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White Paper

Handling Protocols: Key Considerations in the Highly Potent API Market

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HPAPI handling at Verona, WI facility

Navigating the unique challenges of HPAPI manufacturing

The manufacture of highly potent active pharmaceutical ingredients (HPAPIs) has become increasingly attractive to contract manufacturers due to significant advances in clinical pharmacology and oncology research. The Antibody-Drug Conjugate (ADC) market, which requires HPAPIs in the form of linkers/payloads, has experienced a rapid growth rate and is predicted to maintain double-digit year-over-year growth through 2028. However, while the development and manufacture of HPAPIs present exciting prospects for the pharmaceutical sector, entry into this market brings significant challenges. The main challenges include planning, proper equipment and facility design, personnel requirements, and the implementation of the necessary procedures to safely handle potent compounds. Knowledge gained through experience is invaluable, and robust systems must be employed throughout the HPAPI handling program from initial project evaluation through equipment cleaning to waste disposal.

Handling requirements

Manufacturing highly potent molecules is a complex process, mainly due to the containment requirements. The requirements are significantly different from those needed for handling biomolecules or traditional APIs. When handling biomolecules, avoiding contamination from humans involved in the production process is key, and processes are carried out in a controlled cleanroom environment at a positive pressure to prevent the possibility of contamination. However, with HPAPIs the key is protecting workers from the agent itself, which requires more complex handling requirements and a high level of specialized containment. These processes are carried out at negative pressure to prevent materials from entering the lab environment, with workers often wearing full protective gear. This presents a significant challenge compared to facilities that are only set up to handle non-potent APIs, with the major cost being the specialized containment that ensures the employees, the facility, and the environment are protected from exposure. Specialization in the manufacture of highly potent compounds requires that facility design and controls are in place to assure product containment and safe handling. These include product isolation strategies such as the use of closed systems and containment equipment, including HEPA filters, glove boxes, weighing hoods, rapid transfer ports, local exhaust ventilation, and closed-system cleaning processes.

Because of the rapid growth in demand, dedicated new HPAPI facilities, including specialized facilities for HPAPI-ADCs that incorporate both potent small molecule compound handling and biologics processing capabilities, are needed. To safely handle the most potent HPAPIs, engineering controls must be in place to ensure single-digit nanogram containment levels. These facilities usually require a significantly higher investment than a typical GMP production facility.

Personnel considerations

Ensuring personnel safety when operating an HPAPI facility necessitates that a robust HPAPI handling program is in place. This handling program should include:

- Program Management
- Hazard Identification
- Exposure Control
- Communication, education, and training

Program management includes the proactive evaluation of the handling program and setting objectives, goals, and standards for potent compound handling. This also includes ensuring that there is a budget for continuous improvement in procedures and facilities. A committee with responsibility for handling HPAPIs, ideally comprising a mix of senior management, manufacturing, occupational health, and development scientists, should oversee the SOPs and general company policy for handling the HPAPIs.

Hazard identification requires the establishment of a formal hazard communication program and process hazard evaluation program. This is to ensure that all parties are aware of the dangers in handling potent compounds as well as what mitigation strategies are available to ensure safety.

Limiting employee exposure involves a hierarchy of controls. Facility design/environmental controls, closed system operations, and appropriate personal protective equipment (PPE) are just some of the strategies included in an HPAPI handling program. Employee exposure could potentially result in serious adverse health effects and/or sensitization, and it is essential to initiate appropriate medical surveillance and monitoring. Regular reviews of material safety data sheets and toxicological literature should be performed, with relevant occupational safety and health literature checked for information regarding the compounds used.

Communication, education, and training are extremely important and should include detailed operating procedures for donning PPE, equipment use, and process execution. A robust training program and even a training facility focused on practical application of skills learned through SOPs are essential for ensuring operational success and safety. Emergency response plans must also be put in place to ensure appropriate reaction to an unplanned event, while the involvement of local authorities in emergency response planning and training is also important. These measures are essential to ensuring personnel are both informed and protected.

HPAPI handling systems and control hierarchies

It is also imperative that HPAPI handling systems and equipment are tested and verified to meet the necessary isolation and containment requirements. Having knowledge of compound OELs is important for appropriately setting containment performance targets for equipment prior to testing. System testing typically requires the use of both air and surface industrial hygiene sampling methods. As sampling and testing methods for products in early preclinical or clinical trials have often not been developed, surrogate products are regularly used to complete equipment testing. When possible, system testing on actual HPAPIs may be performed to further ensure safety.

Potent compound handling systems should ideally incorporate five levels of cascading protection:

- Elimination
- Substitution
- Engineering controls
- Administrative controls
- PPE

Elimination and substitution are often difficult in HPAPI manufacturing, as changing synthetic pathways can introduce other program and regulatory challenges. Still, experienced process development teams may be able to optimize a process to remove or replace hazardous operations, toxic solvents and reagents, and minimize potent handling steps.

Engineering controls can be broken down into the following categories:

- **Process isolation**
  Closed system glassware and reactors, α/β valves.
- **Containment equipment**
  Glove box isolators (unidirectional where possible), ventilated laminar flow enclosures, rapid transfer ports, local exhaust ventilation, closed system cleaning via CIP.
- **Facility design**
  Air pressurization, high number of air changes, single-pass air, restricted access, airlocks, safe-change filters, misting showers.

Administrative controls were covered in depth in the prior section but are worth mentioning again as they are an important aspect of ensuring a robust system is in place.

PPE should be seen as the final line of defense and involves the use of chemical-resistant suits and hoods, PAPR or supplied air, and proper glove selection.

Ultimately, appropriate production and handling procedures depend upon the toxicity, potency, and occupational exposure limits of each product. While the HPAPI market undoubtedly offers major opportunities for Contract Development and Manufacturing Organizations (CDMOs) and research organizations in the pharmaceutical sector, the barriers to enter the market are significant. Compromises and shortcuts to safety are not allowed. The fact that many pharmaceutical companies outsource HPAPI manufacturing at the commercial scale is testament to the levels of investment, expertise, infrastructure, and technology that are required to achieve sustainable market share.

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