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THE APIS MARKET BETWEEN CHALLENGES AND OPPORTUNITIES

According to a recent report from Italy's Chemical Pharmaceutical Generic Association (CPA) [link 1], the traditional active pharmaceutical ingredients (APIs) market is facing a series of challenges which include rising competition, Governments' pressure on drug prices aiming at reducing healthcare spending, regulatory burden, enormous investments required for the launch of a NME, environmental, health and safety costs, and labor costs among others.

In addition, the traditional generic APIs business is struggling, and many big generic APIs suppliers are changing their strategies, shifting from the traditional generic APIs field to emerging therapies, most of which in the biotech area.

Another analysis [link 2] about the industry released on January 2019 informs that the global APIs market is estimated to reach USD 245.2 billion by 2024 from USD 182.2 billion in 2019, at a CAGR of 6.1% during the forecast period. The increasing incidence of chronic diseases, growing importance of generics, and the increasing uptake of biopharmaceuticals are some of the major factors driving the growth of the global APIs market.

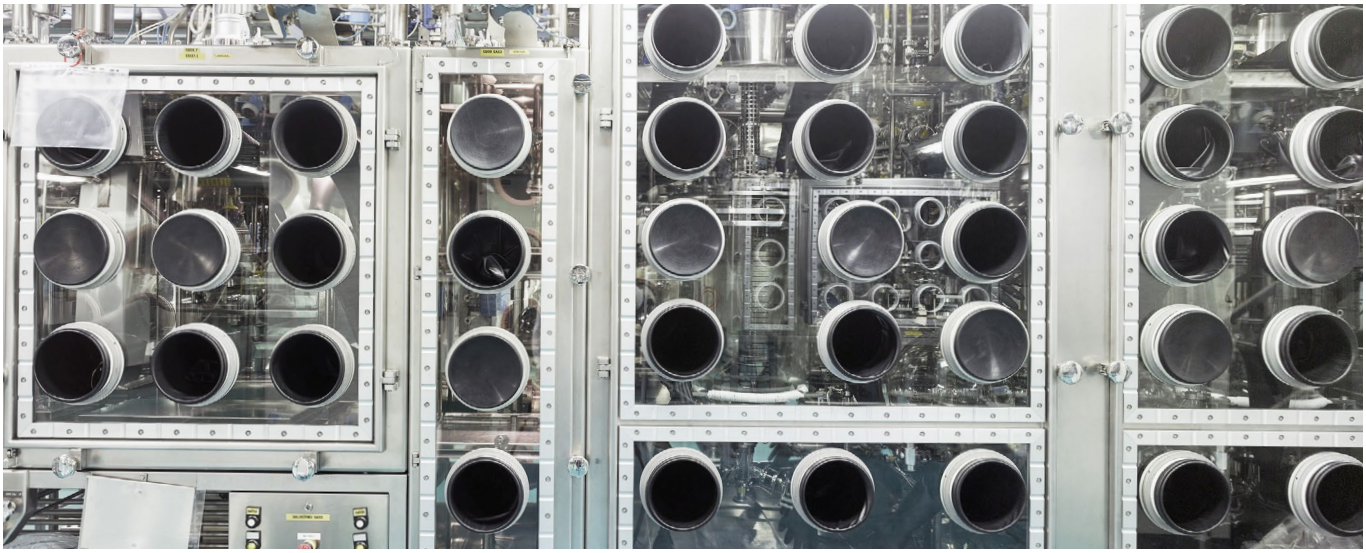
On the other hand, concerns are growing about quality lapses, Good Manufacturing Practice (GMP) violations and compromised data integrity at low-cost manufacturing plants for APIs: those concerns have revived demand for reliable sources of supply in the US and Europe.

Sourcing APIs from economically attractive

locations such as India or China hasn't got so appealing anymore in recent years mainly due to quality and safety issues. It's not by chance that regulatory agencies in the US, and other markets highly dependent on outsourced or offshored pharmaceutical production, have stepped up scrutiny of manufacturing facilities abroad.

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 there are cases not only of weak data collection, processing and storage, but also of deliberate violations and data falsification.

HIGH QUALITY HPAPIS: AN INCREASING DEMAND



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

Estimates for the size of the global HPAPI market vary, but most analysts agree that strong growth can be expected over the next 5–10 years. MarketsandMarkets™ estimates that the global HPAPI market will expand at a compound annual growth rate (CAGR) of 8.7% from $17.72 billion in 2018 to $26.84 billion in 2023 (MarketsandMarkets™, *"High Potency APIs /HPAPI Market worth 26.84 Billion USD by 2023," Press Release, April 2018)*.

Given such a scenario, the market is increasing its demand of high-quality HPAPIs and pharma companies are more frequently outsourcing to specialized CDMOs, given the need for specialized technologies and a high reliability of supply.

A large portion of the HPAPI market serves demand for highly potent cancer drugs: the rapid expansion of the global oncology market indicates where HPAPIs are going, as populations age, new therapeutic options extend survival rates, and cancer drug candidates dominate pharmaceutical R&D pipelines.

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. IQVIA says that a total of 63 new cancer drugs have entered the market within the past five years.

On the other hand, advances in drug development have generated more targeted and potent drugs, and also antibody-drug conjugates, with fewer side-effects, again in the fields of oncology and also for other age-related or chronic diseases. This has fueled strong market demand and growth for HPAPIs worldwide as well.

FACING MANUFACTURING CHALLENGES OF A HIGH-QUALITY HPAPIS PRODUCTION

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

Upgrading existing API facilities requests specialized containment provisions to make sure employees and their environment are protected from exposure to toxic substances. Such a choice, instead of investing in brand new capabilities tailored specifically to HPAPIs, may be not very cost-effective. Manufacturers must also face the need 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/m^3 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 especially for early stage NCEs (in such a case, a conservative approach has to be adopted having in mind the safey first).

Indeed, 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.

INNOVATIVE TECHNOLOGY AND QUALITY FOR A REAL COMPETITIVE EDGE

Given the challenges emerging in the global market for HPAPIs, CDMOs have to face the manufacturers' increasing requests of expertise, safety and high quality products.

Indena, the world's leading company in the identification, development and production of active principles derived from plants, for use in the pharmaceutical, health-food and personal care industries, has being investing for years in innovative technologies and services, to further broaden its technological offer.

As a strategic approach, Indena treats other companies as partners rather than customers: that's why the company is able to offer a full commitment in order to develop new HPAPIs from early clinical stages up to commercial manufacturing.

The last important investments of Indena are related to recent new plants at its Settala main production site: a kilolab dedicated to HPAPIs and two more new suites.

The new kilolab dedicated to HPAPIs (natural, semisynthetic and total synthetic) has been opened at the beginning of 2018. The kilolab is designed to handle the production of toxic substances endowed with an Occupational Exposure Limit (OEL) of 20 ng/m^3. This investment complements the already existing large scale suites and is capitalizing on more than thirty years of experience in handling HPAPIs.

Moreover, in 2019 the company will inaugurate two new suites: a pilot pharmaceutical plant for small scale GMP productions and a new spray drying system, both available from next June.

The new Indena's pilot pharmaceutical plant will summarize all the technologies available at the company, but will be dedicated to productions requiring a smaller scale (hundreds kg/year)

and a higher flexibility. In this way, Indena will be able to produce APIs for clinical trials (up to phase 3) and for small commercial requirements, assuring a complete compliance with cGMP guidelines. The new plant will work for extraction, chromatographic purification and synthesis. Equipped with hastelloy, glass lined, stainless steel reactors, the new pilot plant can manage processes at a temperature ranging from -80°C to +200°C; reactors capacity ranges from 200 to 1000 liters, suitable for batches from few kg to 30/50 kg of APIs.

The second suite Indena is about to complete is a PSD2 spray dryer. It will complement the existing equipment devoted to large scale spray drying from organic solvents, an activity the company has been carrying out for more than 20 years.

The PSD2 new spray drying system is a medium size equipment for clinical and commercial needs.

The new equipment can handle organic solvents and is designed to carry out the production of APIs and pre-formulated APIs (through spray drying in the presence of excipients) with an Occupational Exposure Limit (OEL) of ≥10 µg/m³. The new spray dryer will be completed with ancillary equipment to manage all the production processes, including secondary drying, sifting, blending, packaging, thus supplying a complete service. Full analytical capabilities are supporting the spray drying activities.

A further expansion is already planned and foresees the installation of another new smaller spray dryer (evaporation rate of 2 kg of water per hour), able to handle APIs with an OEL of ≥1 µg/m³.

On top of that, a multipurpose fermentation plant, suitable also for toxic APIs, from 1000 to 20000 liters is also available.

THE IMPORTANCE OF A WELL TRAINED STAFF

In such a high-risk area as HPAPI production, the deep preparation of the staff who manages and handles HPAPIs on a routine basis is such important as the quality and efficiency of the equipment and the facilities.

From Indena's point of view, the "human element" – meaning highly qualified, motivated and trained technical staff – as well as corporate culture strongly oriented to quality and to tight HSE policies are the two fundamental requirements to ensure that HPAPI operations run safely, seamlessly and efficiently.