

Analysis of Future Directions and Growth of Biotechnology in China

by

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Despite the global economic gloom in the third quarter of 2008, China's biotechnology is all aglow in the horizon. Read on for a detailed dissection of the strategies and development that put biotechnology in China in a vantage position.

The current global economic situation has pushed some of China's key manufacturing indexes to record lows; yet Western economists are still projecting an 8% annual growth rate for China in 2009. Some of this growth will come from investments and growth in China's biopharmaceutical sector. Recent collaborations, and a slew of other investments in China's biotech

industry, represent a sustainable growth trend, despite retreating global investments and business opportunities in other sectors.

We believe that current events in the biopharmaceutical market provide indicators for how China's biotech industry will weather the economic storm, and how the industry itself may take shape over the coming decade. According

to Bioplan Associates' recent analysis of the biopharmaceutical manufacturing sector, *Directory of Top 60 Biopharmaceutical Manufacturing Organizations in China*, investment and growth in this emerging industry segment will outstrip both global, and Chinese manufacturing sector expansion. Recent events in China point to this growth, which include increased investments, joint ventures

and R&D collaborations between Western and Chinese organizations. Some of these recent activities that boost the confidence level of the industry were:

On Nov 21, 2008, GlaxoSmithKline (GSK) signed an exclusive Cooperation Agreement with Neptunus Interlong Bio-Technique Co. Ltd. (NIBT) for the co-development of influenza vaccines for Greater China.

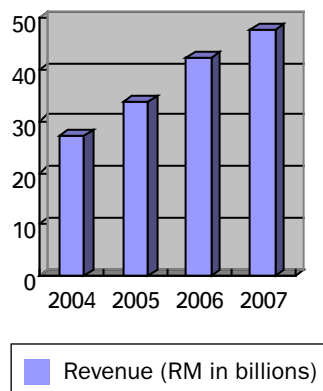
- In November 2008, Novo Nordisk announced plans to invest US\$400 million for an insulin manufacturing facility in Tianjin. This will function as the company's primary production site in China and serve the entire Asia-Pacific region.
- China's R&D in biotechnology is also generating outside interests. In 2007, Sanofi-Aventis announced plans to collaborate with the Chinese Academy of Science on cancer-related stem cell research.
- Cambridge, Massachusetts-based Genzyme Corp. plans to build an R&D center in Beijing as part of its continued global expansion. The company expects the facility to open in 2010, with project costs reaching US\$90 million.

Trend 1: A Robust Growth Industry

Since China's first genetically engineered drug interferon 1b was granted approval and the first biotech company was established in 1989, China's biotech has seen robust growth. In recent years, the sector picked up its pace, boosted by soaring market demands for vaccines, monoclonal antibodies (Mabs), and blood products (Chart 1). Though biopharma currently remains a small portion of China's pharmaceutical industry (8.56% compared with 55%

of chemical medicine and 27.3% of Traditional Chinese Medicine, according to China's Bureau of Statistics), biopharma's compound annual growth rate (CAGR) and profit margins are higher than those segments.

Chart 1. China's biopharma industry revenue during 2004-2007 period



Source: Bureau of Statistics China

Observers have reason to be relatively optimistic about market prospects, as China's upcoming Medical Reform is expected to expand national health insurance coverage and make healthcare more accessible to its 1.3 billion population. For example, the Ministry of Health announced in November 2008 that rural healthcare infrastructure will receive 4.8 billion RMB (US\$702 million) to upgrade facilities in more than 13 000 clinics and hospitals. We would expect government money to also move into reimbursement for drugs, which would see more biological medicines (e.g., more expensive MAb) covered by national health insurance. In addition, the national immunization program, paid by government and free of charge to recipients, more than doubled the number of vaccines offered in 2008 from 6 to 15, by adding

Hepatitis A vaccines, Meningitis vaccine, and Meningococcus Vaccine, among others. Some municipal governments, such as Beijing, have also been providing free flu vaccines to residents, making the pie larger for both domestic and foreign vaccine makers.

The total Chinese biotech market, though still small compared to most Western countries, has attracted attention from multinational corporations (MNCs) with its robust growth. In 2007, China imported US\$336 million in biological medicines, reporting a 51% annual growth (National Development and Reform Commission (NDRC)). Meanwhile, statistics from China's Patent Bureau show that through 2007 the bureau received 27 418 biotech patent applications, with 51% from foreign countries. Among patents granted, 62% are from foreign countries. The MNCs building up biotech IP strategy is consistent with their interests in China's biotech market.

Trend 2: Structural Changes in Biological Product Consumption

China is moving beyond the importation of biological medicines from industrialized countries, China's industry is now making serious efforts to catch up in the R&D and process development side of biologicals. China's "National 863" grant program has made research and commercialization of biotech a priority for the country. Now, dozens of bio-medicines (mostly biogenerics) developed by Chinese researchers, including genetically engineered IFN (interferon), EPO (erythropoietin), CSF (colony-stimulating factor), IL (interleukin), GH (growth hormones), have made their way into Chinese markets.

The next drugs in the pipeline are Chinese-innovated.

Though recombinant products remain a significant portion of biological medicine market, its market share could decrease if the consumption of blood products, vaccines and therapeutic antibodies continues their strong growth. The increases in purchasing power, and the overall size of China's middle-class, have made surgery more affordable to patients in the more affluent regions. This subsequently gives rise to demand for blood products. In 2006 albumin became the Top No. 1 medicine consumed in hospitals, and sales of albumin reaches 13 million bottles (10g/bottle) in 2007 (worldwide consumption is 43 million bottles). Ever since 2007, there has been a severe shortage in supply of albumin and Human Coagulation Factor, so much so that the State Food and Drug Administration (SFDA) had to grant Bayer's Kogenate(R) FS fast-track approval.

China's vaccine market is also expected to continue its yearly growth of more than 17% (compared with 10% worldwide) for at least the next few years; not only does the National Immunization Program cover more vaccines, but the greater product awareness after SARS incidents have also made most Chinese more willing to pay for vaccines not covered by national programs. Interestingly, high-end vaccines not covered by the National Immunization Program experienced even greater growth. Novartis alone reported a 55% annual growth rate in 2007 with sales of over 50 million RMB (US\$8.3 million) according to the director of Vaccine Department, Novartis China.

Recent policy moves would make more vaccines available at



both the Center for Disease Control (CDC) system and hospitals. These policies would grant local CDC purchasing-decision power and are expected to have positive impact on the growth of the vaccines market. China is also encouraging more R&D efforts in vaccines, whose recombinant diarrhea and cholera vaccines are among the first marketed in the world. Lured by the market opportunity, various MNCs, including GlaxoSmithKline, Sanofi-Aventis, etc, have started manufacturing vaccines in China (they used to import vaccines manufactured overseas and dispense in China).

Despite China's remarkable growth for vaccines and blood products, demand for therapeutic antibodies, especially those for cancer treatment, still lag far behind that of mainstream markets and only claims an insignificant portion of drugs consumed. However, these products hold great potential as targeted cancer therapy gradually becomes more mainstream in China. Rituximab, for instance, witnessed an annual growth rate of 46% in 2005 and 20% in 2006, while Merck's Erbitux grew at a rate of 70% for the first half of 2008, making China one of the top 10 markets for the antibody. Not

only are MNCs busy introducing new antibodies into China, Chinese developers are also trying to make their patent-protected me-too (or me-better) versions. In 2007 news broke out that China is going to launch its version of Nimotuzomab for cancer treatment, the first China-made therapeutic antibody approved by SFDA which also claims to have utilized a mammalian cell expression system. The Chengdu-based Huashen Group also introduced its iodine-[131I] Metuximab monoclonal antibody into China in 2008, and more made-in-China therapeutic antibodies are on the way.

Trend 3: R&D Bottleneck and Sino-West Collaborations on the Rise

Though the market is promising, China's biotech has long been bothered with a lack of R&D and innovation capability. China is now home to more than 580 biopharma companies, among which over 500 are small enterprises with net asset less than US\$10 million. Making investment into R&D is difficult in this climate. Promoting such new products into overseas mainstream markets would be virtually

impossible. While the Chinese government has invested heavily into biotech research, most of the funding goes to research institutions and universities who are mostly motivated by publications and who know little about market demands. The long existing separation between Chinese industry and academia, a legacy of the planned economy, makes commercialization of biotech innovations more difficult than it has to be. Venture capital, a vital force in nurturing R&D-based biotech start-ups into mature companies in the U.S. and Europe, are not

active in China's biotech. China has plenty of research talent (both domestic and western-educated) in the biotech field and its biotech research is often considered to be not far behind that of Western countries especially in certain areas such as gene therapy and stem cell. However, China's commercialization of biotech innovation, process development, and manufacturing are often decades behind mainstream markets.

The difficulty of Chinese biotech industry to commercialize the discoveries of its domestic Chinese biotech scientists, combined with

MNC big pharma's need to find drug candidates and innovative technologies at a less costly price, has led to a rise in Western licensing and investments. In 2008, Roche and Merck established licensing offices in Shanghai (Roche just expanded this office in Zhangjiang Incubator); Boehringer-Ingelheim also dispatched licensing professionals to China several times in search of candidates. As Stella Xu, director of Roche Licensing puts it: "We are here mostly not because licensing deals in China are cheaper; we are here to reach the Chinese talents."

Table 1. Partial List of Drug Candidates from China licensed to companies in industrialized countries

Chinese Researcher	Licensee	Drug Candidate
China Military Academy of Medical Science	Phytopharm (Britain)	NJS
Shenzhen Chipscreen	HUYA (U.S.)	HBI 8000 (Chidamide)
	HUYA	HBI 3000
Chinese Academy of Science	HUYA	S-52 (an alkaloid)
Chinese Academy of Science	Debio Pharma (Swiss)	ZT-1
Changchun HuaPu Biotech	SBI Biotech (Japan)	3 nucleotide drugs
Shijiazhuang Pharma	Unidentified U.S. Pharma	Butylphthalide
	IL Dong Pharmaceutical (Korea)	Butylphthalide

Source: Industry news source

Currently, most reported drug candidates licensed to Western companies are small molecule compounds, such as ZT-1 from the Chinese Academy of Science to Debiopharm, HBI 3000 and HBI 8000 from Chipscreen to HUYA, etc; but interest in big molecule candidates are also on the rise. This past October, SBI Biotech Co., Ltd, a subsidiary of the Japanese SBI

Holdings, Inc., and Changchun Huapu Biotechnology Co., Ltd. announced a license agreement to develop future novel class of nucleotide drugs. The three licensed compounds, which SBI Biotech acquired from Changchun Huapu, are a potential new class of nucleotide drugs which induce apoptosis of B cell neoplasms and modulate immune responses.

Another returnee-founded R&D start-up, Shanghai Zensun, has also attracted MNC's licensing interests with its NEUCARDIN™, a recombinant human neuregulin peptide for the treatment of heart failure. With strong government funding support for biotech research as witnessed by the recent "Mega Drug Development Program," analysts have reason to believe that

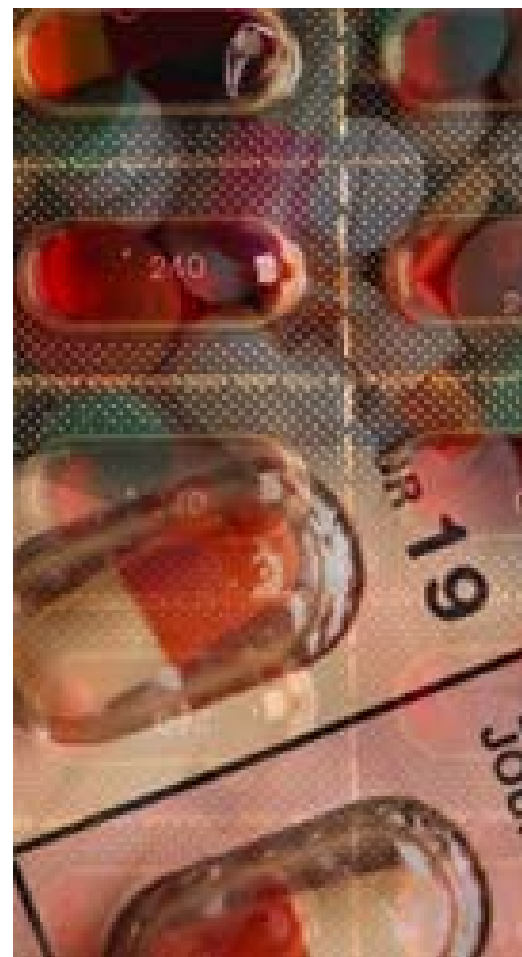
more out-license of biological drug candidates will take place in the future, thus providing an option for Chinese biologists to commercialize their discoveries in overseas regulated markets.

While out-license (licensing discoveries from China to overseas) makes headlines easily, in-license (licensing discoveries from overseas to China) are also taking place quietly. Currently, many Chinese biotech companies are still looking for biogenerics to fill their pipeline, but stricter IP enforcement is putting the practice into question or at least making it more costly. Ms Yan Zhao, medical director of Novartis China, once commented that Novartis was well aware of the biogeneric version of antibodies made by domestic biotechs, and “our IP lawyers are watching their moves very carefully”. There have been litigations between MNC and domestic drug makers on generics of small molecule drugs, and litigations on biological drugs may follow suit. Ex-CEO of Sanofi-Aventis, Mr. David Preston, once put it this way: “The IP law in China has progressed to a stage where most MNCs are getting a reasonable hearing, not always a fair hearing, but a reasonable hearing on IP cases.... The key is that you have to send an extremely strong message to the local players that the bars are up in your company, and you do not want to go up against MNCs patents as they will use every single means to protect their patents”.

Under the changing IP environment, China has in-licensed multiple technologies or drug candidates in recent years. In 2007, Russia-based Novartis Therapeutics out-licensed the China rights for two compounds aimed at treating cancer and hepatitis patients to Lee’s Pharmaceutical Ltd. of Hong Kong.

Lee’s Pharma will be responsible for all clinical development, regulatory filings and commercialization of the compounds in China. In 2008, Microbix Biosystems of Toronto (TSX: MBX) also licensed its proprietary Semen Sexing Technology (SST) to a Chinese breeding company, the Animal Fine Breeding Station of Hebei Province. Whereas Chinese companies usually do not have very deep pockets, in-licensing deals “would have to rely more on royalties rather than up-front payments”, as Dr Allan Liu, Forsun’s licensing director, puts it. There have also been cases about Chinese companies licensing biotech products that failed to get FDA approval and trying to commercialize it in China after upgrading, such as Shanghai Sunway’s H101 and Simcere’s endostatin. While Simcere’s huge success with endostatin seems to prove the feasibility of this model, Sunway is still struggling to promote its H101.

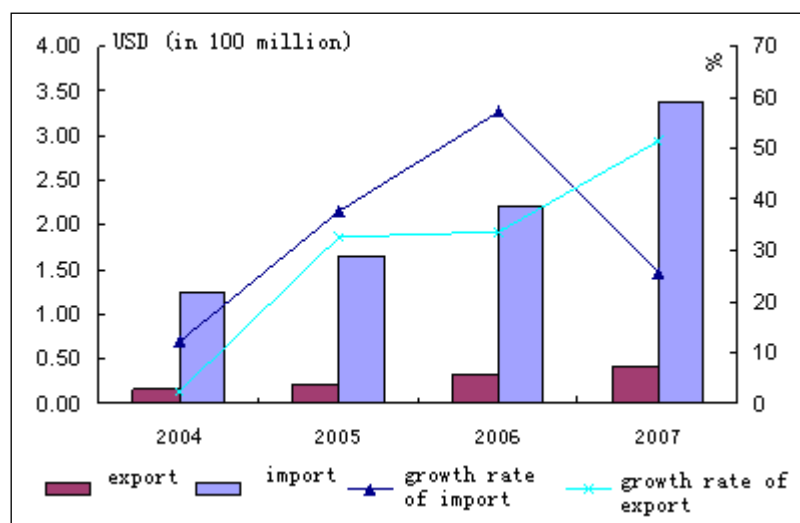
For those Chinese biotech companies with a vision to expand their global presence, sometimes licensing is a must for entering the mainstream market where IP enforcement is stricter. Genepharma, a Suzhou-based siRNA company, is a good case in point. This March the company signed a non-exclusive worldwide license to use the Kreutzer-Limmer siRNA patents belonging to Alnylam Pharmaceuticals (NSDQ: ALNY). The license, which is the first transaction Alnylam has signed with a China biotech, covers the right to manufacture and provide RNAi research products and services. After getting the license, GenePharma is able to manufacture RNAi reagent products for research use both in China and worldwide and see its export to mainstream markets grow rapidly after the deal.



Trend 4: Biotech Export – Reagents May Lead the Way

Though both exports and imports of biologics are growing quickly (Chart 2), unlike other industries, China’s biotech imports far exceed exports. In 2007, China imported US\$336 million in biologics, but only exported US\$41 million. While China’s chemical drug-makers are trying to explore the mainstream market by applying abbreviated new drug application (ANDA), observers may well wonder if China’s more than 200 biogenerics company with over 2000 biological products would like to follow the steps of Huahai (the first Chinese drug-maker to be granted ANDA) and export biogenerics overseas.

Chart 2 Growth of export-import of biologics during 2004-2007 period



Source: China Customs

Though the U.S. Food and Drug Administration (FDA) has yet to open the door to biogenerics, these products have already become a reality in Europe. There have been talks about European market potential for China's biogenerics, but cGMP certification, facility upgrading, staff training, etc remain strong obstacles, especially in the aftermath of the heparin and melamine scandals which tainted the image of made-in-China drug and food products. Over the next three to five years, it would be very difficult for Chinese biogeneric makers to test the waters in mainstream markets; instead, developing countries including those in the Middle East and Asia may be easier initial targets. And these are the markets that some biogeneric makers such as Wison Bioengineering have been trying to explore.

While biogeneric drugs have to wait for acceptance from the outside world, export of bio reagents may pick up the pace quickly. China has been exporting bio reagent such as research-use antibodies for years, but mostly as raw materials to overseas

reagent makers. Now they may be able to sell their reagents with their own branding to Western users—the growth of Genepharma serves as a good example here. A start-up founded by a returnee scientist, the company's SiRNA products first established a stronghold in the Chinese market. Now, after the licensing of technology from Alnylam, the company's exports to the U.S. and Europe have skyrocketed. As president of the company, Dr Peter Zhang stated: "Our oligos are as good as, if not better, than those from Western competitors, and our price is much cheaper." The company has signed distribution agreements with the U.S. distributors, and is contemplating opening offices overseas in the near future. The economic recession may actually benefit Chinese reagent makers; after all, manufacturing and staff costs are much cheaper in China, and the possibly funding shrinking amidst recession would make researchers more cost-sensitive and more likely to try the less expensive new brands.

Positive Outlook

With the economic boom, aging population and strong backing from the Chinese government, the biotech industry in China surely represents a growth market that cannot be overlooked. While truly innovative biological drugs remain out of reach for Chinese biotech companies in the near future, Sino-West R&D collaborations are on the rise, as MNCs reach out to find biotech talent in China. Subsequent out-license deals may help Chinese researchers commercialize their own discoveries in overseas markets, and domestic Chinese biotech players find they can utilize in-licensing strategies to boost their reagent export to mainstream markets. As the winds of change blow through China's biotech landscape, plenty of new business opportunities arise. These will be especially attractive to those with in-depth knowledge of China's biotech industry, who are able to find them.

About the Author

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About BioPlan Associates, Inc.

BioPlan Associates (Rockville, MD) is a life sciences market research and publishing company that has been serving international companies since 1989. Readers who are interested in China's biotech could refer to Bioplan Associates' studies on the China biopharmaceuticals market, which shed new light on this fast-growing industry.

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