Pharmaceutical Manufacturing

trends and investment opportunities in 2013

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The manufacture of ethical pharmaceutical products is a critically important process in the provision of healthcare. The process is both technical and carefully regulated, and staffed by highly trained professionals, and thus the business enjoys high barriers to entry. Although the industry itself is global, regulations are national, with precise requirements varying slightly from one country or region to the next. This adds a further barrier to entry – the ability to provide materials and products that meet the precise requirements of the territory in which they are to be sold.

The pharmaceutical industry is undergoing a period of great change, with exciting new treatments becoming available, while older drugs are becoming generic and thus open to competition. Payers are also becoming more critical about what and how much they are prepared to pay for these treatments. However, the underlying prospects for the industry remain good, as the average age of the population is increasing, with older people needing pharmaceuticals and, importantly, an increasing proportion of the global population becoming able to pay for modern healthcare. Such factors tend to be more resistant to economic cycles, and to the informed investor offers good growth potential with relatively secure long-term revenues.

In this review, we focus on pharmaceutical manufacturing, and the history, risks and opportunities associated with this important aspect of the healthcare business sector.

Types of manufacture

There is more to pharmaceutical manufacture than simply making pills – the components that go into them first have to be manufactured. Active pharmaceutical ingredients, or APIs, are the 'business end' of a pharmaceutical product, and can be either a small molecule, made by some form of chemical synthesis, or large biologics, which are made by fermentation. The manufacture of the ingredients is termed primary manufacture. These components – plus non-active excipients – are the building blocks used in the secondary manufacture process, the formulation of drug products. Finally, the drugs are packaged for distribution to patients and pharmacies.

Key players

Historically, pharmaceutical companies discovered and developed drugs, and then manufactured them in-house. In the past couple of decades, however, pharma companies have moved to outsource increasing amounts of the manufacturing process to contract manufacturing organisations (CMOs). At first, this was often early stage intermediates – precursor chemicals of APIs – which would then be elaborated into the APIs in one of the company's own facilities. Over time, the tendency to outsource moved further down the value chain, to advanced intermediates and the APIs themselves to the finished dosage forms taken by patients.

For its first few years on the market, only the originator pharma company that holds the relevant patent is allowed to sell a drug. Once the patent expires, it becomes a free-for-all, and any company who can produce a copy that meets regulatory requirements can apply for market authorisation and launch its own generic version. Generics have become big business, as many big-selling blockbuster drugs have lost their exclusivity, opening them up to competition. While this almost always greatly reduces the price they can command in the market, a small margin on a large-volume product can still represent significant income. This is particularly the case now that governments and health insurers are encouraging and, in some cases, enforcing, the use of cheaper generic medicines to reduce their drugs bills.

The growth in generics has also increased the number of players who manufacture APIs. Many companies, particularly in India, who manufacture generic drug products also make APIs, and sell them to third parties. This expanding demand for generics has also led to a rise in demand for outsourced APIs, as companies without their own manufacturing capabilities look to take a slice of the lucrative market.

Many CMOs have developed significant chemical synthesis capabilities, and are now able to take on complex chemistries. They can also design new and improved routes to make API molecules more cheaply and efficiently. If a better, more cost-effective synthetic route can be devised, particularly if the IP is protected in some way, this can enable CMOs to gain advantages in the manufacture and supply of individual APIs to secondary manufacturers.

Regulation, compliance and IP

Whether APIs and dosage forms are made in-house or outsourced, it is vital that all regulatory rules and standards are fully complied with. GMP – good manufacturing practice – standards ensure patient safety and prevent substandard or contaminated materials entering the supply chain. While the precise requirements vary slightly between the different regulatory bodies, for example for levels of residual heavy metals derived from catalysts, any good CMO should be able to guarantee that the materials they supply to their customers will comply with all relevant regulations. When manufacturing problems arise, the fall-out can be disastrous. For example, the manufacturing issues at Genzyme's Allston plant in Boston, Massachusetts led to a shut-down so a viral contamination problem could be addressed. This, and other concurrent manufacturing issues, have been suggested as contributory factors in Genzyme's eventual acquisition by Sanofi Group in 2011.

Intellectual property issues are also an important consideration. There have been concerns that a handful of CMOs have had a cavalier attitude to customer IP in the past; a company that is outsourcing its precious projects needs to be sure it can trust its CMOs. A great deal of effort is generally required to ensure the manufacturers have the necessary approvals, as well as processes and capabilities, to maintain the proper manufacturing of these key components of medicinal products.

Recent history

For all commodity products, manufacturing profitability is driven by selling prices, and selling prices are driven by supply and demand. However, this is supply and demand in volume terms, not value terms. Generics are the commodity products of the pharma world, particularly those sold in large volumes – whether long-established products like aspirin and paracetamol or some of the earlier 'modern' drugs like beta-blockers, antiulcer drugs and ACE inhibitors. These drugs are used by large patient populations, and the doses are frequently large, generating a big market for outsourced APIs in volume terms, albeit at a low price.

The APIs of drugs that have lost their patent protection more recently are likely to be lower volume and higher value. Even if the patient population is large, in most cases, the dosage is much smaller, reducing volume demand for the API. Contrast Lipitor with Zantac, for example. Even the rarely-prescribed maximum dose for Lipitor of 80mg/day (20mg is more normal) is dwarfed by the recommended maximum daily dose of Zantac, at 300mg/day, which is commonly prescribed.

While the dosage may be lower, the complexity of the molecule is much greater. For example, newer APIs are much more likely to include one or more chiral centres – carbon atoms attached to four different groups that can exist in two mirror image forms, only one of which is required. Zantac is a relatively simple and easy-to-make achiral molecule, whereas Lipitor's active ingredient poses much more significant synthetic challenges, including two chiral centres.

Typical daily dosages of top 10 best-selling small molecule drugs, 1985 and 2011

1985	mg/day		2011	mg/day
Tagamet	800	1	Lipitor	20
Zantac	150	2	Plavix	75
Adalat	60	3	Seretide	0.5/0.1 (fluticasone/salmeterol)
Feldene	20	4	Crestor	10
Inderal	160	5	Nexium	40
Tenormin	100	6	Seroquel	300
Naprosyn	750	7	Abilify	10
Voltaren	100	8	Singulair	10
Aldomet	1000	9	Zyprexa	10
Claforan	2000	10	Cymbalta	60

Source: IMS Health/Wood Mackenzie/prescribing information leaflets, US where available

Big Pharma has steadily been reducing its manufacturing capacity for APIs and intermediates in recent years. Even 20 years ago, when those early blockbusters had started to go generic, manufacture was still largely carried out in-house by the pharma companies themselves. As soon as the patent expired, it immediately opened up significant opportunities for contract manufacturing companies to offer the APIs that generic companies now required to make their products. Thus a substantial proportion of the manufacture, both primary and secondary, moved from the pharma companies to the generic and CMO sector.

Since those days, originator pharma companies have steadily reduced the amount of in-house manufacturing for their still-exclusive products, relying to a greater or lesser extent on CMOs for chemical synthesis. The extent varies from company to company – some, like GlaxoSmithKline, will keep just the final step, or a couple of late key steps, of the synthesis in house and outsource everything else, whereas others, such as Merck, will only outsource the very early steps.

So now, when a drug goes generic, not only is the API volume required likely to be much lower because of the smaller doses, but a proportion of the manufacturing process is already carried out externally. Rather than a wholesale switching from the pharma companies and their early stage CMOs to generics, by the time the patent expires CMOs are already making commercial quantities of late-stage intermediates, if not the APIs themselves.

Those CMOs who supply big pharma companies with their patented products will take a hit once the product loses exclusivity. In the past, they tended to resist working with generics companies for fear of upsetting their big pharma partners, but increasingly there are examples where CMOs are also supplying intermediates and ingredients those rival generics companies. The ability to remain competitive on pricing is key, although there is the initial advantage of already being geared up for manufacture of the ingredients. For example, many different companies developed their own synthetic routes to the chiral side-chain of Lipitor – the most difficult part of the synthesis. Once CMOs have entered the generic space, they are finding opportunities to use technology capabilities to bring competitive offers to generic companies. Those companies who traditionally have not worked in the generic space, and are slow to move into the area, are suffering.

Overall, the result is that pharma companies need less manufacturing capacity of their own, and some are becoming almost completely virtual, entirely reliant on CMOs for manufacturing. AstraZeneca is generally cited as an example of a large pharma company that has outsourced much of its manufacturing, although it retains manufacturing sites in key territories. The CMOs have needed to add capacity and capability to handle these newer products, while at the same time maintaining the ability to make those older, higher volume generics. For example, SAFC has invested heavily in developing the capability to manufacture highly potent APIs, which require effective and expensive containment facilities for safety reasons.

The generics companies are also experiencing change. Their future business will no longer have a primary focus on the synthesis of relatively simple molecules, where the synthetic routes contain just a handful of steps. Many of those drugs that are now losing patent protection are complex to make, often needing many different steps, some of which are difficult to perform. So not only is a lower volume of API required, but the synthesis is longer and more complicated. Thus while the volume is lower, the price that can be commanded will be higher.

With this new customer base in the generics companies, the CMOs now have a business where the risk is lower. Working in partnership with a pharma company on the manufacture of a drug that is in the late stages of clinical trials is fraught with risk because of the possibility that it might not be approved. This can prove catastrophic if a fails in Phase III, yet the capacity for large-scale manufacture has already been implemented.

Future trends

Ageing populations

The World Health Organisation predicts that the proportion of the global population aged over 60 will double from 2000 to 2050. Older people are more likely to be taking a range of different medicines to keep them healthy – it would not be unusual for a relatively healthy person in the developed world to be taking, say, an ACE inhibitor for elevated blood pressure, a statin to improve their cholesterol levels, and anti-inflammatories to ameliorate arthritic symptoms. Add diabetes, heart disease or depression into the mix, say, and that's a significant annual volume of APIs just in one patient. Multiply that across the population, and the numbers become enormous – and are growing. Even healthy people may, in some cases, benefit from taking medicines as a preventative measure – for example, statins appear to reduce the incidence of cardiovascular disease in low-risk patients (Tonelli et al, CMAJ, 2011, 183, e1189). Many of these drug needs are now served by low-cost generics, but as new breakthroughs are made there is still the potential for big-selling new drugs, even though we are unlikely to see another Lipitor in terms of sales.

The patent cliff

The industry is now well over the edge of the much-vaunted patent cliff, where many of the world's biggest selling drugs lose their exclusivity. The consequent increase in API volume required has led to a range of opportunities for those CMOs who are willing to take up the challenge.

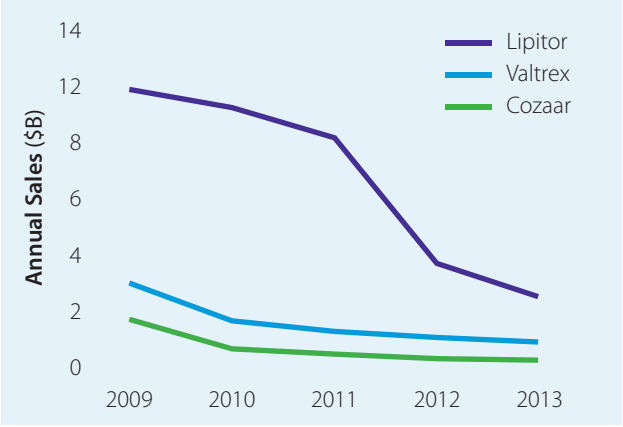
Major small molecule drug patent expiries

2013	Cymbalta
	OxyContin
	Aciphex
	Xeloda
	Zometa/Reclast
	Lidoderm
	Temodar
	Asacol
	Niaspan
2014	Nexium
	Celebrex
	Evista
2015	Abilify
2016	Crestor
	Zetia

As the graph below shows, the market size for a drug can drop dramatically once its patent expires – not because of a dramatic fall in sales volume, but because generic competition erodes the price. For these three examples, the patents expired at the end of 2009 for Valtrex and Cozaar, and 2011 for Lipitor, with sales falling off dramatically once exclusivity was lost.

While this means lower profits for the originator companies, it is also indicative of increased opportunities for generics companies – and the API manufacturers who supply them. Indeed, the sales in volume terms are more likely to increase, as the reduced price means more people who might benefit from the drug will be able to afford them, and payers will be more inclined to fund them.

Total annual sales in millions of dollars, with projected figures for 2012 and 2013



Emerging markets

There has been a trend among big pharma companies in recent years to expand their horizons by gaining market share for their products in emerging countries. However, in these countries the products that are in demand are often generics as the latest, still-patented, premium-priced medicines are unaffordable. This is often compatible with a generic push, and these days most pharma companies has a second brand generic company that offers these lower priced, higher volume products.

The BRIC countries (Brazil, Russia, India and China) are becoming wealthier, with the population demanding a better standard of healthcare. In these territories, the pharma companies are actively selling their full range of product, including those premium priced still-exclusive ones.

Pharma companies have been putting more effort into maintaining sales of newly generic products – after all, a 1% market share for such a big selling drug as Lipitor is still a substantial amount of product. In this case, Pfizer kept a lot of the complex chemistry involved in the manufacture in house, so there has been a significant opportunity for technically capable CMOs to develop their own synthetic routes to make the molecule to sell to generic companies.

Pricing pressures

As government and health insurer budgets have been squeezed in recent years, so the prices they are prepared to pay for medicines have reduced. Some, like Germany, have even introduced reference pricing systems where the maximum they will pay for any drug in a particular therapeutic category is set at a level based on cheaper members of that category, regardless of the additional benefits a new drug might offer. Others have brought in budget cuts and caps, requiring pharma companies to reduce their prices across the board. While the tactics may vary, the outcome is a downward pressure on pharmaceutical prices, and recently a market entry and reimbursement advice industry has developed as a result. Getting the right price for products is now a critical step in gaining market access, and the product becoming commercially successful.

In this more challenging environment, pharma companies are keen to retain as much of their profit margin as they can, and thus the pricing squeeze is being passed down the chain to suppliers. Conversely, those CMOs who are able to develop new, more cost-effective synthetic routes, will be able to retain, if not gain, business by reducing the prices they need to charge for their intermediates and APIs.

Technical capabilities

With the increasing complexity of most APIs on the market, those CMOs who are able to take on these technical challenges will be in a good position for future growth. By investing in one or two hi-tech technologies, they will differentiate themselves from competitors by being able to offer services that many cannot. Admittedly, some of these require expensive equipment, but carefully chosen and implemented, the expanded capability can give a CMO the edge. Examples include:

- Cryogenic capabilities, for carrying out highly exothermic reactions at low temperature.
- Containment facilities, for the manufacture of highly potent APIs.

- Capabilities in working with difficult, dangerous chemicals, such as phosgene or ozone.
- Proprietary catalyst technology, whether chemical or enzymatic, that is capable of carrying out specific processes more rapidly or more effectively.
- Capacity acquisition from pharma companies who are looking to divest assets, particularly if this includes an ongoing contract to supply product back to the divesting company. There are several successful examples, including Aesica's 2011 acquisition of three sites from UCB, Minakem's purchase of AstraZeneca's Dunkirk site where omeprazole, esomeprazole and budesonide are manufactured, and the acquisition of Roche's Boulder, Colorado facility by ICIG in 2011.
- Adding capability and capacity for secondary manufacture, enabling an integrated offering to generics companies with limited (or no) manufacturing capability of their own.
- Expansion into new geographical areas to supply the local market, particularly Latin America, where the market is growing rapidly – Espicom Business Intelligence predicts that the total pharma market size in the eight major markets (Brazil, Mexico, Argentina, Chile, Colombia, Cuba, Peru and Venezuela) will reach $80 billion in 2013 – up from $50 billion in 2010.
- A diversification away from small molecules into biotech-derived products such as proteins, peptides, oligosaccharides and RNAi.

Value drivers and investment opportunities

People, capabilities and IP

When determining the potential of any business, there are a number of factors that generate value. Perhaps the most important of these is the potential of the products that it generates, particularly in terms of volumes and margins. The uniqueness, quality and usefulness of its key assets are also value drivers. Is its know-how backed up by patents or trademarks that protect these assets from competition on the open market? And without a business's people, then any asset is generally bricks and steel – intellectual property is generated by those people. In the pharmaceutical industry, compliance with all relevant regulations is a key requirement. Qualified personnel who understand not only the rules and regulations but, importantly, how to operate a business that complies with these regulations. In any pharmaceutical asset, value is a function of the combination of all these elements.

Carve-outs

Assets that had previously been core to a company's business can become non-core, perhaps because the product manufactured at that site becomes subject to generic competition. In many cases, these assets are extremely valuable, but the current owner is not best placed to ensure its future development. However, if the site is to be divested, it is important to understand that it may not exist as a separate legal entity, so there may not be any independent validation of the costs associated with running the site, nor the revenues it can generate in the marketplace. In a carve-out, the asset first has to be separated from the larger entity, and then either merged with another company, or operated as an independent business. Doing this correctly is critical. There are several recent examples of manufacturing plants where the original owner still required a key product or products to be supplied, but the new owner failed to develop the business potential of the site outside of this. This is where an experienced transaction advisor can be invaluable.

Consolidation

All consolidations are driven by the desire for business and technological synergies, or economies of scale that can be generated by removing costly activities that are duplicated across both companies. In reality, the mergers that are most likely to generate value in the long term will offer the potential for both synergies and cost savings

Future potential

For those companies who provide compelling services and products, there are many opportunities to make consistent revenues and margins. In many cases, these are less sensitive to the prevailing economic climate. The pharmaceutical industry and the general healthcare business remains a traditional safe haven in difficult economic times. It is, however, very exposed to government regulations at both a macro and a micro level. In particular, failures in compliance with regulatory standards can be profoundly expensive, and difficult to resolve.

Navigating through the myriad of business opportunities and operating pitfalls is demanding – a little like walking up the highest mountains on a network of steep and narrow paths. But an expert adviser can provide the surefooted guidance that will help business goals be reached without tumbling into the abyss below. It is essential that, in any acquisition, the fundamental value drivers are present – and correctly valued. An advisor who is an expert in the industry and well-versed in all the potential pitfalls is invaluable.

About the authors

Sarah Houlton is a freelance science journalist specialising in pharmaceuticals, chemistry and chemicals. Prior to becoming freelance in 2001, she was editor of *ManufacturingChemist* magazine in the UK, a publication for which she still writes every issue. Sarah writes regularly for various other chemistry-based publications, including *Chemistry World* and *Chemistry & Industry*, and undertakes one-off writing projects for numerous publications, companies and organisations. She also writes, designs and edits *Chem@Cam*, a news-and-science magazine for the chemistry department at the University of Cambridge in the UK. She has a PhD in synthetic organic chemistry from Imperial College London, has worked in pharmaceutical research, and is based in Boston, Massachusetts, US.

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Kevin has been involved in the successful divestment and acquisition of many businesses, acting as advisor to major pharmaceutical and biotechnology companies. Successful transactions he lead whilst at PharmaVentures included the sale of 2 Sanofi research sites to Covance, divesting Dow Pharmaceuticals API manufacturing division to Dr Reddy's Ltd, the sale of manufacturing businesses from UCB to Aesica, the divestment of Merck's research site in Newhouse, Scotland to Biocity and in 2012 the divestment of Zentiva's (a Sanofi Group Company) Hlohovec plant to Wood Pharma Holding. In the last five years his divestments have resulted in the successful transfer of over 3,700 jobs to new owners and significant value creation for clients.

Kevin also has extensive experience in licensing of research compounds, technologies, IP and pharmaceutical products.

During his career Kevin has held senior positions in pharmaceutical research, alliance management, business development and transactions. He has worked at Hoechst (Sanofi) , Quintiles, Roche Pharmaceuticals, Inpharmatica and PharmaVentures, where until August 2012 he was Head of Transactions.