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CRITICAL CONSIDERATIONS FOR THE SAFE AND COMPLIANT MANUFACTURE OF HIGHLY POTENT DRUGS

The demand for highly potent active pharmaceutical ingredients (HPAPIs) has been increasing over the past decade, mainly driven by oncology research. The overall HPAPI market is predicted to reach USD $31.5 billion by 2029, with more than 25% of drugs currently on the market formulated with HPAPIs.[1]

The safe and successful manufacture of HPAPIs and associated drug products requires carefully developed equipment, processes, and expertise to:

- ensure compliance to GMP regulations for regulatory submissions;
- reduce exposure risk to CDMO operators and related personnel;
- prevent cross-contamination with other products; and
- respect timelines and budgets for sponsors.

IN THIS ISSUE

We examine the intricacies involved in manufacturing HPAPIs, including a review of the relevant guidance, classification systems, and safety processes. We also delve into how CDMO facilities, equipment, and processes for HPAPIs should be adapted to maximize safety and success for your development projects.

DEFINING HIGH POTENCY FOR AN API

The definition of high potency for an API varies depending on the literature, but generally is defined by one or more of the following:

- a pharmacologically active ingredient or intermediate with biological activity at approximately 150 µg/kg of body weight or below in humans (therapeutic daily dose at or below 10 mg);
- an API or intermediate with an occupational exposure limit (OEL) at or below 10 µg/m of air as an eight-hour time-weighted average;
- a pharmacologically active ingredient or intermediate with high selectivity (i.e., ability to bind to specific receptors or inhibit specific enzymes) and/or with the potential to cause cancer, mutations, developmental effects, or reproductive toxicity at low doses;
- hormones;
- certain steroids, and/or;
- any novel compound of unknown potency and toxicity.

Potency Categorization

HPAPI potency is categorized by OELs in µg/m—lower values indicate more potent compounds, requiring greater levels of containment and safety precautions at the manufacturing site. OELs and related criteria such as toxicity and carcinogenicity are used to determine performance-based exposure control limits, which ensure appropriate procedures for safe-handling of HPAPIs based on their potency categorization.

Operational exposure band (OEB) systems are often used in cases where there is insufficient data available to define an OEL for a compound (e.g., new drug candidates at preclinical stage of development). Banding systems categorize compounds from low to high potency and define the handling/containment requirements based on the band. Level 1 is the lowest risk/least restriction; up to Level 5, which requires the use of glovebox isolators with rapid transit ports (RTP) and closed/dust tight systems with closed transfer.

An example of a typical potency classification system is given in Table 1.

Table 1. Typical Potency Classification for APIs

OEB	**1**	**2**	**3**	**4**	**5**
OEL (µg/m³)	≥100	10-100	1-10	0.1-1	<0.1
Potential Exposure Effects	None to minor	Minor to moderate	Moderate to serious	Serious	Very serious
Requirements	GMP/PPE	GMP/PPE	Containment	Containment	Containment and robotics

DETERMINING EXPOSURE POTENTIAL

To assess the exposure potential (EP) during manufacture of an HPAPI, factors to consider include:

- the quantity of material to be handled
- the percentage of material that is active (i.e., the relative proportions of the HPAPI and any excipient components)
- the dustiness of the material
- the task duration

For example, the rapid production of small (gram) or medium (kilogram) quantities of a substance with low dust potential, such as a tablet, solution, suspension, or liquid-filled capsule, where powder API is wetted out in the vehicle, would be associated with a low exposure potential. In contrast, the exposure potential of an extended production process resulting in large (ton) quantities of a powder product would be high, as demonstrated in Table 2.

Table 2. Typical EP Classification for APIs

		DUSTINESS POTENTIAL				
		Low	Medium	High		
QUANTITY HANDLED AND PERCENT ACTIVE	Small (g) or Medium blend (kg)	EP-1	EP-1	EP-2	Short (mins)	TASK DURATION
		EP-1	EP-2	EP-3	Long (hr)	
	Medium (kg) or High blend (ton)	EP-1	EP-2	EP-3	Short (mins)	
		EP-2	EP-3	EP-3/4	Long (hr)	
	High (ton)	EP-2	EP-3	EP-3	Short (mins)	
		EP-3	EP-4	EP-4	Long (hr)	

Containment and Control Strategies

Once the exposure potential is established and an EP band assigned, an appropriate containment strategy and overall control approach is put into place, as shown in Tables 3 and 4.

Table 3: Band and Containment Strategy

Containment Bandling Levels (Based on Product OELs)	Band and Containment Strategy				
	Band	EP1	EP2	EP3	EP4
	F (<0.01µg/m^3)	5	5	5	5
	E (1 to 0.01µg/m^3)	4	4	4	4
	D (10 to 1µg/m^3)	3	3	4	4
	C (100 to 10µg/m^3)	2	3	3	4
	B (1000 to 100µg/m^3)	1	2	2	3
	A (>1000µg/m^3)	1	1	1	2

Table 4: Control Approach

Control Approach				
Containment Strategy 1	**Containment Strategy 2**	**Containment Strategy 3**	**Containment Strategy 4**	**Containment Strategy 5**
General ventilation	Downflow booth/laminar air flow	Downflow booth/laminar air flow with barriers	Containment isolator	Containment isolator with transfer parts/valves

Certain dosage forms are particularly well suited for use in HPAPI manufacture. Suspensions and solutions, where the HPAPI is dissolved in a liquid or cream, and not airborne, minimize operational exposure to toxic materials. **Liquid-filled capsules (LFCs)** are also an excellent option, as the HPAPI powder is dissolved in a closed system and delivered to a capsule filling machine. Operators are thus minimally exposed to airborne particles during manufacturing.

For more information on LFCs, read some of Altasciences' material, including a Playbook, and special issue of *The Altascientist*.

ENGINEERING CONTROLS FOR HPAPI MANUFACTURING

Rigorous engineering controls are necessary to guide the manufacturing process and ensure the selection of equipment, technologies, and procedures meet applicable GMP standards. The type of engineering control required is based on the OEL or OEB category of the API and the risk of operator exposure to inhalable or dermally transmissible particles during the manufacturing process, as explained above. Improper or inadequate containment of HPAPIs and related materials, from receipt to storage through waste disposal, presents a risk to staff, can decrease product yields, and cause cross-contamination with other batches of drug product.

Scientists with expertise in HPAPI manufacture must perform risk assessment and provide clear guidance throughout planning and implementation, to minimize risk while reducing cost and shortening timelines. This is especially important when working on new chemical entities (NCEs), whose potency may be unknown at the time of starting development. A CDMO with in-house analysis capabilities will be well positioned to ensure materials are properly classified and handled.

Once the OEL and/or OEB are established, a suitable manufacturing and laboratory analysis process, with appropriate and rigorous control on material handling, choice of equipment, environmental protection, and GMP requirements, is put into place.

Current HPAPI manufacturing practices apply a "containment at source" strategy, in combination with appropriate PPE, to mitigate the risk of operator exposure. Engineering controls such as local exhaust ventilation (LEV) devices, full hard-shell or flexible containment, and closed transfer systems are used. In addition to the primary engineering controls, containment at source is ensured by facility designs such as air change rates, high-efficiency particulate air (HEPA) filtration, and airlocks. Administrative controls including strict SOPs for safe methods of working and rigorous operator training are employed.

In the laboratory, operator safety remains a critical factor, although the containment strategies can be adapted due to the lower quantity of API being handled (i.e., milligram compared to kilogram scale).

REGULATORY REQUIREMENTS FOR HPAPI PRODUCTION

Regulatory agencies around the globe have specific requirements for the safe and appropriate manufacture of HPAPI products, particularly as regards segregation of operations and cleaning validation. Generally, segregated facilities and equipment for product manufacture according to compound are required (see Table 5).

The combination of quality risk management and a health-based approach to shared manufacturing facilities introduced by the European Medicines Agency (EMA) is a popular methodology for pharmaceutical manufacture. This approach uses toxicological data to inform risk and determine relevant cleaning residue limits, and provides direction on adequate operational and technical measures to control operator risk. Segregation of facilities for materials where toxicology data cannot support a controllable risk (e.g., sensitizing compounds such as β-lactam antibiotics) is still an expectation for both approaches.

As there is significant variation in the regulations between geographic areas, it is important to partner with a CDMO that has in-house expertise in analyzing requirements and determining the most appropriate path forward for your particular program.

When manufacturing drugs for marketing in multiple regions, it is advisable to apply the most rigorous applicable guidelines.

Table 5: Segregation Requirements for Classes of Drugs From Different Global Regulatory Authorities

Pharmaceutical Ingredients	Brazil ANVISA	U.S.A FDA	Europe EMA	Canada HC	WHO	PIC/S
Hormones	X	Certain*	Certain*	Certain*	Certain*	Certain*
Immuno-suppressants			Certain*	Certain*	Certain*	Certain*
Cytotoxic Agents	X	Certain*	Certain*	Certain*	Certain*	Certain*
HPAPI	Certain*	Certain*	Certain*	Certain*	Certain*	Certain*
Biological Preparations	X	X	Certain*	Certain*	X	Certain*
Steroids		Certain*	Certain*	Certain*	Certain*	Certain*
Sensitizing Pharmaceutical Ingredients	X	Certain*	Certain*	Certain*	X	Certain*
Antibiotics	Some*		Certain*	Certain*	Some*	Certain*
Cephalosporins	X	X	X	X	Certain*	X
Penicillin	X	X	X	X	X	X
Carbapenems	X	X	X	Certain*		X
Beta-lactam Derivatives	Others*	X	X	Certain*		X

*Verbatim from the different GMP documents. The regulatory requirements adopted by various countries worldwide only partially define the different segregation levels essential for the production of certain classes of drugs, and the meaning of the terminology is not always clearly provided.

Shared Manufacturing Facility Control Strategy

The control strategy for a shared manufacturing facility is multi-factorial, and some of the key points to consider in the manufacture of HPAPI products include the following:

Toxicological and Potency Analysis

- Access to both expertise and data for occupational safety and toxicology is used to analyze the hazard presented by the compound to staff at the CDMO, clinical pharmacology unit, and ultimately, patients.
- These data inform all downstream processes in HPAPI manufacture and are critical to the success of a program.

Facility Safety and Security Measures

- Room pressure controls for containment, including alarmed monitoring and verification of effectiveness, must be in place within the main HPAPI-handling area (negatively pressured to the surrounding rooms).
- Airlocks around the manufacturing and laboratory spaces must provide gowning and de-gowning areas with proper pressure control.
- Only trained employees may have access to the HPAPI-handling areas.
- Heating, ventilation, and air conditioning (HVAC) systems must be designed with risk-based consideration of the appropriate degree of air handling unit (AHU) sharing, and filtered recirculation or 100% fresh, single-pass air.
- Safe-change filters inside isolators, ventilated enclosures, general HVAC exhaust system, etc., must be used in the filtration and capture of contaminants.

Equipment and Processes

- Risk analysis must be performed to identify containment requirements to limit exposure to staff and the risk of cross-contamination.
- The ISPE's Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP) process is often applied to manage the risk of cross-contamination and maintain an appropriate balance between product quality and operator safety.
- Containment strategies (e.g., general ventilation, localized vacuum systems, manipulation into isolators with open or closed systems, and clean-in-place). Guidelines published by the EMA are a valuable resource.

People

- Manufacturers must ensure sufficient training for those responsible for the handling and manufacture of HPAPI products.
- Processes must be analyzed and designed by experts, to protect the safety of operators. An expert team that has many years of experience in handling and containment, and toxicology expertise, is important.

Transportation and Waste Management

Transportation of HPAPIs is governed by DOT regulations and is the responsibility of the drug company sponsor. A CDMO partner can provide support by:

- offering packaging solutions to reduce the impact of any anticipated temperature fluctuations during storage and transport, particularly during idle time or transition; and
- planning for the appropriate disposal of potent materials, and providing the best approach for cleaning or disposing of contaminated containers.

Altasciences' Case Study–Manufacture of a Nano-Milled HPAPI (Loteprednol Etabonate)

Overview

Altasciences develops and manufactures drug products that often contain highly potent APIs. A long-term client contracted us to manufacture a nano-milled suspension of a loteprednol etabonate intermediate, for ophthalmic application. Loteprednol etabonate is classified as a corticosteroid and requires HPAPI safety procedures, handling, and operator protection protocols.

Product characteristics: nano-milled suspension

API: loteprednol etabonate

Therapeutic indication: ophthalmology

Product development stage: development R&D through commercialization (repeat client)

OEL/OEB: Level 3

Methods

The design and implementation of the HPAPI safety program followed traditional industrial hygiene programs. Hazards were anticipated, all events with potential drug exposure were recognized and evaluated, and all exposure events were controlled.

API Identification

Loteprednol etabonate is classified as an OEB 3 compound based on its available toxicological data. It is a reproductive toxin when inhaled, and toxic to aquatic life.

Potential Exposure Events

Once the OEB was established and the safety hazards recognized, our scientific experts identified all instances where potential exposure could occur, from pre-formulation work to commercial manufacturing. The highest risk of exposure for loteprednol etabonate was determined to be during the dispensing and addition of the API to the vehicle, when the potential to aerosolize is greatest.

Engineering and Administrative Controls

At a minimum, it was required to wear PPE to prevent inhalation. To maximize safety, controls included the use of a face mask or respirator, full skin protection, double nitrile gloves, liquid-proof full body coveralls, and safety goggles. Containment systems were used with any open product, to further reduce airborne particulates.

We manufactured the product in our completely segregated Grade C suite, designed to keep airborne particulates down. This area has pressure controls for containment, with monitoring and verification of effectiveness, within the main HPAPI-handling area (negatively pressured to the surrounding rooms). Airlocks around the manufacturing and laboratory spaces provide the gowning and de-gowning areas with proper pressure control.

The air was filtered and controlled based on laminar flow principles, and operators were trained to minimize disruptions in the laminar flow. When handling micronized loteprednol etabonate, additional containment strategies were applied to reduce aerosolization.

All waste generated was properly documented and sent to a regulated chemical treatment plant for disposal.

WHY PARTNER WITH ALTASCIENCES?

We have invested heavily in our capacity to handle highly potent compounds. Our facilities contain segregated Grade C and D clean rooms, and our operators are highly trained in the particulars of HPAPI manufacture. At the start of each HPAPI program, operators receive refresher training on the specifics of engineering controls required for that product. All our CDMO pharmaceutical manufacturing operations take place on a single campus with analytical, manufacturing, and cGMP warehouse capacity.

For more information on Altasciences' significant experience and expertise with highly potent drug manufacture, we invite you to review the resources below.

ALTASCIENCES' RESOURCES

Webinar

High Potency Manufacturing Solutions

Video

Quick Chat With Ben Reed, General Manager, CDMO Services on HPAPI and Controlled Substances

Webpage:

Potent Handling Capabilities

REFERENCES:

Global HPAPI Market Analysis. https://www.ihealthcareanalyst.com/global-highly-potent-active-pharmaceutical-ingredients-market/ accessed July 4, 2023.

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.