

Biopharma CMOs In China

Will 45% excess capacity drive the industry?

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WITH \$25 BILLION IN EXCESS pharmaceutical production capacity in China, and almost half its production facilities standing idle, many Chinese pharmaceutical factories are looking for higher-value production opportunities. Many are evaluating the potential for biopharmaceutical production. Although recombinant proteins are often considered more technically complex, and can pose greater regulatory hurdles than other therapeutics, biopharmaceuticals are also seen as a potential strategic opportunity.

China is a huge market with international scientific and technical capabilities in biopharmaceuticals. It has a growing number of domestic research institutions that must build new biopharmaceutical facilities in order to manufacture emerging products. With these developments, China is beginning to position itself as a significant competitor on the world biopharmaceutical production market.

According to the joint study to be released this month (June 2006) by BioPlan Associates and the Society for Industrial Microbiology, *Advances in Biopharmaceutical Technology in China*, one of the dilemmas in contract manufacturing in China today is how excess production resources within the pharmaceutical industry will be allocated.

"The reason we chose to conduct contract manufacturing for international pharmas is exactly to solve the problem caused by idle production capacity," said Changchun Wang, manager of contract manufacturing at Xi'an Chiho Pharmaceutical Co., Ltd., a major contract manufacturer in China. "We've been

evaluating how to make the best use of our spare production capacity and create long-term value and profits. We feel that contract manufacturing is the solution. The significance to us of conducting international contract manufacturing is strategic. We not only want to make effective use of our idle production capacity, we want to upgrade our management system to a higher level by gearing to international standards."

Dr. Xiangdong Chai, general manager of Shenzhen Interlong Biotech Co., is very positive about the future development trends toward biopharmaceutical contract manufacturing in China: "Our company plans to become a first-class biopharmaceutical manufacturer in China as well as a very competitive biopharmaceutical contract manufacturer in Asia over the next five to 10 years." He cited China's highly trained and educated workforce, and its background in biological sciences. He added, "Also, the Chinese pharmaceutical industry has decades of experience working with small molecules, especially the necessary quality and regulatory requirements."

It's not just the pharmaceutical manufacturers that are recognizing the strategic importance of biopharmaceuticals in

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China. The Chinese State Food and Drug Administration (SFDA) sees contract manufacturing as a long-term goal. "Now is the right time to seriously talk about pharmaceutical contract manufacturing in China," said Dequan Ren, former Deputy Commissioner of the State Food and Drug Administration (SFDA). Following the implementation of GMP certification in China, the overall production level of the pharmaceutical industry has been improving. The SFDA also has accumulated sufficient experience for monitoring and management of biopharmaceutical facilities. Consequently, manufacturers in China feel it is time for the Chinese government to encourage contract manufacturing in the industry.

And it is not only the Chinese who see opportunity in their biopharmaceutical contract manufacturing. Bernard Pepperstraete, M.D., a principal at MASA Life Science Ventures, a VC fund in Washington D.C., also sees potential: "There is a cost advantage [in China] in infrastructure, raw materials, and manpower that will last five to 10 years. Preclinical animal testing is 20% of the cost of doing it anywhere else. And the government there has invested \$1.5 billion in initiatives to build creativity, innovation, and pursuit-of-patents. They are sending strong signals that they are addressing IP pitfalls. There is an enormous talent pool, and the cost of an equivalent experienced scientist in China is a third of what it would cost in the U.S. Although labor costs in Shanghai and Beijing are increasing, this differential should continue to exist, at least for the near-term."

But that doesn't mean China is without hurdles. The U.S. FDA will send auditors to a facility when it knows a therapeutic is manufactured and intended for the U.S. market. "This is a bit of a chicken-or-egg situation," according to Pepperstraete. "Getting the FDA to inspect will be a hurdle [to Chinese CMOs], given the current limited commitment from U.S.-based companies. To get U.S. approvals, a Chinese CMO will need to develop a relationship with a U.S.-based drug developer first."

Other hurdles may require time and resources to overcome. Cultural differences, IP protection, and adapting to different business styles will continue to require attention. In some situations, the costs associated with managing internationally can sometimes offset the benefits of overseas outsourcing. According to Mr. Pepperstraete, while none of these are insurmountable, in the short-term, it will require "nerves of steel to make this happen."

Chinese Government Policies

China's pharmaceutical contract manufacturing industry began relatively late primarily due to government-imposed restrictions, but the current increase in production capacity and the decrease in production facility utilization have pushed the government to take serious actions to encourage contract manufacturing businesses. The general expansion of China's pharmaceutical industry, particularly after GMP-certification for Chinese pharmaceutical manufacturers, has also played a role. During the past few years, the Chinese government has started to make efforts to establish an open and well-controlled system to facilitate the sound and steady development of pharmaceutical contract manufacturing.

Prior to 1999, the Chinese government heavily restricted

pharmaceutical contract manufacturing. In fact, it was considered illegal. The 1985 edition of Chinese "Drug Administration Law" defined drugs produced by manufacturers who had not obtained Production Approval Numbers as "counterfeit drugs".¹ This provision posed a huge obstacle to the contract manufacturing industry in China.

In October of 1999, the SFDA issued its "Announcement concerning regulations on drug production in different places and entrusted drug processing".² This allowed for drug contract manufacturing under certain circumstances. In the announcement, crude drugs, blood products and vaccines were specifically prohibited from production by contract manufacturers. Following that, the SFDA revised relevant policies to catch up with the steady expansion of contract manufacturing in China. Article 13 of the new edition of "Drug Administration Law" issued in February 2001 stipulated, "A drug manufacturer may accept contract production of drugs upon approval by the drug regulatory department under the State Council, or by the drug regulatory department of the people's government of a province, autonomous region, or municipality directly under the Central Government authorized by the drug regulatory department under the State Council".³ The new law legalized pharmaceutical contract manufacturing in China.

In August 2003, the SFDA clarified in the trial version of the "Regulations on Processing Drug for Export" that Chinese drug manufacturers may conduct contract manufacturing for a pharmaceutical company outside China.⁴ In August 2004, the SFDA issued the "Provisions for the Supervision of Drug Manufacturing" and lifted the ban on contract manufacturing of crude drugs. The provisions also pointed out that the SFDA would be responsible for the acceptance, examination and approval of any "cross-province contract manufacturing or contract manufacturing for injections, biologics (not including vaccines and blood products)".⁵ The most recent SFDA-issued regulation concerning contract manufacturing, which went into effect on January 1, 2006, was the "Requirements for Record-keeping of Pharmaceutical Processing Entrusted by Overseas Drug Manufacturers." This regulation clarified that a GMP-certificated Chinese pharmaceutical manufacturer may accept contract processing of drugs from foreign companies, provided that the processed drugs are not sold inside China.⁶ In all the SFDA regulations vaccines, blood products and Chinese herbal injections are excluded from the contract manufacturing drug list because these products require more strict production conditions.

The Chinese government remains cautious about relaxing restrictions on drug contract manufacturing to assure an orderly transition to this form of manufacturing. The government is taking into account drug safety and manufacturing standardization as it keeps pace with changes in international policies and regulations. These trends are likely to continue as China opens its doors to the outside world.

Current Situation

China completed Good Manufacturing Practice (GMP) certification on all the drug manufacturers present in China in July 2004. Manufacturers had been required to modify their facili-

ties according to the GMP standards before passing inspections. At the end of 2005, more than 5,000 Chinese drug manufacturers had obtained their Chinese GMP certificates. Although the GMP certification had eliminated a number of small-sized manufacturers, the overall production capacity of Chinese pharmas has risen dramatically as the result of GMP modification. This aroused concerns about excess production capacity.

A survey conducted by the China Pharmaceutical Enterprise Management Association in 2005 showed that the majority of GMP-certificated manufacturers in China do have excess production capacities. After GMP certification, the overall production capacity of Chinese manufacturers increased 75%. Chinese pharma manufacturers have invested a total of 150 billion RMB (\$18.75 billion) to modify their facilities to meet the GMP requirements, an average of 86 million RMB (\$10.6 million). During the first half year of 2005, the overall facility-utilization rate for drug manufactures was 55.4% (Injections: 71.5%, Soft Capsules: 70.84%, powder for injection: 67.09%, Oral Liquid: 38.3%).

The China Pharmaceutical Enterprise Management Association submitted a report to the SFDA suggesting that the government should relax restrictions on pharmaceutical contract manufacturing. The report also suggested that the SFDA should allow drug manufacturers to accept the contract production of health products and allow drug manufacturers to obtain production approval through other drug manufacturer's production facilities.⁷ The *Annual Report on the Chinese Pharmaceutical Statistics* also indicated that the overall facility utilization rate was 57.2% in 2002, 56.7% in 2003, and 55.0% in 2004, which revealed a gradual declining trend.⁸

Consequently, it has become a task for the Chinese government to increase the utilization of the 45% excess facility capacity, and give priority to the pharmaceutical contract manufacturing industry.

China's pharmaceutical industry had maintained a steady growth in recent years. In 1999, the gross annual output for the pharmaceutical industry was 198 billion RMB (\$24.2 billion). In 2004, this figure has reached a total of 458 billion RMB (\$56.5 billion). Pharmaceutical contract manufacturing in China has expanded silently, led and driven by the growing domestic market demands. Incomplete statistics suggest that around 13% of the 458 billion RMB in 2004 was generated by the contract manufacturing industry.⁹ China's recent pharmaceutical contract manufacturing increases are also partly the results of the impact of international cooperation.

CMOs in China

API CMOs

While most CMOs in China are not yet directly involved in biopharmaceuticals, many have been developing or acquiring the expertise, regulatory knowledge, and technical ability to participate on the world stage. Since the 1990s, a growing number of Chinese drug manufacturers have been involved in overseas contract manufacturing for crude medicines or Active Pharmaceutical Ingredients (API). An official record showed that Chinese manufacturers have acquired 246 valid Drug

Master File (DMF) numbers issued by the U.S. FDA as of the end of September 2005. The Chinese manufacturers with the largest number of DMFs include:

- Zhejiang Hisun Pharmaceutical Co.
- Shanghai Pharmaceutical (Group) Co.
- Shandong Xinhua Pharmaceutical Co. and
- Tianjin Pharmaceutical (Group) Co.

Other major API CMOs in China include Shandong Meiji Lukang Pharmaceutical Co. (Colistin Sulfate), Dalian Pfizer Pharmaceutical Co. (Cefoperazone), and Aurobindo (Datong) Biopharmaceutical Co. (6 -APA).¹⁰

Zhejiang Hisun Pharmaceutical Co. has been involved in contract manufacturing for overseas pharmas since the early 1990s. The company is one of the largest raw material drug manufacturers in China for antibiotics, anti-tumor drugs and other chemical drugs. The company's first crude drug, Tobramycin, was approved by the U.S. FDA in 1992. Following that, 13 bulk drugs (Adriamycin, Rubidomycin, Mitomycin, etc.) have been approved by the U.S. FDA and 10 bulk drugs (Simvastatin, Lovastatin, Ivermectin, etc.) have been approved by the COS (European Union). Four-fifths of Hisun's products are exported to Europe, America and Southeastern countries.¹¹ In 2004, Hisun's anti-tumor bulk drugs (Rubidomycin, Adriamycin, Mitomycin, etc.) accounted for 60% of the generic bulk drugs market in the U.S. Over the past few years, Hisun has cooperated with several multinational pharmas. In August 2005, Eli Lilly signed an agreement with Hisun to transfer the Capreomycin manufacturing technology gratis to Hisun. Lilly also invested an initial stake of more than \$1 million in Hisun. In December 2005, a U.S. venture capital firm, Vivo, acquired a 40+% share of Hisun. It has been reported that Lilly may be planning to acquire Hisun through the venture capital fund.

Shanghai Pharmaceutical (Group) Co. has been in negotiations with 20 leading pharmas about contract manufacturing 16 bulk drugs with more than 150 million RMB (\$18.5 million) in sales revenue. One of this company's subsidiaries, Shanghai Sine Pharmaceutical Factory, began construction in October 2004 of a solid preparation facility that will meet FDA and European cGMP standards. Suzhou Lederle Pharmaceutical Co. was once a contract manufacturer for Wyeth. It eventually was acquired by Wyeth.

The biannual China International Pharmaceutical Ingredients Fair (API China), the largest pharmaceutical ingredient fair in China, has attracted increasing numbers of international pharmas who are seeking to produce their therapeutics by CMOs in China. The 55th API China Fair held at Hangzhou in November 2005 attracted more than 32,000 professional visitors and 1,100 exhibitors from different parts of the world. A new specialized Outsourcing Manufacturing Service Zone showcasing exhibitors providing contract manufacturing services, customized manufacturing services, etc. was among the highlights of the exhibition.¹²

Pharmaceutical Preparation CMOs

Compared to contract manufacturing of crude drugs, there are very few Chinese manufacturers qualified to accept overseas

contract manufacturing. In 2005, crude drug exports from China reached \$7.9 billion, while drug preparation exports were \$378 million. A significant barrier for Chinese manufacturers is the different manufacturing standards set by various countries. In some cases, at least today, these standards may be much higher than Chinese GMP standards.

However, Chinese manufacturers are making efforts to meet the international production standards, especially the U.S. and European Union. For example, Shanghai Sine Pharmaceutical Factory's solid preparation factory, which was built according to FDA and European cGMP standards in October 2004, is expected to produce five billion pills annually.

In January 2005, Shanghai Fosun Zhaohui Pharmaceutical Co., Ltd. and the Danish LEO Pharma announced a cooperation to produce Fudicin Cream in China. This agreement (worth \$6.2 million annually to the Chinese company) was the first time in China's history that a Chinese pharma obtained a contract manufacturing project for finished drugs other than crude drugs from a European or American company. Following that, Xi'an Chiho Pharmaceutical Co., Ltd. passed the MHRA (Medicines and Healthcare products Regulatory Agency) examination in June 2005 and signed a manufacturing contract with a British company to produce hypertension therapeutics.

Biopharmaceutical Contract Manufacturing

Although biopharmaceutical contract manufacturing in China is at an early stage, the potential market is expected to be large. According to Desheng Zhou, the general manager of Beijing Kawin Biotech Co., a biopharmaceutical CMO in China, "Today, the biggest challenge for Chinese Biopharma CMOs in winning overseas manufacturing contracts is to build confidence with overseas pharmas." Even though the cost of scientific and production staffing is lower in China, it still requires funds to build world-class facilities. Beijing Kawin has a fully-automatic production line in China with an output of 100 million vials of Interferon each year. The six-month output of this production line can supply the whole country's market for one year. The company is technically supported by the Chinese Center for Disease Control and Prevention, and the National Key Laboratory for Virology and Genetic Engineering. It is aiming to become a world-class biopharmaceutical CMO and CRO.

Luo Yilong, the vice general manager of Beijing Pharmaceutical Group, predicted that more Chinese biopharmas would follow Beijing Kawin in seeking contract manufacturing, contract research, and marketing opportunities at home and abroad.

Other biopharma CMOs in China include Hangzhou Acon Biotech., Shenzhen Watsin-gene Engineering Co. Some Bio-Parks in China, such as the Liuyang Biopharmaceutical Park, have declared that they aim to become the largest contract manufacturing base in China.

Challenges and Opportunities

Currently, one of the biggest challenges for the Chinese Contract Manufacturers is to pass the corresponding inspections and examinations from key countries. Chinese contract

manufacturers must modify their facilities and train their staff to meet the requirements of international biopharmas, including the FDA cGMP or EU COS certification. So far, very few Chinese drug preparation manufacturers have managed to earn this passport.

To help Chinese pharmas overcome some of the obstacles on the way to the U.S. market, the U.S. FDA sponsored a cGMP training program in China in December 2005. The program provided the latest updates from the FDA on current regulations and guidance. More than 100 Chinese companies were represented by the 270 attendees. To date, around 130 Chinese drug manufacturers have obtained the cGMP certification issued by the U.S. FDA, and 50 manufacturers have received more than 90 COS certifications from the European EDQM. The Chinese government has paid great attention to the development of pharmaceutical contract manufacturing in China. More new policies will be promulgated by the SFDA in 2006 to enlarge the contract production scope. After China's entry to WTO, more Chinese drug manufacturers are seeking international partners. Contract manufacturing is becoming one of the most promising businesses in China as western pharmas recognize its lower material costs and its technical resources. ■

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