CDMOs: Endless summer?

Pharmaceutical CDMOs are still extremely bullish about the state of business now and for the foreseeable future. Andrew Warmington spoke with industry leaders at CPhI Worldwide 2019

Business leaders are not known for talking down the state of business but when everyone is overwhelmingly positive for years on end, it has to be true. For at least six years, pharmaceutical CDMOs with a base in Europe and North America have thrived. Their outlook at CPhI Worldwide in Frankfurt on 5-7 November was no different.

The main reason is the bulging drug pipeline. Last year saw a record 59 FDA approvals – 42 new molecule entities (NMEs) and 17 biologics. A growing proportion of this coming from small companies, who do not have – and never will have – manufacturing capabilities and who therefore look to CDMOs. These companies continue to find venture capital and IPO funding reasonably easy to access.

According to FDA and GlobalData industry analyst Adam Bradbury, a record 43 drugs in 2018 had one or more expedited reviews, while 34 orphan-designated drug NMEs were approved and 65% of these were outsourced. This was a record high. Of the NMEs, 23 had fast track status, significantly more than in 2017. And 70% were outsourced, partly because so many were developed by small and medium-sized pharma companies. These trends will continue, creating further opportunities in the short term, Bradbury said.

Meanwhile, Big Pharma is outsourcing ever more of its manufacturing needs as it focuses on R&D at one end of the chain and sales and marketing at the other. This partly reflects a choice to invest in biological manufacturing, even though growth rates for large molecules are not much faster than those of small molecules.

As Stuart Needleman, chief commercial officer at Piramal Pharma Solutions, remarked in Frankfurt: "I've been hearing about how biologics are the future for 25 of the 38 years I have been in this industry but I still think small molecules are going to be big. The future is still small molecules in our space, particularly in orphan drugs."

Back from China

Another major driver has been the 'China effect'. This began years ago as customers who took their business to Asia learned that low prices did not always mean low costs, leading to a 'flight to quality'. The process has accelerated immeasurably now that China has started closing down vast swathes of its coastal chemicals industry for environmental reasons.

Even the best facilities are not safe, should they be located in a chemical park that closes because of a single 'bad apple'. Pharma companies in particular cannot risk being left with only a single supplier and some who thought they had two have found that they did not. They increasingly want starting materials and intermediates from Western suppliers who can offer – and document – long-term security of supply.

Add to this the increasing complexity of molecules – by some estimates, the average number of steps has doubled from eight to 16 in the past decade – the compressed timelines for low volumes and accelerated approvals, and it all adds up to a rosy picture, albeit

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Future investment plans include highly potent solid dosage forms at Plankstadt, continuous manufacturing at Chenôve, France, and large-scale solid phase peptide synthesis capacity in Colorado, as well as HPAPI development capabilities. The company will look to further expand its network, acquiring new sites that fit with its needs in technology terms.

Asia to US

In the past year, Korea's SK acquired Ampac Fine Chemicals and incorporated all of its pharma-facing businesses into a new entity called **SK Pharmteco**. The former BMS launch site for new molecules at Swords, Ireland, is part of this, as SK Biotek Ireland. Existing identities and cultures are being maintained.

"We hosted a lot of meetings here at CPhI and they have been very productive with regards to customer commitment to sending projects to us", said CEO Dr Aslam Malik. "We also had a lot of customer-based production meetings and a lot of people showing up at our customer-only event."

As with most CDMOs, the company was seeing Big Pharma, biotechs and virtual pharma about all kinds of projects. "Things have really picked up a lot. Some projects that we used to consider small or early phase are now moving so fast through the FDA approval process, they are leaving rubber marks on the road," said Malik.

Molecules are becoming more complex, with more steps, and thus more likely to need services like chiral chemistry or Ampac's specialities, like simulated moving bed chromatography and energetic chemistry. The FDA now increasingly demands validation earlier in the process: seven to eight steps might be done under cGMP, driving customers to CDMOs for their R&D and engineering capabilities as well as manufacturing.

In addition, added Patrick Park, VP of business development, starting materials are becoming more complex and have to be custom-made. Ampac and other CDMOs are thus having to back-integrate. Additional capacity has been added at Swords and the ex-Boehringer Ingelheim site in Virginia. The firm is also adapting its heritage in continuous processing from the aerospace and oil and gas markets to the smaller volumes and shorter timelines of pharma.

Based in China and the US is WuXi AppTec subsidiary **STA Pharmaceutical**. Dr Xiaoyong Fu, senior VP for API development and commercialisation, said that the company's business is being driven by the same tailwinds as the market in general.

Strong demand from customers, notably in oncology and orphan drugs, is a more specific driver, as are new modalities, such as oligonucleotides and peptides. STA has greatly expanded its peptides and oligonucleotides capacity lately and can handle both solid and solution phase manufacture, unlike most specialised oligonucleotide or peptide CDMOs.

The company is also expanding its API capacity in China. "Every year we add one or two plants into our operations, so we have very big expansion plans," said Fu. "We are also adding to our capabilities, such as various delivery technologies in oral solid dosage form. We are a true CDMO, active the whole way through the development chain to the commercialisation stage."

STA, he added, is also investing in technology capabilities, notably HPAPIs, biocatalysis and flow chemistry. The focus is mainly on using flow to solve technical, chemistry and safety challenges that arise in batch, rather than trying fit particular reactions into flow.

Since the show, STA has been named as the preferred CDMO partner for Impact Therapeutics, a Chinese clinical-stage biopharmaceutical company. This will cover the entire product development process for Impact's pipeline of oncology drugs.

Indian summer

Also rooted in Asia but with extensive Western assets is **Piramal Global Pharma**. New CEO Peter DeYoung said that the company "is seeing really robust demand for our services and offerings". It is investing particularly in four differentiated areas, all anchored in Western facilities: ADCs, sterile fill-finish, HPAPIs and APIs for emerging pharma in the early stages.

Investment will soon take place at Aurora, Ontario, for a major expansion. This is particularly targeted at customers moving compounds into Phase III and seeking certainty of supply. The engineering work is done and it should progress early next year at the latest.

"We are seeing exponential growth in integrated projects across these sites," said DeYoung. "A lot of that is about reducing complexity and improving speed, and it comes from both emerging and large companies. It's really about speed to market more than accelerated approvals as such. The other advantage we can offer is back-integration into our facilities in India."

Kantipudi – China effect also helping India

PATIENTS AT THE HEART OF IT

Piramal Pharma Solutions has become the first CDMO to appoint a chief patient-centricity officer, in the form of industry veteran Stuart Needleman. Speaking at the launch of the CPhI Annual Industry Report, Needleman noted that this trend began in Big Pharma, with AstraZeneca and a few others creating positions like his. Hopefully, the rest of the CDMO space will also move in this direction.

Needleman – The patient is also the CDMO's customer

The concept, he said, is "about putting the patient first in an open and sustained engagement". It is linked to the development of personalised medicine but more about the fact that, ultimately, the customer is the patient. "The patient is who pays the pharma company, but is also the one who pays us."

"If you put the patient at the centre of the universe from a CDMO perspective, it changes the way you behave internally," Needleman continued. "It changes the mindset of an operator on the shop floor who goes home at 5.00 p.m. and therefore the drug doesn't get shipped and someone didn't get a vital medicine."

Traditionally the CDMO business is one step removed from the patient. If it can develop a new mindset of not going home until the job is done, said Needleman, "this should resonate with our customers and enhances our common purpose."

To achieve this, Piramal has begun inviting patients to talk to workers at its plants so that they can appreciate what their work means. It is also appointing patient awareness councils, made up of a cross-section of people at each site, to discuss what the company can do better and the metrics to measure this.

CEO Peter DeYoung added in a separate interview: "We regard patient-centricity as the logical extension to our customer-centricity. Put simply, it's sharing the same mission with our customers and understanding what motivates them, which is the patient, so we can better partner with them."

Cleaning of a nutsch filter at Saltigo's Leverkusen site

and consequent repatriation of projects is filling up capacity in the West," Blocher said.

"There are some Big Pharma mono-plants out there for sale, but they are not always useful for multi-purpose contract manufacturing. In addition, not having R&D at the same site as manufacturing is a disadvantage when processes are being squeezed so fast due to accelerated approvals," he added.

Meanwhile, oncology is an increasingly dominant part of the pipeline and China is becoming a fast-growing market for oncology drugs, albeit an unpredictable one at times of trade wars and tariffs, with price pressure on branded generic drugs and uncertainties on how pricing is handled for innovators. In the longer term, Chinese pharma companies may become a customer for Western CDMOs, Blocher said.

Saltigo is also performing well, said Andreas Klein, head of marketing and sales. Many customers are building Western-centred supply chains for starting materials, intermediates and APIs, and CDMO capacity is heavily booked. Some customers, he said, expect to see this and consequent cost pressures lead to a consolidation in the CDMO sector.

"Nobody really thinks things will go back to normal next year," Klein remarked. "Everyone is preparing for this situation to continue for three to five years or even longer, because the consolidation in China will continue and China will move to a different quality, safety and environmental standard level."

For now, it is not always easy to change from one day to the next, particularly for complex and heavily regulated products, when customers are looking for rapid implementation and long-term solutions. Saltigo is thus asking for four- to five-year commitment from customers to campaigns.

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