Opportunities in Biopharmaceutical Outsourcing to China

by Yibing Zhou

Spiraling costs of biopharmaceutical research and development (R&D) and manufacturing have driven an increasing number of multinational biopharmaceutical companies to consider outsourcing their activities. Reducing costs and increasing efficiency and productivity are vital to maintaining competitiveness. It takes 10–15 years to bring a new medication to market, and it can cost more than US$800 million in the West. By comparison, the cost of developing a new drug in China may be 20% of that amount and often with shorter development time (**1**).

According to a newly released study on the Chinese biopharmaceutical industry by BioPlan Associates, Inc. (BioPlan) and the Society for Industrial Microbiology (SIM), a reduction in costs can support the development of new drugs and open opportunities in new markets for biotherapeutic products in the world's most populous country. Therefore, China is rapidly becoming an important geographic center for global biopharmaceutical companies seeking outsourcing and partnering options. Despite the opportunities, however, some substantial strategic and operational considerations remain.

China's rapidly expanding economy has made it the "world's manufacturer" for many labor-intensive products; however, biopharmaceuticals are in a different technical class. To secure a competitive position, China is expanding its outsourcing services in life sciences and healthcare. The Chinese government has prioritized the life sciences sector and plans to boost its overall services industry. China's Ministry of Commerce is budgeting for projects to establish outsourcing facilities over the next three years, according to *China Daily*. The goal is to bring in up to 100 multinational corporations that will transfer technology and outsourcing business to China. This effort is expected to create 1,000 large-scale international service outsourcing enterprises in China (**2**).

Home of the once "Forbidden City," Beijing (along with Shanghai and the rest of China) is open for biotech business. SOLOMON JONES (WWW.SXC.HU)

"The single biggest opportunity in China is its lower labor costs and increasingly high-quality labor services. This, coupled with excellent infrastructure, puts it in some contrast to India," said Glenn Rice, PhD, CEO of Bridge Pharmaceuticals, Inc., a fast-growing CRO headquartered in the United States with a 100,000-ft^2 facility in the Beijing Zhongguancun Life Science Park. Rice predicts that in five years, "The single biggest technical factor [affecting Chinese and Western pharmaceutical companies] will be the need for increased productivity — the greatest impact for China in this regard is the trend towards globalization of drug development. Cutting costs in a quality manner across research, manufacturing, and development will largely be done through outsourcing to places like China and India, and for some tasks, Eastern Europe. But quality will need to meet or exceed current western standards."

Biopharmaceutical companies are increasingly considering outsourcing R&D and production of drug candidates, especially for early stage drugs. According to the BioPlan study involving 377 biopharmaceutical manufacturers and CMOs, 60% of biotherapeutic developers will be outsourcing at least some of their

mammalian cell culture production, and 58.2% will be outsourcing at least some of their microbial fermentation production by 2011 (3). In the future, more drug products will be developed and produced with technical support from external experts. According to Rice, "This will involve all aspects of protein development, formulation, manufacturing, screening, optimization, toxicogenomics, toxicology, development of biomarkers, and clinical trials. Efficiencies will be improved . . . all with the understanding of who is the boss — the FDA!"

Why China?

China's large biotechnology research facilities and skilled worker pool, combined with its lower resource costs, make the country attractive to biopharmaceutical companies considering overseas outsourcing. The Chinese government has been amending policies, increasing investments, and enhancing intellectual property (IP) protection to attract investment.

China today is a $10–$13 billion pharmaceutical market — putting it amonth the top 10 pharmaceutical markets worldwide. While those global markets grew 7% in 2005, China's pharmaceutical sales grew 20.4%, making that the third consecutive year its market has achieved more than 20% growth (4). Boston Consulting Group (BCG) forecasts indicate that China will become the world's fifth-largest pharmaceutical market in the next five years (5). The Chinese government is actively encouraging this growth through policy reform, thus creating opportunities for established biopharmaceutical companies.

Whereas each American spends about US$700 on medicines yearly, the Chinese spend only $18 (6). As a sizable middle-class expands across the country with China's improving economy, drug spending is predicted to rise dramatically. Some business observers predict that China will become the world's third largest pharmaceutical market after the United States and Japan (7).

Western Companies in China: China's biopharmaceutical talent pool and lower costs have made it attractive to biopharmaceutical companies worldwide. Global companies with a presence in China include Novo Nordisk, AstraZeneca, Eli Lilly, Roche, GlaxoSmithKline, and Pfizer. All have established relationships with Chinese counterparts or established R&D facilities in China. Many others have set up joint-venture operations in partnership with Chinese institutes. AstraZeneca has been outsourcing pharmaceutical R&D to China through its collaborations with 139 Chinese hospitals and research institutes.

"China has unparalleled cost advantages compared with the developed countries, attracting multinational pharmaceutical companies to offer their outsourcing contracts to China," said Xiaoming Zhou, director of the China Chamber of Commerce of Medicines and Health Products Imports and Exports. In addition to significantly lower labor costs, "China is also very competitive in raw materials, energy, and other auxiliary facilities. The overall production capacity of Chinese pharmaceutical manufacturers has increased significantly following the nationwide GMP certification [completed in 2004]. This was the result of China's 4,000 pharmaceutical manufacturers investing US$40 billion to [improve] their facilities."

Global Outsourcing Market Size and Growth: The global pharmaceutical outsourcing industry was estimated at US$48 billion in 2002 and rose to US$60 billion in 2005 (8). Outsourcing includes drug discovery research, preclinical testing, clinical trials, manufacturing, packaging, distribution, and even marketing and sales. Typically, CROs can provide drug discovery and development, preclinical, clinical, drug registration support, and regulatory consulting service to their clients. CMOs usually provide small-scale synthesis, large-scale synthesis, facility design, and manufacturing support with the ability to supply intermediates, active ingredients, and formulations. Contract sales organizations (CSO) have increasingly become partners for marketing and sales of newly approved products by providing postlaunch support.

Biopharmaceutical companies have increased their outsourcing expenditures dramatically over the past decade, with an estimated 40% of pharmaceutical drug development expenditures committed to outsourcing (9). Globally, the biopharmaceutical outsourcing industry is estimated to reach US$60 billion over the next five years (9). Early drug discovery outsourcing is growing at an annual rate of 15%, with revenues expected to reach US$7 billion in 2009 (7). The United States accounts for the majority of these expenditures; however, Europe and Asia will both represent the largest beneficiaries of these investments.

The worldwide CRO market size was estimated at over US$12 billion by 2005, with revenues increasing at an annual rate of 14–16%, according to CenterWatch estimates (10).

The global market for biopharmaceutical contract manufacturing is predicted to reach US$2.5 billion in 2006, with only a small percentage of this work to be conducted in Asian countries (11). However, Asia's percentage is expected to grow as

Table 1: Biopharmaceutical* and pharmaceutical sales revenue in China (Exchange rate — USD:RMB=1:7.97) (**6**)

	Biopharmaceuticals		Pharmaceuticals		
Year	billion RMB	billion USD	billion RMB	billion USD	Share
2005	30.31	3.80	402.0	50.44	7.5%
2004	24.90	3.12	347.6	43.61	7.2%
2003	22.34	2.80	296.2	37.16	7.5%
2002	16.04	2.01	246.4	30.91	6.5%
2001	14.80	1.86	206.0	25.85	7.2%

* Biopharmaceuticals include both biological products and biochemical products

pricing pressures in biopharmaceutical markets increase, intellectual property issues are effectively managed, and production quality continues to improve.

The biopharmaceutical industry spends US$15 billion on outsourcing manufacturing, formulation, and packaging. Contract manufacturing is expected to grow at an annual rate of 10–15%, with most analysts expecting the overall biopharmaceutical industry to grow at a rate of 8–10% in terms of volume (**7**). Biopharmaceutical manufacturing outsourcing is expected to grow rapidly given that many companies have limited facility capacity.

Market Summary for Biopharmaceuticals in China: China's biopharmaceutical industry began in the 1980s and has experienced rapid growth since then. The BioPlan report indicates that China's biopharmaceutical sales revenue in fiscal year 2005 achieved US$3.8 billion, a 30% growth over the previous year, which accounted for 7.5% of the country's total pharmaceutical sales (Table 1). The country's biopharmaceutical industry production value is projected to exceed 100 billion renminbi (RMB) (US$12.5 billion) in 2015. This growth in the Chinese domestic biopharmaceutical industry has helped fuel the development of its services sector as well. As growth continues, more western pharmaceutical companies will seek access to Chinese markets.

Improving the IP Environment: China's pharmaceutical environment experienced radical changes over the past 25 years. In 1980, China joined the World Intellectual Property Organization, an event that marked the beginning of a modern Chinese intellectual property rights (IPR) protection and enforcement system. Another historic milestone was China's entry into the World Trade Organization (WTO) in 2001. The government has emphasized its commitment to welcome foreign investment and services and products while enforcing IPR protection in China. This is a significant factor in the increased "offshoring" to China. Since joining, the country has made impressive progress in protecting and enforcing IPR. Many foreign companies have demonstrated growing confidence in Chinese IPR systems by filing patent applications in China.

According to Michael Wise, a partner in the Los Angeles office of Perkins Coie, "China must be considered as a potential country in which to file patent applications for any international patent portfolio."

Cost Advantages: Western pharmaceutical companies are establishing production and research facilities in China to take advantage of lower-cost skilled workers and special tax-exempt policies for foreign investment enterprises. Cost advantages are found in R&D, raw materials, and labor in China. An investigation conducted by Excel PharmaStudies, a Chinese CRO, showed that the costs for different stages of drug R&D in China range from 15% to 60% of the costs of the West ("Drug R&D Cost" box). Similarly, hiring a research professional in China with a PhD degree obtained in the United States would cost US$10,000–20,000, much lower than in western countries.

Chinese Government Investments in Biopharmaceuticals: The Chinese government has listed biotechnology on its national five-year plans since the 1980s. It has invested billions of renminbi to stimulate the expansion of this sector. In past decades, the government invested RMB$15 billion (US$1.9 billion) in biotech development, and this level of investment is likely to continue (**13**). China's State Food and Drug Administration (SFDA) is also amending policies to stimulate the country's outsourcing industry. Central and local governments have invested in more than 100 biotech parks and offer many favorable tax concessions to the companies located in these parks. For example, newly-established foreign-invested (including both Sino–foreign joint venture and wholly foreign-owned) companies with an operation period of over 10 years are exempted from income tax for the first two years, starting from the first profitable year, and will be levied half the income tax (tax rate 7.5%) from the third to the fifth year (**14**).

Streamlined Approval Process: The approval process for a new therapeutic takes five to eight years in China. By contrast, it requires an average of eight to 10 years in the United States (**15**). Despite the shorter timeframe, China's approval process is similar to that in the United States and includes investigational new drug (IND) applications followed by three phases of clinical trials. Figure 1 shows the procedures for conducting clinical trials in China (**16**).

China's Biotech Talent Pool and "Hai Gui": China has around 20,000 researchers in the life sciences, and its biotech talent pool is quickly achieving world-class status. In the past two decades, Chinese universities have trained about 100,000 biotech researchers. Nearly 1,000 universities

R&D Cost Comparisons (12)

Preclinical
Chemistry: 30% to 60% of westerm cost

Other Preclinical
Toxicology: 30% of western cost

Animal Testing: 30% of western cost

Clinical
Phase 1: 15% of western cost

Phase 2–3: 20% of western cost

and colleges in China offer biology-related courses, and more than 500 universities and colleges offer biology-related programs. More than 20,000 university students graduate each year in biology-related fields. Additionally, one-third of the 300,000 overseas Chinese students are currently enrolled in various biology programs (**17**).

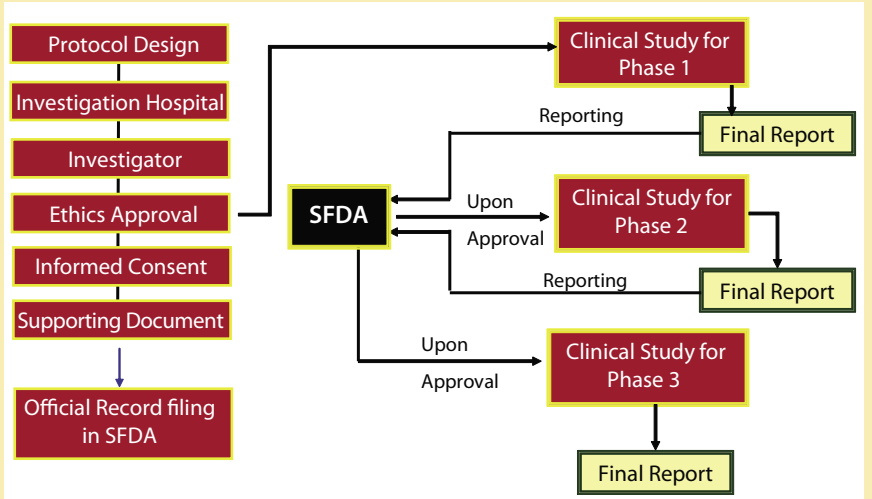
Many Chinese biotech research institutes and biopharmaceutical companies are founded or directed by "hai gui." These are Western-trained Chinese returnees who have stayed overseas for many years. Such people have acquired commercial experience and have been exposed to cutting-edge academic and commercial research technologies. These talented professionals are playing an indispensable role in helping China keep pace with the world's advanced biotech and pharmaceutical fields.

Production Capacity in China: China's biopharmaceutical industry today is relatively small-scale, with around 400 small-to-medium sized biopharmaceutical companies producing 2,000 biological products. Further, the majority of Chinese biopharmaceutical manufacturers produce biogenerics.

However, Chinese research-based biopharmaceutical companies have recently launched and patented 10 novel recombinant products. These include

• recombinant human Ad-p53 injection (Shenzhen SiBiono GeneTech, www.sibiono.com/en)

Figure 1: Chinese procedures for conducting clinical trials (phase 1–3)



• recombinant human adenovirus type 5 injection (Shanghai Sunway Biotech, www.sunwaybio.com.cn)

• recombinant endostatin (Yantai Medgenn, www.medgenn.com/en)

• recombinant human brain natriuretic peptide (Chengdu Rhodiola Bio-Pharma Co. Ltd., www.xzyy.en/english.asp)

•recombinant thrombopoietin injection (Shenyang Sunshine Pharmaceutical Co. Ltd., www.3sbio.com).

All Chinese pharmaceutical companies completed Chinese GMP certification before July 2004. One unexpected consequence generated by national GMP certification was that the overall production capacity of Chinese pharmaceutical companies increased dramatically. Excess production capacities have become a strong driving force for Chinese companies to seek contract manufacturing opportunities. The State Food and Drug Administration of China (SFDA) is also under pressure find a way to keep the 45%-idle facilities running. Thus, the Chinese government is beginning to modify policies to attract more foreign companies to place outsourcing contracts in China (**18**).

Chinese CROs and pharmaceutical CMOs are also making efforts to improve their research and production level to achieve international standards. China has 300 CROs of all sizes. Additionally, 259 pharmaceutical products associated with 130 Chinese manufacturers have obtained CGMP certification from the US Food and Drug Administration (FDA), and 50 manufacturers have obtained 90 European Certificate of Suitability (COS) certification. Among them 10 finished drug manufacturers have received CGMP certification from the US FDA.

In short, political, economic, and technological factors are beginning to create a favorable environment for global pharmaceutical and biopharmaceutical companies to consider outsourcing to China (Table 2).

Choosing Outsourcing Partners in China

China has more than 1,000 domestic biotech and pharmaceutical research institutions and 400 biopharmaceutical manufacturers. These institutions and companies are open to contract research and manufacturing opportunities. As part of the BioPlan study, a database was developed that details biopharmaceutical research institutes and manufacturers in China. This database was developed to help Western companies identify and locate potential outsourcing partners in China.

The number of CROs and CMOs in China is growing. To meet increasing needs for clinical research and manufacturing services today, there are now more than 300 Chinese and western CROs. These companies form an integrated service chain,

offering a wide variety of services from the earliest stage of drug discovery and development though clinical studies, new drug application, and postapproval research. Biopharmaceutical CROs in China are now also providing technical services such as nucleotide sequencing and synthesis, protein expression, chemical custom development and other chemistry-based, drug screening, and clinical development services (Table 3 provides a summary list).

Table 2: Supportive factors for outsourcing to China

Political	• Increasing government investment in biotech R&D and training • Relaxation of government policies associated with outsourcing • Shorter and controlled approval process • Growing government commitment to IP protection
Economic	• Low R&D and production cost • Low labor and raw material costs • Preferential taxation policies for foreign investment

Technological	• Large biotech talent pool
	• Many biotech research institutes
	• Rich clinical and disease resources
	• Shorter time to complete clinical trials
	• Production
	  • Improved production facilities after GMP certification
	  • High production capacity

Market	• Large market potential • Double-digit growing market • Increasing demand for medications

Table 3: Typical CROs in China and their services

CRO	Ownership	Location	Service
Wuxi Pharma Tech	Chinese	Shanghai Pudong	Drug R&D, chemical synthesis
Shanghai Genomics Inc.	Chinese	Shanghai Zhangjiang	Drug gene R&D
Shanghai Lead Discovery Pharma	Chinese	Shanghai Zhangjiang	Drug R&D
Shanghai Pharma Engine Co. (CRO)	Chinese	Shanghai Zhangjiang	Regulatory and clinical study
Pharmaron Pharmaceutical Technology	Chinese and United States	Beijing	Organic synthesis and R&D
Excel PharmaStudies Inc.	Chinese	Beijing	Regulatory and clinical study
Guangzhou Pudu Pharma Sci & Tech Development	Chinese	Guangzhou	Drug R&D
Quintiles Transnational Corporation	United States	Beijing and Shanghai	Regulatory and clinical study
Bridge Pharmaceuticals Inc.	United States	Beijing	Preclinical study
MDS Pharma Service	United States	Beijing	Clinical study
Beijing KendleWit Medical Consulting Co.	Chinese and United States	Beijing	Regulatory and clinical study
Shanghai InCROM Pharma Development Co.	Japanese	Shanghai	Clinical study
Center for Clinical and Basic Research (CCBR)	Denmark	Denmark	Clinical study
VenturePharm CRO Service	Chinese, United States, and Canadian	Beijing	Clinical study
Starvax Inc.	Chinese	Beijing	Toxicology, pharmacology, and animal studies

Generally, major Chinese CROs are concentrated in Beijing and Shanghai, especially in two large life science parks: Shanghai Zhangjiang Biopharmaceutical Park and Beijing Zhongguancun Life Science Park. Beijing's park alone boasts more than 100 CROs, many of them specializing in clinical trial services. CROs in Shanghai are more focused on drug development. The Shanghai Biopharmaceutical R&D CRO Service Base and Shanghai Pudong Biopharmaceutical R&D Service Center host more than 30 CROs and plan to become Asia's largest CRO facility. The centers operate under US good laboratory practice (GLP) standards.

To date, 20 more preclinical research laboratories in China have received SFDA-issued GLP certifications. These laboratories primarily include many national and provincial centers for new drug safety evaluation across China. It is estimated that 30 laboratories will receive GLP certification by the end of 2006.

Compared with the fast-growing contract research business, biopharmaceutical contract manufacturing in China is lagging behind. So far, vaccines, blood products, and Chinese herbal injections are excluded from the contract manufacturing drug catalog by the SFDA because these products require more strictly controlled production conditions. Many Chinese biopharmaceutical CMOs (e.g., Beijing Kawin Biotech Co., Hangzhou Acon Biotech, and Shenzhen Watsin-Gene Engineering

Trends in Biopharmaceutical Outsourcing to China

- Increasing IP protection enforcement
- Emphasis on R&D innovation
- Regulatory reforms
- Increased investments in biotech outsourcing
- Venture capital development
- Health insurance reforms
- Adoption of international standards
- Government policies to support China's becoming a major biotech player

Things to Consider

Intellectual Property: The government keeps IP protection high on its agenda following China's entry to the WTO. However, enforcement is still problematic. While intellectual property protection is improving rapidly in China, most investors remain cautious.

Immature Capital Market: One of the biggest problems for most Chinese biopharmaceutical companies is the lack of financing channels. According to Zero2IPO statistics in 2004, China's pharmaceutical industry acquired only RMB$ 270 million RMB (US$34 million) of venture capital. Overseas VCs remain hesitant to invest in the Chinese biopharmaceutical market. A major concern is that China has not established an effective venture capital withdrawal system.

Management Staff: Despite their wealth of talented scientist, one of the major issues facing organizations in China is a limited pool of talented mangers. The Chinese government is addressing these issues by actively recruiting expatriates to return to China. Incentives are provided to managers with Western experience, and technical capabilities to return to China to support this growing sector.

Language barriers: China had a closed-door policy to the outside world for decades prior to 1980s. Chinese people were not encouraged to learn foreign languages. As a result, today many Chinese, particularly older Chinese, do not speak English.

Co.) are actively looking for overseas contract manufacturing opportunities.

When choosing a right partner in China, western biopharmaceutical companies should consider seeking assistance from local government agencies, especially the administration offices in various high-tech or biotech parks. This will help ensure a good understanding of favorable or unfavorable policies. Identifying potential partners or consultants with good business records is a next step. Foreign enterprises can save time and resources by managing risks and identifying the right partner for working in China.

Strategic Considerations When Outsourcing to China: Despite the opportunities, there are still some substantial strategic and operational considerations to be managed. Chinese enterprises tend to be small and their research efforts limited. The lagging technology in domestic research results in inefficient and less-innovative systems for research and production of complex protein therapeutics. In addition, some functional issues are still being resolved. According to the BioPlan study, issues include intellectual property protection, immature capital markets, limited management staff, and language barriers ("Things to Consider" Box).

Outlook

Although today China currently accounts for less than 2% of the world market, its growth opportunities are promising. With the world's largest population, supportive government policies, and rapid economic expansion, the environment for a strong biopharmaceutical outsourcing sector in China has formed. Chinese CROs and CMOs are preparing to embrace more outsourcing opportunities in the coming years. As a result, biopharmaceutical outsourcing in China will continue to expand.

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