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Biogenics in China: An Evolving Industry

China's large domestic market potential and its competence in producing biogenics are driving its future direction

Development of biogenics today is more a function of intellectual property (IP) and politics rather than scientific factors. With the approval of biogenics no longer a hypothetical, the global industry must now determine pathways for efficient development. China's rapidly growing biopharmaceutical industry plays a significant role in the biogenics picture. A key question, addressed in *Advances in Biopharmaceutical Technology in China*, a recent study conducted by BioPlan Associates and the Society for Industrial Microbiology, is whether China's biogenics industry is moving in the right direction, or in a disorganized way with little consideration for IP issues (See *Biopharm International* Column, May 2007, "For Biopharma Considering China, Are IP Fears Unfounded?")

Most healthcare policymakers in China and in the West recognize that generic drugs are important to healthcare policy. Because biopharmaceuticals are currently among the most expensive therapeutics on the market and many blockbuster biopharmaceuticals are losing patent protection, the biogenics industry will clearly expand.

In China and India where regulatory and IP standards for biogenics are more liberal, a biogenics industry is already thriving. In China, the presence of a substantial biogenics industry reflects a growing need to provide modern healthcare to its domestic populations, at a reasonable cost. Although China sells its products primarily domestically, many western drug innovators [QA: Where? In which countries?] struggle with the impact such biogenics may have on commercialization opportunities and IP protection.

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BIOGENICS AND BARRIERS TO EXPANSION

Biological products in China are mostly biosimilars or biogenics of Western-invented products. This situation is changing as Chinese biopharmas invest in product innovation. However, the country's relatively low investment in R&D and the late development of its recombinant DNA technologies have resulted in

Table 1. Imported drugs with administrative protection in China

Owner	Product Name	Generic Name	Application Date
Novartis	Zometa inj.	Zoledronic acid	2004
Schering-Plough	Aerius tab	Desloratadine	2001
Sanofi-BM Squibb	Aprovel tab.	Irbesartan	2000
Novo Nordisk	NovoNorm tab.	Repaglinide	1999
Pharmacia-Upjohn	Parmorubin	Epirubicin RD	1998
Glaxo Welcome	Epivir	Lamivudine	1998
Pfizer	Trovan	Trovafloxacin Mesylate	1998
Amgen	Infergen	Interferon alfacon-1	1998

Source: China's SFDA announcements

Table 2. Expired or expiring proprietary biopharmaceuticals

Brand name	Generic name	Company	Expiry year
Neupogen	G-CSF	Amgen, Roche	2006
Novolin	Human Insulin	Novo Nordisk	2005
Protropin	Growth Hormone	Genentech	2005
Activase	t-PA	Genentech, Boehringer Ingelheim, Mitsubishi, Kyowa Hakko Kogyo	2005
Epogen/Procrit	EPO- α	Amgen, Johnson&Johnson, Sankyo	2004
Nutropin	Growth Hormone	Genentech	2003
Humatrope	Growth Hormone	Eli Lilly	2003
Avonex	Interferon β 1a	Biogen	2003
Intron A	Interferon α 2b	Schering-Plough	2002
Humulin	Human Insulin	Eli Lilly	2001

most biologics production being based on non-Chinese IP. In recent years, however, government support has encouraged greater innovation in biological products marketed in China. Still, there are obstacles hindering the industry's success. These continue to impact innovation, and include:

- Low levels of product commercialization: Inexperience in manufacturing processes increases production costs and makes large-scale production difficult.
- Inadequate market expansion: Products that may be highly successful in the US, such as erythropoietin (EPO) and growth hormone (GH), tend to yield smaller sales revenues in the Chinese market. Population structure, health insurance systems, and retail pricing of these drugs are relevant factors contributing to the disparities.
- Small-scale production with duplicated investment: 21 genetically engineered drugs and vaccines have been approved for marketing in China. Of the world's top 10 biologics, eight

can be manufactured in China. While just one or two manufacturers could meet market demands, multiple manufacturers duplicate production. For instance, more than 10 enterprises manufacture EPO and interferon α 2b and α 2a in China; more than 20 enterprises produce GM-CSF and G-CSF.

- Relatively few products have proprietary IP rights: The technology behind many products is not adequately protected—many are produced on a small scale, with small profit margins.
- Limited managerial and technical leadership: There is a need for

more experienced, high-quality managers, and talented technical professionals.

PHARMACEUTICAL INDUSTRY BACKGROUND

China produces more generic drugs than any other country in the world. Since the 1950s China has manufactured these products to supply its domestic demand. Today, generic drugs still dominate the Chinese pharmaceutical market. However, we are seeing more domestic innovation, and the market share of innovative drugs increased from 17% in 1997 to 20% in 2003.¹ For healthcare policy, economic, and scientific reasons, generic drugs have played a key role in the Chinese pharmaceutical market over the past several decades, and this trend will most likely continue in the future.

China began developing innovative drugs only recently. Its ability to innovate remains relatively limited, partly due to the current capital investment climate. In contrast, most Chinese drug manufacturers have produced generic drugs for several decades. China's technical competence in producing generic drugs and its advantage in raw materials have made the country a global off-patent crude drugs processing center. Abundant raw material and basic manufacturing talent support China's generics drug production.

Beginning in the early 1980s,

Table 3. Comparison of maximum retail price of interferons (IFN) controlled by National Development and Reform Commission (NDRC)

Product name	Brand name	Manufacturer	Specification	Retail price (\$)
rh IFN α -2a	Roferon-A	Roche	3 million IU	\$24.75
rh IFN α -1b	Intron A	Schering-Plough	18 million IU	\$158.00
rh IFN α -2a	Chinese biogenerics		3 million IU	\$5.75
rh IFN α -2b	Chinese biogenerics		3 million IU	\$6.67
rh IFN α -1b	Chinese biogenerics		50 μ g	\$11.00

Source: Excerpted from NDRC announcement 2005 [1762] Sep. 18, 2005

In the West, concept of biogenerics is seen as an IP and policy issue. In China, it is a healthcare issue.

the Chinese pharmaceutical industry began to modernize. However, Chinese pharmaceutical companies did not develop innovative drugs because of financial and technical obstacles. Patent laws were not a significant consideration. In fact, when China's patent law was first enacted (effective April 1985), it excluded drugs from patent protection. China's Drug Administration Law (July 1985) specified that pharmaceutical products that had never been manufactured in China were 'new drugs.'

China has a short, but very rapidly evolving history of protecting IP rights for pharmaceutical products. Practical patent protection for pharmaceuticals was simply not available in China until 1993 when China's patent law legalized drug patent protection. Since 1998 China's State Drug Administration (SDA) Protection Office has authorized administrative protections for 155 drugs from 12 different countries as of July 2005.² Table 1 lists these drugs.

Following China's entry into the World Trade Organization (WTO) in 2001, more aggressive measures were taken by the government to address IP shortcomings. These included, in 2002, the definition of 'new drug' to harmonize with the Trade-Related Aspects of Intellectual Property Rights (TRIPS). China issued new Drug Registration Regulations in 2002 to improve its patent protection system. China's patent law was amended again in 2002 pursuant to the TRIPS to harmonized China's patent system with other WTO member countries.

Over the past several years China's IP protection for pharmaceuticals has conformed with international standards. In June 2006, Pfizer won its patent protection lawsuit for Viagra in China, ending dozens of Chinese companies. The fact that the Chinese companies

appealed this decision (instead of ignoring it) suggests a significant shift in recognition for the rule of law. Table 2 lists expired or expiring proprietary biopharmaceuticals in China. [QA: Is it ok to call out Table 2 here?]

HEALTHCARE IN CHINA

With over 1.3 billion people, China has the world's largest population, and arguably the greatest need for biogenerics. Although China's gross domestic product (GDP) reached \$2.28 trillion in 2005 the per capita GDP was only

Table 4a. Major biogenerics in China

Biogenerics	Indications	Manufacturer(s)
IFN α -1b	Hepatitis B, Hepatitis C	Shenzhen Kexing Shanghai Institute of Biological Products Beijing Tri-prime
IFN α -1b (eye drop)	Viral keratitis	Changchun Institute of Biological Products
IFN α -2a	Hepatitis B, Hepatitis C	Changchun Institute of Biological Products ChangSheng Gene Pharma Sunshine Pharma Sundiro Pharma Liaoning Satellite Shanghai Wanxing
IFN α -2a (Suppository)	Gynaecological diseases	Wuhan Tian'ao Changchun Changsheng
IFN α -2b	Hepatitis B, hepatitis C	Anke Hansheng Huaxin Dingli Yuance Hualida Neptunus Interlong Reahar Changchun Institute of Biological Products
IFN α -2b (gel)	Herpes	Hefei Zhaofeng
IFN γ	Rheumatoid	Shanghai Institute of Biological Products Shanghai Clone Livzon Pharma
Interleukin-2 (IL-2)	Adjunctive therapy for cancer	Four-rings Huaxin Changchun Institute of Biological Products Sunshine Pharma Changsheng Gene-Science Ruide Jinsili Kangli

Table 4b. Major biogenerics in China

Biogenerics	Indications	Manufacturer(s)
125 IL-2	Adjunctive therapy for cancer	Beijing SL Pharma
125Ser IL-2	Adjunctive therapy for cancer	Shandong Quangang Liaoning Satellite
—	Leukopenia	Hangzhou Jiuyuan Gene Eng. Beijing SL Changchun GeneScience Suzhou Zhongkai Shanghai Sunway Beihai Fangzhou Amoytop Shandong Kexing Xinpeng GeneLeuk Lilu Chengdu Rongsheng Reahar North China Pharma
—	Leukopenia	Xiamen Amoytop North China Pharma Beijing Medical Univ. Pharma Reahar Hainan Huakang Gene-Science Shanghai Huaxin Liaoning Satellite
Erythropoietin (EPO)	Renal anemia	Sunshine Pharma Huaxin Shandong Kexing Shanghai Clone Chengdu Diao Shandong Ahua Four-rings Biologicals North China Pharma
Hepatitis B vaccine (yeast)	Prevention of hepatitis B	Shenzhen Kangtai Beijing Institute of Biological Products

\$1,700, ranking 100th in the world. Similarly, China's per capita drug spending is among the lowest in the world—less than \$20.00 annually. Furthermore, for the majority (80%) of Chinese who live in rural areas, yearly drug spending is only \$5.00 per capita. By contrast, Americans spend more than \$700.00 on medicines each year.² Clearly, generic drugs make up a vital component of the domestic Chinese healthcare situation.

LIMITED INSURANCE COVERAGE

According to China's Social Science

Institute, 65.7% of Chinese citizens are not covered by any kind of medical insurances. In 2005, only 133 million urban employees were covered by the "National Basic Medical Insurance." Inexpensive Chinese generic drugs and traditional Chinese medicines (TCMs) account for about 90% of the Basic Medical Insurance Drug Catalogues. Expensive imported medicines are prohibited or severely restricted from China's social medical insurance (See Table 3). As a result of the high cost of medicines, China's National Development and Reform Commission (NDRC) drafted plans

to cut the price of a number of commonly dispensed drugs.

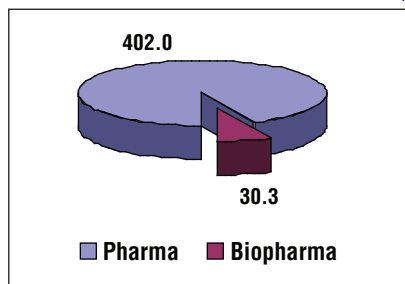
BIOGENERICS VERSUS INNOVATION IN CHINA

The concept of biogenerics in the West is seen as an IP and policy issue. In China it is a healthcare issue. Chinese biogenerics today include both off-patent biological products and generic biological products developed by Chinese biopharmaceuticals prior to China's entry into the WTO. Since biogenerics account for over 95% of China's biopharmaceuticals, the biopharmaceutical industry in China today is virtually a biogenerics industry.

China's biopharmaceutical industry began in the 1980s when the Chinese government introduced a series of national programs (e.g., the 863 Program, 85 and 95 Key Tech R&D Program) and placed biotech and related industry as one of the "major development sectors." Since the first Chinese-developed biotech drug, recombinant human interferon α 1b (produced by Shenzhen Kexing Biotech Co.), entered the Chinese market in 1989, China's biopharmaceutical industry has undergone rapid expansion. Today, Chinese biopharmaceutical companies have marketed 361 recombinant biogenerics (including therapeutics and vaccines) and 25 biotech drugs.⁴ More than 10 innovative biotech drugs have been launched into the market, and more than 100 biopharmaceuticals are currently at clinical trial stages. China is able to produce eight of the world's top 10 genetically engineered drugs or vaccines.

Biopharmaceutical production value has grown rapidly, from \$30 million in 1986, to \$4.2 billion in 2005. China's biopharmaceutical sales revenue has grown at 20–30% over the past five years. In 2005, biopharmaceuti-

Figure 1. China's pharmaceuticals and biopharmaceuticals sales revenue 2005



als accounted for 7% of the pharmaceutical market (Figure 1). According to the China Biopharmaceutical Engineering Industry Outline, the country's biopharma industry production value is projected to exceed \$12.5 billion by 2015.

BIOGENERICS MANUFACTURERS

There are over 2,000 biological products made by more than 200 Chinese biopharmaceutical companies, 95% of which could be classified as biogenerics. Chinese biogenerics include a wide range of biologics, such as genetically engineered drugs, vaccines, blood products, antibodies, and diagnostic agents. The major biogenerics and manufactures are summarized in Table 4.

Some Chinese biogenerics (e.g., rh G-CSF and EPO) have been manufactured and sold legally in China. G-CSF is manufactured by more than 30 Chinese biogenerics companies. Amgen applied for administrative protection for its Neupogen (G-CSF) and Epogen (EPO) in 1993, but did not win approval from the Chinese regulatory authorities. Other court cases are pending.

Some products are more likely to succeed as biogenerics. Several are currently under development by companies and many are already marketed in China and other developing countries. Short to mid-term biogenerics opportunities include hGH (registered), Insulin, Interferon-alpha, Interferon-beta,

G-CSF, GM-CSF, and FSH. Other longer term opportunities may include: Abciximab, Rituximab, Basiliximab, Infliximab, Trastuzumab, Alemtuzumab, and Adalimumab.⁵

CONCLUSION

Generic drugs have made significant contributions to China's healthcare system since the 1950s. In the past few years, China has begun to develop its own innovative drugs; yet generic drugs will continue to play an important role. China's biopharmaceutical industry continues to expand and is likely to continue its steady growth through the foreseeable future. Chinese state and local governments are making concerted efforts to push for innovation, better R&D, and greater early-stage funding.

To assure continued industry growth, Chinese authorities recognize the importance of enhancing their country's IP protection systems for both domestic and foreign biologics. The fact that Chinese companies are using the court systems and lawsuits to seek remedies indicates a major change in the Chinese pharmaceutical business environment. China's large domestic market potential and its solid competence in producing biogenerics are key factors driving its future direction. ♦

REFERENCES:

1. The journey of generic drugs to overturn innovative drugs (in Chinese). *Medicine Economic News*. 2004; Dec. 30.
2. http://www.oecd.org/document/25/0,2340,en_2649_201185_34967193_1_1_1_1,00.html.
3. <http://www.sfda.gov.cn/cmsweb/webportal/W4291/A64003794.html>.
4. China's bio-tech and industry appears rapid expansion trend. A report (in Chinese). 2006; Apr. 22. Available at <http://www.chinabgao.com/freereports/10264.html>.
5. Rader R. *Biopharmaceutical products in US and European markets*. 5th Ed. BioPlan Associates, Inc. 2006.