termsheet

October 2020
Issue 31

Heads of Terms

Invest to Divest

Dr Fintan Walton
Founder & Chief Executive

At PharmaVentures, we have spent over 28 years assisting companies in their deal making activities. In many respects, the basic fundamentals of deal making in whatever form, i.e. licensing, fund-raising and M&A , are much the same, as long as the seller has an offering that is of commercial benefit to the buyer and the buyer is willing to pay for it at a price that can be mutually agreed.

Twenty years ago, we started to advise major pharmaceutical companies in the divestment of their manufacturing facilities. Although the fundamentals of the exercise were similar to any deal making process, our clients gained a significant amount of knowledge from us about how companies can best position themselves to be successful in divesting these important assets.

One of the key lessons our clients learned is that investing in the divestment plan is really essential. This is for the simple reason that the most likely outcome from divestment is that a once operational cost-based manufacturing facility will transition to a future profitable manufacturing facility owned by a CDMO. The biggest mistake that can be made by our clients is not to understand the current and future value of the facility from both a buyer's and a seller's perspective. This can often mean that the divestment is a non-starter. This is where we can help with the important first step of a divestment process. We can provide an independent Valuation and Positioning (V&P) assessment using our advanced and robust valuation methodologies. These methodologies have been built on our considerable experience with potential buyers and from actually selling these facilities on behalf of our clients.

From such exercises, our clients can make the right decisions about the future of the manufacturing facility before they start the process of finding a buyer. Our extensive network and years of building working relationships with potential buyers world-wide mean that the divestment process can be a lot quicker and smoother. Finally, and equally important, is our ability to work seamlessly with our large pharma management clients to ensure a successful outcome.

The most basic lesson our clients have learnt over the years is that it is wise to invest in order to divest.

Industry Insight

Is Nationalism Transforming the Pharma Manufacturing Map?

The last few years have seen a rise in nationalism and populism across the world. In 2016, the US voted in the populist Donald Trump on his promise to 'Make America Great Again'. In 2018, Hungary re-elected its national conservative prime minister Viktor Orbán with the slogan ' For us, Hungary is first'. And in 2019, India re-elected its Hindu nationalist ruler, Nehendra Modi, and the UK elected (with a large majority) the Eurosceptic Boris Johnson on his pledge to 'Get Brexit Done'. Other nationalist world leaders retaining their support base include Binyamin Netanyahu in Israel, and Rodrigo Duerte in the Philippines.

A shift towards healthcare nationalism?

This shift from global to local thinking is leading to protectionism in healthcare. Trump has stated that the US will not join the World Health Organization's worldwide Covid-19 vaccine initiative, Covax. The US has also pledged to leave the WHO, declaring it corrupt. Trump's administration, in March 2020, secured priority access to Gilead Science's remdesevir, which showed effectiveness against SARS-CoV-2, the virus that causes Covid-19. The administration also reportedly attempted to acquire German company CureVac in order to get exclusive access to its Covid-19 vaccine. This raises concerns about patient access to Covid-19 vaccines and treatments in the future, particularly for low- and middle-income countries.

Bringing manufacturing home

The trend towards nationalism is happening in the manufacturing sector as well. The Trump Administration is pushing a 'Buy American' policy, to encourage American manufacturing of pharmaceuticals and to reduce reliance on overseas manufacturers, especially those in China. This drive would also include streamlining the approvals process for US-manufactured products, as well as more labelling of country of origin. The aim behind this is to encourage manufacturers to invest in domestic production facilities. Acts include the Strengthening America's Supply Chain and National Security Act, which would require companies to provide the FDA with information on the API supply chain, and the Coronavirus Aid, Relief, and Economic Security Act, which includes routes to mitigate drug shortages.

continued on page 2 . . .

Industry News

Another successful transaction

PharmaVentures is pleased to announce that it was the corporate finance advisor to **Novartis** on the divestment of its manufacturing facility in Barberà del Vallès, Spain, to **Siegfried Holding AG**, a global contract development and manufacturing organisation (CDMO).

Industry Insight

. . . continued from page 1

It's not just happening in the US. The UK's Brexit vote showed a desire to 'Take Back Control' and the NHS Federation and medical charities are calling for more drugs to be manufactured in the UK. The UK imports 75-80% of finished drugs, with India as the UK's biggest supplier. Some are also imported from Europe, which is potentially going to become more complex now that the UK has left the EU, and the end of the transition period is fast approaching on 31 December 2020 following the completion of Brexit.

In Europe, the European Fine Chemicals Group (EFCG), an association representing API manufacturers, has requested the creation of a European database for supply chains and issues relating to supply, as well as accelerated approval for alternative suppliers for APIs. It is also seeking funding to rebuild the European drug manufacturing through newer and greener technologies.

The French government is also seeking to increase production internally, and Sanofi has pledged to create a company in Europe that will allow the move of manufacturing away from Asia.

The Japanese government is providing $2 billion in subsidies to support Japanese companies with an aim to move supply chains back into the country, and is working with over 400 companies to boost domestic production.

The Indian government has announced incentives to encourage manufacturers to move there, and Vietnam, Cambodia, Myanmar, Bangladesh and Thailand are all seeing boosts. As an example, Vinatic Organics, based in Mumbai, India, saw a 25% increase in orders for an essential ibuprofen ingredient between February and May 2020, potentially as a result of companies looking to shift away from China.

An increasing dependence on outsourcing

Pharma and biotech companies have increasingly been moving from having their own manufacturing plants to outsourcing to contract manufacturing organisations (CMOs) and contract development and manufacturing organisations (CDMOs) over the last couple of decades. In the early 2000s, both biopharma companies and CDMOs came under pressure to cut costs, and manufacturing moved to Asia, particularly India and China. Here, land and facilities were cheaper, shipping and transaction costs for materials were less, and environmental laws were often not as strict. Wages were also lower, with overall manufacturing costs being 30-40% lower than those in Europe or the USA. India and China also had the manufacturing skillsets based on a history of producing generic copies of Western drugs. More recently, the 'reverse brain drain' has seen scientists and other skilled and experienced people who have been educated and trained in Europe and the USA returning to India and China.

This has resulted in an increasing dependence on India and China as a source of active pharmaceutical ingredients. In 2017, the UK MHRA estimated that Chinese manufacturers made around 40% of all active pharmaceutical ingredients (APIs) used worldwide. And in 2019, around a third of the manufacturing sites for APIs for the US market were in India or China (*Figure 1*).

This trend towards outsourcing is reflected in the rate of growth (*Figure 2*). The fastest growing CDMO market is Asia Pacific, particularly India and China, with a CAGR of 8.9%. Europe and North America have the lowest CAGR at 4.8%.

An area bucking the trend is the development role. While China and India are the major suppliers of APIs, the USA remains the biggest location for outsourcing drug development.

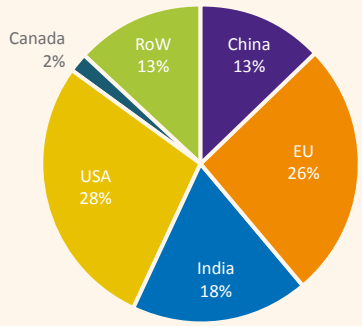
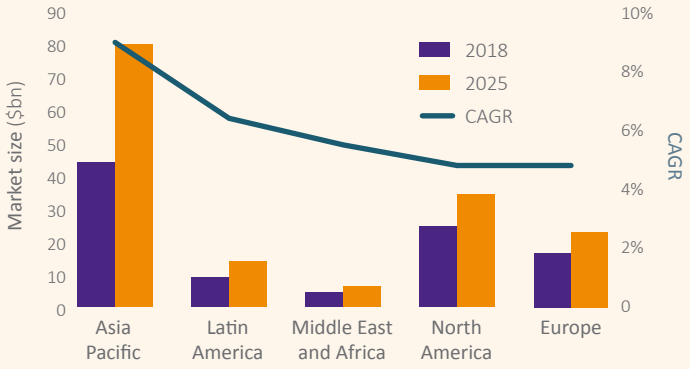


Figure 1
Manufacturing sites of APIs for US market, August 2019
Source: FDA



Market size predictions were made before the Covid-19 pandemic.

Figure 2
CDMO market by region
Source: PharmaVentures/PWC

Coming home from China

One of the reasons cited for bringing manufacturing home is the reliance on long-distant supply lines, which have been particularly vulnerable during the global pandemic. Factories in China were closed early on in the pandemic as the country moved to contain the early spread of the virus. As Indian manufacturers source the majority of their APIs from China, this had a knock-on effect to countries sourcing finished drugs from India. As a result, the Indian government stopped exporting 26 drugs and drug ingredients. But this export ban wasn't just restricted to India. During the pandemic, more than 50 countries restricted drug movements, leading to shortages and threats of shortages, which are still ongoing. As an example, in September 2020, there were 198 medicines that could not be exported from the UK or hoarded; there were 29 at the beginning of 2020. Pharmaceutical companies may be concerned about setting up agreements with new suppliers, and may lean more heavily on well-established relationships.

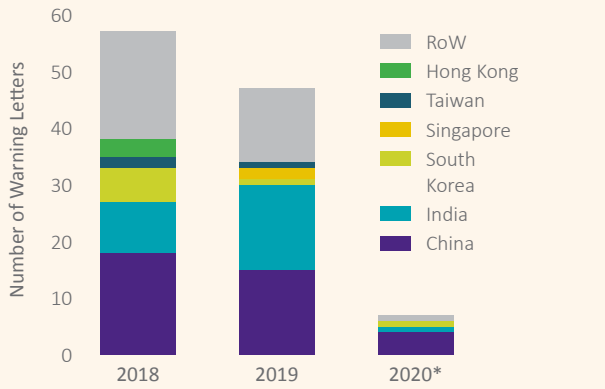
Another issue that is used in the shift towards local manufacturing is that of quality. Of the 57 warning letters issued by the US FDA's Office of Manufacturing Quality in 2018, 18 went to manufacturing plants in China and nine in India, with 11 more going to other plants in Asia. In 2019, Chinese and Indian manufacturers received 15 warning letters in each country from a total of 57, with four further in South Korea, Singapore and Taiwan (*Figure 3*).

This concern is further supported by the inspection scores given to measure a site's compliance to cGMP regulations (*Figure 4*). While India and China's scores indicate an acceptable level of compliance, they are statistically lower than the global average.

An example of quality issues in China's manufacturing base was associated with the manufacturing of valsartan and other angiotensin receptor

Industry Insight

. . . continued from page 2



* Data up to September 2020; likely to be incomplete because of the Covid-19 pandemic

Figure 3
FDA warning letters sent out by the FDA's Office of Manufacturing Quality 2018-2020
Source: FDA

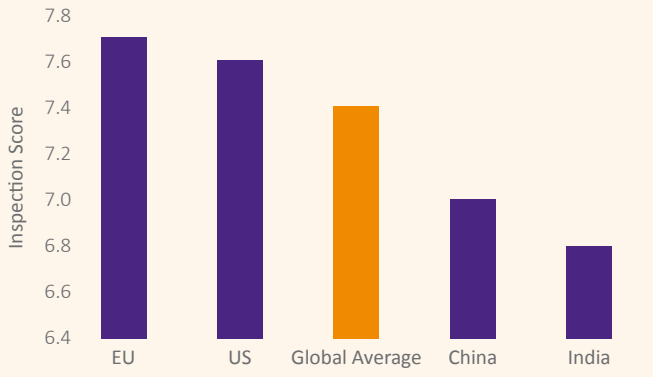


Figure 4
Inspection score
Source: FDA

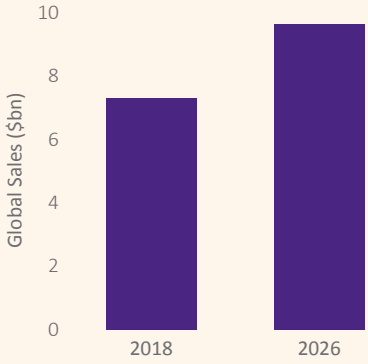


Figure 5
The value of the global ARB market
Source: Reports & Data

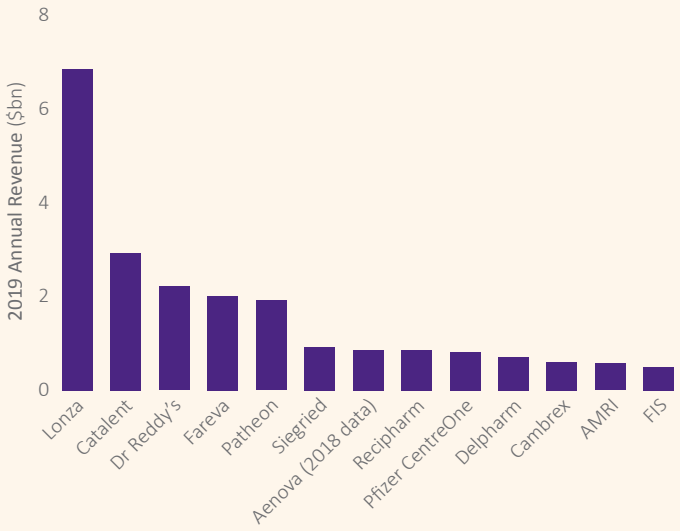


Figure 6
Selected CDMOs and CMOs by 2019 revenue
Source: Various

blockers. In mid-2018, a Chinese manufacturer, Zhejiang Huahai, detected N-nitrosodimethylamine (NDMA) in the valsartan active pharmaceutical ingredient it was manufacturing. Also known as dimethylnitrosamine, it is found in low levels in cured meat, fish, beer and tobacco smoke. NMDA is a potential human carcinogen at low levels, and can damage the liver at higher levels. The levels found in drugs pose a very low risk of cancer, but the European Medicines Agency, the Food and Drug Administration and other health authorities cracked down on the generics manufacturers, with drug recalls, withdrawals of authorisation and measures to stop distribution. NMDA and another impurity, NDEA (N-nitrosodiethylamine) were also founds in other angiotensin II receptor blockers (ARBs), including losartan and irbesartan. Companies and repackagers affected by the contaminated valsartan also made voluntary withdrawals. To reduce shortages, and the knock-on effect on drug prices, the FDA accelerated the approval of a new generic valsartan.

The angiotensin receptor blockers market is a very valuable one (*Figure 5*), predicted to grow at a CAGR or 3.5% between 2018 and 2016. This is driven by increasing levels of obesity, diabetes, kidney disease and hypertension. Shortages of ARBs because of drug recalls would have a huge impact, particularly in Western markets where the levels of obesity and hypertension are increasing.

Nitrosamine impurities have also been found in ranitidine, used to treat peptic ulcer disease, gastroesophageal reflux disease, and Zollinger–Ellison syndrome, and the antidiabetic medication metformin. There were recalls of certain lots of both drugs. In 2020, all marketing authorisation holders were asked by the CHMP to review all their drugs for the presence of nitrosamines, and look into their manufacturing processes.

Ironically, making improvements can also lead to shortages. In 2018, China's State Council released its 2018-2020 'Three-Year Plan on Successful Defence of Blue Sky', also known as the Blue Sky Action Plan, to curb air pollution. This tightening of environmental controls led to plant closures and increases in costs, as well as issues of low stocks of certain drugs.

Reshaping of the CDMO landscape

The CDMO global market is very fragmented (*Figure 6*). While a handful of companies have very high annual revenues, the five leading CDMOs hold just 15% of the market share. Around three-quarters of CDMOs have annual revenues of less than $50 million.

The sector has been consolidating, with a shift towards bigger pharma companies simplifying their supply chain, seeking one-stop-shops and forming more strategic-based relationships. In response, CMOs and CDMOs are expanding their remit in response to the needs of the pharma and biotech industries, by becoming beginning to end service suppliers. They are reaching this goal by acquiring smaller companies to gain expertise, or to enhance their strength regionally. The consolidation trend is similar to that seen with clinical research organisations (CROs), which used to be equally fragmented, but now where the top five companies now account for 70% of the market share.

Industry Insight

. . . continued from page 3

Looking at some of the mergers and acquisitions over 2019, there are examples of European or US companies expanding domestically or regionally, potentially to secure manufacturing away from China:

- Recipharm (Sweden) taking over Consort Medical (UK)
- MercachemSyncom (Europe) buys Dutch facility from Alcami (USA)
- Olon (Italy) acquiring CapuaBioservices (Italy)
- LGM Pharma (USA) acquiring Nexgen Pharma's development and manufacturing operations (USA)
- Thermo Fisher Scientific (USA) acquiring Brammer Bio (USA)
- Catalent (USA) acquiring Paragon Bioservices (USA)

However, the locations gaining from the shift away from China may not be the USA or Europe. In 2019 there were deals where Asian companies acquired assets in the West, for example:

- SK Holdings (South Korea) combining SK biotek (South Korea), SK biotek (Ireland) and AMPAC Fine Chemicals (USA) to form SK pharmteco
- Hitachi Chemical (Japan) acquiring apceth Biopharma in Germany
- Seikagaku (Japan) acquiring Dalton Chemicals Laboratories (Canada)
- Fujifilm (Japan) acquiring Biogen's biologics manufacturing site in Denmark
- Fujifilm expanding its Texas, USA site
- Strides Pharma (India) acquiring the only FDA-approved integrated soft gel capsule manufacturing facility in the USA from Micelle
- Piramal Enterprises (India) acquiring G&W Laboratories' drug manufacturing facility (USA)

Chinese CDMOs are looking to secure non-Chinese sites, which may be an attempt to gain a stronghold in an area where the manufacturing quality is higher. As an example, WuXi Biologics (China) took over Bayer's plant in Leverkusen, Germany, for its own use but also to provide backup supply for Bayer's haemophilia drug Kovaltry if needed.

There are still some companies outside the Asia-Pacific looking to the region, but with a focus on India:

- Zentiva (Czech Republic) acquiring Sanofi's manufacturing facility in India
- Olon (Italy) acquiring a manufacturing facility in India

There has also been increasing interest from private equity companies in CMOs and CDMOs, for example Ampersand Capital Partners acquiring German company Vibalogics.

Covid-19 may also affect the timing of mergers and acquisitions between CDMOs, as agreements underway are delayed by agreements and due diligence taking longer to conclude. It will be interesting to see, as data emerges over a longer term, whether the pandemic will make companies more cautious about seeking mergers and acquisitions, or more keen to enter into deals that provide a greater security and economies of scale.

Finding the solution

There are concerns about depending on a single country or region for supplies of something as critical as finished drugs or APIs, as anything that affects that region, be it an outbreak of disease, a war, or an internal uprising will make the supply lines for APIs or finished drugs vulnerable to disruption.

It is too early yet to see if the response to the concerns about manufacturing in Asia driven by quality issues and the global pandemic will drive a major shift away from Asia and back to domestic markets, or whether it will simply mean a reshuffle that maintains the diversity of suppliers, but just in different locations. The security of diversity of sourcing, reducing the dependence on a single country, needs to be balanced with the confidence of sourcing locally. Changes in manufacturing technologies, however, could help to make it financially worthwhile to bring domestic manufacturing back. This would mean a shift from traditional batch production to the lower-cost continuous manufacturing and 3D printing, and requires greater flexibility.

As the demand for personalised medicine increases, pharma and biotech companies need to be able to produce a broader portfolio of shorter run drugs, whilst keeping costs down. Pfizer's approach is its portable, continuous, miniature and Modular (PCMM) development and manufacturing approach, based around prefabricated modules, known as PODs. The PODs are different parts of a pharmaceutical continuous manufacturing line, such as clean rooms or control systems, which can be put together as needed for operation on site. Once a project is completed, the self-contained and autonomous modules can be redeployed as needed. The lead time from planning a new facility to assembly on site is less than a year, providing flexibility to take advantage of new manufacturing technologies, reducing the time to market for a new drug, or allowing companies to work with changes in demand. Technologies like Pfizer's PCMM could also allow a number of pharma companies or CDMOs to share utility overheads in a large warehouse, while retaining confidentiality within their own PODs.

Download the full white paper

Industry Insight

Data Room Structure Guidance Notes for N-Site

At PharmaVentures, a data room is used as a location to store essential documents that are needed during an M&A or Divestment transaction. It is an essential part of the due diligence process which interested buyers' access prior to closing a transaction. We routinely use Virtual Data Rooms (VDR) from third party providers of which there are many. All provide similar functionality, but three essential features are the ability to permission document access to an individual user level, feedback on user activity and a copy of all activity that took place in the VDR as an audit trail.

Download the full white paper

Industry Insight

InSights

Overcoming Divestment Challenges

In this special edition of PharmaVentures Insights, we explore the challenges faced by pharmaceutical companies during the manufacturing divestment process, and how to accelerate the divestment process to achieve a successful outcome.

Paul Larsmon spoke with leading experts including:

Mark Bamforth, President and CEO, Arranta Bio
Stéphane Lepeu, Directeur Général Délégué / Chief Commercial Officer, DELPHARM
Jansen Jacob, Vice President, PharmaVentures.

Watch the interview now

Talk to us

Before your next divestment programme, simply talk to our globally experienced M&A team, who will:

- Demonstrate how our experience and depth of knowledge gained advising on over 40 site divestments globally can benefit you and your team
- Connect you with the buyers actively looking for R&D or manufacturing operations within your space
- Discuss your business needs, any challenges you face, and how the proper process should be tailored for your company to ensure your site is divested safely
- Advise you on how to safeguard the security of supply and retain jobs to ensure consistent high-quality production continues
- Support you through the complexities and manage the divestment process to provide extra resource as and when you need it to determine the right deal terms for the best return

divestments@pharmaventures.com

Conference Update

- **CPhI: Festival of Pharma**
  Virtual Event, 5 – 16 October 2020
- **Bio-Europe Autumn**
  26 – 29 October 2020

Licensing and partnering can be transformative for your company, especially with the optimal strategy and best execution.

To meet with our experts please send an email to:
enquiries@pharmaventures.com

Team News

PharmaVentures in Action

Biotechgate Digital Partnering
1 – 3 September 2020

Summer Park, Senior Business Development Director attended this virtual event.

KoNECT-MO, HW-MFDS International Conference
9 – 11 September

Summer Park, Senior Business Development delivered a session on **Doing a Deal with the Post-Deal Alliance in Mind** during the event.

SeoulBioHub Virtual Conference
24 September

Adrian Dawkes, Managing Director and **Summer Park**, Senior Business Development Director delivered a number of sessions on Day 1 of the conference.

- BD101: Business Development for Beginners (Korean),
- Negotiating a Deal for a Successful Partnership (English)
- Changing Deal Trends: How do Korean Biopharmaceutical companies fit into the Deal landscape? (English/Korean mix)
- YouTube Live Q&A (Korean)

PharmaVentures Ltd
Triumph House, Parkway Court, John Smith Drive, Oxford Business Park, Oxford OX4 2JY
www.pharmaventures.com

PharmaVentures
Experts in deals and alliances