Fine chemicals

Stringent regulations prompt return of manufacturing to the West

Pharmaceutical ingredient manufacturers are witnessing a rise in demand, and they remain positive about the near-term outlook for the industry. Increasingly stringent regulations on manufacturing standards, however, are causing some manufacturing to return from Asia to the West. Nevertheless, companies in countries such as India do not see their roles diminishing, and they expect to be crucial in the worldwide industry in the future.

Industry players and experts say that the environment in the pharmaceutical ingredient manufacturing industry is positive yet challenging. The European Fine Chemicals Group (EFCG; Brussels), an industry association that forms part of Cefic, says, "The environment is positive as increasing API [active pharmaceutical ingredient] business is being reported as innovator and generic customers are moving [away from] total dependency from Asian suppliers, plus there are new outsourcing opportunities. The environment is also challenging because of the need to be compliant with continuing regulatory changes globally and where new investment decisions are needed to cope with the extra demand," says Tony Scott, adviser at EFCG. Formed in 2004, EFCG is the representative body for Europe-based producers of fine chemicals.

Demand for APIs "continues to grow at a consistent rate, while the supply of APIs manufactured with international GMP [good manufacturing practice] standards and world-class documentation is not keeping pace with this demand," says Aditi Kare Panandikar, managing director of Indoco Remedies (Mumbai). "The scenario remains challenging due to competition that exists in 'me-too' molecules." A me-too drug is a compound that is structurally very similar to already known drugs manufactured and marketed by a large number of companies. "The competition in the me-too segment has kept the prices and profitability under check. However, there is an emerging trend to offer novel polymorphs, noninfringing processes, with new molecules that are yet to go off-patent. This trend has helped in creating a niche to command a price that would improve profits to support innovation via R&D and sustain the investments made in maintaining high GMP and regulatory standards," Panandikar says.

Indoco Remedies, which was established in 1947, is a manufacturer of APIs and finished-dosage forms for various therapeutic segments. "Unlike most Indian pharmaceutical companies who commenced their business with APIs and then forward integrated into formulations, Indoco started with the finished-dosage form business and forayed into API business as a backward-integrated

initiative to support its captive demand," Panandikar says. "Having fulfilled our captive demand, we are now registering our APIs with regulatory authorities across international markets and are also undertaking audit certification by major international regulatory bodies for GMP standards. The multiton API facility at Patalganga, India; and the API kilolab at Rabale, India, have already been inspected and approved by the US FDA and Australia's [Therapeutic Goods Administration]."

Indoco's total sales in the fiscal year ended 31 March 2014 grew 15% compared with the previous fiscal year, to 7.17 billion Indian rupees ($116.5 million). The company's API business reports growth of 34% in annual sales, to Rs460.0 million. Indoco expects to grow its revenue further.

"Indoco's captive consumption of APIs will rise significantly in the current fiscal year. As a result, in value terms to third-party consumers, the growth is likely to rise by 20–25% in the current fiscal year," Panandikar says. "We continue to focus on [supplying APIs to] large, multinational pharmaceutical companies, however, these companies take a substantial amount of time to qualify a new vendor in order to comply with elaborate regulatory processes. Indoco also intends to launch at least three to four new generic molecules every year and file DMFs [drug master files] with the US FDA and other international authorities at least three to five years before these molecules go off-patent," Panandikar says.

Indoco says that it is planning to expand capacity at its Patalganga API facility. The company has not divulged further details about this project.

Indoco and DSM entered into an agreement in 2012 to commercially cooperate on eight APIs. APIs manufactured by Indoco will, under the terms of the deal, be marketed and sold by DSM, and the alliance leverages Indoco's product-development and manufacturing capabilities, as well as DSM's market access. "The alliance is working in the right direction, though it has not yet yielded meaningful results. We have streamlined our activity under the alliance to achieve faster results and expect it to deliver results in the next three to five years," Panandikar says.

FDA has since 2013 issued warning letters to several API manufacturers in India for deviations from cGMP. These letters have has been a blessing in disguise, Indoco says. "Despite the warning letters to some manufacturers, India still continues to have the largest number of FDA-approved production sites outside the United States for APIs and finished drugs. The possible reasons for these warnings are a lack of training and knowledge of the staff on the shop floor or the analyst in the lab and, in a few exceptional cases, could even be due to the lack of awareness of shop floor activities at the top management level. However, most companies have implemented corrective measures, keeping in mind the long-term business potential in the US market. These warning letters have also turned out to be blessings in disguise for API manufacturers in India as [they have] provided huge insight, especially in terms of systems and documentation expected," Panandikar says.

PANDIKAR: *Planning API capacity expansion.*

ROTTHIER: *Alarming signals in antibiotics business.*

The outlook for the pharma ingredient manufacturing industry in India is positive because the country will remain a manufacturing hub for APIs, Indoco says. India's API industry faces a challenge, however, on account of extraordinarily high manufacturing-site fees and DMF trigger fees levied by the US FDA and with the need to bring in discipline in the organizational culture to keep pace with stricter regulatory standards, Indoco says.

DSM Sinochem Pharmaceuticals (DSP; Singapore) says that it sees "alarming signals" in its core business. DSM and Sinochem completed a deal in 2011 to establish DSP as a 50-50 joint venture for DSM's former anti-infectives business. Sinochem acquired a 50% stake in the anti-infectives business for €210 million ($243.0 million), creating DSP. The jv develops, produces, and sells raw materials, intermediates, and APIs for anti-infectives, such as antibiotics and antifungals, and APIs for other therapeutic classes, such as cholesterol-lowering medicines.

"DSP's core business is antibiotics, and I see alarming signals there," says Karl Rotthier, president of DSP. "I see a storm of policy and stakeholder pressure developing around the antibiotic supply chain. Issues such as [antimicrobial resistance], pollution from production plants, product-quality concerns, and security of supply are all driving increased business risks," Rotthier says.

DSP recorded sales of €368.0 million in 2013 and expects to improve its financial performance. "Excluding the exchange rate impact and despite a challenging business environment, DSP improved its performance compared to previous years in 2014. We saw robust sales growth versus 2013 due to our value strategy and modest volume growth. While 2015 will be another challenging year, I expect this trend to continue, as I see further growth in all our products and our new business initiatives, such as the opening of our new statins plant in India and our drug product endeavors starting to contribute visibly," Rotthier says.

DSP started up a production facility in the second half of 2014 at the company's site at Toansa, India, to manufacture the API atorvastatin using DSP's proprietary biotechnology route. Atorvastatin is the generic version of cholesterol-lowering drug Lipitor. "The new facility will help to meet the increasing strong demand for DSP's atorvastatin and build a strong position in defined therapeutic segments, such as cardiovascular. In 2014, DSP produced the API rosuvastatin, which is the generic version of the cholesterol-lowering drug Crestor, with the help of manufacturing partners. In the course of 2015, we will start the supply of rosuvastatin API from our own facility [at Toansa]," Rotthier says.

DSP intends to strengthen further the company's beta-lactam antibiotics business, expand the API portfolio, and move forward selectively into drug products or finished-dosage forms. "We are continuing to grow our API portfolio and added new beta-lactam molecules, such as cefaclor," Rotthier says. "I believe sustainable enzymatic production, or green chemistry, as it is also called, is the future of antibiotics manufacturing."

DSP says that the near-term outlook for the pharma ingredient manufacturing industry is positive. "We very much believe in the future of the pharmaceutical ingredient manufacturing industry; but, manufacturers must adapt to the changing economic environment and the increasingly stricter environmental and regulatory laws," Rotthier says. "We expect a further increase in regulation in all markets in the coming years. China, for example, introduced a new environmental law on 1 January, and we already see the effects of that with producers coming under increased scrutiny from authorities and regulatory bodies and

having to invest to upgrade or install adequate systems for environmental protection to be in compliance. We also expect stronger environmental regulation in other countries, as governments move to ensure companies do not pass on parts of their production costs to society but manufacture in a sustainable and responsible way," Rotthier says.

A BASF pharma ingredients and services subsidiary produces a range of APIs and excipients and provides exclusive synthesis services for the pharmaceutical industry. BASF does not disclose the annual sales of this business but says, "We are confidently within the top suppliers of excipients, bulk APIs, and custom synthesis services, and we target to grow above the growth rate of the market."

The environment in the pharmaceutical ingredient and excipients industry "continues to be challenging and competitive due to the ever-increasing expectations and needs of the regulators and our partners," says Daniele Piergentili, v.p./global marketing, R&D and head/North America at the pharma ingredients and services segment. "However, we are optimistic that BASF's solution platforms, i.e. for skin delivery or solubilization, have a continued value proposition in the market." BASF's skin-delivery platform provides services and materials for delivering drugs to or through the skin.

"BASF['s pharma ingredients and services segment] will continue to expand and strengthen its excipients' solution platform with new products and new capabilities," Piergentili says. BASF says that it is planning to expand production capacity for its polyvinylpyrrolidone (PVP) excipients. Further details of this planned capacity expansion have not been disclosed. BASF manufactures PVP excipients at Geismar, LA; and Ludwigshafen.

"In addition, we will maintain our commitment to serve and grow with generic and originator companies with key products, such as omega-3 fatty acids and ibuprofen. As the pioneer in the field of omega-3 fatty acids, innovation will be a key focus in further developing our API portfolio," Piergentili says..

BASF says that collaborations are also crucial in its growth strategy. "Collaborations with technology leaders in the industry are increasingly important to overcome some of the major challenges formulators are facing today," Piergentili says. BASF is working with Bend Research (Bend, OR) jointly to develop solutions to enhance the solubility and bioavailability of poorly soluble drugs. Bioavailability is the measure of the amount of drug that is actually absorbed from a given dose. BASF also continues to work with Catalent Pharma Solutions (Somerset, NJ) to provide products and services to overcome bioavailability challenges of new molecular entities with solubility or permeability issues.

"Despite all the challenges, the pharmaceutical ingredients and excipients industry is a growing and profitable market. Key[s] for success will be a right mix of products and technologies and a close eye on costs and competitiveness," Piergentili says.

EFCG says that more than 70% of all APIs currently sold in the European Union are produced at non-EU sites. Echoing the views of API manufacturers interviewed by *CW* during the CPhI trade fair, held in Paris last October, EFCG confirms that its members are observing a trend of API manufacturing returning from Asia to the West for various reasons,

including issues related to regulatory compliance in countries, such as India. The European Union's Falsified Medicines Directive (FMD), which came into force in July 2013, is designed to minimize counterfeit medicines entering the EU market. FMD introduces two options for overseas API producers to inform EU authorities of the quality of imported APIs: being listed by the European Commission or sending a "written confirmation." About 1,500 non-EU sites are identified in the top 18 countries exporting bulk APIs to the European Union, and most of them issue written confirmations, EFCG says. Authorities in China and India have limited the number of sites allowed to export to the European Union via written confirmations, and the European Union has prevented has certain Indian sites reported to be noncompliant with EU GMP from exporting to the EU market, EFCG says. EFCG members have picked up new business as a consequence of FMD, EFCG says.

EFCG aims to help create a more level playing field in the worldwide API manufacturing industry, and to achieve this, EFCG "keeps advocating to the main Western regulators—the European Commission, European Medicines Agency [(London)], and the US FDA—to maintain high levels of GMP manufacturing and distribution standards and to align them wherever possible and, via mutual recognition agreements, to seek the same high standards with other regulators on a country-by-country basis," Scott says.

Regulations are helping to achieve a level playing field, but more needs to be done, EFCG says. "EFCG believes that whilst the FMD has reduced some of the risk to patients from substandard/counterfeit APIs and medicines, more needs to be done to level the playing field by checking industry self-regulation and by harmonizing regulations where possible," Scott says. Mandatory inspections of API sites in the European Union are performed by EU regulatory authorities, but there are no mandatory inspections of non-EU API sites.

EFCG proposes that the EU commission should reconsider the case for stricter enforcement of the FMD and related directives by the EU authorities with tough sanctions to punish offenders; employ more EU inspectors and train all inspectors to improve detection of falsification and fraud; ensure a more harmonized approach to the transposition of the FMD by EU member states; subject APIs imported as finished/semifinished products to the same rules as for bulk APIs; and change the FMD to include mandatory GMP inspections by the EU authorities of all API sites supplying the European Union irrespective of their location and paid for by industry, as is the case with FDA's Generic Drug User Fee Amendments (GDUFA), or arrange mutual recognition agreements with countries that have EU GMP standards.

GDUFA became effective on 1 October 2012. It is designed to speed public access to safe and effective generic drugs and reduce costs to industry. The law requires industry to pay user fees to supplement the costs of reviewing generic drug applications and inspecting facilities. The program also ups the number of inspections of US and overseas manufacturers of generic APIs and finished pharmaceuticals.

FDA announced last year the rate for the generic-drug API and finished-dosage forms facility user fees for fiscal 2015. These fees became effective on 1 October 2014 and will remain in effect through 30 September 2015. The total estimated fee revenue for fiscal 2015 is about $312.2 million. The total number of API facilities identified through the self-identification process, mandated in the GDUFA, is 795. Of these, 103 are domestic facilities and 692 are foreign facilities, FDA says. The total worldwide API-facility fee revenue is expected to be $43.7 million in fiscal 2015. The domestic API-facility fee is $41,926, and the foreign API-facility fee is $56,926.

PIERGENTILI: *To expand PVP excipients production.*

SCOTT: *Members gaining new business due to FMD.*

FDA says that it is on track to meet all GDUFA goals. "One of the goals of GDUFA was to achieve parity of risk-based inspection frequency across foreign and domestic geographies, and the FDA was and is committed to achieving this goal. The Food and Drug Administration Safety and Innovation Act [(FDASIA)], which includes GDUFA, made several changes that are helpful to this end," FDA says. "The FDASIA and GDUFA both emphasize and require risk-based inspection paradigms, which replace the prior, time-based,

CLOSER TIES: *US FDA commissioner Margaret Hamburg (l.) talks to Chinese pharmaceutical executives.*

inspection regulations. FDA is implementing these required changes, which will benefit public health."

About 80% of APIs and 40% of finished drugs in the US market come from outside the country, FDA says. FDA has been intensifying efforts to work with its counterparts in China and India and to increase its presence in these countries. FDA commissioner Margaret Hamburg visited China in November 2014. "A key reason for the trip is the important and growing collaboration between FDA and its counterpart agencies in China to ensure the safety of the large volume of foods and medical products exchanged between our two nations. China is the sixth-largest provider of drugs and biologics to the United States," FDA says.

FDA currently has 13 staff members stationed in China, primarily in Beijing, and they help to ensure that the food and medical products being exported from China meet FDA standards. "Given the volume of US trade with China, we are working to more than triple the number of American staff we place in China. Placing more FDA experts in China will allow FDA to increase significantly the number of inspections it performs in this dynamic, strategic country as well as to be more effective partners with our colleagues in China. Such dramatic staffing increases will also allow FDA to enhance its training efforts and technical collaboration with Chinese regulators, industry, and others," FDA says.

FDA also signed an implementing arrangement with the China Food and Drug Administration (Beijing) to help frame the work that FDA inspectors will do in China and create mechanisms for collaboration on inspections.

Hamburg also visited India in February 2014—her first official trip there. Hamburg, during the visit, signed a statement of intent that allows FDA and Indian regulators to collaborate. FDA said last year that it had received approval from the Indian government to add 7 drugs investigators, which will increase its presence to 19 US staff based in India, including 10 dedicated to drugs. **—DEEPTI RAMESH**