



Trends in the World Small Molecule API Manufacturing M&A Market

Key drivers reshaping the industry in 2009:
Following the economic turmoil in the latter
half of 2008, what are the key business drivers
now affecting this industry in 2009, and what
now are the future prospects for the primary
API manufacturing sector?

A white paper by

Ruth Barrett, Ph.D.
Consultant



PharmaVentures
Experts in deals and alliances

Table of Contents

Introduction	3
1	
Overcapacity in the West from historical success	4
2	
Overcapacity from changes in new therapies approved and under development	4
3	
Growth of the generics sector	5
4	
Growth of the Asian CMO sector	6
5	
Increased manufacturing out-sourcing by Big Pharma	7
6	
Highly fragmented CMO market now ripe for consolidation	8
Who's buying?	8
Concluding remarks	10

Introduction

The pharmaceutical small molecule API manufacturing industry is now experiencing a period of rapid change. This change is being driven by factors such as the changing nature of the drugs being made, expiry of patents covering the top-selling pharmaceuticals, the growth of the API manufacturing industry in India, China and Asia, shrinking margins causing downward pressure on pricing and the drive by governments to cut spending on drugs. This paper takes a look at how these trends are helping shape mergers and acquisitions (M&A) activity within this dynamic sector.

Last year (2008), global pharmaceutical fine chemicals production was valued at around \$70 B, a figure predicted to rise to \$106 B by 2015,¹ giving a CAGR of 6.3% over this period. During this time frame, the Asia Pacific region is set to overtake Western Europe as the world's top producer, predicted to grow at 9% annually 2008-2015. The strongest growth is expected to come from India and China, largely driven by elevated pricing pressure in the West and the growth of the generics market. However, it should be noted that the Western European segment itself will be growing at a healthy 5.5% CAGR (*Figure 1*).

There are currently a number of trends that are affecting M&A activity in the pharmaceutical fine chemicals sector:

- 1 **Overcapacity in the West from historical success**
- 2 **Overcapacity from changes in new therapies approved and under development**
- 3 **Growth of the generics segment**
- 4 **Growth of the Asian CMO sector**
- 5 **Increased manufacturing out-sourcing by big pharma**
- 6 **Highly fragmented CMO market now ripe for consolidation.**

These points will now be considered in turn.

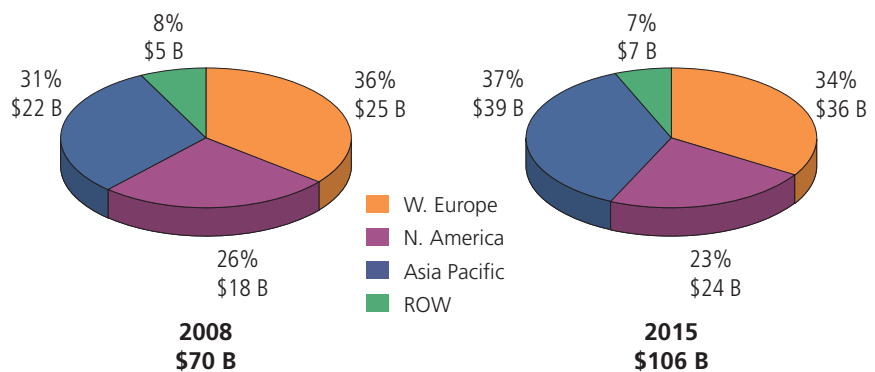


Figure 1 – Global pharmaceutical fine chemicals production by region, 2008 and 2015.²

¹ Acmite Market Intelligence. Study: World Pharmaceuticals Fine Chemicals Market, March 2008.

² Calculated from data in reference (1).

1

Overcapacity in the West from historical success

A decade ago, NCEs were still being approved by the FDA at a good rate (an average of 39 per year in the period 1996 -1999). These were typically drugs that were given at a high dose, and so needed large manufacturing facilities to meet demand. Globally, there was a projected capacity shortage. To meet demand, big pharma built their own facilities and kept manufacturing in-house. Profit margins in the manufacturing sector were comparatively high; Western fine chemicals manufacturers have since suffered decreasing EBITDA margins over the period 1997-2004.³ Over the next ten years or so (1997- present), many new facilities were built, the high-dose top-selling NCEs came off patent, drugs increased markedly in their potency, NCE pipelines began to dry up and the FDA increased its stringency in approving NCEs. This combination of factors (in conjunction with those listed in addition below such as the growth of the API/intermediates manufacturing sector in India and China) has resulted in an estimated 25-40% overcapacity in the West (*i.e.*, Europe and the US) today.⁴ Many leading pharmaceutical companies have inflexible manufacturing facilities manufacturing high-margin, patented, average dose, small molecule APIs. As these APIs come off patent and the drugs are subject to generic competition these facilities become surplus to requirement. Therefore many large pharmaceutical companies are now attempting to divest a range of their manufacturing assets.

2

Overcapacity from changes in new therapies approved and under development

The nature of the new drugs being developed and approved is changing. From the high-dose low-potency relatively simple small molecule drugs of yesteryear, newer small molecules are increasing in potency and becoming more complex to synthesize. Add to this the rise of biologics, and it is easy to see that older manufacturing facilities are often out-of-date, and/or surplus to requirements. The result is often strategy-driven attempts to divest such assets.

On average, a higher-potency molecule requires lower capacity for its manufacture as it is given at a lower dose. The trend towards increased potency over the last two decades is seen clearly when comparing the daily doses of the top 10 selling drugs across this time window (*Table 2*). Also, as these drugs come off-patent and a flood of generics manufacturers (many of whom are in India or China) enters the markets, the patent owner is left with excess capacity.

In addition to this general increase in molecules' potency, there is now also a trend towards "High Potency APIs" – HPAPIs; a specific class of exceedingly highly potent molecules with specialized handling and safety requirements – that is adding to the overcapacity issue in the West. Typically, a molecule will be classed as an HPAPI if it has an occupational exposure limit of under 10µg/m³ of air. These molecules require

³ <http://www.contractpharma.com/articles/2006/09/the-western-fine-chemicals-industry>

⁴ Acmite Market Intelligence. Study: World Pharmaceuticals Fine Chemicals Market, March 2008.

1985		1995		2005		
Drug	mg/day	Drug	mg/day	Drug	mg/day	
1	Tagamet	800	Zantac	150	Lipitor	20
2	Zantac	150	Prilosec	40	Zocor	20
3	Adalat	60	Vasotec	10	Zyprexa	10
4	Feldene	20	Prozac	20	Procrit/Epex	na
5	Inderal	160	Zocor	20	Prevacid	15
6	Tenormin	100	Capoten	150	Norvasc	5
7	Naprosyn	750	Voltaren	100	Advair	100
8	Voltaren	100	Zovirax	800	Paxil	20
9	Aldomet	1000	Augmentin	1000	Fosamax	10
10	Claforan	2000	Ciprobay	1000	Zoloft	50

Table 1 – The top-selling drugs from 1985, 1995 and 2005 with their daily doses.

a high degree of containment to be worked with safely, and facilities with the correct exposure-control technology must be used for their manufacture.⁵ Growth of the HPAPI sector now stands at 12% per year.⁶ HPAPIs will continue to take an increasing proportion of this market due to advances in clinical pharmacology/ oncology research plus the large number of HPAPIs in development. HPAPIs require specialized facilities for their manufacture; empty facilities once used to make non-HPAPIs are not suitable, adding to the overcapacity issue in the West.

Companies are also choosing to move strategically towards other therapy types, such as biologics, proteins, peptides and oligonucleotides, rendering small molecule facilities redundant. This move is borne out by the observation that while the pharmaceutical market is predicted to grow at almost 4% per year between 2007 and 2014, this growth is split between the 9.8% yearly growth expected for biologics, compared to the tiny 1.3% yearly growth predicted for conventional technologies, the mainstay of which is small molecule chemistry.⁷

3 Growth of the generics sector

There is one trend that may help to reduce some of the world's overcapacity through acquisitions: the strong growth seen in the generics sector, which is expanding in value at 9% per year.⁸ Generics products now account for 63.7% of the total US pharmaceutical market volume. This growth is primarily driven by patent expiries of blockbuster drugs. Research-focused large pharmaceutical companies will see their exposure from patent expirations to increase from \$17 B in 2007 to \$20 B in 2008.⁹ The relentless march of generics is significantly influenced by pharmaco-economic and political decisions, plus intense competition amongst generics producers to get a piece of this valuable market. The generics market's value expansion in the West is dampened by the move of generic manufacturing to India and increasingly

⁵ www.safebridge.com/pdf_docs/APIs&Fine_Chemicals.pdf

⁶ Dave Bormett, Pharmaceutical Technology Europe, Volume 20, Issue 10, 1st October 2008

⁷ Evaluate Pharma

⁸ Evaluate Pharma

⁹ Intralinks Industry Insights

China (ultimately allowing for more price competition of the final products), where a great number of new facilities (many of which are FDA compliant) have been built to house production at a lower cost.

4 Growth of the Asian CMO sector

Growth in the CMO sector in India and China will ensure that the Asia Pacific region becomes the world's top producer of APIs by 2015. This growth is mainly driven by the ability of Indian and Chinese producers to significantly undercut Western producers on account of their low cost base coupled with the increasing pressure faced by pharmaceutical companies to cut costs. Putting further pressure on Western companies, Asian producers are increasingly competing on quality of manufacturing too having accumulated many years of specialised competencies and succeeding in obtaining FDA certifications. By the end 2008 there were over 60 FDA approved plants in India and more than 200 with WHO GMP compliance.

An increase in M&A activity is accompanying this growth and results from two main drivers. The first is that Indian manufacturers are now looking to go global, to acquire facilities in the West or US. They aspire to a competitive advantage in the technologies they can offer, access to a wider customer base and the ability to offer a more integrated local service for large Western customers, as such customers often value a quick response, a more suitable time zone and close contact with their outsourcing partner.

The second driver of consolidation is the high fragmentation of the competitive landscape that exists in India and China. Thus far, the barriers to entry to begin CMO operations in these countries were relatively low in comparison with doing so in the West, resulting in many new Asian CMOs springing up. Build costs have been cheap (reportedly sometimes only 10% of the Western cost) and wages low (average 2006 figures: \$3,750-\$7500 p.a. compared to \$50,000 in Western Europe), and to date there have been few environmental regulations to be adhered to. Consolidation of Asian CMOs helps them to achieve critical mass and become attractive partners. This is further covered in point 5 below.¹⁰

However, the beneficial differences experienced by the Asian sector are shrinking, meaning that the Asian CMO growth will not continue unabated: with the improving living standards and high demand for educated workforce wages are rising fast and environmental restrictions becoming tighter. Raw materials are often more expensive to acquire than in the West and energy costs can be great, especially if on-site generators are needed to protect against power cuts.¹¹

In addition to these changes, there is a set of existing restrictors that will continue to limit the Asian CMOs, at least in the short term, relating to the level and type of service they can provide. Western pharma companies have voiced concerns over adherence to GMP, confidentiality, quality of the products, the ease of communications, and the ability to stick to a schedule/risk of disruption of supply.

¹⁰ <http://www.contractpharma.com/articles/2006/09/the-western-fine-chemicals-industry>

Add to this the time and cost involved in validating and monitoring Eastern suppliers, and it becomes more financially sensible for many pharmaceutical companies to stick with their Western suppliers, especially if they can leverage the Asian alternatives to negotiate a price reduction with them.¹² These concerns will doubtless be allayed over time as Asia gains more experience in the sector and continues to catch up with the West. Assisting this acceptance will be the FDA, which has now opened offices in China and India to work more closely with manufacturers to share best practices and to ensure that producers build quality and safety in to their processes. Inspectors positioned in these countries will assess the facilities that export to the US and work with government agencies/the private sector to develop certification programmes.¹³

The growth of the Asian CMO market has had a clear knock-on effect on the M&A activity among Western CMOs and pharmaceutical fine chemical producers. Asian producers tend to be fairly undifferentiated, making intermediates and APIs that are relatively simple to manufacture, such as older generics. The low cost of Asian bulk API production has forced Western producers to differentiate themselves in order to maintain a clear value proposition: offering proprietary or sophisticated technologies or the ability to make HPAPIs. Becoming a trusted partner at the clinical phase and maintaining very high quality standards with quick turnaround times help Western CMOs to keep winning business and be seen as an attractive target for acquisition. Companies that are unable to show differentiation (such as those assets built in the 1990s to manufacture high-volume low-dose small molecules) are less likely to be bought, and many such assets on the market in the West may remain unsold.

5 Increased manufacturing out-sourcing by Big Pharma

A trend that is stimulating M&A in the CMO and pharma sector is the continuing practice by big pharma to save financial and strategic resources through out-sourcing the manufacturing of mature in-line products. Pharmaceutical companies around the world are restructuring in an effort to increase margins and refocus their internal resources in the face of patent expiries and an excessive infrastructure that ballooned to unsustainable levels over several decades of high growth. Many conclude that small molecule manufacturing is not part of their core skill set. It is anticipated that pharmaceutical companies will outsource 30-50% of their manufacturing in the near future. Fourteen of the world's top 20 pharma have announced closures or divestitures of manufacturing assets in the last two years.¹⁴ Pfizer announced in April 2008 that they planned to sell 13 more manufacturing sites as part of their \$2 B cost reduction programme.

A common divestment strategy of big pharma is to sell their assets to a CMO with whom they would also then enter into a supply contract to continue to manufacture the chemicals already being made in those assets. For example, on 1st January

¹¹ www.contractpharma.com
September 2006 feature article,
Enrico Polastro

¹² www.contractpharma.com
September 2006 feature article,
Enrico Polastro

¹³ <http://www.hhs.gov/news/press/2009pres/01/20090115a.html>

2008, PRWT Services announced that they had acquired Merck & Co.'s API plant located in Riverside, PA, and that they had entered in to a five year supply agreement with Merck worth some \$100-200 M per year. And on the 11th December 2008, Hovione announced that they are to acquire Pfizer's Lipitor intermediates plant in Cork, Ireland, and also to provide Pfizer with manufacturing services (terms of the transaction were not disclosed). This trend looks set to continue as resource rationalization carries on within the pharma sector.

Whilst outside of the core scope of this paper, it is worth noting that although big pharma are keen to outsource API manufacture, they still keep in house secondary manufacturing including packaging and labelling to maintain partial control over the supply chain and ensure adherence to the regulations of multiple countries.

Additionally, pharmaceutical companies aim to maintain strong control over the full manufacturing of strategically important, newly launched potential blockbusters that will enable them to effectively manage their cost structure and the quality of production until these products are well established and matured in their markets.

6 Highly fragmented CMO market now ripe for consolidation

The CMO market is highly fragmented, especially in Asia. Frost and Sullivan recently estimated that the 'critical mass' that a CMO should aim for to become an attractive partner to the majority of potential clients is sales of around \$100 M per year.¹⁵ M&A activity resulting in such a company will benefit from economies of scale, cheaper marketing, a spread of risk over many different projects and a reduction in competition. In particular, a large custom manufacturing CMO would ideally have more than one Phase III project so that the business is not dependent on the success of any one of them. In addition, there are a number of synergies that exist between Asian CMOs and Western pharma that make each other attractive partners for a merger: the Asian company needs market access, and wishes to move up the value chain in to more proprietary areas; the Western CMO wants to reduce manufacturing costs, possibly expand in to generics. Together, the extended company has a larger portfolio with reduced risk and products at a wide range of lifecycle stages.

Who's buying?

The current economic climate's impact on financing facilities is having a profound subduing effect on M&A activity in the pharmaceutical fine chemicals sector world-wide, affecting each of the three buyer groups listed below. It is a buyers' market for those who can raise money; a lack of access to cheap funds is preventing many would-be buyers from acting. Companies who have immediate access to

¹⁴ Lincoln International LLC presentation, Pharma ChemOutsourcing conference, Sept 2008

¹⁵ Frost and Sullivan 'European Fine Chemicals Markets – Investment Analysis and Growth Opportunities, 2006.

Date	Acquiring Company	Target Company	Deal value	Highlights of Assets Sold	Rationale for Acquirer
30.04.08	Dr Reddy's	DowPharma assets	Undisclosed	Custom manufacturing, IP, technology licence.	Highly differentiated UK business with a broad Western customer base. ¹⁶
30.04.08	Dr Reddy's	BASF	Undisclosed	OTC/RX generics manufacturing business and plant (US), inc. business, contracts, NDAs, ANDAs.	US customer base, FDA approved facilities, range of dosage forms.
11.06.08	Daiichi Sankyo	Ranbaxy	US\$4.6 B	Generic pharma company: manufacturing/sales	Cost-effective Indian operations, plus a strong foothold in generics for Japanese market.
16.11.07	Cambridge Major Labs	Chemshop	Undisclosed	EU GMP manufacturing site including HPAPIs	HPAPI facility, EU presence and customer base.
21.01.08	Actavis	Pfizer	Undisclosed	Italian oncology product manufacturing site	Broad manufacturing capabilities in plant, plus a multi-year supply agreement with Pfizer.
11.12.08	Hovione	Pfizer	Undisclosed	Lipitor intermediate site in Ireland, 427m ³ . Multi-purpose; specialized chemistry/spray drying capabilities	Manufacturing services for Pfizer, increased capacity, strengthen leading position in spray-drying, tax efficient location.
06.02.08	3i	Alpharma	US\$395 M	Injectable generic API manufacturing business. Sites in Scandanavia, Europe and China.	3i attracted by fast-growing segment/ business's potential for further growth.

Table 2 – Selected deals in the API manufacturing space from the last 18 months, with the rationale for the deal, plus the deal value where this was disclosed.

large cash piles will be somewhat immune, such as private owned or family run businesses. Buyer groups may be partitioned into Western Strategic, Asian Strategic or Private Equity.

Western Strategic:

Looking to generate differentiation through acquiring proprietary technologies or more sophisticated chemistry capabilities. May also be looking to bring in-house reduced cost manufacturing through Asian acquisitions.

Asian Strategic:

Want to obtain access to the key markets through acquisition of premises approved by the major regulatory authorities. Many companies are now looking to go global and expand in to major markets. They may also want to expand their technology base to make more complex molecules or move up the value chain in ways of process differentiation. Buyers are becoming bolder as the Asian economies become stronger.

Private Equity:

Tend to look for profitable independent businesses with annual sales of over \$20 M with potential for high growth following additional cash injection. As strong growth is continuing in Asia, quality companies in this region with large pharma contracts may be attractive to this buyer group, who will be looking to exit in a timeframe of four years or so.

¹⁶ PharmaVentures acted as Dow's advisors for this deal: <http://www.pharmaventures.com/aboutus/press/news/1183>

Over the last three years, through the API manufacturing business divestments that we have handled, we have charted the drop in Private Equity/financial buyers' involvement in transactions as the economic climate has worsened. In terms of a percentage of interested parties executing CDAs to progress through our auction processes, Strategic buyers (Western and Asian) have become relatively more prominent as Private Equity interest has waned (*Figure 2*).



Figure 2 – Relative interest shown by Strategic and Private Equity buyer groups expressed as a percentage of parties having executed CDAs in three of PharmaVentures' API manufacturing divestments 2007-2009.¹⁷

Concluding remarks

The pharmaceutical fine chemicals sector is in a state of flux. Who is manufacturing what type of molecule, where that occurs in the world, and whether it is made in-house or out-sourced, is rapidly changing. Robust M&A opportunities are accompanying these trends. Over-capacity in the West has resulted in many assets becoming available for purchase, while the growth of the generics sector may help stem some of this issue. However, with the movement of generics and increasingly custom manufacturing to Asia, many of these Western facilities will likely remain unsold. The growth of the Asian sector has resulted in strategic synergies between Western and Asian companies. This dove-tailing of needs will continue for years to come, but eventually the Indian and Chinese economies will catch up with the West's to the point where the currently substantial Asian advantage disappears. The increased out-sourcing by pharmaceutical companies has led and will continue to lead to the divestment of their manufacturing assets, especially to CMOs. Lastly, a period of consolidation may now be seen as companies aim to reach critical mass to increase their customer base. These trends look set to continue for several years to come as strategic Western, Asian and Private Equity players compete to stay ahead of the wave.

¹⁷ Data courtesy of Kevin Bottomley, Senior Principal, PharmaVentures

This paper was written in March 2009

About the author

Dr Ruth Barrett, PhD – Consultant

Ruth is an expert advisor in M&A in the pharmaceutical fine chemicals sector. Most notably she was instrumental in The Dow Chemical Company's divestment of its DowPharma assets to Dr Reddy's (<http://www.prwebdirect.com/releases/2008/4/prweb831844.php>) where PharmaVentures acted as transaction advisor to the Dow Chemical Company.

Dr Barrett is also experienced in licensing, analysis of deal-making strategy, valuations, and commercial diligence. Before joining PharmaVentures, Ruth gained five years' experience in the biotechnology industry as a founding member of Daniolabs (now Summit). Ruth has an undergraduate degree in Biological Sciences from Keble College, Oxford University and was awarded her PhD in developmental genetics from Corpus Christi College, Cambridge University.