Containment of High-Potency Products in a GMP Environment

by Trevor Calkins

Many modern medicines are highly potent, with only tiny doses required to achieve a therapeutic effect. But a nanomolar medicine poses extra hazards during manufacturing, whether the product is a biologic or a small molecule. These issues have to be evaluated and addressed in the design of a manufacturing facility for such products. Not only is it vital that the product not become contaminated, but employees and the general public must be protected from the product. Exposure to just a small quantity of a highly potent compound can pose significant health risks.

Highly potent products have their individual manufacturing requirements. But the issues pertaining to safe handling are often common and not product specific. Potency is often a function of structural class, but it cannot be predicted for new molecules or new biological products without sufficient testing. A dramatic increase in development of new drugs, particularly in oncology, is more likely to require engineering controls for containment. My company tends to err on the conservative side and handle each product as potent, then relax restrictions as more information is gathered during a its development cycle. Proper handling of these materials involves specialized facilities that are carefully designed to minimize containment risks.

Isolators are integral to SAFC Pharma's facility in Madison, WI.
(WWW.SAFCGLOBAL.COM/SAFC-PHARMA/EN-US/HOME.HTML)

Facility Design

Some facility design requirements are common to all product types. Most significant is process isolation: ensuring that all product remains within its manufacturing equipment and process piping, including during cleaning procedures. Enclosed equipment such as sealed reactors and dryers are key here, as are product transfer systems for moving materials through a process train. A facility should also be designed with equipment such as isolators, laminar flow hoods, and local exhaust ventilation appropriate for potent compound handling.

Airflow within the facility should be single pass to prevent cross-contamination or concentration of materials. Exhaust air should be filtered to ensure that escaping product is captured before its release to the external environment. In addition, proper air-pressure differentials must be established to keep potent compound–handling areas negative to all adjacent vestibules or airlocks. Equipment and facility engineering controls apply not only to the manufacturing areas, but also support areas such as process development and quality control laboratories.

Even with extensive engineering controls, personnel working with potent compounds should wear suitable personal protective equipment (PPE), including respiration equipment for those working around the most potent products. Proper training on procedures for operation and maintenance of containment and isolation equipment is critical. Staff members must understand why the use of engineering controls is crucial for a manufacturing process.

Product Categories

Before work begins on any drug product, it must be evaluated and characterized to assess potential hazards. For contract manufacturers, the first call is clearly to the customer, who should have information about a product's safety and toxicology. Other information can be gleaned by making comparisons with similar products with known toxicological properties. The drug is then categorized according to its potential hazards so correct handling procedures can be established.

The performance-based exposure control limits (PBECL) categorization system links compound toxicity and potency to procedures for safe handling practices. This system was established in the late 1980s by health and safety departments within large pharmaceutical companies working on development projects for which insufficient data were available to determine occupational exposure limits (OELs). The industry uses many different categorization systems — including three, four, and five-tier systems — but this most common system has four categories.

Category 1 compounds are low potency with higher dosage levels. They have minimal acute or chronic health effects and good warning properties. These products will have no genic effects and will not be sensitizers. Absorption will be slow, and no medical intervention will be required following exposure to them.

Category 2 compounds have moderate acute or chronic toxicity, but their effects are reversible. They may be weak sensitizers. Most have fair warning properties, a moderate absorption rate, and no genic effects, but medical intervention may be required after exposure to them.

Category 3 compounds have elevated potency, with high acute or chronic toxicity. These effects may be irreversible. The products may be moderate sensitizers, and their warning properties are likely to be poor or absent. Their absorption rates may be rapid, they may have suspected or known genic effects, and moderate to immediate medical intervention will be required. At SAFC Pharma, we consider this to be the default category.

Category 4 compounds have high potency and extreme acute and chronic toxicity. They cause irreversible effects and are likely to be strong sensitizers, with poor or no warning properties and a rapid absorption rate. These products will have known genic effects and require a higher degree of medical intervention. They may also affect sensitive subpopulations to a greater extent than the public overall.

All potent products fall into category 3 or 4, depending on their cumulative risk factors. Requirements for containment and protection vary among the categories, and the precise ways they are put into practice differ. The details depend on whether a product is an infectious biologic such as a viral vector or vaccine, a highly potent small molecule (made by chemical reaction or fermentation), or an antibody drug conjugate that links a biologic to a potent small molecule.

Containment of Hazards

A facility manufacturing a high-potency active pharmaceutical ingredient (API) will resemble a standard API manufacturing plant, but it will house additional containment equipment (such as isolators and single air-pass systems) and facility engineering controls. For nonhazardous chemicals, ingredients can usually be added to an open reactor. For highly potent compounds, they cannot. To prevent escape, everything must be sealed throughout the manufacturing process, from raw material addition to the reactor through to the packaging of a final product.

For a category 1 molecule — which offers little risk during manufacturing — generally safe laboratory practices and gowning are sufficient. Open handling may be acceptable for small quantities of product, but local ventilation is advisable for handling larger quantities. However, no containment is needed. Standard laboratory practices and gowning are enough for category 2 as well, but the cut-off point for local ventilation is lower, and containment is needed for high-energy, dust-generating operations such as milling.

If a molecule falls into category 3, then it requires high-potency manufacturing methods. Operators need additional gowning and respiratory protection when handling powders, which should not be handled openly. Although small quantities of such products can be handled within a laminar-flow enclosure, processing at large scale presents more complex challenges. Operators wear protective clothing, but process isolation equipment is the primary control at our company. Additional facility controls need to be in place for containment, notably closed-system solution and solid transfers, even at glassware scale. Material handling takes place in an isolator glove box, and charge bottles are filled with raw materials, which are added to reactors through closed-system technologies such as α–β valves.

Category 4 products (the most hazardous) require full gowning and supplied-air respiratory protection in a specialized facility in addition to all the requirements for category 3. In addition to full containment of all solutions and powders as well as restrictions against open handling, deactivation and/or verifiable dissolution and rinsing are required for cleaning.

Using process isolation and containment equipment is the most important means of protection. By ensuring that an entire manufacturing process is carried out in closed systems — from raw materials to product packaging — the chances of employee exposure can be minimized. At SAFC Pharma, we have engineered glassware and fixed equipment around closed-system transfers. The functions that require employee input (such as weighing samples) are fully contained. Materials are kept out of the operating environment using a ventilated balance enclosure, rapid transfer ports, and local ventilation.

Personal protective equipment should be regarded as a secondary control measure. Employees wear coverall suits and ventilation hoods, the correct type of gloves, and full chemical suits when necessary because of the nature of the solvents or

reagents in the category 4 manufacturing process. This is a precautionary measure, however, because primary isolation and containment measures are designed to prevent highly potent compounds from escaping. In addition, all personnel should be fully trained in necessary procedures and policies, and their health should be monitored regularly for signs of exposure.

Those criteria must be kept in mind when design expectations are being established for a category 4 facility. A company should determine equipment containment criteria (such as <1 μg/m^2) as part of user requirement specifications for selecting vendors and equipment to support potent compound handling.

Requirements for Different Product Types

Many general requirements for chemical API plants are the same for facilities manufacturing highly potent biologics, but there are some important differences. **Viral vectors and vaccines** are manufactured in sealed bioreactors, and because they are infectious, these products must be carefully contained. Operators and the public must be protected in the event of an escape. As with chemical facilities, air should be single-pass and HEPA-filtered, with each manufacturing suite exhausting separately through further HEPA filters to prevent cross-contamination. People, equipment, and raw materials should all flow from clean to dirty areas, with exit vestibules providing the final line of containment.

Cross-contamination is an even greater issue with virus-based products. One means of prevention is the use of disposable bioreactors with a minimum of hard piping. This eliminates the problem of infectious materials remaining inside bioreactors after cleaning and sterilization. Each reactor itself is sealed once a process is finished and product isolated, and the remains are disposed of as a biohazard. Single-use technology might seem to add cost through consumables, but it removes the need for cleaning and validation, which allows much faster changeover between different products. That's particularly important in multipurpose facilities that produce many different viruses and vaccines.

An **antibody–drug conjugate** combines an antibody that targets a specific site in a patient's body with a small-molecule payload that provides a therapeutic effect. As high-potency small molecules become more frequent in bioconjugates, containment issues become crucial. Not only do the chemical issues have to be considered, but manufacturing the antibodies also requires a biologic facility — and biologic and chemical facilities have very different requirements. Facilities designed for conjugating antibodies to small-molecule potent compounds must combine the two facility types to ensure that containment, cleaning, and proper aseptic handling techniques are incorporated.

It makes more sense when designing a facility for manufacture of antibody–drug conjugates to introduce chemical handling capabilities into a facility designed for biological manufacturing rather than vice versa. This can be done by installing a containment isolator (complete with airlock, rapid transfer port, and utility connection plate) into an aseptic environment that also contains a biological safety cabinet and other equipment necessary for biologics. Essentially, introducing all the equipment for high-potency API manufacture within a biologics facility adds greatly to its complexity.

Secondary metabolites involve current good manufacturing practice (CGMP) compliant manufacture of highly potent small-molecule drugs using biologic systems, generally organisms such as yeast or fungi. A growing number of APIs and advanced intermediates are being manufactured in bioreactors. Just like small-molecule pharmaceutical chemical products, their containment issues depend on the precise nature of each chemical, so a full assessment must first be carried out to evaluate the risks. If the purified product poses enough risk, then purification process will need to be carried out under containment.

If a secondary metabolite product is highly potent, then a combination of biological- and chemical-enhanced containment will be necessary, with level 2 large-scale biological safety alongside the ability to isolate highly potent compounds up to category 4. Each separate manufacturing suite will require single-pass HEPA air supply and separate exhaust complete with room pressure differentials and full airlocks and vestibules around each manufacturing suite as well as directional flow (from clean to dirty) of personnel, materials, and waste. For multipurpose facilities of this type, strict changeover procedures must be observed using automated steam- and clean-in-place (SIP and CIP).

Rise to the Challenge

Many modern drugs are toxic and potent. Specific manufacturing techniques must be observed if they are to be handled safely, protecting the product, employees, and the environment. Several features are common to all types, whether biologic, small molecule, or a combination of the two. These include single-pass airflow with containment pressurization and multiple layers of protection for both products and employees. Complexity increases in a multipurpose facilities that need effective cleaning and sterilization procedures to ensure no carryover of product from one batch to the next. However, there is no reason why all this cannot be done safely as long as the appropriate cascade of controls have been established and procedures are strictly adhered to.

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