Cytotoxic drug manufacturing market

Outsourcing, a preferred business model in this domain

The cytotoxic drug and HPAPI manufacturing market is currently considered one of the fastest growing sectors in the pharmaceutical industry. The resurgence of new anticancer treatments, notably antibody-drug conjugates (ADCs), has generated significant demand for expertise in development and manufacturing. Outsourcing has become a preferred business model in this area, offering increased flexibility, reduced costs and rapid drug launch.

Demand for HPAPIs continues to grow

According to Cancer Facts and Figures 2023, published in January 2023 by the American Cancer Society, an estimated 1.9 million new cancer cases will be diagnosed in 2023, among which prostate cancer is estimated at 288,300, followed by 238,340 cases of lung cancer, and 300,590 cases of female breast cancer.

Spending on cancer drugs reached $196 billion globally in 2022, and is expected to reach $375 billion by 2027, driven by continued innovation and offset by continued adoption of biosimilars across major markets.

The United States remains the largest market in the world, followed by major European countries.

The solid portfolio of next-generation biotherapeutic products in oncology presents significant potential as well as a wide range of uncertainties, both clinically (efficacy, durability of response, and safety) and commercially. The combination of these factors contributes to the baseline outlook for $19 trillion growth in global spending by 2027 (current global spending is $3 trillion), which is significantly lower than the high-end scenario, but reflects the range of unknowns surrounding this groundbreaking research, according to IQVIA.

The number of products under development in oncology has grown significantly over the past decade, with more than 2,000 products currently under development. The growing number of new generation molecules should stimulate the HPAPI production market, while the development of targeted therapies such as antibody-drug conjugates, which contain highly potent cytotoxic payloads, has also played a key role in the number of new molecules in development.

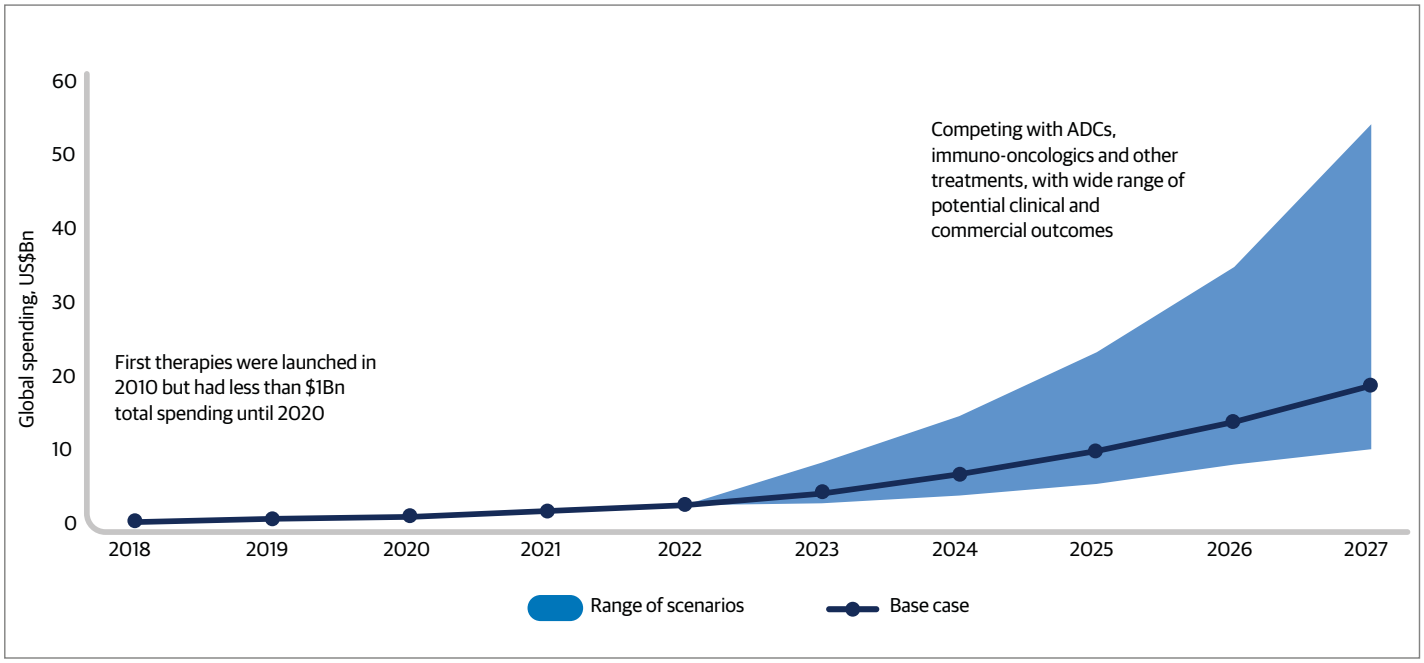
Global high potency API (HPAPI) market size is expected to grow from USD 26,853.45 million in 2023 to USD 41,831.63 million by 2028, at a CAGR of 9.27% over the forecast period, according to Mordor Intelligence.

The cytotoxic drug and HPAPI manufacturing market is one of the most powerful and dynamic

FAREVA SITE IN PAU

Source: Fareva

THE OUTLOOK FOR NEXT-GENERATION BIOTHERAPEUTICS IN ONCOLOGY INCLUDES SIGNIFICANTLY UNCERTAIN CLINICAL AND COMMERCIAL SUCCESS



Source: IQVIA Institute, Apr 2023
1. Subject to customary closing conditions; closing expected H2 2023
APRIL – a proliferation inducing ligand. ERA – endothelin A receptor antagonist. FALCON – fatty acid ligand conjugated oligonucleotides. IgAN – immunoglobulin A nephropathy

sectors in the pharmaceutical industry. 21 oncology novel active substances (NAS) were initially launched globally in 2022, with 176 in total since 2013.

Providing cost-effective manufacturing in small batches

The challenges of developing and marketing innovative drugs containing HPAPI reside largely in striking the right balance between safety and profitable production.

Manufacturing highly potent APIs and cytotoxic drugs requires an adequate working environment, strict manufacturing protocols, and a workforce trained to rigorously handle highly potent APIs and cytotoxic drugs. Producing high-potency drugs requires expensive infrastructure that is often complex to design, install and maintain.

Emerging biopharmaceutical companies (EBPs) created 70% of new oncology drugs in 2022 and launched 71% of their own products. EBPs rely on third-party service providers to leverage their technologies for manufacturing potent and cytotoxic compounds and achieve greater operational flexibility. The expertise inherent in CDMOs is expected to reduce the time to market a product and provide significant financial benefits.

CDMOs are paving the way for a new era in the pharmaceutical industry, which is based on the construction of strategic partnerships with EBPs for the production of small batches of drugs with high added value.

The development of more personalized and targeted therapies and the increase in the number of orphan drug approvals in smaller patient populations have increased the number of lower-volume drugs entering the market, thereby increasing demand for small production runs.

As HPAPI demand is expected to increase, CDMOs are investing heavily to provide their biopharma partners with the scalability required for these projects. These changes will focus on the complexity of small-volume production operations with flexible, technically innovative facilities configured to meet low-volume batch manufacturing requirements.

The huge capital investments in dedicated capacity and facilities required for safe and compliant manufacturing of HPAPIs may not translate into an immediate return on investment.

CDMOs are strengthening their expertise with a lot of acquisitions.

In June 2023, **Lonza** acquired **Synaffix B.V.**, a biotechnology company focused on commercializing its clinical-stage technology platform for

the development of ADCs. While ADCs offer widespread and targeted treatment potential against cancer, they present a range of complex development and manufacturing challenges. Supported by a team of scientific experts, the Synaffix technology platform, which includes payload and site-specific linker technologies, will enhance and extend Lonza's integrated ADC services, including its early-phase offering.

Combining Lonza's development and manufacturing capabilities with the Synaffix ADC technology platform will provide customers with a comprehensive service to rapidly discover, develop, scale up and commercialize novel and differentiated ADCs. These enhanced capabilities will streamline the path to clinic and commercialization.

Since July 2023, **Evonik** and **Heraeus Precious Metals** have been collaborating to expand both companies' range of services for highly potent active pharmaceutical ingredients (HPAPIs). The cooperative effort leverages the specific HPAPI competencies of both companies and provides customers with a fully integrated offering from the pre-clinical stage to commercial manufacturing. Heraeus Precious Metals' pharmaceutical ingredients CDMO covers a full range of development and manufacturing services for cancer therapy, focusing on producing highly potent small molecules (HPAPIs), such as payloads including linkers and toxins for Antibody-Drug Conjugates (ADCs). The partnership with Heraeus Precious Metals builds on the company's track record of delivering complex APIs to meet the clinical and commercial supply needs of biotech and large pharma customers around the world.

The range of services includes development and manufacturing under GMP for clinical trials, photochemistry in batch and continuous flow mode, high-containment systems for OELs (Occupational Exposure Limits) < 10 ng/m3, state-of-the-art equipment, CMC documentation for global approval and regulatory support.

Holistic concept for safe and efficient handling of HPAPIs

The development and manufacture of highly active substances was initially intended for the pharmaceutical manufacture of solid oral dosages and since also used in biotechnology, such as in antibody-drug conjugates.

The toxicological properties of HPAPIs require health-based risk management for handling the active ingredient in the workplace to ensure optimal employee protection. It is also essential to exclude a negative impact on other products, i.e. cross-contamination. As a result, comprehensive and rigorous management systems are required for safe handling and containment of highly potent molecules.

• **Dangerousness classification (OEB, LEP)**

In the pharmaceutical industry, an occupational exposure scale (OEB) developed by the US National Institute for Occupational Safety and Health (NIOSH) 2 is used to classify chemicals into specific categories. The Occupation Exposure Band (OEB) is a technique of accurately classifying chemicals into "bands" or "categories" based on their adverse health effects. It only takes the toxicity of the pure substance into account. It is based on the principle that the more toxic a product is, the higher its classification.

The classification of the toxicity and dangerousness of a product is based on a certain number of data: acute toxicity, eye damage, skin and respiratory sensitization, corrosion and skin irritation, carcinogenicity, etc. From the classification obtained, it is possible to determine the equipment allowing safe handling. Depending on the degree of dangerousness, the operator may need a containment space certified OEB1 (less dangerous) to OEB6 (more dangerous) so that he is protected from risks.

The OEL value (Occupational Exposure Limit) corresponds to the weighted average concentration of a substance

OCCUPATIONAL EXPOSURE BANDS

	A	B	C	D	E
Particulate/Dust	>10 mg/m³	>1 to 10 mg/m³	>0.1 to 1 mg/m³	>0.01 to 0.1 mg/m³	**≤0.01 mg/m³**
Gas/Vapor	>100 ppm	>10 to 100 ppm	>1 to 10 ppm	>0.1 to 1 ppm	**≤0.1 ppm**

Source: McKernan et al. 2016

Most large pharmaceutical companies develop highly potent drugs in-house

in the air on site. It is measured during a previously defined period. In this environment, there is no risk of acute or chronic damage to the health of employees as long as the value is not exceeded. Expressed in mg/m3, fibers/CC or parts per million (ppm), the classification aims to protect exposed personnel against occupational diseases.

The figure also gives high-level guidance on handling requirements appropriate to a certain OEB. It is recommended that certain classes of active ingredients should be manufactured in dedicated or specifically equipped facilities.

Each High Potent drug project begins with a risk assessment, which takes into account the entire manufacturing process, from manufacture of the HPAPI through to the finished and packaged pharmaceutical product. The study consists of assessing the risks that may arise, and the extent of the immediate danger for users and the environment. This exhaustive study must take into account the dangers associated with product transfer systems, cleaning procedures, upkeep and maintenance of equipment and production premises, plant security, containment concept and highly qualified and well-trained personnel

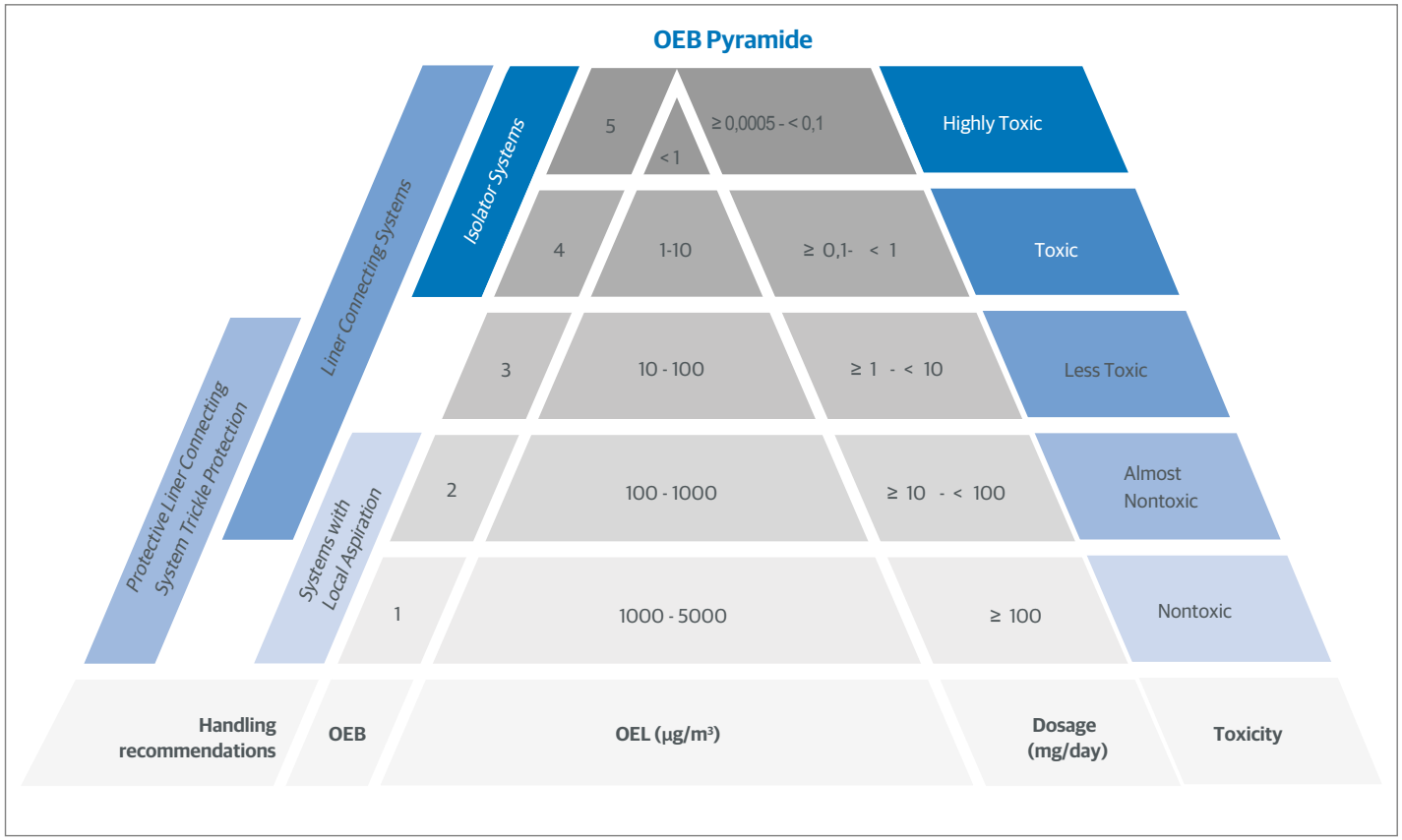
During the project, the characteristics of the primary and secondary containment to be implemented will be studied. Primary containment refers to any technologies that enclose the substance and prevent it from spreading. Secondary containment consists of preventing any further spread of the substance which might not have been slowed by primary containment.

For each project, the appropriate solution depends on the potency of the product and the size of the batch handled, laboratory, small scale or commercial use.

The manufacture of very potent drugs therefore requires highly technical expertise, perfectly mastered technologies and appropriate containment facilities.

The most significant barrier for companies to produce HP products is capital expenditure and operating costs. Indeed, the production of high-power APIs is a costly activity and the choice of insulation technologies is

OVERVIEW OF OEB, OEL AND POTENCY OF COMPOUNDS



Source: Aenova Group.
Graphic adapted from NIOSH https://wwwn.cdc.gov/Niosh-oeb/

a crucial question to ultimately ensure the profitability of the installations.

Most large pharmaceutical companies develop highly potent drugs in-house, but there are therefore strong fiscal incentives to outsource them. This outsourcing becomes essential when it comes to medium-sized structures or EBPs.

Key HP CDMO Market Insights

Choosing a contract development and manufacturing organization to develop and manufacture highly potent drug products is a complex process, requiring a high level of due diligence.

Currently, more than 170 companies around the world have the capabilities required to offer the development of highly potent active pharmaceutical ingredients (HPAPI) and cytotoxic drug contract manufacturing services at various operational scales.

Among these, 55 CDMOs in Europe and the United States offer manufacturing and packaging services for High Potent drugs (OB3 and above). Very few are pure players (10%) offering only expertise and specialized facilities for high potential production. The majority of CDMOs are generalists and offer development and fill and finish services on one or more of their factories. 29% only offer expertise and production services for solid cytotoxic forms, including one company specializing only in semi-solid forms. 35% only offer expertise and production services for sterile forms. 36% offer services and expertise for solid and liquid forms

The headquarters of the 55 CMDOs are split half between the USA and Europe. The 55 CDMOs bring together more than 120 industrial sites with the required capacity to produce finished pharmaceutical forms for clinical and commercial (OEB 3 and above). The number of industrial sites is more strongly represented in the countries of the European Community, with more than 60%, and only 40% on the North American continent. The majority of industrial sites with High Potent production activity are located in Italy, Germany, Ireland and the UK. Nearly 40% of global installed manufacturing capacity is available in facilities located in the Europe region. ■

EXCELLA SITE

Source: Fareva