CMOs and Final Dosage Manufacturing in China

The far east market evolves

By **Oliver Mueller and Clifford Mintz**
Suzhou Pharma Services BioInsights

CMOs offer a wide array of manufacturing services to the pharmaceutical and biopharma industries. These services can range from production of small quantities of materials for R&D purposes, larger amounts for clinical study usage and ultimately full-scale production for commercial purposes. The global contract manufacturing market primarily includes solid and liquid dosage forms and injectables. The growing use of generic drugs and complex pharmaceutical products has also induced many CMOs to offer active pharmaceutical ingredient (API) manufacturing services to their clients.

In 2011, total global spending on contract manufacturing reached $31.9 billion according to a 2012 *Informa* report entitled, "The CMO Market Outlook to 2017." The CMO industry has experienced double-digit growth in the past two decades and that trend is expected to continue for the next five years.[1] By 2017, the size of the global contract manufacturing market is expected to grow to about $63 billion. While there has been a steady growing demand for API manufacturing in recent years, solid dosage formulation remains the largest segment of the CMO industry by revenue. The solid dosage market is expected to expand over the next five years at an annual rate of 12.5% and as much as $55 billion will be spent by 2017 on CMO-based solid dosage manufacturing.[1]

In the past, the decision to outsource manufacturing was primarily based on the need to acquire a new skill or to compensate for a lack of in-house, internal capacity. However, in the last decade or so, the decision to outsource has been strategically embraced as a way for pharmaceutical companies to: 1) reduce costs, 2) lower drug development risks, 3) adapt to shifting manufacturing requirements, 3) gain access to manufacturing expertise and, 4) reduce drug commercialization development times.

Factors Driving Outsourcing

Cost control is one of the main reasons that pharma companies are increasingly turning to CMOs for manufacturing help. The need for pharmaceutical companies to assiduously control costs has been caused by: 1) impending "patent cliffs" resulting from recent blockbuster drug patent expiry, 2) increased regulatory scrutiny, 3) decreased new drug approvals and, 4) genericization and downward pricing pressures on branded prescription drugs.

Over the next few years, patents for as many as 19 blockbuster drugs (products with more than $1.0 billion in annual global sales) will expire.[2] For example, six of the top 10 largest selling medicines — including Lipitor, Plavix, Advair, Diskus, Nexium and Seroquel — will lose patent protection by 2015.

According to the Generic Drug Association, the 2011 global market for generic drugs expanded to approximately $100 billion—representing more than 10% of worldwide drug market.

Oliver Mueller is president at Suzhou Pharma Services, a CDMO and subsidiary of Amerigen headquartered in NJ, with a China-based, FDA- and SFDA-approved solid dosage tablet and capsule manufacturing operation. He can be reached at omueller@suzhoupharma.com. **Clifford Mintz, Ph.D** is a freelance science writer at BioInsights, Inc.

The increased reliance by physicians and patients on generic medications, coupled with ongoing patent expiry of many blockbuster drugs and decreasing profit margins on branded drugs, is forcing most pharmaceutical companies to outsource manufacturing to control and contain costs.

In addition to patent cliffs and generic encroachment, drug makers' revenue growth is being negatively impacted by recent increased regulatory scrutiny by U.S. and European authorities. Over the past five years or more, regulatory agencies have demanded that companies increase the number and size of clinical trials for approval of new molecular entities (NME). This, in part, has caused R&D spending to rise from $8.4 billion in 1990 to $70 billion in 2011. Yet, despite massive increases in R&D spending, the number of NMEs approved in the U.S. each year has steadily declined from 27 in 2000 to 21 in 2010.[5] Industry experts contend that rising U.S. and European regulatory scrutiny is unnecessarily driving up the cost of new drug development and consequently stifling pharmaceutical innovation.

Finally, rising prescription drug prices and global healthcare reform initiatives have driven insurance companies and other healthcare payers to control healthcare costs. Increasingly, patients are asked to switch from branded medications to lower cost generic equivalents (when available) to help payers lower healthcare costs. Not surprisingly, this has cut into the sales revenues of many branded drugs and forced drugmakers to consider outsourcing manufacturing to help to control production costs. Additionally, an increase in generic drug substitution rates has created further outsourcing demand as generic drugmakers look to CMOs to supplement their own manufacturing capacities and capabilities.

Benefits of Contract Manufacturing

Dedicated manufacturing facilities require high capital investments in equipment, personnel and facilities management. By some estimates, manufacturing absorbs as much as 23% of total sales revenues generated by a typical pharma company. Companies that outsource manufacturing can avoid or substantially reduce these costs and reallocate capital, resources and personnel to other corporate activities. This is especially true for startups or smaller and midsize companies that are often technology rich but cash poor.

Contract manufacturing also helps to reduce some of the risks associated with new drug development and commercialization. For example, in the past, companies with pending or newly approved drugs would have to build expensive, dedicated manufacturing facilities. Outsourcing manufacturing to a CMO obviates these capital expenditures and concomitant operating costs and also provides a company with the flexibility to scale up or scale down production to meet commercial product demand. Moreover, continually shifting specialty manufacturing demands — e.g., biologics, parenteral drugs, transdermal formulations and controlled release — is inducing more drugmakers, both branded and generic, to consider outsourcing because they lack the financial resources or internal expertise to manufacture the products themselves.

Because of a constantly changing regulatory environment and a greater emphasis on maintaining product quality, many drugmakers do not possess the requisite personnel, facilities, equipment or expertise to keep pace with best manufacturing practices. To that point, CMOs offer direct access to a variety of manufacturing capabilities, regulatory and manufacturing expertise, equipment and state-of-the art production facilities. Similarly, by leveraging the resources and expertise available at CMOs, drug makers can avoid oversights or costly mistakes made by inadequately trained personnel. This, in turn, can shorten product development and commercial manufacturing lead times that typically translate into substantial cost savings.

Contract Manufacturing in China

The outsourcing of pharmaceutical manufacturing is growing most rapidly in Asia. Recently, PriceWaterhouseCoopers named China as the most attractive Asian country for outsourcing. At present, more than 100 drug manufacturing sites in China are manufacturing API or finished products for approved branded and generic drugs.[6]

While China accounted for only $1.9 billion of the $31.9 billion global CMO revenues in 2011, Chinese CMOs have emerged as preferred outsourcing partners for many pharmaceutical companies for a variety of reasons. These include: 1) cost containment, 2) improvements in China's infrastructure, 3) improved regulatory oversight and adherence to current good manufacturing practice (CGMP) standards, 4) better enforcement of intellectual property laws, and 5) a skilled Chinese workforce.

One of the main drivers of the emergence of the Chinese CMO industry is cost savings. Because China is a low labor wage country, pharma manufacturing costs can be reduced by as much as 40% or more.[6] Also, lower capital and overhead costs (as compared with the U.S. and Europe), tax advantages and an undervalued currency can translate into significant cost savings for companies that outsource manufacturing in China.

The opening of China's borders and growth of its middle class has increased its government's focus on drug discovery and healthcare. To that end, China has been investing heavily to develop its own pharma industry. Also, the country has invested in infrastructure improvements that have strengthened transportation and supply chains throughout the country.

Further, creation of the State Food and Drug Administration (SFDA) and a restructuring of its regulatory system to improve product quality have greatly increased the number of western pharma companies doing business with Chinese CMOs. However, while the SFDA created its own set of CGMP guidelines, concerns persist about how well Chinese manufacturers adhere to them. Today, more than 4,000 pharmaceutical manufacturers in China are believed to have received Chinese CGMP certification. In 2008, FDA opened local offices in China to monitor manufacturing practices and to train Chinese regulators on expected U.S. quality standards and CGMP requirements.

Despite vast improvements, concerns still persist about enforcement of U.S. and European intellectual property (IP) and patent laws in China. However, it is important to note, that as part of the agreement that allowed China to become a member of the World Trade Organization in 2001 the Chinese government made a commitment to more stringently adhere to and uphold these laws. Moreover, in recent years, the SFDA has

stepped up it activities to prevent IP and patent infringement by Chinese pharma companies, making conditions more favorable for foreign drugmakers to do business with Chinese CMOs. Finally, the Chinese government is acutely aware of concerns about patent and IP protection in China and continues to enact new legislation to improve enforcement and compliance.

Another factor that has been driving the explosive growth of the Chinese CMO industry is the country's huge talent pool of western-trained scientists and pharma workers. Many Chinese nationals return to China to find work after training in the west because of tough immigration policies and high unemployment among American and European pharma workers. Also, a growing number of drug companies, including Novo Nordisk, Merck, AstraZeneca, Lilly, Roche and Pfizer have established or plan to establish R&D centers in China, making it a job destination for many life scientists and pharma professionals.[7] The growing pharma presence in China will almost certainly spur Chinese innovation.

Finally, by 2020, China is expected to become the largest pharmaceutical market in the world. Because of this, many western companies are eager to establish business relationships with Chinese life sciences companies. To that end, working with Chinese CMOs is a convenient way for foreign drugmakers to build relationships and penetrate the Chinese pharmaceutical market. According to a report by ChinaKnowledge, several American and European drugmakers, including J&J, Roche, Bayer, AstraZeneca, GSK, Novartis, Novo Nordisk, BMS and Pfizer have either partnered with Chinese CMOs or established their own manufacturing facilities in China.

Chinese CMO Landscape

Most of the CMOs operating in China today offer mainly API and bulk drug materials manufacturing. China recently surpassed India as the world leader in the manufacture of APIs and bulk drug materials (India still exports substantially more finished dose medications). Some of China's leading API and chemical intermediate CMOs include: Asymchem Laboratories, Beijing Second Pharmaceutical, Chongqing Huapont Pharmaceutical, Porton Fine Chemicals, Shandong Xinhua Pharmaceutical, Tianjin Pharmaceutical, Venturepharm Laboratories, WuXi AppTec, Zhejian Hisun Pharma and Zhejiang Huahai Pharmaceutical.[8]

While API manufacturing is common in China, most Chinese CMOs are limited in the solid and liquid dosage manufacturing services (branded or generic drugs) that they offer. Most Chinese production facilities have not yet received U.S. or European CGMP certification and consequently cannot manufacture finished dosage products for sale in these regions.

Of the leading CMOs listed above only Chongqing Huapont, Zhejian Hisun and Zhejiang Huahai currently offer solid dosage manufacturing in U.S. or European CGMP-compliant production facilities. Although these companies offer this service, it is unclear whether or not any of them are currently performing any solid dosage manufacturing on behalf of Western drugmakers.

In addition, several smaller CMOs, including Suzhou Pharma Services, Harbin Pharmaceuticals and the Shanghai Pharmaceutical Group, offer similar solid dosage manufacturing services.[8] However, while opportunities exist for Chinese CMOs to enter the global solid dosage manufacturing market, they must possess or receive Chinese and Western (U.S. FDA and/or European) CGMP certification and approval, and strongly demonstrate to foreign clients a firm commitment to Western manufacturing and quality standards. At present, commercial solid dosage manufacturing services offered by Chinese CMOs represent only a minute fraction of their total annual sales revenues.

What Does the Future Hold?

Ongoing pricing pressures, generic drug competition and economic challenges will continue to force pharmaceutical companies to seek the cost advantages offered by outsourcing manufacturing. China's low-cost skilled labor force, coupled with a government focus to improve and maintain high quality product standards, suggests that Chinese CMOs are positioned to continue to capture a growing portion of the global contract manufacturing business. To that end, according to the *Informa* report, the Chinese CMO market is expected to grow at an annual rate of almost 18% and reach $5.0 billion by 2017[1]. More than 90% of that growth is projected to take place in final dosage manufacturing.

While most Chinese CMOs still specialize in API and chemical intermediate manufacturing, many of the large CMOs have invested heavily in the construction of final dosage manufacturing facilities. However, the ability of Chinese CMOs to compete successfully in the global final dosage manufacturing market will likely depend upon their ability to overcome quality and safety concerns. This can only be accomplished by respecting and strictly adhering to western CGMP regulatory requirements. ■

References

1 The CMO Market Outlook to 2017 Emerging Markets, Key Players and Future Trends, Informa 2012

2 The Blockbuster Drugs Outlook Optimum Management Strategies Throughout The Product Lifecycle. Business Insights, 2001

3 Drug Patents Expiration in 2011 & 2012 – A Bumpy Ride Ahead for Big Pharma as Big Drugs Lose Patent Protection, IHS Healthcare Blog 2011 http://healthcare.blogs.ihs.com/2011/10/28/drug-patents-expiration-2011-2012-a-bumpy-ride-ahead-for-big-pharma-as-big-drugs-lose-patent-protection/

4 IMS Institute for Healthcare Informatics, The Global Use of Medicines: Outlook Through 2015. May 2011

5 U.S. Food and Drug Administration New Molecular Entity Approvals for 2010 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm242674.htm

6 Bhandari V, Erhard A, Tejwani S of A.T. Kearney. *Will China Lose Its Cost-Competitiveness In Pharma Manufacturing By 2015?* Life Science Leader, September 2010 http://www.lifescienceleader.com/component/k2/item/3546-will-china-lose-its-cost-competitiveness-in-pharma-manufacturing-by-2015

7 China Knowledge.com. http://www.chinaknowledge.com/Business/CBGdetails.aspx?subchap=3&content=12

8 The Top 10 CMOs in China Market dynamics, competitive positioning and trends Business Insights, 2011