Handling Protocols
Key Consideration in HPAPI Market

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Over the past 10 years, 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. In addition, with factors such as fewer FDA drug approvals, over-supply and stiff competition from Asia-Pacific producers putting pressure on profitability and margins in the 'traditional' API sector, the rapidly growing HPAPI segment has an annual double digit growth rate and has become something of a 'promised land' for CMOs. However, while the development and manufacture of HPAPIs present exciting prospects for the pharmaceutical sector, entry into this market brings significant challenges, primarily in terms of planning, proper equipment and facility design, personnel requirements and the implementation of the necessary procedures to safely handle the compounds. Knowledge gained through experience is, therefore, 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 because of the containment requirement needed when dealing with high-potent compounds. Here we have an environment that is significantly different from that needed for handling biomolecules or traditional APIs. When handling biomolecules, avoiding contamination from humans involved in the production process is key, so 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 entails altogether 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 environment, with workers wearing full protective gear. This presents a significant upgrading challenge compared to facilities that are only set up to handle non-potent APIs, with the major cost being the specialized containment that ensures employees and the environment are protected from exposure. Because of the rapid growth in demand, dedicated new HPAPI facilities requiring investment of millions of dollars beyond typical GMP production facilities are needed, including specialized facilities for HPAPI-antibody drug conjugates that incorporate both potent small molecule compound handling and biologics processing capabilities.

Personnel considerations

Operating an HPAPI facility also necessitates that various systems, policies, training programs and standard operating procedures (SOPs) be put in place to protect workers. Employee exposure could potentially result in serious adverse health effects and/or sensitization, so it is essential to initiate appropriate medical surveillance and monitoring. Regular reviews of material safety data sheets and toxicological literature should be undertaken, with relevant occupational safety and health literature checked for information regarding the compounds used. This should also include personal protective equipment (PPE) and engineering processes.

Overseeing these procedures should be a committee with responsibility for HPAPIs, ideally comprising a mix of senior management, handling staff, experts, occupational health and senior scientists. This committee's primary focus should be the development of a general company policy and SOPs for potent compound handling, including designating which members of staff have access to/are able to handle HPAPIs; training programs; evaluation; categorization; and on-going updates of procedures and processes. 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 key.

Plant and equipment

It is also imperative that HPAPI handling systems and equipment are tested and verified to meet the necessary isolation and containment requirements. 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.

Engineering controls should be employed as the primary source for containment and isolation of potent compounds, with PPE utilized, as secondary protection for employee exposure control. Potent compound handling systems should ideally incorporate five levels of cascading protection – the first two being the primary methods of product isolation:

- Process isolation: closed system glassware and reactors, α/ß valves
- Containment equipment: glove box isolators, 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
- PPE: Saranex™ coveralls and hoods, PAPR or supplied air, proper glove selection, chemical suits when needed for solvents/reagents
- Personnel: training, procedures/policies, education, health monitoring.

Ultimately, the correct production and handling procedures depend upon the toxicity, potency and occupational exposure limits of the particular product.

While the high potency market undoubtedly offers major opportunities for CMOs and research organizations in the pharmaceutical sector, the barriers to market are significant and cannot be undertaken lightly. Neither can compromises be made or short-cuts taken. The fact that there are still relatively few companies producing HPAPIs 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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