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Kinapse White Paper

Opportunities for Global Pharmaceutical Companies in China

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Opportunities for Global Pharmaceutical Companies in China

Kinapse Consulting, 2007

China's pharmaceutical market is the ninth largest in the world and was estimated to be worth US\$19.2 billion in 2005. If projected estimates of growth are correct, China will become the world's fifth largest market by 2010 and the world's largest by 2050. These figures have compelled many global pharmaceutical companies to establish a presence in China but is this investment delivering results? What is the Chinese R&D opportunity and how can global pharmaceutical companies seize this opportunity?

For non-domestic, global pharmaceutical companies, China offers many attractions including a growing domestic pharmaceutical market, emerging academic research prowess, a large potential clinical trial population with established healthcare facilities and a maturing capability in drug discovery and development.

There are, however, a number of outstanding risks which impact global pharma's ability to succeed in China. Complex regulatory approval processes coupled with the costs of integrating local talent into a global company culture have led to claims that R&D activity in China is inefficient. In addition, inconsistent enforcement of intellectual property protection laws has resulted in a reticence to launch new drugs into the market.

Whilst the vast majority of large Western pharmaceutical companies have a presence in China, (usually building that presence from the establishment of a salesforce and manufacturing capability before focusing on R&D), it remains to be seen whether they will successfully tap into the potential of the Chinese R&D environment.

This paper outlines three critical success factors to enable global Pharma to seize the Chinese R&D opportunity. Establishment of excellent relationships with Chinese regulatory authorities will expedite approvals and minimise risks to intellectual property and scientific fraud. This requires investment in the creation of a high-calibre team, with a working knowledge of the local system and culture, as well as global R&D requirements and processes. Finally, given the current R&D climate, global pharmaceutical companies need to build strong networks with domestic Chinese organisations, (especially with China's academic strengths) to develop a truly global drug pipeline. In addressing these three factors, global pharmaceutical companies should find themselves in a good position to seize the Chinese opportunity.

Introduction

China is a country with a land mass the size of Europe and approximately 1.3 billion people, almost one fifth of the world's population. The Yellow River and the Yangtze River roughly divide the country into north, central and southern China.¹ The country is densely populated around the coastal areas in the east and sparsely populated in the west and north east of the country. China has 668 cities, 13 of which have populations of more than two million each.² The largest of these are Beijing, the political centre of China, with a population of 14 million people, and Shanghai with a population of 13 million.²

The Chinese government spends significantly on infrastructure (US\$201 billion or 9% of GDP in 2005)³ with most infrastructural investments focused in urbanised areas. Rural areas of the country lag behind and a stated key focus for the government in the next 5-10 years is reducing the income inequality between



Figure 1: Map of China showing major cities

cities and rural areas.⁴ As a result, the biggest growth is predicted to be in the small and middle-sized cities rather than current metropolises such as Beijing and Shanghai.⁵

China's prominence as a global destination for general manufacturing has been followed by a rapid expansion in research and development.⁶ Foreign biopharmaceutical companies have clustered around the affluent urbanised areas of Beijing, Shanghai and Guangzhou with marketing offices, manufacturing sites and, increasingly, R&D facilities. This has been due to a combination of factors such as access to world class infrastructure (e.g. hospitals), greatest number of patients, best research institutes, living standards and tax benefits. Multinational and domestic pharmaceutical companies benefit from a host of incentives such as corporate income-tax holidays and exemption from the country's 17% VAT for certain drugs (e.g. anti-HIV and contraceptives). There are additional incentives for foreign companies that set up R&D collaborations with Chinese research institutes and those that are registered in High-Tech Development Zones.^{7, 8, 9}

Continued infrastructure investment will make the environment more favourable. It will link up isolated parts of the country and allow more of the country's population better access to healthcare services. Crucially, the incentives which drew pharmaceutical companies to the big cities may be replicated in other parts of China to draw more foreign and domestic investment.

The Opportunity

For global pharmaceutical companies the opportunities

in China are its growing domestic pharmaceutical market, its academic research prowess and its maturing capability in drug discovery and development.

Chinese Pharmaceutical Market

The Chinese pharmaceutical market currently accounts for 4% of the world total. At less than US\$15, China's annual per-capita expenditure on healthcare is one of the lowest in the world, and comparable to India's.¹⁰ Pharmaceutical sales, excluding Traditional Chinese Medicines (TCM), were approximately US\$19.2 billion in 2005,^{10, 11} with domestic players holding 65% of the sales.⁹ At least 95% of drugs on the Chinese market are generics,¹² with the State Food and Drug Administration (SFDA, similar to the US FDA) approving 10,000 generic drugs in 2005 alone.⁹ Traditional Chinese Medicine accounts for nearly 25% of the market.¹² Most global pharmaceutical executives see TCM as complementary to pharmaceuticals, not a competitor.⁹ Some even see TCM as a resource to find new R&D targets.⁹

China has a disparate disease profile. As suggested by the percentage of total drug sales in Table 1, China has the disease profile of a developing nation as systemic anti-infectives are the most commonly sold drugs.⁹ However, the leading causes of death data, also in Table 1, indicate that China has a disease profile of a developed country as more than 80% of deaths in China are due to noncommunicable diseases and injuries.¹³ Moreover, an estimated 160 million people in China suffer from hypertension, and 20 million have diabetes.¹⁴

Like India, there is a division between the primary diseases suffered between the urban and rural populations.⁹ Whilst it is true that noncommunicable diseases account for the majority of mortality,

Category of drug	Percentage of total drug sales	Rank	Disease or injury	Percentage of total deaths
Systemic anti-infectives	34	1	Cerebrovascular disease	18.1
Others	16	2	Chronic obstructive pulmonary disease	14.1
Alimentary Tract & Metabolism	12	3	Ischaemic heart disease	7.7
Cardiovascular	12	4	Stomach cancer	4.6
Anti-neoplastic agents / immunomodulations	9	5	Liver cancer	3.6
Central Nervous System	6	6	Trachea, bronchus & lung cancers	3.5
Blood & blood forming agents	4	7	Conditions arising during perinatal period	3.0
Respiratory system	2	8	Self-inflicted injuries	3.0
Musculoskeletal system	2	9	Lower respiratory infections	3.0
Genitourinary system	2	10	Tuberculosis	2.9

Table 1: Sales of leading therapeutic areas in China in 2003 compared against the leading causes of death in China 2002. (Sources: IMS Health and Global Programme for Evidence in Health Policy, WHO).

communicable diseases and malnutrition continue to take their toll in areas where development has lagged behind, primarily in western China.¹³ Current areas of concern are AIDS, TB, SARS and avian flu. Moreover, these communicable diseases result in conditions that allow deaths to occur due to noncommunicable

Disease	Current situation	Predicted future situation
HIV	840,000 official cases reported in 2003 Mainly between 20-39 year olds	10-15 million cases by 2010
Diabetes	Estimated 20 million cases	150 million cases by 2025
Care of the Elderly	130 million people are older than 60	By 2010 there will be 253 million & by 2025, 446 million people older than 60

Table 2: The major diseases predicted to affect China in the future (Sources^{10, 9, 17})

diseases. For example, more than 100 million people are chronically infected with hepatitis B in China, yet many people actually die from the secondary effect of Hepatitis B infection which include cirrhosis and liver cancer. China has the greatest burden of liver cancer in the world.¹⁵

China's disease profile is expected to increasingly resemble that of Western countries. It is likely that communicable diseases will continue to be tackled aggressively by the government, via better immunization and vaccination programmes.¹⁶ 'Lifestyle diseases' are likely to rise due to increased urbanization of the population, increased spending power due to growing middle-class population (doubling to 200 million by

2010)¹⁰ and an increasing aged population (see Table 2). As a result, the Chinese pharmaceutical market for ethical drugs has been estimated to become the world's 5th largest pharmaceutical market by 2010 and the largest by 2050.¹⁰

Along with the growing middle-class segment, patient access to medicines is also expected to change dramatically. China's healthcare provision has been set up along the lines of the US model, but in 2005 the Chinese health authority decided that this was unsuitable for China.¹⁶ Due to the large population and uneven wealth distribution, the government has decided to further develop its primary care system (community services). Rather than going to hospitals, as they do now, Chinese patients will access healthcare via local service providers. As a result, the over-the-counter (OTC) market in China is predicted to grow from US\$2 billion to an estimated US\$6 billion by 2010.⁹

The predicted growth in the Chinese pharmaceutical market makes it attractive to global pharmaceutical companies. The US annual per capita spend on healthcare in 2002 was US\$5267.¹⁸ If the Chinese per capita spend was even 10% of this the Chinese market

would be worth approximately US\$68 billion, making China a market impossible to ignore. Although the increasing middle class population will drive growth in both segments, there are opportunities for pharmaceutical companies to catalyse further accelerated growth. For example, one of the major transitional challenges is the misconception of the general public that community health care is a second rate service. Also, as the OTC market grows, so will the roles of the independent general practitioner and the pharmacist.⁷ Public and healthcare professional training will thus be a key driver for market growth and may be a key activity for global pharmaceutical companies looking to increase the size of the market as well as their market share.

Education and Academic Research

The Chinese government has not limited its spending to infrastructure. Since 1999, funding for Chinese research has grown 20% per annum,¹⁹ reaching the equivalent of US\$70 billion (Purchasing Power Parity) in 2005²⁰ (US total funding for science in 2004 was US\$118 billion).²¹ Science funding bodies in China have seen their budgets balloon. For example, the National Natural Science Foundation (analogous to the UK's Research Councils) has enjoyed a 26% budget increase in 2006.²⁰

This investment is starting to show results. The number of 'high-impact' papers (those that are ranked amongst the top 1% most-cited papers of each year) that feature at least one China-based author has increased 10 fold between 1993 and 2003 (see Figure 2) and the country's Institute for Scientific Information (ISI) world ranking was 5th in 2005.²⁰ Chinese universities now

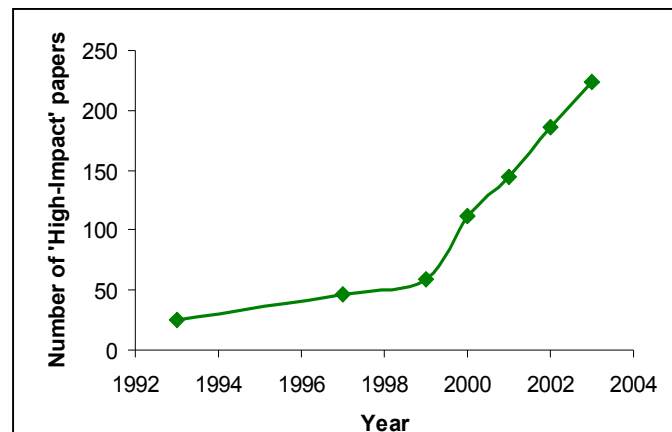


Figure 2: China's number of 'high-impact' papers by year (Source: Thomson ISI Essential Science Indicators)

apply for some 6,000 patents each year – a similar record to that of US universities and six times that of the UK.²⁰

China's core strengths in science are in synthetic chemistry, nanotechnology and understanding natural products derived from TCM. Other 'hot topics' for research are biotechnology, stem-cell research and agriculture technology.²² There has been a conscious drive to move 'from imitation to innovation'.¹⁹

China's scientific prowess has largely been due to the widespread return of overseas Chinese scholars. Their knowledge, training and expertise has been such that

Examples of China's research area strengths

China's academic establishment benefits from the Chinese government's commitment to science and also its liberal attitude in conducting research in contentious areas. For example, scientists in the US and Europe are restricted in stem cell and gene therapy research. By approving Genedicine (developed by Shenzhen's SiBiono GenTech) in December 2003, China became the first country to officially approve a gene therapy for head and neck squamous cell carcinoma.²⁴

Chinese research institutes (such as the Centre for Stem Cell Biology and Tissue Engineering in Guangzhou) have established new primate research centres with the intention of creating transgenic primates to use as models of human diseases and as a global source of primate stem cells. China has been a major supplier of primates to the US and conducting animal testing closer to source will save a large amount of breeding and transportation costs.

Finally, given China's rich natural resources in therapeutic herbs and TCM, China is uniquely placed to find new therapeutics and to commercialise them internationally.

81% of the members of the Chinese Academy of Sciences and 54% of those of the Chinese Academy of Engineering are returned overseas scholars.²³ Approximately 500–1000 Chinese who earned their doctorates overseas return to China each year.²⁴

The country's top-tier life science/biopharmaceutical research institutions are based largely in Beijing, Shanghai and Guangzhou and include the North and South Centres of Human Genome Research, the Beijing Global Biotechnology Centre and the Shanghai Institute of Material Medica; the country's leading centre for pharmaceutical R&D.

Unfortunately, China's scientific resurgence is mirrored by an increase in scientific fraud.^{25, 26} A recent Chinese Ministry of Science study of 180 PhD candidates found that 60% admitted to plagiarizing and paying bribes to get their work published. In addition, two University Deans were recently dismissed over false academic credentials. This perceived 'integrity gap' has been attributed to a lack of governance – the increases in science investment have not been matched by a corresponding boost to China's governance structures.²⁷ The Chinese government announced it would introduce more stringent rules from 2007, although what form these would take are currently unknown. Notably, an increased emphasis on the role of bioethics may improve governance.

Nevertheless, the perceived risk of fraud has not stopped collaborative activity in Chinese academia. For example, the Green Valley Group, a pharmaceutical company focused on TCM R&D, set-up a partnership and co-development agreement with the Shanghai Life Sciences Institute.²⁴ The Green Valley Group will invest US\$6.25 million as start-up funding for projects in the areas of oncology and cardiovascular disease.²⁴ In a separate deal, in 2005, the Yangzijiang Pharmacy Group agreed to build a joint drug discovery facility in Shanghai with Stanford University.²⁴

Despite allegations of fraud, Chinese academia appears to be in healthy shape. As discussed above, China is conducting world class research in selected areas and Chinese partnering activity crosses international borders. Science is well supported by the government by direct funding and tax incentives. Together with infrastructure support and assuming that measures to address fraud deliver results, China will continue to be an attractive destination for life science research. The

challenge for pharmaceutical companies is in understanding how to harness this opportunity through building alliances.

Domestic drug discovery and development activity in China

The domestic pharmaceutical industry

To date, China does not yet have a mature capability in either discovery or development. China has only had two drugs approved internationally, arteannuin (an anti-malaria agent) and Sodium di-Mercaptosuccinate (an anti-Schistosomiasis agent).²⁴

Discovery research is still nascent in China as Good Laboratory Practice (GLP) is a relatively new concept (there were less than 20 GLP-compliant facilities in mid 2005.)²⁴ Nevertheless, China has strengths in lower-complexity chemistry such as analogue preparation and compound synthesis. Assay development, screening and lead optimization expertise is emerging. There is developing proficiency in preclinical toxicology, protein purification and protein expression. China also has biotechnology competence in the areas of stem cell research and the Human Genome Project. However, application of this technology to drug discovery is still some way in the future.⁷

China's development capability is at a more advanced stage. Arguably, China's greatest strength in the R&D value chain is in conducting clinical trials. The country has a decade of experience in running clinical trials as part of local and global trials for multinational pharmaceutical companies, and is particularly strong in patient recruitment, trial management and monitoring. At the end of 2004, there were more than 250 trials in progress (sponsored by multinational companies), an increase of 25% over the 2002 figures.¹⁰

With this unbalanced skill set and the government's focus on basic health needs, China's approximately 6000 pharmaceutical manufacturers primarily produce generic drugs. The market is awash with 'me-too' products that compete mostly on price. To stay in business, manufacturers have developed efficient processes and typically invest far less than 10% of their revenues in R&D. In contrast, leading multinationals invest 15% or more.²⁴

Contract research organisations

Contract research organisations (CROs) arrived in China during the mid-1990's. However it was not until the SFDA issued Good Clinical Practice (GCP) standards in 2003, that the role of the CRO was officially recognised, when it was explicitly documented for the first time that CROs could conduct clinical trials on behalf of their clients.

Since then the sector has experienced huge growth, with a market value of US\$62.4 million in 2004. Currently there are more than 300 CROs, many of which are very small and can only provide limited services. However, at least 100 CROs are providing a range of service such clinical trial management, pharmacogenomics and new drug applications.

The current Chinese CRO market can be divided into three groups: foreign CROs (such as Quintiles), joint-venture companies (such as KendleWits, formed by the American company Kendle International and the Chinese company Acer/Wits), and local CROs (for example, Wuxi Pharmatech). A snapshot of the R&D activities conducted in China, together with a list of CROs is shown in Figure 3. The CRO industry in China is still young and fragmented, but is anticipated to ramp up quickly toward standardization and global

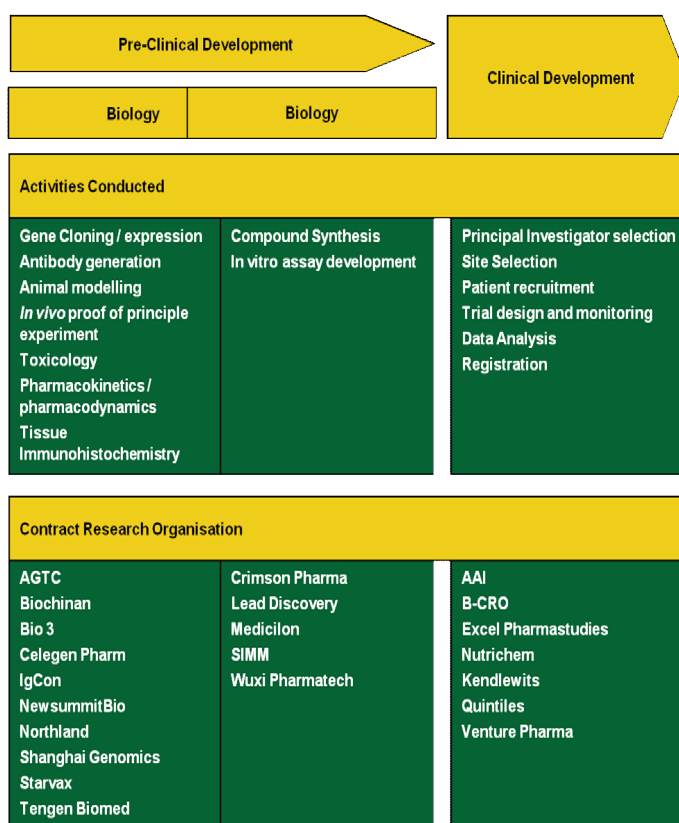


Figure 3: List of preclinical and clinical services and CRO providers in China. (Source: Biotech Entrepreneur to Entrepreneur (Bioe2e) 2005 presentation)

competitiveness. It is estimated to offer serious competition to other Asian countries, such as India, within two to five years.²⁸

Reduced costs and large population base

Part of the reason for the surge in CROs is the

associated cost reduction in running research projects in China. Estimates indicate that the cost of conducting clinical trials and preclinical research projects in China may be one third and one fifth respectively, of those in the US²⁴, with an average post doctoral scientist salary in China only 10% of the corresponding US figure.²⁴

Along with cost savings, China can readily provide access to diverse, large and treatment-naïve populations for clinical testing with faster enrolment compared with the US and Europe.¹¹ With the European Agency for the Evaluation of Medicines (EMA) and Food and Drug Administration (FDA) requiring a baseline percentage of clinical trials to be conducted in ethnic populations and the industry shifting from blockbusters towards pharmacogenomics and individually tailored therapies, China's role in determining susceptibility to disease and the safety and efficacy of drugs to treat it will become ever more valuable.

The Risks

For global pharmaceutical companies, there are three key risks which need to be mitigated to successfully enter the Chinese pharmaceutical marketplace; inconsistent Intellectual Property Rights (IPR) Protection, a complex regulatory process and a lack of 'work-ready' local talent.

Perceived 'weak' Intellectual Property Rights Protection

China has long had a poor reputation regarding IPR protection. The US Pharmaceutical Research and Manufacturers Association has said that IPR protection in China remains of concern.²⁴ The major problems that have been identified are: a complex registration process; a lack of data exclusivity protection, counterfeiting, inconsistent administrative protection and weak enforcement of patent law.^{10, 7} Even after becoming compliant with the World Trade Organisation Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement in 2001, two high-profile cases in 2004 highlighted the remaining problems in IPR protection in China. Pfizer's patent on sildenafil (Viagra) was overturned in July and GSK abandoned its attempt to defend its patent on rosiglitazone maleate (Avandia) in August of that year.

China has moved to address these issues. It has set up a large national group specialising in IPR protection and enhanced technological methods to combat IPR infringement crimes. The government has also established cooperative mechanisms with countries including the US, and intensified its efforts to crack down on cross-border IPR infringement. It is also trying to raise understanding in IP across the country⁷ and has started taking serious steps to curb piracy. In 2004, for example, it closed 691 companies producing counterfeit medicines.⁸ These activities, together with the recent rulings in the Pfizer Viagra patent case (see Case study 1) suggest that China has taken its TRIPS commitments seriously. The pharmaceutical industry has operated in China for a long time which suggests that they see the

Case study 1: Patent setbacks for Pfizer in China^{29, 30, 31}

When Pfizer filed its Viagra patent application with the member states of the Paris Convention in 1994, it fell foul of Chinese regulations covering nonpatentable treatment of disease. Pfizer subsequently amended its claim, limiting it to the use of sildenafil citrate, and Pfizer was awarded its Viagra patent on September 19th 2001.

On the same day, an invalidation request was filed in China, which was subsequently supported by 12 Chinese drug manufacturers. In July 2004, Pfizer's Viagra patent was overturned because of insufficiency, on the basis that the application lacked experimental data to support the technical effects of the drug in treating erectile dysfunction.

Pfizer objected to the State Intellectual Property Office's (SIPO) Patent Review and Adjudication Board decision on the grounds that the rules regarding disclosure were changed after the patent was awarded and then imposed retroactively. In other words, the data the company supplied was sufficient under regulations in effect at the time, and that the regulator was now applying newer and more stringent standards.

Pfizer launched immediate legal action against the SIPO decision, reaching the Chinese court in October 2004. Two years later, on June 2nd 2006, a Beijing court overruled the SIPO Board's decision made in 2004 and thereby, upholding Pfizer's Viagra patent.

This is a landmark ruling in China and providing this ruling is upheld in the face of a counter-appeal by the Chinese manufacturers, demonstrates how far the Chinese IP framework has evolved. Pfizer feels sufficiently encouraged enough to invest more into China, and are currently in talks with the Chinese government to introduce its smoking cessation drug, Chantix, into the Chinese market.

country as a manageable risk. Moreover, some of the major global companies have substantially built upon their initial investments in China. However, IPR remains a risk and companies will need to determine how much of the risk is acceptable.

Complex Regulatory Process

A second risk to global pharmaceutical companies entering the Chinese market is the country's regulatory process. China has complex requirements for the introduction of new drugs, perhaps second only to Japan's.⁹ The SFDA³² is responsible for the regulatory process in China. Drugs intended for the Chinese market must undergo full, local clinical trials, completing all three phases before they can be considered for market approval in China. This is true for all drugs, even those that have undergone clinical trials in other similar geographies such as Singapore or are generics, as the SFDA is not satisfied with standard 'biological equivalence tests'.⁹ For global pharmaceutical companies, product registration is estimated to take 2–5 years.⁹

China also has complex rules for companies wishing to conduct clinical trials in the country. Compounds discovered outside China must undergo a Phase I trial abroad before a Phase I trial can start in China and all trials in China must involve Chinese nationals.⁸ Pharmaceutical companies must make an application to the local regulatory agency followed by an application to the SFDA. Obtaining approval for conducting clinical trials in China is estimated to take 9–12 months.¹¹

Many shortcomings of the current process have been reported by global pharmaceutical companies. They include favouritism to domestic drug companies; limited up front discussion with the SFDA; lack of clarity of how changes to the regulatory process should be implemented and a need to forge and maintain good relationships with officials and agencies in the regulatory process. Moreover, it has been said that the process is not transparent; there is a need to understand the spirit and essence of the guidelines rather than take them at

their face value.⁸

The government has started to crackdown on unethical relationships between the pharmaceutical companies and the SFDA. In 2005, 450 illegal factories were destroyed and 60 production licenses were withdrawn. Several SFDA officials, including the Director of the Department of Drug Registration were arrested on commercial bribery charges in February 2006. Also in April of that year, the SFDA announced a new anti-corruption campaign targeted at drug and device manufacturers and distributors.³³ The stated aims of the campaign are to ensure honest business activity and education in the importance of complying with the law.

Despite attempts to streamline the central regulatory environment the process still involves the cooperation of numerous different central, provincial and local authorities.²⁴ For example a national registration certificate is issued once the quality test process has been completed successfully. Nevertheless, Chinese provincial governments may require additional procedures to be carried out, which may or may not be transparent or consistent.²⁴ Moreover, the clinical trial infrastructure is also starting to become overloaded. For example, in the second half of 2003, the number of applications to conduct clinical trials submitted to the SFDA increased 420% to 2500 and there are currently over 6500 products approved for clinical trial testing.⁸

For these two reasons, good relationships (e.g. via a large and pro-active Medical Affairs group) with the relevant national and local regulatory authorities are a must-have for pharmaceutical companies wishing to successfully enter the Chinese market. Pharmaceutical companies should not underestimate the importance of this activity when entering China. The government's anti-corruption crackdown should help level the playing field for non domestic pharmaceutical companies but caution must be exercised because the relationship with the SFDA is currently a very sensitive area.

Perceived lack of local 'work-ready' talent

Company	Major Locations	Production	R&D initiatives	Partnerships	Investment
Pfizer	Dalian, Suzhou, Wuxi, Shanghai	Dalian plant joint venture with Dalian Pharmaceuticals 1 st to receive GMP certification in China	R&D Centre opened Dec 2005 Provides drug development support (e.g. drug design, results analysis of clinical trials) and training in GCP	In the planning phases – aim to train & develop local talent	Has invested > US\$500 million in China to date Has >1800 employees in China
GlaxoSmithKline	Beijing, Tianjin, Suzhou, Shanghai (Pudong)	4 production sites manufacture OTC, antibiotic & vaccines 3 are joint venture	Two R&D centres: OTC & human vaccines	Recombinatorial chemistry lab with Shanghai Institute of Materia Medica	Has >2300 employees in China
AstraZeneca	Wuxi, Shanghai	US\$134 million invested in production plant at Wuxi.	Intend to set-up AstraZeneca Innovation Centre to be operational 2009 Centre will concentrate on identification & validation of biomarkers for cancer	US\$14 million partnership with Wuxi Pharmatech for compound collection synthesis Collaboration with Shanghai Jiao Tong University to identify the genes linked to schizophrenia Will fund new centre for pharmacoconomics & outcomes research at Beijing University	Has >2200 employees in China
Roche	Wuxi, Shanghai	Includes Xeloda & Cellcept	R&D Centre opened 2004 in Zhangjiang Hi-Tech Park in Shanghai Focus on medicinal chemistry research for lead generation & optimisation	Collaboration with Chinese National Genomes Centres in Shanghai & Beijing to identify genes associated with diabetes, Alzheimer's and schizophrenia	Has >1300 employees in China
Novo Nordisk	Tianjin	Received GMP certification in 2003 for insulin product manufacture	R&D Centre opened 2002 in Zhongguancun Life-science Park in Beijing Company centre of excellence in molecular biology, protein chemistry & cell biology	None reported	Has >790 employees in China
Boehringer Ingelheim	Shanghai (Pudong)	US\$41 million invested in manufacturing plant	None reported	Boehringer Ingelheim's presence in China is a joint-venture with Shanghai Sine Pharma Co Ltd	Has >500 employees in China

Table 3: Selected Global pharmaceutical companies' Chinese operations (Source: Kinapse analysis)

As described above, China's pharmaceutical infrastructure is beginning to get stretched. Even though two million people graduated in 2003 (600,000 in engineering, 200,000 in science and 100,000 in medicine³⁴), to give a total of 23 million graduates in China in 2005³⁵, there is concern that they cannot support China's need for expansion. As many multinational companies have found, there is a shortage of 'work-ready' talent.⁸

A poor command of English appears to be the most difficult hurdle facing multinational companies establishing Chinese operations, followed by cultural fit and communications style. For example, Chinese scientists may not be accustomed to international research norms such as developing detailed research plans, establishing defined timelines and targets or communicating openly with colleagues.

Global companies should realise that they may have to invest significantly more in training and developing new hires than they expect. Education in the importance of IP and increased governance will also be needed.

Seizing the opportunity

What strategies have global pharmaceutical companies taken to establish their presence in China?

It is important to stress that there is no one 'approach' to successfully enter the Chinese healthcare market.¹⁶

China is a market that 'requires patience and long-term commitment'.¹⁶

There are differences in the type of presence between many of the companies (see Table 3), but this may be due to historical reasons such as tax laws. The typical China market strategy has been to first establish a sales force, secondly develop manufacturing facilities and thirdly, build up R&D capabilities in China as companies deepen involvement in the country (see Figure 4).

The motivation for building up R&D in China varies between companies. One reason for building up R&D in China has been to leverage the country's large patient population for clinical trials and tailored therapies. AstraZeneca, for example, sees China as a critical component of its future global clinical trials operations. From being amongst the first of the global pharmaceutical companies to set up clinical trials operations in China in 2002, AstraZeneca has built up its partnerships with academia and is now building its own R&D centre with the intention of accessing data that cover different ethnic populations and genetic variations.

Other companies have built up their R&D capability because of potential cost savings and have chosen to do so strategically, in order to build/strengthen links with the Chinese regulatory authorities. For example, Roche executives have commented they built their \$11 million R&D facility, partly, to establish strong ties with the Chinese regulatory authorities.²⁴

A final motivation has been to build R&D in order to tap

into China's unique TCMs as a source of potentially new targets / molecules for discovery research. Novartis is one company pursuing this course to 'think outside the box'. The company formed a R&D partnership with the Shanghai Institute for Materia Medica to identify compounds derived from TCM, with the hope that they

specific work such as data process and analysis.

For pharmaceutical companies looking to execute their current pipelines, China offers advantages to improve the efficiency of execution. China's cost differentials, large patient populations and experience in clinical trials can all be accessed, again via partnership with a local CRO, taking over a CRO or establishing an in-house clinical trials centre. Again, a buy-out of a local generic company has value in terms of established relationships with local regulatory agencies and ready-made manufacturing facilities for clinical supplies.

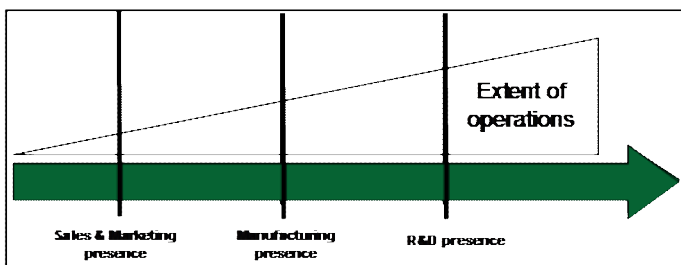


Figure 4: A three-stage strategy for building up operations in China

can be developed by Novartis into new drugs. Novartis have also announced plans to build a US\$100 million research centre in Shanghai, employing 400 scientists to look at TCMs and how they can be exploited in the field of oncology.³⁶

China: A win – win opportunity

China's lack of a discovery pipeline is surprising, given China's eminence in areas of academic research. The contrast between its strong academic position and its weakness in discovery research is striking. There is clearly a challenge in translating pure research into a sustained discovery pipeline. Although continued government support has led to partnerships between public research institutions and domestic pharmaceutical companies, this has not dramatically increased innovative capacity. For global pharmaceutical companies looking to enter the Chinese market, this gap represents an untapped opportunity.

For pharmaceutical companies looking for market approval from the SFDA, teaming up with a Chinese CRO may be helpful. A local CRO with a good working relationship with the SFDA can help accelerate approval, monitor the process and deal with problems efficiently. However, this is can only be a temporary solution. For global pharmaceutical companies who are looking to develop an effective long term presence, a preferred option may be to buy-out a local generic manufacturer.

The acquisition of a generic would mean that global pharmaceutical companies could tap into existing working relationship with the SFDA, so important for expediting approvals, without needing to reinvigorate it on a project by project basis. Global pharmaceutical companies could also take advantage of existing partnerships with academia and set-up new collaborations without having to go in 'cold'. The global pharmaceutical company would also inherit a company, used to competing on price for its products that was lean, with efficient processes. There would be a ready made manufacturing and distribution base for the global pharmaceutical company to springboard its products into the Chinese market. With a suitable base, a discovery platform could be added if required. A buy-out of a local CRO may compliment this strategy by providing in house expertise for clinical trials work or farming out of

Finally, for global pharmaceutical companies looking to add to their pipelines, China offers a unique source of potential blockbuster compounds in the form of TCM as well as cutting edge research. Here, partnership with academia (as yet, an untapped resource) is key and part of building this relationship will involve sponsorship, collaboration and eventually, taking this talent in-house in the form of R&D centres.

In all of these strategies, the element of collaboration and partnership with local academic institutes and biopharmaceutical companies is extremely important. It is only by engaging with local businesses that the global pharmaceutical company is more likely to secure support from the Chinese government,

It is noticeable that it is not only the industry giants who are being lured to China: Western medium-sized and start-up biopharmaceuticals have also a sizeable presence. Moreover, Invitrogen's acquisition of the Chinese competitor Bio Asia in December 2004 signposts that China has become a market *de rigueur* for the pharmaceutical sector. The question has shifted from 'why should you enter China?' to 'how do you enter China?'.

Conclusion

From our analysis, there appear to be three critical success factors to enable global Pharma to seize the Chinese R&D opportunity. Establishment of excellent relationships with Chinese regulatory authorities will expedite approvals and minimise risks to intellectual property and scientific fraud. This requires investment in the creation of a high-calibre team, with a working knowledge of the local system and culture, as well as global R&D requirements and processes. One possible way of achieving this would be the acquisition of a Chinese domestic generics manufacturer. Finally, given the current R&D climate, global pharmaceutical companies need to build strong networks with domestic Chinese organisations, (especially with China's academic strengths) to develop a truly global drug pipeline. In addressing these three factors, global pharmaceutical companies should find themselves in a good position to seize the Chinese opportunity.

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