China appears to be moving forward a more innovation–based pharmaceutical industry.

editorial

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China: moving towards innovation in pharma

Although regulators and pharmaceutical companies have been slow to seize the opportunity for biologic generics in the USA and Europe, a full-blown industry dedicated to it has developed in China during the past ten years. China is quickly gaining pace as innovator, with several new products having been approved by the Chinese authorities and a host of new drug candidates in development.

This is surprising advancement for a country where traditional Chinese medicine (TCM) still plays a major role in the healthcare system. The emergence of a biopharmaceutical industry, in part, can be attributed to China's weak intellectual property system, tax advantages, government investment, favorable policies and entrepreneurial culture. Also, an influx of Chinese who have trained or worked abroad are bringing critical skills to the emerging industry.

How did we get here?

After the People's Republic was established in 1949, China modeled its scientific and industrial systems in large part on that of the Soviet Union. Through programs set up at this time, Chinese scientists were able to produce pure bovine insulin by 1965. Such early successes were followed by the Cultural Revolution that took place between 1966 and 1976, during which most areas of technology and education were suspended. At the end of the 1970s, when Deng Xiaoping came to power and implemented his 'opening up' policy, biotechnology once again began to advance. In the mid-1980s, the '863 program' was initiated to provide funding to various initiatives in the sciences, including biotechnology.

In 1989, results from funding began to manifest, with the development of China's first biotechnology products including interferon α1b by Hou Yunde. Several companies were established by the Chinese government to manufacture the drug; during this time the economy was predominantly controlled by the Chinese government through State Owned Enterprises (SOE). The intellectual property associated with the discovery was held by the Chinese authorities, as no formal system for patents was in place. Today, Shenzhen Kexing remains the largest producer. This development heralded the start of the biopharmaceutical industry in China. In 1993 China first allowed for the patenting of medicines, another major milestone for its pharmaceutical industry. From 1993 to 1996, various projects were pursued, including vaccines and blood products, by China's six largest biologic product institutes.

From 1997 to 1999 an explosion in the number of companies entering the biopharmaceutical industry occurred. Most focused on the imitation of other

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Chinese companies products or copying products from developed countries. According to data from 2001, >30 enterprises were granted licenses by the SFDA to manufacture products within the IFN series and eight enterprises for EPO. Competition intensified, few companies were able to develop their own intellectual property, chronic overcapacity resulted, and margins were greatly eroded. This situation was ironic, given that in numerous cases, government funds were used to help these biologics manufacturers start up in the first place. Despite this hypercompetitive environment, most manufacturers were able to forestall bankruptcy due to local government support and in many cases, outright ownership.

After 2000, other players entered the biopharmaceutical industry due in part to the attention China received from its successful sequencing of 1% of the human genome. Many publicly listed enterprises with no prior experience in biotechnology entered the industry via M&A, private investment, or joint ventures with biotech companies or institutes. Examples include Xin Huangpu (listed on the Shanghai stock exchange, code: 600638) and DaLian International (listed on the Shenzhen stock exchange, code: 000881). In most cases, these biopharmaceutical companies focused exclusively on manufacturing, sales, and marketing, with little capital being re-circulated into R&D initiatives.

However, during this time frame a large number of R&D focused companies were established closer to the more 'traditional' model of that prevalent in developed countries. These startups focused on the discovery and development of their own intellectual property and the commercialization of novel products. Examples include SiBiono GeneTech (which received approval for a gene therapy aimed at nasopharyngeal cancer in 2003), Shanghai Genomics, Sunway Biotech, and Hangzhou Jiuyuan. Some of these companies were founded by returnees with experience at biotechnology companies in the developed world, whereas others were spinoffs from China's life science institutes, such as the Shanghai Institute of Biological Sciences (SIBS). Focus areas for these companies included gene therapy, antibodies, and TCM modernization. TCM modernization, including the HTS of herbal preparations and other techniques aimed at the discovery of active components, is thought by some to be a competitive advantage for China's drug discovery.

Today, many Chinese biotechnology companies and academic institutes have drug candidates in preclinical and clinical development in China. Hutchison Medipharm, a company based in Shanghai, has recently filed an IND with the FDA. With the establishment of so many entities, and the increased emphasis on the development of novel therapeutics, China appears to be moving toward a more innovation-based pharmaceutical industry.

Not just drugs

Along with the development of innovative companies and the generics players, bio-related service companies and suppliers of reagents, consumables, and life science equipment have begun an impressive rise to provide products and services for the local and world markets. Some of these product and service players have become targets for acquisition, as evidenced by Invitrogen's announced acquisition of BioAsia at the end of 2004. In the broader biotechnology context, many fermentation product markets, including citric acid and vitamin C are now dominated by Chinese companies. Enzyme manufactures, such as Novozymes and Genencor International, have long capitalized on China's industrial boom through local manufacturing, sales and marketing, and in the case of Novozymes, even R&D.

Overview of biopharmaceuticals on the Chinese market

Of the more than 150 biopharmaceuticals available on the global market, Chinese companies currently produce >20. Products include the interferon series, interleukin series, colony stimulating factors, epidermal growth factors, fibroblast growth factors, recombinant insulin, human growth hormone, among others. Accurate market information is difficult to obtain in China, but a number of sources place the Chinese market for biopharmaceutical products at >US$1.5 billion. The market for biopharmaceuticals is growing at >15% per year, according to a variety of reports. Most of the market, according to 'China Industrial Statistical Yearbook,' is captured by domestic Chinese enterprises.

As of the beginning of 2005, more than 120 companies had facilities that passed the Chinese GMP to manufacture biopharmaceuticals. These manufactures fall broadly into several categories: subsidiaries of Chinese pharmaceutical groups (e.g. North China Pharmaceutical Company, Qilu Pharmaceutical), companies with core business focused on biopharmaceutical manufacturing (e.g. Shengyang Sunshine, Shenzhen Kexing, Changchun GeneSci) and companies with a global partner or owner (e.g. Shanghai Roche, Shanghai GeneMedix, Nanjing Huaxing). Most biopharmaceutical manufacturers in China are small in comparison with the established global players in terms of sales, employees, manufacturing capacity, and invested capital.

The nature of competition

For most biopharmaceuticals on the Chinese market, more than one manufacturer has received a license from the SFDA for production. Price is often the only means by which manufacturers of the same product compete, making China's biopharmaceutical market a truly generic one. More sophisticated manufacturers are increasingly exporting products to other developing countries, such as Vietnam, where they can develop an exclusive position or maintain higher prices for a set time.

Most advanced biopharmaceutical products are not reimbursed in China, and are unlikely to be reimbursed

for some time. Often, even at cut-throat pricing by manufacturers, most Chinese are not able to afford high-priced biologics, such as antibodies, the prices of which might be several times higher than the average family income. Although the main markets for high priced pharmaceuticals, such as biotech products, include the developed cities on the east coast such as Beijing, Shanghai, and Guangzhou, second- and third-tier cities are becoming increasingly important markets. Drug manufacturers, however are bullish on the future. China currently spends only 4.5% of GDP on healthcare, low even compared with other developing countries.

China's business environment

An important element to consider in China's biopharmaceutical industry, as with any other industry in China, is the role of the Chinese national and local governments. Although the national government sets overall policies, such as approach to intellectual property rights and market mechanisms, in practice these policies must be carried out at the province- and local-levels of government. Many province and city governments support their local champions through tax policies and looking the other way on environmental issues and intellectual property.

Guanxi is another important aspect of business in China. Due to a variety of historical and cultural reasons, relationships between individuals are more critical in China than in most developed countries. Developing deep relationships through repeated contact and socializing, and forging a personal bond of trust with colleagues, business partners, and officials is an important, though declining, way of cutting through red tape, getting to the deal, and reducing contract risk in China.

Regulatory highlights

After China opened up in the 1980s, the Chinese government made great efforts to reform its regulatory system along the lines of developed countries. One critical change included the reorganization of several regulatory bodies into the SFDA in 2000. This effort included increasing the number of departments with specific responsibilities, such as quality, manufacturing certifications, and marketing. Such changes have standardized many procedures and have made accountability more clear, bringing China in closer step with developed countries.

In an effort to consolidate its more than 6000 pharmaceutical companies, China instituted mandatory GMP certification by June 2004. China's GMP standards are not as stringent as those in developed countries. Nonetheless, it has been estimated that >2000 companies failed to pass and are to be shut down.

Intellectual property

Many biopharmaceutical-related patents have not been registered in China. This allows for local companies to manufacture the drugs without having to obtain IP licensing rights. If a Chinese company is producing a product in violation of a Chinese patent, it can be prosecuted. However, enforcement at the local level often remains less than ideal, especially outside of Shanghai and Beijing. Damages can be difficult to collect and the Chinese government in many cases maintains unattractive damage caps. Notwithstanding the former, it must be recognized that China's patent system is still developing and has made great progress within the last several years. With WTO accession and anticipated adherence to TRIPS, China is doing more to improve its intellectual property law and enforcement.

Increased legal activity and some high-profile cases are also a sign that the Chinese government is increasingly catering to the needs of foreign investors and pharmaceutical companies.

Foreign players

Global biopharmaceutical players, along with big pharma, have struggled in China, due in part to their incomplete understanding of the Chinese market. With domestic enterprises in some cases producing generic versions of their products with outright government backing, it is no surprise that branded pharmaceutical companies have been cautious. Most large pharmaceutical companies have sales, marketing, and manufacturing operations in China. Roche's announcement concerning the opening of an R&D center in China heralds a sea change in pharma's attitudes towards China.

Dragon Pharmaceuticals, of Canada and GeneMedix, of the UK have both invested in biogenerics platforms in China. Dragon, in particular, has met with some success in producing EPO for the Chinese and other developing markets.

Opportunities

The biopharmaceutical market in China has much room for growth. Although drugs with many producers in China are priced as generics, most biologics are not available on the China market. This leaves open opportunities for companies to sell products not already produced in China. Complicated products with significant associated know-how are particularly good candidates for a China launch. A careful and candid market assessment is the first step to making informed decisions about entering China's market.

Due to tax, labor cost, and other issues, China could be a good place to manufacture biopharmaceuticals for the Chinese or Asian markets. Building a green-field facility, partnering with, or acquiring domestic manufacturers is a way to get into the market. Acquisition of local facilities may be an interesting option due to several factors, including the traditional valuation of Chinese companies being based on book value and recently compressed margins due to competition.

Chinese scientists have ample experience with basic protein-expressions systems. Work with Chinese Hamster Ovary cells has been a relatively recent phenomenon,

although a number of companies have used this technology for biologic production. In the antibody field, CP Guojian is currently the only manufacturer. Biotech Pharmaceutical, a joint venture between the Cuban and Chinese governments, and Asia Space Pharmaceuticals, located in Dalian, have facilities slated for completion in the first half of 2005. These companies will probably have excess capacity, making them potentially attractive partners for global therapeutic antibody developers.

China is an ideal location from which to base a global biogenerics player. Local capacity exists, and could be updated to pass US and EU GMP. Dragon Pharmaceuticals has already positioned itself in such a role. While selling EPO to the Chinese and Southeast Asian markets, it is able to prepare for entry into the USA and Europe.

Chinese suppliers to biopharmaceutical industry, including manufacturers of cell culture media, bio-equipment, reagents, and consumables are poised for growth. Global producers can reduce costs by sourcing supplies and chemicals from China. Significant savings can also be realized through access to China's emerging basic science, preclinical and clinical development services companies. Laboratory suppliers in the USA such as Invitrogen have already made significant inroads into China through organic growth and acquisition. It is only a matter of time before the biopharmaceutical manufacturers follow suit.

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