls

- Design containment approaches for hazard and risk presented, such as glove box/isolation technology; ventilated enclosures and local exhaust; weigh hoods for powders (laboratory); vertical process trains; intermediate bulk containers; special valves; glove bags; and vacuum transfer.

Verify effectiveness

- Validate performance of engineering controls by IH monitoring of containment devices during handling.
- Perform health surveillance (with special emphasis on evaluating target organs potentially affected by exposure).

Determining and assessing the environmental impact

- Conduct short-term and cost effective 'screening' environmental fate (ie, persistence) and effects tests to determine the proper disposal procedures for waste streams from pharmaceutical operations.
- Assess the impact of pharmaceutical and chemical processes on environmental regulatory compliance and/or the site emission profile.
- Develop the environmental assessment (EA) for regulatory filings.

Source: SafeBridge Consultants, Inc