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SUPPORTING DEVELOPMENT OF HIGHLY POTENT MEDICINES WITH MANUFACTURING FLEXIBILITY

Highly potent active pharmaceutical ingredients (HPAPIs) pack a punch above their weight. These therapies act in low doses, often on specific pharmaceutical targets, providing precision treatment for cancer, autoimmune disorders, infectious diseases, and other medical conditions with reduced side effects.

Packaging HPAPIs in a tablet or another solid dosage form makes them easier for patients to take.[1] Because these compounds can have a major cytotoxic effect in even tiny amounts, their safe handling is a challenge for personnel. It also presents hurdles in meeting requirements for equipment, the environment, and product quality in drug manufacturing and development.[2]

Cancer treatments in tablet forms are easier for patients to take.

Credit: Elnur/Shutterstock

Drugmakers incorporating HPAPIs in their processes must take precautions at every step of production—from the substance's arrival at a facility, through formulation, to packaging and delivery. Those safeguards can seem burdensome when flexibility to handle different substances, formulations, batch sizes and production processes is critical to keeping a drug development project on track, on time, and on budget. Building that flexibility into HPAPI facilities and workflows is key to keeping these drugs moving through the pharmaceutical pipeline, according to Bernd Sterner, head of pharmaceutical development at Aenova's Center of Excellence HPAPI & Oncology Products in Regensburg. Aenova is a contract and development manufacturing organization (CDMO) that processes HPAPI's in 3 of its 14 facilities.[3]

PRECISE POTENCY

HPAPIs represent one of the fastest-growing market segments in the global pharmaceutical industry. As of late 2022, over 40% of all pharmaceuticals in development were highly potent.[4] Market analysts valued the global HPAPI market at $21.2 billion in 2022 and predict it to reach $32.17 billion by 2027.[5]

A harmonized standard for the definition of HPAPI is not established, and classification systems vary by region and company.[6] In general, toxicologists evaluate highly potent substances by their values, such as occupational exposure limit and permitted daily exposure value, as well as by screening results regarding a compound's link to cancer, reproductive toxicity, or genetic mutations.

Typically, an API can be considered highly potent if its occupational exposure limit is below 10 µg per m^3 or if it is known to cause cancer, mutations, or developmental or reproductive harm at low doses. In addition, novel compounds with unknown potency and toxicity or APIs that are designed to have a highly selective effect on a specific molecular target within cells can be defined as HPAPIs.[2]

Examples of HPAPIs include

- sex hormones, such as estrogen or estradiol;
- chemotherapies that target specific proteins overexpressed in cancer cells, such as human epidermal growth factor receptor 2 (HER2) in breast cancer or epidermal growth factor receptor (EGFR) in lung cancer;
- antimetabolites that prevent cell replication, such as methotrexate, which is used to treat some cancers, rheumatoid arthritis, and psoriasis; and
- antibody-drug conjugates used as targeted cancer treatments.[7]

HOLISTIC CONTAINMENT

Delivering targeted treatments via precision and personalized medicine drives interest in developing drugs using HPAPIs. With increased market demand comes an increased need for development and manufacturing capacity. A CDMO with expertise in safely handling HPAPIs can be a valuable partner in the development process. "Operator safety and product quality are the most important parameters for everything we do," Sterner says.

The handling of highly potent active ingredients requires sophisticated production facilities, including isolators to contain material, personal protective equipment, and designated rooms with advanced air-handling systems.

Credit: Aenova

Containment is key to preventing cross-contamination as well as to ensuring operator safety. Aenova approaches containment holistically, Sterner says. Its measures include allotting spaces for HPAPI handling, establishing elaborate pressure zones using building air-handling systems, and using containment equipment and personal protective equipment (PPE).

Aenova's pilot-scale plant in Regensburg, Germany, has rooms designated for HPAPIs are negatively pressurized to prevent substances from escaping. The air pressure in these rooms is lower than that of the space outside, meaning that air only flows into the HPAPI room rather than out of it.

During the most hazardous segments of a production process, operators wear state-of-the-art PPE that resembles a space suit with separate oxygen supply. During less hazardous steps, operators may be able to switch to PPE that is not so restrictive. They would then use different containment solutions or specially designed air-handling systems.

PROCESSING PROTOCOLS

Having quality management and environmental health and safety teams involved in every step of production—from receiving through manufacturing and packaging—is critical to maintaining the highest quality standards when using HPAPIs. Aenova's procedures mandate that safety assessments, cleaning validation requirements, and handling instructions be in place before any new substance is put on manufacturing or dispensing equipment, Sterner says.

The life cycle of a newly introduced HPAPI begins before the compound arrives at a plant. Environmental health and safety personnel assess the compound to define the occupational exposure band level, assess the occupational exposure level, and determine the permitted daily exposure. Based on this assessment, the team then evaluates and documents the requirements for cleaning validation. Finally, as a prerequisite for handling an HPAPI in production, the team develops suitable analytical methods for cleaning validation.

The first time operators handle an HPAPI is for quality testing upon arrival. Areas designated for receiving, storing, and sampling HPAPIs are equipped with safety measures such as glove boxes in the respective sampling cabinet. Common methods for testing powdered APIs include opening containers and removing quality control samples for laboratory analysis. To reduce handling of open containers of powdered material, operators can also analyze samples using noninvasive methods, such as a Raman fiber-optic probe.

When dispensing HPAPIs for production, operators contain the material in isolators. Isolators can be custom-made rigid containers with an atmosphere that is different from the surrounding environment and dedicated air filtration. Isolators typically come equipped with weighing and dispensing equipment, dispensing chambers, and individual glove sleeves and pass box to access the interior. Isolators can also be single-use bags or polyethylene sleeves.

Containers with HPAPIs are opened only in the isolators, and dispensing areas for HPAPIs are completely separated from the dispensing areas for inactive ingredients, or excipients. Rigid isolators require strict cleaning protocols, while single-use isolation products require strict disposal procedures.

After a production run using HPAPIs, operators follow validated cleaning methods for used equipment and the surrounding production area. The cleaning validation concept must be designed in a way that prevents cross-contamination, particularly in facilities where identical equipment trains are used for different HPAPI products, Sterner says.

FLEXIBLE AND AGILE MANUFACTURING

The rapidly changing environment of HPAPI drug development requires flexibility in manufacturing so that production lines can change volumes, processes, and products to meet changing market demands or clinical trial requirements. Yet, the strict processing protocols and containment processes[8]

Facilities designed for flexibility—such as being able to change a mold during the production of cancer drugs—maintain scalable manufacturing of highly potent drugs.

Credit: Aenova

for HPAPI drug development can limit how a production line responds to new requests—unless flexibility is built in from the start.

Aenova's site at Regensburg features what Sterner calls a "colocation manufacturing concept": Development activities and subsequent commercial production happen in the same place, and the facility can transition seamlessly from a pilot-to a full-scale commercial run. "The target of this approach is to have as few changes from pilot to full scale as possible," Sterner says.

Advantages of the colocation concept include

- Scalability: Due to comparable equipment setup for small-, pilot-, and commercial-scale manufacturing, the site can increase production from 0.5 kg to 500 kg.
- Knowledge retention: Product-specific learnings from development remain within the site after launch.
- Risk mitigation: Reduced process transfer efforts lower timeline risks.

Sterner describes a scenario for sudden demand for larger quantities of a new drug after success in early clinical trials. "In that case, the colocation concept can quickly scale up production at the same site without transferring the manufacturing process to a different facility," he says. "Also, the colocation concept allows for greater efficiency in the manufacturing process, as we can quickly adjust the production process based on the feedback from the clinical trials."

By providing more targeted and effective therapies, HPAPIs will transform how we treat cancer and other diseases. And as the number of HPAPIs in development increases, the need for developing partnerships between innovative researchers and experienced CDMOs will only grow.

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