



# Biopharmaceutical Exports: China's New Business Strategy

### Converting China's pharmaceutical manufacturing capacity to biopharmaceutical exports



Eric Langer is president of BioPlan Associates, Rockville, MD, 301.921.9074, elanger@bioplanassociates.com.

More and more biotechnology and pharmaceutical companies in China are considering converting excess capacity to contract manufacturing as part of their overall biopharmaceutical products strategy. However, due to the significant capital investment, high operating costs, and quality requirements associated with contract manufacturing, this segment in China has not expanded as rapidly as it has in other Asian and Western markets. Moreover, until only recently, contract manufacturing of pharmaceuticals was not permitted in China. Even today, the State Food and Drug Administration (SFDA) regulations do not allow vaccines, China's main biological exports, to be contract manufactured.

With \$25 billion in excess pharmaceutical production capacity in China, and much of its production facilities standing idle,<sup>1</sup> many Chinese pharmaceutical organizations are beginning to evaluate the strategic value in biopharmaceutical production. Recombinant proteins are considered more technically complex, and the regulatory hurdles for these are higher, compared with other therapeutics, therefore, moving into this area requires a thoughtful approach.

Dr. DC Yu, of Kanghong Biotechnology Co., Ltd., in Chengdu, China, has seen a move among pharmaceutical firms in China to get into the biopharmaceutical field, including the conversion of existing resources or changes to their business directions. Many firms have started working on biologics, approaching it in a number of ways, said Dr. Yu, "A few approaches these companies are taking include building a biologic division, converting existing space into production facility for biologics, and building new facilities specifically for biologics." According to Dr. Yu, publicly listed companies, in particular, want to add 'sexy' products or capabilities in biotechnology. "A few biotech firms have been recently

## Large biopharmaceutical companies in China will likely become a more significant global resource for APIs and advanced intermediates.

acquired by pharmaceutical companies," said Yu. "The Gendicine manufacturer (Ad-p53, the first gene therapy product in the world) has been recently acquired by a pharmaceutical company, and Endostar (endostatin, which failed in the US in trials) was recently acquired by Simcere, which was recently listed in NYSE."

According to *Advances in Biopharmaceutical Technology in China*, the recent BioPlan Associates and Society for Industrial Microbiology study, an issue in considering contract manufacturing in China today is how companies will allocate excess production capacity, or obtain the resources needed to establish a biopharmaceutical CMO operation. "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 contract manufacturer in China. "We feel that contract manufacturing is the solution. The significance of conducting international contract manufacturing to us is strategic."

China is already an international supplier for active pharmaceutical ingredients (APIs) and intermediates, and as domestic consumption

increases, China will continue to attract the attention of global pharmaceutical and biotechnology companies. As Chinese fine chemical companies increasingly move into more complex areas like biopharmaceuticals, industry experts expect large global biopharmaceutical companies to consider China as a materials, labor, and service resource. Large biopharmaceutical companies in China will likely become a more significant global resource for APIs and advanced intermediates.

According to government statistics, China's biologics market exceeded \$2.5 billion in 2004 and is growing at a rate of 13% per year. This market is primarily dominated by generic manufacturers. Most of these companies are small domestic

## In 2006, China exported a total of \$890 million in biologics to other countries—a 30.61% increase, compared with the previous year.

players that compete on price and tend to have excess manufacturing capacity. With excess capacity and compressed margins, Chinese biopharmaceutical manufacturers are ideal to partner with or acquire.

### GROWING BIOLOGICAL EXPORTS

China's biological product exports are growing rapidly. In 2006, China exported a total of \$890 million in biologics to other countries—a 30.61% increase compared with the previous year. This increasing

focus on exports is likely to include expansion of contract manufacturing services. Tonghua Dongbao Pharmaceutical Co. exported \$8 million of recombinant human insulin products to 10 countries in 2006. Its export destinations included Russia, Poland, Mexico, and other developing countries. The company is planning to enter the EU and US markets by obtaining required certifications in 2009. It is acquiring a Sweden-based plant, which has received both EU and FDA certifications, to be its base for manufacturing Insulin in Europe.

Others are following a similar path. 3 S Bio Inc. is also planning to increase its recombinant human erythropoietin (rh EPO) exports. The company exported a modest \$753,000 in recombinant products in 2006, but plans to expand its exports to other developing countries.

### EVOLUTION OF CMO POLICIES

China's pharmaceutical contract manufacturing industry began relatively late due to government-imposed restrictions. Rapid industry growth and excess in production capacity encouraged the government to modify its policies. Before 1999, the Chinese government restricted pharmaceutical contract manufacturing, which was generally considered illegal. Back then, the Chinese Drug Administration Law defined drugs produced by manufacturers who had not obtained production approval numbers as counterfeit drugs. This provision posed a major barrier to contract manufacturing in China.

**Table 1.** Leading biopharmaceuticals in China

Founding year	Company name	Leading products
1989	Shenzhen Kexing Biotech	IFN $\alpha$ 1b, IL-2, GH, Insulin
1992	Beijing Tri-Prime Genetic Engineering	IFN $\alpha$ 1b
1992	Tianjin Hualida Bioengineering	IFN $\alpha$ 2b
1993	Guangxi Beisheng Pharma. (plc)	IFN $\alpha$ 2b, TF
1993	Shenyang Sunshine Pharma.	EPO, IFN $\alpha$ 2a, IL-2, TPO*
1993	Guandong Techpool Biopharma	Urokinase
1994	Anhui Anke Biotech	IFN $\alpha$ 2b, GH, MAR AsAb kit
1994	Beijing SL Biotech (plc)	IL-2, IL-11, bFGF
1995	Changchun GeneScience	GH
1995	Shanghai Sunway Biotech	G-CSF, H101-103*
1995	Shandong GeneLeuk Biopharma	G-CSF, GM-CSF, TNF- $\alpha$
1997	NCPG GeneTech Biotech Dev.	GM-CSF, G-CSF, EPO, HB Vac
1998	Beijing Tiantan Bio. Products (plc)	Albumin, immunoglobulin
1998	Shenzhen SiBiono GeneTech	rh Ad-p53*
1999	Yantai Medgenn	YH-16*
2000	Shanghai Celstar Biopharma	rmh TNF
2000	Beijing BioTech Pharma.	h-R3*, EGF Vac
2001	Beijing Sinovac Biotech	Vaccines
2002	Tianjin Fusogen Biotech	Sifuvirtide*
2005	Chengdu Hoist Biotech (plc)	I- 131 Monoclonal Antibody*

\* Class I new drugs approved by SFDA since 2004.

Beijing Kawin Bio-tech Co., Ltd.,  
National Engineering Research  
Center for Viral Bio-Technology



In 1999 the SFDA issued its “announcement concerning regulations on drug production in different places and entrusted drug processing.”<sup>2</sup> This allowed drug contract manufacturing; however, crude drugs, blood products, and vaccines continued to be prohibited from CMO production. In 2001 the SFDA stipulated that, “A drug manufacturer may accept contract production of drugs upon approval by the drug regulatory department under the State Council...”<sup>3</sup> The new law legalized pharmaceutical contract manufacturing in China. In 2003, the SFDA clarified its “regulations on processing drug for export,” noting that Chinese drug manufacturers may conduct contract manufacturing for a pharmaceutical company outside China.<sup>4</sup> In 2004, the SFDA lifted the ban on contract manufacturing of crude drugs.<sup>5</sup> In January 2006, a record-keeping regulation clarified that a GMP-certified Chinese pharmaceutical manufacturer may accept contract processing of drugs from foreign companies, provided the processed drugs are not sold inside China.<sup>6</sup> The SFDA regulations continue to exclude vaccines, blood products, and Chinese herbal injections from contract manufacturing.

### CURRENT GMP SITUATION

China completed the good manu-

facturing practice (GMP) certification for all the drug manufacturers present in China in July 2004. Most manufacturers were required to modify their facilities according to the GMP standards before passing GMP inspections. At the end of 2005, more than 5,000 Chinese drug manufacturers had obtained their GMP certificates. Although the GMP certification process eliminated a number of small-sized manufacturers, the overall production capacity of Chinese pharmaceuticals increased dramatically as a result of GMP modification. Manufacturers invested an average of \$10.6 million to modify their facilities. The Chinese government recognized that it must improve the current capacity utilization rate (currently 45% excess facility capacity),<sup>7</sup> and give priority to the pharmaceutical contract manufacturing industry.

### BIOPHARMACEUTICAL CONTRACT MANUFACTURING

Biopharmaceutical contract manufacturing in China is young. According to Desheng Zhou, the GM of Beijing Kawin Biotech Co., one of China’s few biopharmaceutical contract manufacturers, “Today, the biggest challenge for Chinese biopharma CMOs in winning overseas manufacturing contracts is building confidence with overseas pharmas.” Beijing Kawin has a fully

automatic production line in China with a staff of 200 employees, and an output of 100 million vials of Interferon each year.

Other biopharmaceutical CMOs in China include Hangzhou Acon Biotech and Shenzhen Watsin-gene Engineering Co. Also, some bioparks in China, such as the Liuyang Biopharmaceutical Park, have indicated that they plan to become major centers for contract manufacturing in China.

Most of the CMOs in China today are not yet directly involved in biopharmaceuticals. Many have been developing or acquiring the expertise, regulatory knowledge, and technical ability to participate in this arena. The Chinese manufacturers with the largest number of Chinese drug master files include:

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

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

### BIOPHARMACEUTICAL MANUFACTURERS IN CHINA

Since the founding of the first modern biopharmaceutical company in China (Shenzhen Kexing Biotech) in 1989, Chinese biopharmaceutical companies have experienced rapid growth. By the end of 2005, China had around 400 biopharmaceutical manufacturers, among which 40 are capable of manufacturing genetically engineered drugs, 30 manufacturing vaccines, and 34 manufacturing blood products. Over 20 listed

## Challenges for the Chinese contract manufacturers include establishing quality management and passing relevant EU and US FDA inspections.

companies in the Chinese stock market have been involved in the biopharmaceutical industry. These listed companies include the Shanghai Fosun Pharmaceutical Group, Ginwa Group, Beijing Tiantan Biological Co., Ltd., Beijing Four-rings Biopharma, Guangxi Beisheng Pharma, Beijing SL Pharma, Shenzhen Neptunus Bioengineering, and Changchun High-tech. In 2005, the domestic annual sales revenue of biopharmaceuticals in China reached \$3.8 billion, accounting for 7.5% of the total pharmaceutical revenue (including blood products, intermediaries, and vaccines). The majority of Chinese biotech pharmaceuticals remain small.

### CHALLENGES AND OPPORTUNITIES

Challenges for the Chinese contract manufacturers include establishing quality management and passing relevant EU and US FDA inspections. Chinese contract manufacturers recognize that they will need to modify their facilities and train their staff to meet US cGMP standards and EU COS certification. So far, very few Chinese drug preparation manufacturers have met these hurdles. The US FDA sponsors cGMP training programs in China and provides the latest updates from the FDA on current regulations and guidance. In a recent program, 270 people from over 100 Chinese manufacturers attended the training. Over 90 Chinese drug manufacturers have

obtained the cGMP certification issued by the FDA. After China's entry into the World Trade Organization in 2001, Chinese drug manufacturers have been seeking international partners, and contract manufacturing is becoming one of the more promising business approaches that Chinese producers have been evaluating. This approach may expand as western biopharmaceutical companies recognize the technical resources and relatively lower costs available in China. ♦

### REFERENCES:

1. Advances in biopharmaceutical technology in China. Society for Industrial Microbiology and BioPlan Associates, Inc., 2006.
2. Announcement concerning regulations on drug production in different places and entrusted drug processing [in Chinese]. State Drug Administration Office [1999] 300. 1999; Oct. 8.
3. Order of the president of the People's Republic of China, No. 45. Drug Administration Law of the PRC [in Chinese and English]. 2001; Dec. 1.
4. Regulations on processing drug exports (trial version) [in Chinese]. SFDA [2003] No.189. 2003; July 29.
5. Provisions for the supervision of drug manufacturing [in Chinese]. SFDA [2004] No. 14. 2004; Aug. 5.
6. SFDA. Requirements for record-keeping of pharmaceutical processing entrusted by overseas drug manufacturers [in Chinese]. SFDA [2005] 541. 2005; Nov. 5.
7. China pharmaceutical facility utilization survey report: To encourage pharmaceutical contract manufacturing [in Chinese]. Based on a survey conducted by the China Pharmaceutical Enterprise Management Association in 2005 showing utilization rates. 2005; July.