Outlook on China's pharma development — 2004

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Abstract China's pharmaceutical industry is undergoing tremendous positive transformations, spurred both by the government's economic and political policies and the increasing investment/involvement by foreign pharma firms in China. This paper will describe the three major forces driving the changes: economic, regulatory and China's entrance into the World Trade Organization. These changes will contribute to China's emergence in the next decade as a major force in the international pharmaceutical arena, but the speed with which this will happen is contingent on overcoming the still-existing problems of intellectual property enforcement, regulatory capabilities, innovative skills and meeting EU/US good manufacturing practice quality and compliance requirements.

Keywords: *State Food and Drug Administration (SFDA), state-owned enterprise, State Economic and Trade Commission (SETC), active pharmaceutical ingredients (APIs), good manufacturing practice (GMP), quality assurance (QA), certificate of suitability (COS), drug master file (DMF)*

INTRODUCTION

In the past five years, the Chinese pharmaceutical industry has undergone tremendous change. These changes have had a positive impact and will contribute to China's emergence as a world power in the international arena. The three major factors driving China's pharmaceutical transformation are: economic changes resulting from the shift from a planned to a market economy; the State Food and Drug Administration's (SFDA) regulatory changes; and changes resulting from China's entrance into the World Trade Organization (WTO). Concomitant with improvements, particularly in the regulatory arena, is the increasing investment/cooperation by foreign companies in China. There are still factors that hinder the speed with which China can become a major player as both an active pharmaceutical ingredient (API) and a finished dosage supplier, and these must be addressed by the Chinese government to enable China to compete internationally.

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SWITCH FROM PLANNED TO MARKET ECONOMY

Until the early 1990s, China's industry was under central government-mandated planning policies. The state dictated production in terms of product portfolio, quantities, domestic sales and exports. Domestic distribution was carried out via state-controlled companies and exports were carried out via state-owned import and export companies. The switch to a market economy resulted in an unprecedented opportunity for decision making to shift to manufacturers and allowed direct contact with customers for the first time; manufacturers could be proactive in responding to market demands — developing new products/new specifications (eg particle size).

The reduction and, in some cases, elimination of state subsidies forced factories to develop ways to become profitable or risk bankruptcy. Under the planned economic policies of set salaries/pricing, there had been little incentive for factories to invest in process improvement unless the government provided the funds to do so. Financial burdens for large key enterprises, such as North China Pharma or Northeast General, were tremendous. Dubbed 'small societies', factories were expected to provide cradle to grave care for employees, including schooling, medical care, meals, housing and pensions after retirement. In 1999, the State Economic and Trade Commission (SETC) estimated that 32 per cent of state-owned enterprises recorded financial losses. Factories were forced to reform their entire operational system to follow a more rational Western economic model. This transformation had many positive effects — reduction in numbers of redundant employees, increased profits — but also led to numerous bankruptcies and high unemployment rates.

In order to speed up and assist in the change, the government encouraged financially stable companies to acquire failing factories at low cost. The state started to reduce its equity ownership in state-owned enterprises, encouraging factories to list on the Chinese or Hong Kong stock exchanges to raise capital. This also provided opportunities for Chinese entrepreneurs, as well as non-pharma companies, to make investments in the pharma sector, injecting new business practices/marketing strategies into the moribund pharma industry. The Zhejiang Hengdian Group, originally a privately-owned company founded as a textile company, diversified into pharmaceuticals in the late 1990s. This Group's pharma/chemical export value has grown from about $8m in 1999 to $80m in 2004, primarily due to its emphasis on service and Western marketing practices. Factories had the resources to hire qualified personnel and to pay according to ability/experience, not according to the previously dictated tier system, to hire regulatory consultants and to invest in marketing and sales.

Foreign investment in the pharma industry increased with the liberalisation of policies governing foreign investment. While the pharma industry was one of the first to be opened to foreign investment, initially government restricted foreign equity to 49 per cent and there were burdensome export requirements. Encouraging foreign investment was clearly also designed to allow foreign money to replace the state's in terms of funding. Foreign-invested factories have continued to serve as vehicles for educating the Chinese in good manufacturing practice (GMP) compliance, quality assurance management, standard operating procedures (SOPs) and management through training programmes and practice, as multinational managers in China operate by the same stringent requirements worldwide.

Twenty of the top 25 multinational companies have manufacturing operations in China, primarily for the production of finished dosage forms for sale in China. There are now a total of 1,800 foreign-invested pharma firms in China, including a number of generics companies, such as Stada, Zambon, Ranbaxy, Aurobindo, Dr. Reddy's and Antibioticos.

SFDA REGULATORY CHANGES

The SFDA was established in April 2003. This was the third major reorganisation of the regulation of China's pharma industry; in 1998, the State Drug Administration had succeeded the former State Pharmaceutical Administration. The formation of the SFDA gave one

organisation total responsibility for regulating functional foods, health foods, cosmetics and pharmaceutical products. Since 1998, sweeping regulatory changes have been enforced in the government's target to consolidate and improve the overall quality of pharma factories.

GMP regulations

The concept of GMP compliance was introduced in China in the 1980s, and in 1998 the State Drug Administration issued compulsory GMP guidelines (based on World Health Organization (WHO) guidelines) with an enforcement deadline of June 2004. Factories failing to achieve the GMP certificate would have their production licence revoked. In 2001, a revised drug regulation law was put into effect; this established a basic regulatory framework and defined the regulations on drug research, manufacturing and distribution. The SFDA estimates that factories have paid, on average, $2.4–3.6m to implement these changes. The impact is in the numbers — in 1998, there were 7,500 pharma factories; in 1999, there were 6,700. By the end of 2003, there were 4,296 pharma factories, of which 2,800 had obtained GMP certifications. The SFDA anticipates that at least 1,000 factories will lose their production licences by the end of 2005. Currently, the SFDA is discussing the possibility of implementing US current good manufacturing practice (cGMP), with a target date of 2010–2015.[1]

New regulations have been issued both by the SFDA and by other government ministries to enhance intellectual property (IP) protection. Legislation promulgated in 2003 allows for statutory damages for patent infringement, extends patent coverage to 20 years and includes provisions for patent linkage and data protection. Under current law, Chinese applicants for a new drug for production or import must provide a letter of guarantee that the product does not infringe the patent rights of others. The changes, according to SFDA director, Zheng Xiayou, resulted, in part, from China's entrance to the WTO and the 'new demands on the pharmaceutical sector'.[2]

WTO

China was accepted into the WTO in 2003. While lauding the advantages of WTO membership, the Chinese pharma industry regarded admission as a new competitive threat in the domestic market. Enhanced IP regulations, reductions in import tariffs (from 9.6 per cent to 4.2 per cent) and opening distribution, retail and wholesaling to foreigners would enhance opportunities for foreign pharma sales in China. The Chinese pharma industry — still predominantly a generics market, weak in R&D — would be faced with multinational monoliths with innovative product portfolios and superior marketing and sales in the domestic market. The Chinese government responded by declaring that the aim would be the creation within the ensuing five years of 12 major pharma groups that would be competitive in world markets, as well as in China. Funds would be earmarked to invest in innovative drug development, technology and R&D. China's largest firms are also active in seeking investment abroad; in 2003, the 999 Group purchased a small Japanese over-the-counter manufacturer. Entrance into the WTO has forced the Chinese domestic pharmaceutical industry to respond to the perceived threat from foreign competitors through quality improvements, enhancement of regulatory compliance and consolidation within the industry, as well as aggressively seeking long-term partnerships with foreign companies.

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IMPACT: NOW AND FOR THE COMING DECADE

The resultant changes are far too sweeping to be described in a short paper, as they include immeasurable, but still very important, psychological/cultural changes in business practice and mentality. The trends that will positively affect the speed and form of China's pharma industry — and greatly affect China's place in the world market — are as follows:

1. Quality improvements: foreign investment continues to enable the Chinese to learn and implement western quality controls. Investment in software (technical/consultants/foreign agents) and continued drive to file certificates of suitability (COSs) and drug master files (DMFs) will spur this trend. There are currently 55 Food and Drug Administration (FDA)-approved factories and at least 20 additional factories plan to file DMFs/COSs in 2005.[3]
2. Increased R&D spending: current average spending is 1–2 per cent of total annual sales, but most leading companies are planning to increase R&D spending to 4–8 per cent in 2005.[4]
3. Consolidation/acquisition: an excellent example is the formation of Shanghai Pharma Group, a powerhouse formed by merging five API producers, four distributors and seven finished dosage facilities. Since 1996, Shanghai Pharma has invested $120m, on average, per year for expanded capabilities and improvements. Fourteen products are FDA approved and several new plants are being constructed in the Spark Zone (a government-supported high tech industrial park in Shanghai). Shanghai Pharma is currently negotiating to purchase 60 per cent of Lukang Pharmaceutical, Shandong — China's fourth largest antibiotics plant.[5]
4. Stock listing: listing provides not only capital but also exposure to Western accounting practices and the ability to make investments in both hardware and software. Transparency of financial systems is another effect of listing and enhances foreign investment.
5. Privatisation: allowing the existence of privately-owned corporations, as well as allowing privately-owned companies to invest in state-owned enterprises, has added dynamism in terms of development, management and marketing strategy. Remarkably, in 2002, non-state-owned enterprises (which now account for 35 per cent of all companies in China), contributed 60 per cent of China's gross domestic product.[6]
6. Return of Chinese ex-pats: increasing numbers of Western-educated Chinese individuals with R&D/quality assurance experience in Western pharma firms are being recruited by the more dynamic Chinese pharma firms. Hisun Pharma, which has a number of FDA-approved products, employs Americans, Europeans and Chinese-Americans in regulatory, production and quality and assurance roles.[7] The Shanghai Pharmaceutical Group has also retained a foreign FDA consultancy firm and Zhejiang Jiayuan (part of the Hengdian Group), has hired three foreign researchers for its R&D facility. Wuxi Pharmatech is a good illustration of the combination of Western skills, Chinese entrepreneurial skills and low-cost but qualified researchers. Founded in 2001 by a Western-educated Chinese individual with working experience in US biotech, the company already has 200 scientists on staff and collaborations with Merck, AstraZeneca, TargeGen, Inc and PTC Therapeutics.

The positive impact of these tremendous changes is reflected in the statistics; the average profit growth rate from 1999 to 2003 was 28.04 per cent, although the 2004 rate is expected to be 15 per cent. The potential is still enormous; China's *per capita* total expenditure on healthcare as a percentage of gross domestic product was only

5.5 per cent versus 13.9 per cent, according to 2001 WHO statistics. Clearly, China is emerging not only as an increasingly important supplier in the marketplace but as a growing market for both domestic and foreign products.

BARRIERS

Certainly at present, China lacks the global scope, technical development (including quality compliance) and the business capabilities of the leading Indian firms. Product selection is still primarily driven by the traditional 'generics business model', selecting blockbuster products coming off patent.[8] Chinese companies lack the legal resources to carry out extensive patent searches to ensure non-infringing processes and do not yet have the legal sophistication to launch patent challenges outside of China. This is already changing; Hisun Pharmaceutical retains a US patent firm and other large group companies, including Shanghai Pharma, the Hengdian Group and the Shandong Xinhua Pharmaceutical Group, have utilised US-based law firms for production route reviews of existing patents.

IP issues continue to be a major barrier, and the July 2004 revocation of Pfizer's Viagra patent by China's State Property office was a shock for foreign pharma companies in China.[9] Due to foreigners' concern regarding IP issues, China does not currently supply any new pipeline drugs to innovators, but does supply intermediates and older APIs.

Utility costs are rising, as are labour costs, particularly in the more developed coastal areas surrounding Shanghai, but there are considerable cost advantages in China's interior provinces such as Hubei and the northwestern regions. China's emerging middle class in the southern coastal regions has caused continual power outages in Zhejiang province since 2002. Jiayuan Pharmaceutical Company, part of the Hengdian Group, used its own funds to build a power plant that serves the manufacturing facilities of the Hengdian Group, as well as supplying the residents of the Hengdian area.[10] Environmental issues are still a problem, although there have been numerous, increasingly stringent, government regulations for pharmaceutical plants, particularly with respect to worker safety and waste-water treatment systems.

The final push for China's emergence as a world leader will depend both on its internal forces of change and the external assistance of foreign generics and multinational companies. Foreign firms that have been established for two decades or more have continued to be a conduit for western management/quality practices. In addition, a number of foreign generics firms, particularly European ones, are actively seeking partnerships with China for sourcing APIs/intermediates in their own drive to cut costs, and the results will be beneficial to China. In the past, firms had a 'wait and see' attitude with respect to China, and companies preferred to source only from the few approved suppliers. Now, the more aggressive generics companies are investing time, resources and capital to improving their Chinese partners/suppliers via quality assurance training programmes, regulatory assistance and technology transfers. These factors, coupled with the recent changes, will be critical to China's emergence as a world power.

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Appendix 1: China's top 50 bulk chemical drug manufacturers by sales, 2003

Rank	Company	Sales (RMB 10,000)	Profits (RMB 10,000)
1	Harbin Pharmaceutical Group	730,192	45,196
2	North China Pharmaceutical Group	700,000	59,000
3	Hebei Shijiazhuang Pharmaceutical Group	567,684	89,373
4	Tianjin Jinyao Group Ltd	341,841	35,001
5	Shandong Xinhua Pharmaceutical Group Ltd	337,800	8,450
6	Zhejiang Haizheng Group Ltd	183,699	25,268
7	Shandong Lukang Pharmaceutical Group Ltd	182,365	12,162
8	Northeast China Pharmaceutical	172,300	10,500
9	Hebei Gaoying Enterprise Group Ltd	147,133	7,525
10	Hangzhou Huadong Pharmaceutical Group Ltd	135,591	22,222
11	Zhejiang Xinhecheng Co., Ltd	101,760	11,666
12	Shandong Xiwang Group Ltd	89,783	7,952
13	Yishui Land Corn Development Ltd	84,562	4,619
14	Jiangsu Jiangshan Pharmaceutical Ltd	72,669	22,164
15	Zhejiang Zhongbei Jiuzhou Group Ltd	59,410	2,597
16	Hebei Zhangjiakou Pharmaceutical Group Ltd	58,964	–2,915
17	Zhejiang Xianju Pharmaceutical Co., Ltd	58,205	7,371
18	**Roche** Shanghai Vitamins Ltd	57,604	–3,057
19	Henan Tianfang Pharmaceutical Co, Ltd	53,216	8,505
20	Fujian Fukang Pharmaceutical Co, Ltd	50,000	7,000
21	Guangdong Zhaoqing Xinghu Biotech Co, Ltd	47,000	3,800
22	Hubei Biocause Pharmaceutical Co, Ltd	41,863	–4,027
23	Shanghai Hualian Pharmaceutical Co., Ltd	41,196	1,326
24	Inner Mongolia Chifeng Pharmaceutical Group Co, Ltd	41,126	1,274
25	Hangzhou Huiyinbi Group Ltd	38,728	2,576
26	Shandong Zibo Jincheng Industrial Co, Ltd	37,010	1,967
27	Shanghai Sunve Pharmaceutical Co, Ltd	37,690	5,183
28	Shandong Qilu Antibioticos Pharmaceutical Co, Ltd	37,175	2,073
29	Zhejiang Haixiang Pharmaceutical and Chemical Co, Ltd	35,835	3,577
30	Sichuan Pharmaceutical Co, Ltd	33,694	–21
31	Zhejiang Huzhou Beigang Enterprises Group Ltd	33,587	788
32	Hengdian Group Jiayuan Chemical Co, Ltd	33,358	2,654

Appendix 1: *Continued*

Rank	Company	Sales (RMB 10,000)	Profits (RMB 10,000)
33	Jiangsu Lianyungang Hansen Pharmaceutical Co, Ltd	32,508	9,137
34	Zhuhai **United Labs**. Factory Ltd. Zhongshan Branch	32,501	10,186
35	Southwest Synthetic Pharmaceutical Co, Ltd	31,302	–2,734
36	Henan Nanyang Pukang Group Chemical Drug Factory	30,930	3,200
37	Jiangsu Yangzhou Pharmaceutical Factory	30,538	929
38	Zhejiang Huahai Pharmaceutical Co, Ltd	30,304	1,1518
39	**Roche** Zhongya Wuxi Citrate Co, Ltd	28,348	–770
40	Jiaozuo Xin'an Group Co, Ltd	26,540	1,103
41	Guilin Jiqi Pharmaceutical Co, Ltd	25,335	189
42	Hubei Bafeng Pharmaceuticals & Chemicals Co, Ltd	24,161	2,838
43	Guangzhou Longza Fine Chemical Co, Ltd	23,774	7,105
44	Shanghai Wuzhou Pharmaceutical Co, Ltd	23,011	358
45	Shanghai Glucose Factory	22,854	–3,484
46	Tianjin Zhongjin Pharmaceutical Co, Ltd	22,832	2,176
47	Sichuan Leshan Sanjiu Changzheng Pharmaceutical Co, Ltd	22,541	310
48	Zhejiang Zhenyuan Pharmaceutical Co, Ltd	22,483	2,287
49	**BASF** Vitamins Ltd	20,749	55
50	Liaoning Meiya Pharmaceutical Co, Ltd	20,340	2,516

*Companies in bold are foreign-invested enterprises

Source: *China Pharmaceutical Report*, based on 2003 China Pharmaceutical Statistic Yearbook

Appendix 2: China's pharma industry January to June 2004 ($bn)

Total sales	19.7	+14.7%
API sales	5.6	+15.26%
API exports	1.2	+19.7%

API, active pharmaceutical ingredient

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