Developments in high potency API manufacturing

Molly Bowman of **Thomson Reuters** examines trends in high potency API manufacturing

The global high potency APIs (HPAIs) market is expected to reach €13 billion by 2018. HPAIs are able to target diseases more selectively and are extremely effective at small doses. Applications include oncology, hormones, narcotics, musculoskeletal treatments and retinoids. HPAIs require sophisticated facilities and specialised technical capabilities due to their potency and small dosage requirements. Most are manufactured in North America and Europe and this is expected to continue.

A compound is generally defined as highly potent if it has an occupational exposure limit (OEL) of ≤10 µg/m^3, a daily therapeutic dose of ≤10 mg/day or if a 1 mg/kg/day dose produces serious toxicity in laboratory animals. The OEL is determined using toxicology information from published scientific literature and internal studies. OELs of APIs vary enormously, from 5 mg/m^3 in the case of aspirin and naparoxen down to 35 ng/m^3 for ethinyl estradiol.

Most companies have a banding system that categorises compounds based on their toxicity and this dictates the handling containment required to work with the compound. Often companies can determine an exposure limit of a known compound based on the lowest therapeutic dose, but many other factors have to be considered, including the form of the API (liquid or powder), the formulation process and the frequency of contact.

Most new developmental products do not have the toxicity information available. Often companies are asked to work on products where it may be difficult to determine the potential risk of exposure. Currently, there is no official guidance for the safe handling of highly potent compounds.

As containment varies depending on the toxicity of the product, the handling requirements will also differ greatly. Numerous companies use the SafeBridge classification system, while many have developed their own, based on their equipment and facilities (Table 1).

The attraction of HPAIs, in addition to some lucrative product targets, can also include cost reduction since the increased potency means that less API is needed. Often, pilot-scale facilities are large enough to manufacture commercial quantities of HPAIs, where the global demand is less than 100 kg/year. However, the production of HPAIs also requires more frequent, in-depth EHS audits. Banding systems often evolve due to changes in manufacturing technology and containment enhancements.

Since high potency manufacturing requires people with specific expertise and different equipment, many companies have been making strategic deals and investments in the field. Although a great deal is kept in house, over the past few years there has also been significant outsourcing from Big Pharma to CMOs.

Table 1 - Examples of banding systems & categorisation of APIs

OEL (mg,µg,ng/m^3)	SafeBridge Consultants	Merck & Co.	Lonza
10 mg	Category 1: Low toxicity	Category 1	Category 1
1 mg		Category 2	Category 2
100 µg	Category 2: Intermediate toxicity	Category 3	Category 3
10 µg			Category 4
1 µg	Category 3: Potent	Category 3+	
100 ng		Category 4 & 5	Category 5
10 ng	Category 4: Highly potent		
≤1 ng			Category 6

It can be more economically viable to outsource the products as resource demands and the level of specialisation needed increases for small volumes of HPAI. Key manufacturing attributes include facility design, containment level, monitoring capabilities and operational scale, in addition to the protocols, training and experience of staff.

Over the past few years, many companies have touted their partnerships and investments into HPAI manufacturing. Dishman's acquisition of Carbogen-Amcis gave it immediate access to a significant knowledge base in containment and facilitated the construction of a commercial HPAI manufacturing site in India. Both SAFC and Fresenius Kabi have made significant investments into their facilities for handling HPAIs.

In 2012, Aesica opened a high potency granulation facility and announced plans to invest in HPAI manufacturing as well. Novasep invested €3 million in HPAI production in France, while Evonik has invested in both its high potency laboratory space and kilo-scale facility. Lonza has been investing in the expansion of its antibody-drug conjugates (ADCs) capacity in Switzerland, with plans to double the existing capacity for handling both biologics and small molecule HPAIs.

The manufacturing of HPAIs also comes with significant challenges. Operating these facilities requires high containment technologies, protecting employees from dangerous compounds as well as keeping compounds from cross-contamination. There is significant cost in specialised equipment; however, prices are expected to decrease as more flexible systems are developed.

Some of the barriers to entry for companies getting involved in HPAIs include a lack of guidance in design, limited skills outside Big Pharma, and high capital and operating costs. Challenges and regulatory risks associated with standard APIs are increased when dealing with HPAIs. Additionally, compounds may need to be re-evaluated as more data is available.

As medicine becomes more targeted and specialised, the number of highly potent drugs being developed will likely increase. Currently, analysts estimate that 25% of the drugs in development globally are highly potent. ADCs, which combine monoclonal antibodies and HPAIs, allow for more selective cytotoxicity being delivered directly to tumours.

It is expected that competition will further drive new technology developments and likely see more high potency manufacturing being developed in high growth regions of Asia, such as India and China. However, the expertise and experience in dealing with these compounds is primarily located in Europe and the US. Numerous HPAIs will lose patent protection in the next few years as well, which will likely drive more generic drugs companies' investment into high potency manufacturing or partnerships with CMOs to develop these products.

Conclusion

As technology develops and more drugs are created with higher pharmacological activities, the market is expected to continue growing. It is likely that more companies will decide the upfront investment to enhance their capabilities will be worth it, as the market for high potency products grows. Some technology advances, such as single-use production, could see more HPAI manufacturing being done in-house.

However, the lack of a global regulatory framework for handling HPAIs will continue to be a challenge for many. Companies with extensive experience in the area will continue to dominate the high potency manufacturing space, but the continued growth and demand for such products will probably drive more companies into this highly technical space.

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