Meeting The Challenges Of HPAPI Production

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Growing concerns about quality lapses, Good Manufacturing Practice (GMP) violations and compromised data integrity at low-cost manufacturing plants for active pharmaceutical ingredients (APIs) have revived demand for reliable sources of supply in the US and Europe.

The appeal of sourcing APIs from economically attractive locations such as India or China has tarnished somewhat in recent years as regulatory agencies in the US, and other markets highly dependent on outsourced or offshored pharmaceutical production, have stepped up scrutiny of manufacturing facilities abroad.

According to a report by the US Government Accountability Office in December 2016, the Food and Drug Administration estimated that more than 40% of finished medicines and around 80% of active pharmaceutical ingredients in the US drug supply were being produced overseas at that time.

An analysis by Ned Pagliarulo of BioPharma Dive in April 2018 found that 39, or 64%, of the 61 warning letters sent out by the Office of Manufacturing Quality in the FDA's Center for Drug Evaluation and Research were to facilities in India and China, compared with 25, or 57%, of a total 44 warning letters in 2016. Data integrity is also a growing concern as facilities become increasingly automated and the flow of manufacturing data thickens.

One consequence of this waning confidence in low-cost manufacturing plants has been increased investment by Western API manufacturers in new technologies and custom-synthesis facilities, including capacity to manufacture highly potent APIs (HPAPIs).

The Italian company Indena, whose operations span pharmaceuticals, health foods and personal-care products, has followed this trend by opening a new kilolab dedicated to HPAPIs in Settala (see box on page 6).

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– Stefano Togni
Director, BD
Indena

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HPAPI Market Growth

Advances in drug development have generated more targeted and potent drugs, or antibody-drug conjugates, with fewer side-effects, particularly in the fields of oncology and other age-related or chronic diseases. This has fuelled strong market demand and growth for HPAPIs worldwide.

Estimates of HPAPI market sizes tend to vary, in part due to the difficulty of pinning down API values in the captive-production segment (i.e., APIs used by companies for in-house manufacturing of finished dosage forms).

Italy's Chemical Pharmaceutical Generic Association (CPA) has estimated the global market for HPAPIs expanded at a compound annual growth rate of 7.9% between 2004 and 2015, reaching US$13 billion in 2015.

The share of outsourcing in this segment increased from 29% in 2015 to 33% in 2019, the CPA calculates. As Stefano Togni, Indena's director of business development and licensing, points out, there are "two key factors driving the demand for high-quality HPAPIs manufactured by contract development and manufacturing organizations."

One of these is "the general market-size increase; the other is the more frequent outsourcing by originators to specialized CDMOs."

It looks as though these kinds of growth rates will continue into the foreseeable future, if not even accelerate. Since a large portion of the HPAPI market serves demand for highly potent cancer drugs, the rapid expansion of the global oncology market, as populations age, new therapeutic options extend survival rates, and cancer drug candidates dominate pharmaceutical R&D pipelines, is one indicator of where HPAPIs are going.

The IQVIA Institute for Human Data Science believes the global market for oncology therapeutics will be worth as much as $200 billion by 2022, averaging 10% to 13% growth over the next five years. A total of 63 new cancer drugs have entered the market within the past five years, IQVIA says.

Manufacturing Challenges Of HPAPIs

At the same time, HPAPI production has not been immune from the quality and data-integrity problems at non-Western API plants identified by the FDA and other regulators. "The data integrity issue is at its core a cultural problem, and is affecting the industry irrespective of whether we are talking about HPAPIs or non-high potent APIs," Stefano Togni comments.

While rapid market growth in the highly potent segment and the broader shift away from API sourcing in low-cost territories make HPAPIs a winning proposition for Western manufacturers, they also present a number of manufacturing challenges. These include tough specifications for handling and producing high-potency compounds, to guarantee a safe, high-quality working environment free from cross-contamination.

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Upgrading existing API facilities, rather than investing in new capabilities tailored specifically to HPAPIs, can be a costly undertaking, given the need for specialized containment provisions to make sure employees and their environment are protected from exposure to toxic substances. Manufacturers must also take steps to protect the active pharmaceutical ingredients themselves from contamination or cross-contamination by other HPAPIs produced at the same site.

A further complication is the lack of a universally accepted definition for HPAPIs. One generally acknowledged measure is an Occupational Exposure Limit (OEL) of 10 µg/m3 of air or less. The lower the OEL is, the more potent the substance and the greater the need for rigorous containment. That is assuming the manufacturer has the necessary data to classify a substance as a HPAPI, which is not always the case.

Even where data are available from clinical trials, animal studies or other sources, the risk-assessment process needs to take into account factors such as the differences between potency and toxicity (e.g., a high-potency compound may be pharmacologically effective at a low dose but toxic only at a much higher dose); or the difficulty of extrapolating effects from clinical trials, designed specifically to address predetermined endpoints in people with preexisting conditions, to occupational exposure of nominally healthy workers in HPAPI facilities.

Specialized requirements for HPAPI facilities range from appropriate facility design and engineering controls to:

- tailored manufacturing equipment (e.g., isolators, glove boxes);
- innovative containment technologies;
- robust risk-assessment, -management and -monitoring procedures;
- comprehensive quality-management systems;
- continuous education and training;
- standard operating procedures for handling HPAPIs;
- single-pass heating, ventilation and air-conditioning systems;
- room-pressure differentials;
- protective clothing and airlocks around manufacturing or laboratory areas where employees can put on or take off protective clothing;
- Misting showers to rinse protective clothing;
- access restrictions to ensure that only trained and qualified personnel enter areas where HPAPIs are handled;
- strict monitoring of occupational hygiene and employee health;
- third-party certification;
- close attention to cleaning/waste management.

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All of this has to go hand in hand with proven expertise in areas such as synthetic organic chemistry, process development, scale-up, purification and highly sensitive analytical techniques. With concerns building over data integrity in pharmaceutical manufacturing, continuous and comprehensive data review and auditing are also indispensable.

The Human Element

As in all pharmaceutical manufacturing environments, and particularly in such a high-risk area as HPAPI production, the equipment and facilities are only as good as the staff managing them and handling HPAPIs on a routine basis.

"Having a nice glove-box installed is not sufficient per se," Stefano Togni notes. "It is just an expensive tool in an expensive environment without proper handling."

He emphasizes rather the "human element" – meaning highly qualified, motivated and trained technical staff – as well as corporate culture strongly oriented to quality as the two fundamental requirements to ensure that HPAPI operations run safely, seamlessly and effectively.

"We have seen several companies that invested as newcomers in HPAPI manufacturing but had issues with properly running the equipment," Stefano Togni adds.

As far as the regulatory environment for HPAPIs is concerned, high-potency compounds are not subject to any specific requirements beyond the overarching regulations for APIs, which may vary slightly from market to market, points out Indena's R&D director, Pietro Allegrini.

That only underlines how much personal responsibility is invested in manufacturers to make sure that their facilities, equipment, staffing and procedures are geared optimally to the particular challenges of handling HPAPIs.

Global Opportunity

For Indena, its expanded HPAPI capabilities represent a truly global opportunity. "In principle, there are no geographical limitations in terms of target markets," Stefano Togni comments, while adding: "Clearly the most appealing markets, both in terms of size and innovation pace, are the US, Japan and Europe."

Most of this opportunity is expected to come from small-molecule drugs, notwithstanding the decisive shift to more complex biologics in the research-based pharmaceutical industry.

"While a growing share of HPAPIs will be represented by biological products, such as antibody-drug conjugates (ADCs), small molecules are poised to maintain the lion's share in the years to come, considering also the innovation pace for this segment," Stefano Togni predicts.

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R&D Director, Indena

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At the same time, Togni foresees a significant role in the biological arena for CDMOs that manufacture cytotoxic payloads, or small-molecule HPAPIs with chemical linkers for coupling to monoclonal antibodies in the form of ADCs. The advantage of conjugation is selective cytotoxicity, enhancing both the efficacy and safety/tolerability of the treatment combination.

New Challenges

New challenges are likely to emerge in the global market for HPAPIs, as manufacturers respond to increasing demand by investing in the space and raising the competitive stakes on the supply side.

Nonetheless, Indena is confident that the HPAPI segment also provides avenues for niche capabilities.

"From a technical point of view, we have seen the emergence of several molecules endowed with a poor solubility, which creates an opportunity to offer, besides custom-synthesis activities, services for API pre-formulation, such as spray drying with organic solvents or other absorption-enhancing technologies," Stefano Togni explains.

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Indena's New Kilolab In Settala, Italy

This state-of-the art facility extends Indena's traditional capabilities in identifying, developing and manufacturing high-quality active ingredients derived from plants to encompass the production of natural, semi-synthetic and fully synthetic highly potent APIs (HPAPIs) that call for a higher confinement level.

Building on Indena's expertise in cytotoxic medicines and high-containment materials, the Settala plant can synthesize, purify and manufacture toxic substances up to an Occupational Exposure Limit of 20 ng/ m3, handling anything from small-scale batches for toxicology testing to cGMP (current Good Manufacturing Practice) batches for clinical trials and large-scale commercial production.

Indena has been dealing with high levels of containment and HPAPIs since the start of the 1990s, accumulating a wealth of experience with plant-based taxanes as APIs for anticancers such as paclitaxel or docetaxel, and building a robust corporate culture for managing HPAPIs over the years.

"The further expansion was quite a natural move, to capitalize on our existing knowledge and expertise while further expanding to other classes of compounds, both synthetic or natural," Stefano Togni says. "Plus, the private ownership of our company and its sound financial position are facilitating elements toward high-technology investment."

The new custom-services site in Settala is designed to meet US Food and Drug Administration (FDA), European Union (EU) and International Conference on Harmonization (ICH) requirements for cGMP and regulatory-compliant production of HPAPIs.

It enables Indena to expand its offering into a fast-growing segment of the pharmaceutical market while maintaining optimal levels of quality, safety and security in an ever more demanding environment for high-potency compounds.

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