

KEYS TO HPAPI PRODUCTION

High potency active pharmaceutical ingredients (HPAPIs) are in high demand, particularly as key ingredients for anticancer therapies. The manufacture of HPAPIs requires stringent, risk-based containment measures. CARBOGEN AMCIS shares best practices in HPAPI containment.

H PAPIs are the fastest growing segment in the API market. The appeal of HPAPIs lies in their ability to target diseased cells more precisely and in smaller doses than non-high potency APIs. Because of the ever-strong demand for anticancer therapies, more than 25% of new compounds entering clinical development are focused on oncology and are HPAPIs.¹

HPAPI Containment

An API is classified as an HPAPI if it has an occupational exposure limit at or below 10 µg per cubic metre of air. This presents a number of challenges to manufacturers because conventional plants are usually inadequately equipped for the manufacture of HPAPIs.

Before September 2010, when the International Society for Pharmaceutical Engineering issued the Risk-Based Manufacture of Pharmaceutical Products Guide (Risk-MaPP), no scientific risk-based approach was publicly available to manage the risk of cross-contamination in multiproduct facilities.² The lack of expertise in containment chemistry led many HPAPI manufacturers to hire external consultants to handle containment issues. Only a small number of companies anticipated the need for a scientific risk-based approach and gradually built a cross-functional team of experts in toxicology, industrial hygiene and good manufacturing practices that focus on risk assessment and management.

Containment Levels

At CARBOGEN AMCIS, the required containment level is determined based on the substance's pharmacological and toxicological activity, and the exposure potential of the anticipated unit operations, leading to a performance-based exposure control limit or occupational exposure limit in cases where sufficient toxicological data exist. Cleaning limits are calculated by defining an acceptable daily exposure (ADE), maximum allowable carry over and cleaning limits for final rinse and surface contamination. The ADE (µg per day) is calculated based on the lowest clinical dose for the previously prepared API and the maximum recommended dose for the API to be manufactured. In the presence of genotoxic or reprotoxic impurities, the threshold of toxicological concern in line with the current European Medicine Agency's guidelines further corrects these limits.

Contamination Risks

Risks are assessed based on the amount of HPAPI handled, the type of operation performed (routine versus nonroutine), whether the substance is a dry powder or solution, how often steps are repeated and whether the processing happens in a closed or open environment. We apply a so-called 'protection cascade' for facility design to address these risks. To avoid direct contact between the substance and the operator, any process involving a high potency material is confined within specific manufacturing areas and contained within sealed processing equipment, such as reactors, filter dryers or self-contained glove boxes and isolators. Air locks separate the high potency areas from the rest of the building following the 'building within a building' concept with relative positive pressure in clean zones and relative negative pressure in manufacturing zones. This ensures that no airborne contamination reaches the clean zones. The heating, ventilation, air-conditioning system delivers clean air into and out of the facility, preventing the stagnation of any airborne contaminants within the manufacturing cells and eliminating the risk of exposure in the non-manufacturing area. Furthermore, single pass high-efficiency air filtration obviates the need for routine use of personal protective equipment, which is available as backup in case of an emergency.

Emergency measures are ready in the event of accidental exposure and include personal protective equipment for operators and an 'easy-clean' design for efficient decontamination. Standard operating procedures, constant training and a well-defined health-monitoring programme are key measures that further enhance workers' safety and awareness.

Handling Dry Powders

An increasingly important aspect of API manufacturing is particle size distribution because finely ground powders increase a drug's bioavailability. To limit the higher exposure risks associated with handling dry powders, CARBOGEN AMCIS adopted in-line wet milling as a core particle sizing technology during the past 2 years and uses it as the preferred approach for particle reduction where technically feasible. Experience shows that a scientific risk assessment and management approach, combined with modifications to facility design and equipment, the use of risk-minimizing technologies and well-defined operational containment guidelines make the production of HPAPIs safe and protect the health of patients and employees. **Pharma**



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References

1. www.carbogen-amcis.com/pdf/CA_whitepaper3.pdf
2. Baseline Guide: Risk-Based Manufacture of Pharmaceutical Products, ISPE (September 2010).

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