Biotechnology in China

A Guide to the Chinese Biotechnology Industry

by Yijian Tang, June 2004

for

ABSTRACT

This report aims to provide a comprehensive picture of the Chinese biotechnology industry to people who are not yet familiar with it, using both primary (interviews) and secondary (such as Chinese publications) information sources. After an introduction on the relevant economic, political and social aspects of China, the funding system for research, the strategic research areas and the achievements in the Chinese biotechnology field are described. Collaboration between Germany and China in biotechnology research is highlighted and sources of support in Germany for doing business in or with China are presented. The Chinese biotechnology industry is then reviewed in general and by important sectors (biopharmaceutical sector, diagnostics and agriculture). Factors important for the development of this industry in China are also discussed. A sample of ten indigenous Chinese and four joint-venture or foreign-owned companies in the biotechnology industry in China are subsequently described. Lastly, interviews by the author of the report with CEOs of three Chinese biotechnology companies are included for additional insight.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

863 plan	Hi-Tech Research and Development Program of China
973 plan	National Basic Research Program of China
CAS	Chinese Academy of Sciences
CDC	Center for Disease Control
CNCBD	Chinese National Center for Biotechnology Development
CNRRI	China National Rice Research Institute
MOH	Ministry of Health of China
MOST	Chinese Ministry Of Science & Technology
NNSFC	National Natural Science Foundation of China
SFDA	State Food and Drug Administration

1. INTRODUCTION

According to Ernst & Young's Global Biotechnology Report 2003, the overall global biotech revenues totaled more than $41 billion in 2003, and despite of the challenges caused by the prolonged capital market depression, this research-intensive industry (with R&D expenses exceeding $22 billion in 2003) may well achieve profitability by 2010. On its way to that, biotech companies are undergoing consolidation and redefining business strategies. Global partnering, alliances and outsourcing remain essential to the success of biotech companies. The significance of biotechnology in changing our society has also made biotechnology a priority area for research funding by governments across continents. Although this industry still lags behind in the Asian countries, countries there including China are receiving especially heavy government support to build it up.

The modern Chinese biotechnology industry started about 20 years ago with the government's 863 program, and is now already at the turning point for a qualitative change: from follow and copy the Western countries to begin to innovate. China's accession into WTO has undoubtedly contributed to this change. In the biopharmaceutical sector, alongside the recombinant protein drugs there is already world's first gene therapy drug produced in China. In the molecular diagnostics sector, various biochip products for clinical use have been brought to market by Chinese biotech companies. In plant biotechnology, China has come up with its own genetically engineered insect-resistant cotton, and has been progressing with very big projects such as the Animal Mammary Gland Bio-reactor Project.

Due firstly to its market potential and its inexpensive labor force including those with a university degree, China has been attracting foreign companies and investment. Now this starts to happen in the biotechnology industry also.

The purpose of this report is to serve as a guide for companies, especially the German companies who have an interest in China, as well as those who have not looked in this direction so far. Some in the latter group may discover that "making it to the Great Wall" can be a good strategic move.

What's covered in this report:

overview of the current economic, political and social environment in China relevant to biotechnology;

overview of the current state of the biotechnology in China – the science base, the strategic areas funded by the government, and achievements;

overview of support for collaborations between Germany and China;

overview of the Chinese biotech industry; aspects important for the development of the industry; examples of indigenous Chinese companies; and examples of joint ventures and wholly owned foreign companies as case studies to illustrate strategies in doing business with/in China.

2. ECONOMIC, POLITICAL AND SOCIAL CONDITIONS

2.1 Economic conditions

China is an "advanced" developing country with a GDP of 1.02 trillion RMB (RenMingBi, name of the Chinese currency) Yuan (in 2004, roughly 1 EURO = 10 Yuan). Its GDP growth rate was 9.1% for the year 2003 (National Bureau of Statistics of China, 2004). In fact its GDP grew at a rate between over 7% and over 11% for the past ten years (National Bureau of Statistics of China, 1995-2004). With a total trade volume of over 620 billion USD, and an over 20% growth rate in both import and export in year 2002, the country, excluding Hong Kong, was the fifth largest exporter and the sixth largest importer in world merchandise trade in 2002 (WTO, 2003). In overall GDP, China will match Germany by 2010, and growing by the size of Spain every 5 to 7 years, overtake the USA by 2040, according to J. Woetzel, in an interview over his book Capitalist China (Mckinsey, 2003).

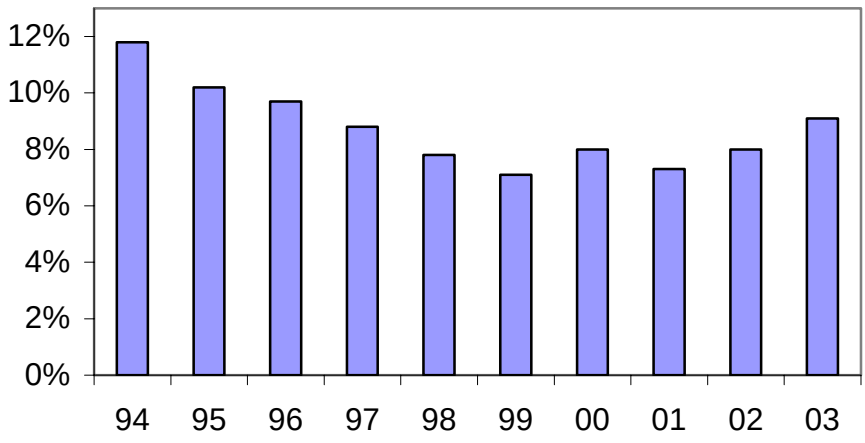


Figure 1: Annual growth rate of the domestic total economic output in China in the past 10 years. Source: National Bureau of Statistics of China

Foreign investment in China has been growing. In 2002, China for the first time became the world's largest destination for foreign direct investment, attracting over $50 billion (Xinhua Infolink, ca. 2003). As of the end of 2003, 6.8 billion Euro from Germany was invested in China and 660 German companies were doing business in China (AHK, 2004). These companies included not just VW, Siemens, Bayer, BASF, but also companies in the biotech industry such as Qiagen, Eppendorf, Bicoll, Miltenyi, and the laboratory supply company Julabo.

The Chinese Ministry of Science & Technology's High Tech Products Catalog for Foreign Investment published in July 2003 listed over 900 products in 11 technical fields including biomedicine and medical instruments, new materials, environmental protection and modern agriculture (MOST, 2003a). To further improve foreign investment climate, the State Administration of Foreign Exchange issued the Circular on Improving Foreign Exchange Management of Foreign Direct Investment, which came into effect on April 1, 2003, with provisions on ten major aspects of the management - from capital flow-in, to qualification examination and registration, to capital flow-out (MOST, 2003b). Since China's accession to the WTO, restrictions for foreign investment are being gradually removed. For instance, the insurance market has started to open up after WTO accession and the Regulations on China-Foreign Joint Venture School Business of the People's Republic of China effective since September 1, 2003, opened school businesses for the first time to foreign investment (MOST, 2003c). In this context, the most recent German-Chinese investor support and protection agreement signed at the end of 2003 aims to further encourage German investment in China, as such agreement is a prerequisite for the investment guarantee from the state against non-commercial risks in doing business in China (BMWA, 2003).

Currently the best means for companies wanting to cash in on the fast growth of the Chinese economy is believed to be direct investment (private equity), for reasons including the limited number and the questionable quality of the Chinese companies listed on the Chinese stock markets. Xcelerator Capital Group in Australia, for instance, reportedly signed a $4 million protein research joint venture with the Shanghai Institute of Biological Sciences in 2002 (The Hindu, 2003). As a matter of fact, many well-known Chinese research universities and institutions list technologies for commercialization on their web sites and have established technology transfer and commercialization offices, like Shanghai Institute for Biological Sciences does (http://cttc.sibs.ac.cn), although their web contents are frequently available in Chinese only.

For an overview of venture capital investment situation in China, please see Section 4.1.1 - Capital market and exit channel in this report.

2.2 Political conditions

Politically China is a socialist state controlled by the Chinese Communist Party. The Chinese economy is characterized by itself as a socialist market economy. The shift away from a totally state-planned economy to a more market-oriented economy started with Deng Xiaoping's "open door" policy in 1978. The weight of the state-owned enterprises in total industrial output decreased from 64.9% in 1985 to 34% in 1995 – almost halved in ten years (National Bureau of Statistics of China, 2001). According to J. Woetzel in an interview (Mckinsey, 2003), companies in China now mostly determine their own fate, and that competitive advantages such as innovation and consolidation have replaced government relationships as success factors.

As compared to other industries, healthcare is still predominantly state-owned. However, even healthcare will likely open up to a certain degree to competition and to foreign investment. To support the health insurance system introduced in 1998, the Chinese government has initiated a reform to introduce a mechanism of competition among medical institutions and a market operating mechanism for medicine production and circulation to achieve better medical service at lower cost (People's Daily, ca. 2002). In addition, following the commitments under the terms of its WTO accession, China has been gradually opening up previously closed markets, as mentioned before, hence restrictions for foreign investment in healthcare will likely be less in the future as well. The current state of health insurance system in China will be described in the following Section - Social conditions.

Problems exist in many state owned enterprises, especially in the small and medium-sized enterprises (SMEs) at the bottom of a hierarchy, as voiced by a recent report by Liaoning Provincial Economic Research Center (2000) done under the framework of the Industrial Restructuring and Investment Promotion of the EU – China LIEP programme (Liaoning Integrated Environmental Programme) (www.eu-lnip.com). Having operated under a planned economy for a long time, these enterprises cannot keep up with the market economy, unable to choose new projects and raise capital independently, and show instead great dependence on the government. Decision-makings there are still order-oriented instead of market-oriented. These enterprises are also burdened with a large number of retired workers to whom they must pay retirement pensions. However, China is further developing its market economy and further privatizing state enterprises.

China Daily (2003a) reported in November 2003 that the Central Committee of the Chinese Communist Party decided to accelerate the shift of state ownership to private ownership and to maintain total state ownership of a very

few enterprises in strategic industries only. The party stated for the first time that it would vigorously develop a mixed economy with stock ownership playing a dominant role. The government hoped that foreign investors would take stakes in state enterprises, thus bring better technology and management to these companies. There are also attempts to make the privatization process more transparent and fair because privatization in China has been associated with local corruption and insider deals in which government officials and managers acquire the companies at low cost. Many large state enterprises in China are planning their initial public offerings (IPOs). Examples are banks and other enterprises like the Shanghai Pharmaceutical Group, China's last state-owned pharmaceutical conglomerate which accounted for 8% of the total sales of the fragmented Chinese pharmaceutical industry in 2003 (China Daily, 2003b). The world's largest IPO in 2003 was China Life Insurance, the biggest life insurer in China (Renaissance Capital, 2003). According to Renaissance Capital, China Life went up 27% in its US trading debut despite of its $ 3 billion offering size, reflecting investors' interest in the fast-growing Chinese economy.

2.3 Social and medical conditions

With a population of 1.292 billion in year 2003 (National Bureau of Statistics of China, 2004) (roughly 1/4 of the world's total) and the "one-child" family policy gradually shifting the population structure towards the gray zone, improving health care and agricultural production are the most important issues China is concerned with. China believes that biotechnology will help solve problems in both areas, and therefore is essential to its sustainable development.

According to the National Bureau of Statistics of China (2004), in 2003, about 40.5% of the population lived in cities and towns and 59.5% in the rural areas. Since the economic reform there has been massive influx of people from the rural into the urban areas. In the urban areas, disposable income per capita was 8472 Yuan (ca. 847 Euro) and in the rural areas income per capita was only 2622 Yuan (ca. 262 Euro) in 2003 (National Bureau of Statistics of China, 2004). It's worth noticing that China faces challenges characterized by both developing and developed countries due to the uneven development among areas, especially the difference between the urban and the rural areas. This for instance, is reflected in the disease profile in China. While incidence of infectious diseases remains high in the rural areas, diseases common to developed countries like obesity, diabetes and hypertension are increasing rapidly in the urban areas. In the late 1990's, the Chinese government has started to introduce a set of social security and welfare

programs such as social security system, old-age insurance system, basic medical insurance system, unemployment insurance system, social welfare system, etc (People's Daily, ca. 2002). These programs cover mostly urban residents so far. The Sino-German social insurance agreement came into existence in 2002 (Koppitz, 2002) .

In the old socialist days with a totally planned economy (from 1949 to the late 1970's), China's health care was provided almost free to people in the city. Workers got reimbursed by their "working units", and since nearly all the people able to work were employed for life then, this meant a free coverage for all working in the city. Although people in the countryside had to pay out of their own pockets, health care was inexpensive then. With the economic reform, private enterprises mushroomed, and the healthcare system also went through changes. One of the outcomes has been the rapid increase of the healthcare costs, and an increasing amount of people in the city paying for healthcare on their own.

In 1998, the Chinese government issued the Decision on Establishing the Basic Medical Insurance System for Urban Employees, introducing a basic medical insurance system to those employed in the cities (People's Daily, ca. 2002). Under this system, employers and employees both contribute to the basic medical insurance premium. To ensure that the basic medical service charges do not increase too rapidly, the government has strengthened its administration of medical services using measures like specifying a list of medicines, healthcare service items and standards of healthcare facilities to be covered by basic medical insurance, somewhat similar to the practice in Germany. By the end of 2001, 97 percent of prefectures and cities had started such healthcare reform programs, and 76.29 million employees had participated in basic medical insurance programs. Free medical service and other forms of healthcare insurance systems covered still more people - over 100 million people in the city then (People's Daily, ca. 2002). According to the National Bureau of Statistics of China (2004), in 2003, 108.95 million people in China (still only less than 10% of the total population) were covered by medical insurance, presumably by the basic medical insurance program as well as other forms of health insurance.

3. CHINESE BIOTECHNOLOGY RESEARCH

3.1 Current state of research and funding

China has attracted international attention by being the only developing country to contribute to the Human Genome Project. The Chinese National Center for Biotechnology Development (CNCBD) of the Chinese Ministry Of Science & Technology (MOST) (Wang, ca. 2003) has characterized the Chinese biotechnology as undergoing a qualitative change: from follow-and-copy to innovate, and from doing research in the laboratory only to beginning to commercialize research results. Currently, there are about 200 Key Laboratories in biological research, with over 20,000 R&D personnel. In many universities the best students choose to major in biology. However, although China has some well-developed areas in applied research, particularly those related to genomics, its overall basic research is still weak and needs to be strengthened.

An article by Wu (2003) at Cornell University described the current status of basic life science research, the amount of funding and the fund allocation system in China:

In the areas of biochemistry and molecular biology, according to the estimation of Wu, China has about 500 scientists only who are doing high-quality research which can be published in international journals with high impact. In comparison, for instance, while the US population is about ¼ of that of China, it has over 40,000 scientists engaging in high-quality research. Chinese scientists tend to focus on low-risk projects lacking originality and creativity and publish therefore mostly in domestic journals. Causes include insufficient research funding, shorter duration of funding (2 to 3 years), problematic funds allocation, lack of collaboration among scientists, and an educational system that does not cultivate critical and creative thinking.

In 2000, life science funding in China was about 20 billion Yuan RMB (ca. 2 billion Euro), equal to 0.02% of the GDP of the year. Although in 2003, the overall R&D funding has increased from 1.1% in 2000 to 1.3% GDP (National Bureau of Statistics of China, 2003), most of the funding is channeled towards applied research. In addition, non-governmental sources of funding for basic research hardly exist in China.

Most of the basic research in China is funded through the Chinese Academy of Sciences (CAS), the Ministry of Science & Technology (MOST) – especially through its 973 plan, and the National Natural Science Foundation of China (NNSFC). Among them, the NNSFC reportedly has the strongest peer review system and is open to all applicants. Although the NNSFC funding system is similar to that used by the National Science Foundation in the USA, there is often a lack of experts familiar with certain specific research areas. In addition, the important big projects in NNSFC are funded without peer review. However, since two years ago, NNSFC has started to invite reviewers from the USA for its proposals. The MOST's 973 plan is also experimenting with incorporating overseas reviewers to evaluate its projects. It announced its first trial in August 2003 (MOST, 2003d), to invite more than 20 scientists from the USA, Great Britain, Canada, Sweden, Japan, Australian, Hong Kong, etc, to participate in the first round of evaluation. These overseas scientists were to make up about 10% of all the reviewers.

Since 1986, the MOST has set up the Hi-Tech Research and Development Program of China, called 863 plan (www.863.org), which funds applied research in strategic areas. The first 15 years have brought a good number of achievements in areas including biotechnology. In 2001, the plan continued into the 10th governmental five-year plan period (2001 to 2005) and biotechnology is the area that is receiving the largest amount of funding now (Wang, ca. 2003). The research areas under this plan are determined around improving the economy and living standard. It's probably no exaggeration to say that the 863 plan jump-started the modern Chinese biotech industry.

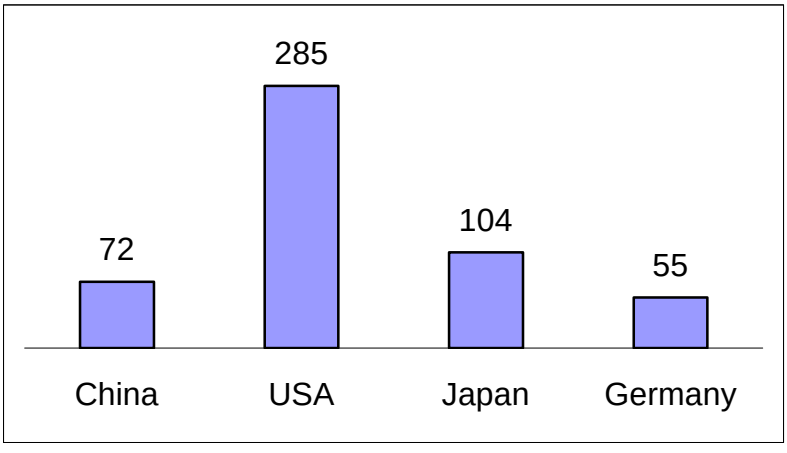


Figure 2: R&D expenditure in 2001 – 2003 (in billion USD). Source: OECD's Science and Technology Statistical Compendium 2004

3.2 Strategic research areas and recent achievements

Strategic research areas

The National Basic Research Program of China, the 973 plan, has specified the following strategic areas for applications in 2004 (MOST, 2004).

In agriculture:

- functional genomics of important agricultural plants and animals, and basic research regarding the quality and safety of important agricultural animals

In resource and environment:

- ecological system protection and repair

In population and health:

- functional genomics and proteomics, molecular and cellular basis for health and important diseases, basic research in preventive and curative measures for important diseases

In multidisciplinary research:

- basic research in photosynthesis

A list of projects already running can also be found at the 973 web in English (http://www.973.gov.cn).

The 863 plan research areas for the period 2001 – 2005 fall under the following programs (MOST, ca. 2002):

- Bio-engineering technology program
- Gene manipulation technology program
- Bioinformatics technology program
- Modern agriculture technology program

Achievements in basic research

According to the "Chinese Biotechnology Industry Development Report" (2002) edited by the Chinese National Development Plan Committee's High-technology Industry Development Department and the Chinese Biotechnology Society, beginning with its participation in the international Human Genome Project in 1999, China has established its capacity in genome analysis. This

includes facilities and platforms for sequencing (sequencing capacity was about 50 MB per day in 2002), bioinformatics, proteomics, genotyping, and genome dynamics. The achievements related to genome research (Beijing Genomics Institute, 2004a, b) include:

- completed the working draft and the fine sequence map of the rice indica genome, made the sequence data public; sequenced and analyzed rice chromosome 4
- completed the genome survey and whole transcriptome sequencing of pig - a Sino-Danish Pig Genome Consortium project
- completed sequencing of the silkworm genome
- collaboration with the USA and Europe in the Chicken Genome Project
- the ongoing Chinese Superhybrid Rice Project
- participation in the International Haplotype Map (HapMap) Project to make a 10% contribution

Achievements in human medicine

China has strength in the research and development in therapeutic cloning, in human embryonic stem cells and related embryonic technology. While reproductive cloning is forbidden by the guidelines published by the Ministry of Health of China in 2001 and last modified in 2003 (MOH, 2003), China permits therapeutic cloning and funds it as a strategic area. Interested readers can take a look at the Nature article "Stem cells rise in the East", listed in chapter 6, which portrays the stem cell research scene in China. Achievements in this area (Yang, 2003) include:

- generation of fertile cloned rats by regulating oocyte activation (Zhou, et al, 2003)
- embryonic stem cells generated by nuclear transfer of human somatic nuclei into rabbit oocytes (Chen, et al, 2003)
- reconstruction of human embryos derived from somatic cells using human egg (Lu, et al, 2003)

Other than stem cell research, China was the first to position and clone the genes causing some genetic diseases such as a form of neurological deafness, dentinogenesis imperfecta Shields type II and brachydactyly type A-1 (Cyranoski, 2001).

Achievements in agriculture

China has been active and successful in modern plant biotechnology. A publication in Science (Huang, et al, 2002) identified 35 institutes that conducted research in tissue culture, genetic engineering, marker-assisted selection, diagnostic technology, microbiology, or other related areas. The same publication revealed that Chinese scientists were using over 50 plant species and more than 120 functional genes in plant genetic engineering, making China a global leader in the field. The following is a more detailed account of the achievements, according to Cui and Guo (2002) and Hou (2002), unless otherwise noted.

In 1993 China conducted a large-scale field trial for its first transgenic, virus resistant tobacco. In 1997, the first transgenic long-shelf-life tomato was approved for commercialization, the commercial use of GM cotton was approved and Bt cotton varieties from publicly funded research institutes as well as from a Monsanto joint venture were available to farmers. China has successfully researched a large number of transgenic agricultural products, including rice, wheat, corn, cotton, tomato, pepper, potato, cucumber, tobacco, petunia. Transgene features include disease resistance, insect resistance, herbicide resistance and quality improvement. However, in consideration of export of agricultural products, China slowed down or temporarily stopped granting approval since 1998. Up till year 2002, a total of seven transgenic plants were approved for commercial production in China. These include three varieties of cotton (two Chinese-made, one from Monsanto), virus-resistant tomato and sweet pepper, long-shelf-life tomato, and a color-altered petunia. However, only cotton, also the single commercial transgenic plant with Chinese own intellectual property, has been planted in very large scale. According to the International Service for the Acquisition of Agri-biotech Applications (ISAAA, 2004), the planted transgenic crops in China (referring to cotton) totaled 6.9 million acres in 2003, making China the fifth largest country in GMO planting area, after the USA, Argentina, Canada and Brazil.

In rice research, up till year 2002, China has created over 100 kinds of transgenic products, over 80 of which were in environmental release stage, and 1 in demonstration stage. These include rice with blood-lowering effect, with Helicobacter pylori killing function, or diabetes prevention and treatment function, according to news from the China Rice Info Net run by China National Rice Research Institute (CNRRI, 2003).

China has also created various transgenic animals including pig, sheep, cow, rabbit and fish, and has cloned sheep and cow. Its first transgenic domesticated animal was created in 1990.

3.3 Support for collaboration between Germany and China

Support for research collaboration is described first.

"Cooperation between research institutions in different countries is often the prerequisite for the development of innovations and for the opening up of new markets. New products can thus be placed much more easily on the world market." - stated a report by the Federal Ministry of Education and Research in Germany – BMBF (2002).

The Sino-German cooperation on science and technology based on intergovernmental agreements started as early as in 1978, and the major German partners involved are the BMBF, other federal ministries (such as the Federal Ministries for Environment, Nature Conservation and Nuclear Safety - BMU; of Consumer Protection, Food and Agriculture – BMVEL; of Health and Social Security - BMGS), and some state (Länder) ministries (BMBF, 2002). Other institutions involved are the German Research Foundation (DFG), the Max Planck Society (MPG) in the field of basic research, the Fraunhofer Society in applied research, the Alexander von Humboldt Foundation which awarded the largest number of grants to the Chinese scientists for several years now and other science-oriented foundations (BMBF, 2002). According to BMBF (2002), further, all the important German research or mediating organizations have their own contracts with Chinese partner institutions and have significantly increased their contacts over the past years. There are more than 300 collaboration projects between German and Chinese higher educational institutions, the largest number of such cooperations between Germany and an Asian country. In the following, the collaborations of BMBF, DFG, Max Planck Society and Max Delbrueck Center for Molecular Medicine will be described in more detail.

BMBF

BMBF, through its Asia Concept with new forms of collaboration, contributes to a stronger presence of German science in Asia including China. Over time, the BMBF's collaboration programs with China have been expanded and are increasingly being organized to cover projects with specific targets and to find solutions to important problems (BMBF, 2002).

The funding activities of BMBF are market-oriented in many respects, and economic and industrial interests play an important role in cooperation, according to the report by BMBF (2002). BMBF participates actively in bodies of the Asia Pacific Committee of German Industry. In implementing joint projects, BMBF attaches importance to participation by companies in addition to research institutions. "Technology advisors", introduced by BMBF and financed by BMWA (Federal Ministry of Economics and Labour), provide services in this. In China, such advisors are working at the Fraunhofer liaison office in Beijing and at the German Chamber of Industry and Commerce Abroad in Shanghai.

With the agreement on cooperation in the field of biotechnology of September 12th, 1991, researchers in China and Germany have been encouraged to get together and do common research projects. The International Cooperation Office of BMBF at DLR in Bonn covers their transportation costs for mutual visits. The first projects started 10 years ago, in 1994. After 1-2 years, promising small projects which evolve into bigger ones could receive, after further evaluation, more funding from BMBF. At this stage the so called 2+2-projects should preferably involve companies from both countries, especially innovation-oriented SMEs. Up to now there are two running projects with participation of two German companies and one Chinese company. They focus on probably new compounds for drug development out of microorganisms to find new agents to treat cancer or other diseases. The microorganisms isolated from plants with play a major role in Traditional Chinese Medicine (TCM) offer an appropriate platform to find new compounds for drug development.

Agreements are in place to address the intellectual property ownership issues concerning these collaborations. At the end of 2002, Germany and China signed a Sino-German Model Contract for Know How- and Patent License (Deutsch-chinesischer Standardvertrag für Know How- und Patentlizenzen), which is obtainable from the publications concerning China at the web site of the German Office for Foreign Trade www.bfai.de. This model contract can be used by German institutes and companies for collaboration with China, either

as it is or with own modifications. The general practice has been that the Chinese partners own patent rights in China and the German partners own patent rights outside China. For the BMBF funded collaborations, 14 projects done so far have yielded 8 patents already.

DFG

According to the report by BMBF (2002), DFG has developed partnership with the National Natural Science Foundation of China (NNSFC) since 1986. As an outcome of this partnership, the Sino-German Center for Science Promotion was established in Beijing in 2000. The center's tasks include the support and promotion of joint research projects and the preparation of such collaborations. The Center supports researchers to find suitable partners, can provide funds for the preparation and development of projects, and can organize conferences, workshops and seminars for scientists in both countries. The 20 million Yuan RMB (ca. 2 million Euro) budget is co-financed equally by DFG and NNSFC.

Max Planck Society

Max Planck Society (MPG) has exchange of scientists and research collaboration with the Chinese Academy of Sciences (CAS) for already 30 years, starting in 1974. Collaborations cover all MPG’s research fields, with material science being one of the strong areas. MPG focuses on basic research.

In life sciences, MPG and CAS have established the independent junior research team in China since 1995 and have appointed a total of 6 team leaders so far. These team leader positions are advertised in internationally known top scientific journals like Science. Team leaders are selected by a committee made up of international experts in the field. Funding is for 5 years, with roughly 3/4 coming from CAS and 1/4 from MPG which is 50,000 Euro per year. The team leader has complete freedom in choosing research topics and personnel, as well as in deciding how to use the part of funding coming from MPG – such as subscribe to international journals, buy books from overseas, hiring additional staff or use part as own income, etc. These positions are very attractive to young Chinese scientists finishing up their training in the West and are looking for good opportunities in China to return to. Competent young researchers are thereby given the opportunity to conduct independent research in order to qualify for science management positions in China.

MPG has also established 10 partner groups in China. Former recipients of grants who have conducted research at Max Planck institutes are leading

partner groups to promote networking and relations between Chinese scientists and German research institutions, especially former German host institutes. Further, the Shanghai Institute for Advanced Studies (www.sias.ac.cn), an institute of the CAS, is strongly supported by the Max-Plank Society, the BMBF, and also by the Volkswagen Foundation, as a center for exchange of ideas and information across all scientific disciplines. The institute's German director Dr. Schwarz comes from MPG. Most recently, in 2003, the CAS Kunming Institute of Zoology launched a collaboration between the CAS, MPG and the University of Chicago to train China's next generation of conservation biologists: the International Center for Biodiversity and Evolutionary Biology, with half of the advisory board members from MPG.

In all these activities, including the Junior Scientist program, what MPG has been contributing the most is knowledge and experience in identifying good scientists, good research projects and in bringing people together. This kind of science management expertise is what China lacks and needs urgently, perhaps even more than money, according to Dr. Spielmann at the MPG.

MPG is interested in building a long-lasting relationship with China, and the purpose behind the above-mentioned activities is to support China in establishing a modern scientific research structure.

Already now MPG's engagement in the Chinese science has been bearing fruits. For instance, the first MPG Junior research team leader Pei Gang is now the president of the Shanghai Institute of Biological Sciences and engages in frequent and intensive dialogue with the scientists at MPG. China has been trying to set up a competitive research system, and among the different models to follow, one is the MPG model. The CAS is already establishing its own independent junior research teams, for instance. What's more, talented young Chinese scientists are attracted to MPG to do research due to MPG's reputation in China.

It is therefore good news for the German industry that German research institutions such as those of the Max Planck Society have been building a lasting relationship with the Chinese scientific community, because business opportunities often come into existence because of the existing personal ties. Concerning the Chinese biotech industry where overseas-trained Chinese scientists play an important role right now, as examples in chapter 4 will show, such relationships can be even more important in leading to business collaborations between China and Germany.

Max Delbrueck Center for Molecular Medicine

In December 1997 a joint lab was opened at Fu Wai Hospital in Beijing (Sino-German Center at Beijing Fu Wai Hospital) with the Max Delbrueck Center for Molecular Medicine in Berlin as the German partner (BMBF, 2002). The joint lab enables scientists from both sides to do research on the genetic causes of cardiovascular diseases. Researchers there have, for instance, identified genes related to the heart development and arteriosclerosis as well as genetic mutations related to myocardium (Consulate General of Switzerland, 2001).

In the future, there will likely be more industrial involvement in Sino-German collaborations. According to BMBF (2002), among the tools to be implemented regarding these collaborations is increased integration of industry in Science & Technology cooperation and in preparatory and supportive measures.

A note on the Chinese side: the MOST's 973 plan encourages international collaboration and its projects are open particularly to European scientists: European scientists and Chinese scientists can jointly apply for funding and carry out 973 projects (www.973.gov.cn). 863 plan also encourages exchange and collaboration with international partners as well as the involvement of industry.

In the following, major sources for support for companies interested in doing business in or with China are described.

German Industry and Commerce (GIC)

The offices of German Industry and Commerce (GIC) in Beijing, Shanghai, Guangzhou and Hong Kong, under the Association of German Chambers of Industry and Commerce (DIHK), support German companies to establish and extend their activities in China, and help Chinese enterprises to develop their business in Germany.

According to its web site (www.china.ahk.de, formerly: www.ahk-china.org), GIC in China supports especially small- and medium-sized enterprises (SMEs) in their efforts to explore their potential and business opportunities in China. The core services are the provision of economic data and monitoring of developments, the search for suitable business partners and the individual consultation of companies. Mediation of trade disputes as well as vocational training is also part of the service. Moreover, regular organization of

seminars, symposia, business luncheons, round table discussions, presentations and press conferences is used to facilitate communication and the exchange of useful information among business communities for the benefit of the economic relations of Germany and China.

The offices of German Industry and Commerce in Beijing, Shanghai, Guangzhou and Hong Kong are operating independently in their assigned geographic areas and work in concert on cross-regional projects such as China wide consultation and research. At their internet site www.chin.ahk.de, one can find very good information on China, services offered and publications, including proprietary Chamber information not available elsewhere. The scope of their services include: China economy (short presentations, investment guide, current statistics, business headlines, German companies – a database of German companies doing business in China, banks & financing, consulting, reports & analyses, etc.), publications, business contacts China, China & WTO, law (law offices, legal documents), training services, trade fair, environment & business (environmental services, information), China government (ministries, administrative changes, web sites), and event calendar. Many of the services are especially practical for SMEs with limited own capacities in dealing with the issues associated with expanding into the Chinese market.

German Office for Foreign Trade

The German Office for Foreign Trade (bfai) (http://www.bfai.de) is another source of information and service for doing business in foreign countries, it is however not focused on China only. According to the bfai web site, its spectrum includes: economic data and trends, sector analyses, foreign economics and taxation law, customs procedures and tariffs, international invitations to tender, public and private financed projects, business opportunities from German and foreign companies, organization of information and networking events and coordination of the foreign trade portal iXPOS. One can order country-specific publications from the web. Among the many China-specific publications covering all business aspects, for instance, is the “Deutsch-chinesischer Standardvertrag für Know How- und Patentlizenzen”.

IHK

Local chapters of IHK in Germany also offer China-specific information and service, such as the IHK Pfalz (http://www.pfalz.ihk24.de). China is one of the several foreign countries IHK Pfalz’s international services cover. Local chapters also organize events (such as together with associations like

Ostasiatischer Verein e.V.) disseminating information and facilitating exchange of information and business experiences concerning China.

German Centers

Companies new to China may find German Centers useful. The Bayerische Landesbank has established the German Center Shanghai (www.germancentreshanghai.com) since 1994. Tenants there can get support from the center's management team and from the office of the German Chamber of Commerce (AHK) located permanently on the premises. Similarly, the Landesbank Baden-Württemberg has established the German Center Beijing (www.germancentre.org.cn) since 1999. It offers office for rent, conference facilities, training facilities, meeting facilities, Business Center, technical & digital equipment and consulting. Service providers include the German Chamber of Industry and Commerce Beijing. Both centers belong to the network of German Centers located also in other foreign cities.

Others

In addition, several institutions have Chinese studies as one of their focuses, such as the Institut für Asienkunde (IFA) in Hamburg. Those are also information sources for business, social issues and culture in China.

3.4 Potential areas for collaboration

The following are just some examples of collaboration areas where China offers distinctive advantages and/or unique resources and at the same time shows a need and interest for development.

In molecular medicine

Molecular medicine had a late start in China. However, according to Chien and Chien (2003), the following areas offer opportunities for collaboration between China and the Western countries:

- Uncovering new hereditary risk factors as well as biological markers for common diseases by analyzing the Chinese population for phenotypes and genotypes.

- Primate research in China can be used for collaboration in neural and cardiovascular disease research. China could build up a primate-based technology platform for drug safety and efficacy research with cost advantage.

- Cardiovascular diseases are increasing in China and the number of patients will likely reach 0.1 billion in several years. The cost for hospitalization is relatively low in China. These two factors combined makes it attractive to conduct research for new diagnostic and treatment methods in some advanced medical centers in China. In addition, the economic level in China prevents it from using currently available expensive diagnostics and treatments at a large scale, adding to the need for inexpensive and more advanced treatment methods.

In genomics related areas

China plans to sequence more genomes of both scientific and economic importance, in collaboration with international partners. (Beijing Genomics Institute, 2004c)

Study of traditional Chinese medicine using genomics tools is a focus of China. For example, Beijing Genomics Institute reportedly was working to identify and then manufacture the active ingredients of traditional Chinese medicines such as Gingsen (Murphy, 2001).

In biodiversity

China is one of the richest countries regarding biological resources. As compounds from plants offer the best chances for the development of new lead structures in drug discovery, collaboration in this area can be very interesting, for instance.

Worth mentioning here is that local governments in China have come up with policies to attract investment and expertise to commercialize biotechnology. For instance, Yunnan, one the hot spots of biodiversity in China, has provincial governmental support for pharmaceutical projects, including for overseas researchers intending to do their high-tech research in Yunnan, with special funds and other means (Xinhua News Agency, 2003). To encourage innovation, Yunnan government announced that scientists who have developed new drugs can become shareholders using their research results as registered capital, following the practice in the West.

A driving force for Chinese biotechnology is the large number of overseas-trained Chinese who returned to work in China, bringing with them knowledge and contacts. With some 20,000 Chinese scientists working in the West as of 2002 (The Economist, 2002), this trend is unlikely to stop. Many of the scientists who returned to China now head key research projects, found and manage biotech companies. They often play an important role in international collaborations. Examples in the following chapter “Chinese Biotechnology Industry” illustrate this.

4. CHINESE BIOTECHNOLOGY INDUSTRY

4.1 Overview of the industry

According to the "Chinese Biotechnology Industry Development Report 2002" edited by the Chinese National Development Plan Committee's High-tech Industry Development Department and the Chinese Biotechnology Society, China did not yet established a comprehensive statistics system concerning its biotechnology industry as of 2002 and the available data came from somewhat systematic data collections in 1986 and 1996 and a partial follow-up in 2000. The estimation by the above-mentioned report is that up till year 2002, there were about 300 companies engaged in biotech research and development, and most of them were in healthcare and agriculture sectors. Half of these were small- and medium-sized enterprises established within the last five years. Around 150 companies had production capacity, of which about 60 companies received manufacture permit for genetically engineered drug and vaccine, and the rest produced diagnostic kits, blood products, and biochemical drugs. Only several have grown into sizable enterprises and have achieved relatively good profitability. According to the Chinese National Center for Biotechnology Development (Wang, ca. 2003), there are about 500 modern biotech businesses in China employing over 50,000 people. Of those, over 300 enterprises are in the medical biotechnology area. About 100 new biotech companies are formed each year.

Total number of companies	500
Number of companies in medical field	over 300
Total employment	50000

Table 1: Chinese biotechnology industry in 2003
Source: Chinese National Center for Biotechnology Development

The "Chinese Biotechnology Industry Development Report 2002" covered the following areas in the healthcare sector: biopharmaceuticals, antibiotics, clinical diagnostic reagents, biochips, stem cell research and commercialization, and human genome project related. It also covered transgenic agricultural products, plant cell tissue culture, herbicides & pesticides, feed additives, and rice genomics related in the agriculture sector. Based on the relevant chapters of the above mentioned report on biopharmaceuticals (Xu, et al, 2002), molecular diagnostics (Hao, et al, 2002), biochips (Chen, et al, 2002), and transgenic agriculture products (Cui and Guo, 2002) (unless cited otherwise), a summary for each sector follows.

4.1.1 Biopharmaceutical sector

Before 1996, biopharmaceutical industry in China was mainly imitating foreign products and the funding for R&D came mainly from the government. After 1996, the government invested more in biotech R&D to speed up the ongoing projects and to strengthen the research leading to innovative new drugs. The industry began to realize the potential of biotech and became more and more interested in investing in it. As a result, the 863 plan contributed to about 20% of the total R&D capital only for products related to 863 projects in the biotech field after 1996. The majority of the R&D funding in the biotech industry came from the enterprises themselves.

According to a report from the Chinese National Center for Biotechnology Development (Wang, ca. 2003), 21 recombinant pharmaceuticals such as recombinant interferon, insulin and GCSF have been commercialized since China's first genetically engineered drug (recombinant human Interferon a1b) was brought to market in 1993. Of the world's top 10 selling biopharmaceutical drugs in 2002 China could produce 8 of them. As of 2002, in clinical trial stage, were more than 150 biopharmaceuticals (30 of which had type A New Drug status), 7 proprietary gene therapy drugs including those for malignant tumor and hemophilia B, and 6 tissue engineering products (bone, cartilage, skin, tendon, etc). These numbers looked a bit different according to the "Chinese Biotechnology Industry Development Report 2002". According to this report, about 30 biopharmaceutical drugs were in clinical trial phase up till 2002 and about 100 biopharmaceutical drugs and healthcare products were in R&D stage.

The biopharma's sales revenue was 6% of the total Chinese pharmaceutical industry revenue in 2000, and was over 24 billion RMB Yuan (ca. 2.4 billion Euro) in 2001. Brands regarding biopharmaceutical drugs as well as biopharmaceutical enterprises are being established. Well-established companies included Shenzhen Kangtai (HBV vaccine), Beijing Research Institute of Biological Products (HBV Vaccine), Shenzhen Kexing (Interferon), Shenyang SanShen (English name: Sunshine Pharmaceutical Co. Ltd; Interferon, Interleukin 2, EPO), Beijing Shuanglu (G-CSF, Interleukin 2), Anhui Anke (growth hormone).

Having grown into sizable enterprises, several of the biopharmaceutical companies have been investing in R&D leading to new drugs. Sunshine pharmaceutical Co. Ltd., for instance, has set up LifeGen Inc. in Maryland, USA, for upstream research, according to the company (www.3sbio.com).

Recent significant events in the biopharmaceutical sector included:

- In October 2003, the Chinese State Food and Drug Administration (SFDA) issued drug license to Shenzhen SiBiono Gene Technologies Co. Ltd. (www.sibiono.com) to commercially produce the world's first gene therapy drug Gendicine, for the treatment of head and neck squamous cell carcinoma (Pearson, et al, 2004). Gendicine uses an adenoviral vector + p53 tumor suppressor gene delivery system. More aspects related to this are covered under "Manufacturing aspects" and "Clinical trials" in this section.

- In November 2003, SFDA approved a SARS vaccine made of inactivated virus for clinical trial, putting the Chinese company ahead of competing groups. The vaccine was developed by Beijing Kexing Biotech Co. Ltd. (English name: Sinovac Biotech Co. Ltd.) (www.sinovac.com). In January 2004, the company reported that 30 volunteers would be inoculated with the vaccine to determine whether it is safe to use in humans – a phase I clinical trial.

Readers interested in a review of the Chinese pharmaceutical industry at large are referred to Section 6 for a recent report by the International Federation of Pharmaceutical Manufacturers Association (IFPMA) entitled "Accelerating Innovative Pharmaceutical Research and Development in China: a case study".

4.1.2 Clinical diagnostics sector – molecular diagnostics

Before 1980, the medical laboratory sciences in China lagged 20 years behind the West. Between 1985 to 1990, a large number of technologies from the West were imported and many diagnostics companies were set up. In the early 1990's, the number of clinical biochemical reagent manufacturers exceeded 100, and that of immunological diagnostics companies exceeded 300. This resulted in intense competition which helped to advance the application level of diagnostics products. However it resulted in a chaotic market also, due to products of various quality because of regulation loopholes. Some companies operated without manufacture permit. Since 1993, the government started to regulate this sector. By 2002, the number of diagnostics companies stabilized at about 80.

The total diagnostics market in China in 2002 was 3 to 4 billion Yuan RMB (about 0.3 to 0.4 billion Euro) in total revenue, with clinical biochemistry and immunology products taking the lead. In general, the Chinese diagnostics companies are small in size, with a narrow product spectrum. The market was fragmented with the top ten domestic companies combined taking about 20%

of the market in 2002. Foreign companies have been selling directly to the Chinese market through their own sales organization also, and in 2002, these companies took about 10% of the Chinese market.

Among the top 10 Chinese diagnostics companies based on sales revenue in 2002, three had molecular diagnostics product offering, one company focused totally in this area. The three companies involved in molecular diagnostics were Shanghai FuXing Enterprise holding Co, Ltd., Sino-American Biotech company, and Zhongshan (Sun Yat-sen) Medical University DaAn Gene holding Co., Ltd.

The molecular diagnostics market in China, up till 2002, was made up of PCR-related products. Since 2000 the State Food and Drug Administration (SFDA) has granted reagent new drug permit to semi-quantitative and quantitative PCR reagents. China is advanced in market development and the degree of maturity in the application of such products. Since 2002 Chinese biochip companies such as Shanghai HealthDigit, have come up with products for clinical diagnostics. More on the biochip sector in the next section.

Although the R&D investment was low for the clinical diagnostics sector in general, some companies have started to establish their own R&D center and research institutes. For instance, Sino-American Biotech Company has been permitted by the government to establish itself as a post-doc research station. One of the challenges faced by the Chinese diagnostics companies was the capability and capacity for producing automated equipment for use with the reagents.

4.1.3 Biochip sector

China recognized the potential of biochip technology early in 1997. To avoid a lack of own intellectual property (IP) rights as was the case with the Chinese IT industry, biochip research and development received a lot of government support. The MOST has started functional genomics and biochip projects under its 863 high-tech projects in 2002. Two national centers have been set up: the National Engineering Research Center for Beijing Biochip Technology, which is an affiliate of the Capital Biochip Corporation, and the Shanghai Engineering Center for Biochip, which is an affiliate of Shanghai Biochip Co., Ltd. (SBC).

According to Capital Biochip Corporation (www.capitalbiochip.com), it was founded in 2000 with a total funding capital of 376 million Yuan (ca. 37.6 million Euro). 240 million Yuan came from the four founding stock holders and

106 million Yuan from venture capital firms. The MOST was to provide a total of 200 million Yuan for research during the first 5 years.

SBC (www.shbiochp.com) was founded in 2001. In 2003 the State Plan Committee commissioned SBC to establish the Shanghai Engineering Center for Biochip with a total investment of 290 million Yuan (ca. 29 million Euro) (People's Daily, 2003).

There were at least 100 biochip companies in China in 2002, but most of these were in the initial phase of R&D only. There are over 20 major players, including both companies and universities, in the research and development of biochip. Companies with products on the market already include Shenzhen Yishentang Biological Products Co. Ltd. (www.szyst.com), Shanghai HealthDigit (www.health-digit.com), Shanghai United Gene Holding Co. Ltd. (www.unitedgene.com), and Capital Biochip Company (www.capitalbiochip.com). Shenzhen Yishentang Biological Products Co. Ltd has brought to market HCV Antibody protein chip detection kit (granted type A New Drug certificate by the SFDA) and HBV drug resistance gene chip detection kit, which the company co-developed with the Academy of Science for Military Medicine. Shanghai HealthDigit, Shanghai United Gene Holding Co. Ltd. and Capital Biochip Company will be described in detail later in chapter 4.3.

In general, products in the biochip equipment area are limited and are in the early phase of research and development still. Companies making equipment include Chendu Baiao Science and Technology Co., Ltd. (product development done by the Institute of Optics and Electronics, Chinese Academy of Science) and HealthDigit who has developed its own data analyzing system. In general, China lags behind concerning software products in the biochip sector.

4.1.4 Agriculture biotech sector - transgenic products

In 2002, transgenic cotton was planted in over 40% of the total cotton growing areas in China. the company Biocentury the key player in this field. Biocentury will be described in more detail later in chapter 4.3.

Shenzhen Lupeng Agricultural High-tech Enterprise Co., Ltd. is the major player in the industrialization of transgenic animal products. A description of Lupeng will also be provided in chapter 4.3.

According to Wang (ca. 2003), China has a production line with 10,000 Ton capacity for recombinant nitrogen-fixing bacteria as well as 5 kinds of recombinant microbial products for animal use including vaccine. Permits for

commercial production have been issued for 3 microbial herbicides/pesticides including a transgenic BT microbial product.

For a detailed overview of the Chinese Agri-biotech, please see Chapter 7 for readings like "China: Agricultural Biotechnology Opportunities to Meet the Challenges of Food Production".

4.2 Factors important for development

China has made impressive progress in the last 20 years building up its biotechnology industry. However, there's a lot of challenges the industry has to face. With China's accession into WTO, there is no choice for the industry but to innovate in order to succeed in the global market which China is a part of. Issues which received a lot of criticism in the past such as the protection of intellectual property rights have been continuously improved. Strictly speaking though, the current Chinese biotech industry still lags behind the Western countries in all these aspects: technology, capital, qualified human resources and management. This, for one, underlines the need on the Chinese side to collaborate with international partners, for another, shows also the opportunities for this industry in China. In the following, factors important for the development of the biotech industry in China will be discussed in detail. This includes: capital market and exit channel concerning venture capital (VC), manufacturing aspects, clinical trials, regulatory issues as well as intellectual property issues.

4.2.1 Capital market and exit channel

The importance of venture capital for the establishment and development of high and new technology-based industry like biotech industry is generally acknowledged. In China the venture capital market is underdeveloped. The majority of the Chinese biotech companies are related to public sector institutions. According to Zhang Mu, chief of the medicine department at the Chinese National Center for Biotechnology Development, venture capitalists in China are either too cautious (risk adverse) or have trouble picking innovative, high-tech projects (lack of experience and expertise) (Jia, 2003).

In 2003 China has set up more than 250 venture capital institutions with a capital scale of more than 40 billion Yuan (ca. 4 billion Euro) since 1994, of which 10 billion Yuan (ca. 1 billion Euro) are foreign investment (Xinhua InfoLink, ca. 2003). Most of the Chinese capital is from government-related agencies (Tang, et al, 2003). It is a common practice among the Chinese VCs to match foreign investments by several folds, according to Dr. Tang, president and managing director of the World Technology Ventures in the

USA (C. M. Tang, personal communication, March 2004). Foreign venture capital has extended from Beijing and Shanghai to other areas of China. For instance, Shandong New and Hi-tech Investment Co., Ltd. with Singapore United Overseas Bank and British Oxford and Cambridge Group reportedly set up a venture capital fund company, involving an initial total investment of 300 million Yuan (ca. 30 million Euro) (Xinhua InfoLink, ca. 2003).

VC investment in biotechnology was about 8.5% (68 projects, ranking biotechnology in the top 5 of 18 sectors as defined by China's VC Yearbook 2002) of its total investment, so about 340 million Euro, according to one source (Tang, et al, 2003). According to another source (Liu, 2003), China had only about $100 million VC funding for biotechnology, and in comparison, the US and European biotechnology sectors attracted $2.7 billion and $950 million in venture capital in 2002. Further, it was estimated that 81% of the $325 million raised by Asian VCs between June 1999 and June 2003 for biotechnology are invested in US firms (Liu, 2003). Foreign VC investment in Chinese biotech does exist although the total sum is limited. One example is the Xcelerator Capital Group in Australia, already mentioned early in this report. Reportedly this group signed a $4 million protein research joint venture with the Shanghai Institute of Biological Sciences in 2002 (The Hindu, 2003). Problems associated with exit channel and IP protection are cited as factors that have been keeping foreign VCs away.

Venture capital has a very short history in China. In 1999, the Chinese State Council issued decisions and opinions to support the cultivation of capital markets and venture capital for the development of high-tech industries and stated that a venture capital industry was necessary for the technological innovations of small and medium sized enterprises (Xiao, 2002). The government has also been developing a legal framework for the venture capital industry, and planned to open a technology board in Shenzhen Stock Exchange to improve exit channels for VC. The plan, however, has not yet been materialized due to banking scandals (Liu, 2003). Local governments have been following suit in their policies to encourage venture capital investment as well. To encourage foreign VC investment, China has published the provisional procedures on using foreign investment to reorganize state-owned enterprises and the provisional procedures on qualified foreign institutional investors making securities investment in China (Shanghai Online, ca. 2003).

Hindrances to develop a VC industry exist regarding exit channel and IP protection, many believe. IP issues in China will be discussed later in this chapter. Concerning VC exit channel, for one, the capital structure mandated by Chinese company law limits the free transferability of equity. The law

segregates shares into domestic-only and foreign-only ownership, and only the foreign shares may list on foreign securities exchanges (Fu, 2002). This constricts exit strategy.

Limitation also comes from an immature Chinese domestic stock market. Individual investors and institutional investors alike speculate instead of invest, and scandals have been generated due to improper regulations and insufficient enforcement of the securities laws, and consequently problems associated with listed companies (Green, 2001). For instance, although the Chinese securities laws call for continuous disclosure and mandate financial reports, neither the laws nor common practice in China defines the content or structure of financial disclosure, and the Chinese accountancy rules are relatively immature (Fu, 2002). Further, China's stock market currently does not support listing of innovative technology-based companies due to requirements such as profitability requirements, a situation similar to the German stock market before the creation of the growth sector, the Neuer Markt, which led to the current TecDax on the Frankfurt Stock Exchange. It seems mandatory that the Chinese stock market be brought up to international standard first before a growth sector can be introduced. As an alternative, VCs in China can list their companies in Hong Kong stock exchange which is linked to the London stock exchange and which has a technology board.

Problems VCs in China have to face also include information asymmetry between company management and outside investors as well as a lack of service professionals such as law firms, accounting firms and assessment centers to support venture capital firms, according to Wei Xiao, Managing Director and Vice President of Beijing International Trust & Investment Corporation and Beijing Venture Capital Company (Xiao, 2002).

China is progressing fast, so its stock market and related conditions may improve in the near future and become more conducive to VC development. Until that happens, the major source of funding for the Chinese biotechnology research remains the government.

Government funding

The government funds almost all of the plant biotechnology research in China with a total investment in 1999 of some $112 million, and in 2001, China planned to raise plant biotechnology research budgets by 400% before 2005 – if achieved, one-third of the world’s public plant biotechnology spending would come from China (Huang, et al, 2002). There is also some niche funding from non-profit international organizations available to Chinese

scientists for certain projects in this area such as from the Asian Development Bank, United Nations, World Bank and Rockefeller Foundation (Tang, et al, 2003).

The government has been using favorable policies in taxation, financing, attracting talents, and import and export, to support biotechnology industry, and over 20 biotech parks have been established in Beijing, Shanghai, Guangzhou and Shenzhen (Wang, ca. 2003). Companies with R&D spending equivalent to or above 5% of its annual sales revenue are qualified as "high-tech" enterprises (China, 2002). To promote small- and medium-sized scientific and technological enterprises, the Innovation Fund for these enterprises was established in 1999, and 660 million RMB Yuan (ca. 66 million Euro) was arranged to support R&D activities in the field of electric information, biology, medicine and photoelectricity in 2000 (China, 2002).

4.2.2 Manufacturing aspects

The concept of Good Manufacturing Practice (GMP) was introduced to China in the ninety eighties. China published its first GMP rules in 1988 and they were last modified in 1999 by the Order number 9 of State Food and Drug Administration – SFDA (1999). The SFDA (www.sda.gov.cn), previously named SDA, is responsible for the certification of GMP, the training, examination and appointment of GMP auditors. The Drug Safety Surveillance and Administration department of the SFDA carries out the above-mentioned tasks.

According to SFDA (1999), to qualify for GMP certificate, drug manufacturing firms submit application and supporting documents to SFDA. The Drug Safety Surveillance and Administration organizes experts to inspect the sites. If the inspections meet requirements and are passed by the SFDA, a Drug GMP Certificate is issued by SFDA and is valid for 5 years. If the requirements are not met, candidates can reapply after one year.

GMP facilities are necessary for the approval of pharmaceutical and clinical diagnostic products worldwide. Several years ago, China set up rules for its existing drug manufactures to meet GMP requirements in different stages and by different deadlines based on their drug categories (SFDA, 1999). Those not able to comply by the deadline had to terminate their production. Rules were also made to prevent reappearance of low-quality manufacturers by requiring both new drug manufacturers and generic drug manufacturers to get GMP certificate first before they can apply for Drug Manufacture Permit. In 2003, China gave an ultimatum to all its pharmaceutical companies to comply with GMP by June 30, 2004, or to close down (SFDA, 2003). Because of

GMP requirements, the number of drug manufacturing companies in China has decreased in the last several years. The over 6000 drug manufacturing companies in 2001 (most of whom did not meet GMP requirements at that time) were reduced to over 4,000 in 2002, and the number is expected to reduce further to around 3500 in 2004.

Concerning biotech manufacturing technologies, relatively poor industrial arts, in terms of purification and/or fermentation, is a serious flaw in Chinese biotech research and development institutes, according to Peng Zhaohui, chairman of SiBiono Gene Technologies Co. Ltd. (www.sibiono.com), the Chinese company that developed world's first commercial gene therapy drug (Jia, 2003). Further, in his opinion, while China might lag behind the United States by five or seven years in biotech theories, in practical lab technologies, it lags behind by more than 15 years. SiBiono, for instance, imported its manufacturing facilities from an US company (Eichenbaum and Sattan, 2003). It is interesting to note that the technology specialist for this product in the US company is Chinese. Another high-profile Chinese biotech company Sinovac Biotech Co. Ltd. (www.sinovac.com), the first to enter clinical trial phase with a SARS vaccine, also had its plant for one of its two major vaccine products done by European companies. According to the company, the design of the plant for Healive vaccine was done by the Italian company Sterile with major equipment and facilities imported from the Spanish company Telstar, and the installation and debugging processes completed by the FDA-approved French company SVS (Sinovac, 2004; Pan and Li, 2002)

4.2.3 Clinical trials

Ethical and quality issues in clinical trials determine whether the data collected can be used for approval internationally. When such issues are effectively addressed by the SFDA in China, foreign companies may prefer having their clinical trials conducted in China to lower drug development cost whenever possible. Conforming to international ethical and quality standards in clinical trials is equally important for Chinese pharmaceutical companies interested in exporting their products. According to Pharmaceutical Research and Manufacturers Association (www.phrma.org), although most of the clinical trials conducted by international pharmaceutical companies are being done in the developed countries, in recent years, companies have increased testing in developing countries. Companies are also developing an increasing number of medicines for diseases having a higher prevalence in developing countries, hence must test there. While clinical trials are conducted in accordance with applicable laws and regulations as well as locally recognized good clinical practice, companies wanting to use the data to have a medicine approved in the US, Europe or Japan must comply with standards published

by international organizations such as the International Conference on Harmonization (IHC), details of which can be found at www.fda.gov/cber/ich/ichguide.htm. Whether clinical studies done in China can be accepted for approvals outside China is judged by regulating agencies case by case. For instance, the relevant general guidelines of FDA can be found in its Guidance for Industry: Acceptance of Foreign Clinical Studies at www.fda.gov/oc/gcp/guidance.html.

China is moving fast to formulate and to improve regulations governing clinical trials in order to move in line with international standards. Talks and information exchange involving SFDA of China and other countries can be found at meetings like the Forth IFPMA Asian Regulatory Conference (www.ifpma.org/site_docs/Events/ARC_Program_March30.pdf) and the Drug Discovery & Development Summit. As an example, in the 2nd International Drug Discovery and Development Summit in 2003, the SFDA (Cao, 2003) presented on current regulatory requirements for human pharmaceutics in China covering the establishment, amendment and execution of regulations on drug safety evaluation, description of the codes and the guidance regarding Good Laboratory Practice, Good Clinical Practice, and Good Manufacturing Practice, as well as the procedures for filing and approving IND and NDA submission, inspection and audition of clinical centers that conduct clinical trials, and the programs for training clinical trial auditors. The next section will provide some details on the specific regulations in China concerning clinical trials.

Advantages in conducting clinical trials in China include a very large number of patients, in addition to low cost. The huge patient pool makes organization of trials faster and consequently shortens time in which the statistically meaningful data can be collected – hence shortening time to market. This was cited by SiBiono as one of the reasons for its being the first with a gene therapy drug on the market (Pearson, et al, 2004). SiBiono conducted trials on head and neck squamous cell carcinoma, a common cancer in China which accounts for about 10 per cent of the 2.5 million new cancer patients annually (Pearson, et al, 2004).

4.2.4 Regulatory issues

Both drug GMP and clinical trial quality control are the responsibilities of the Drug Safety Administration of the State Food and Drug Administration (SFDA) of China. SFDA has an informative web site, however it is in Chinese only. Information such as pricing policy for drugs (somewhat similar to that of

Germany) can be found on the SFDA web site as well. Some relevant information from the web site will be summarized here.

A sample of relevant laws and orders:

1.) People's Republic of China’s Drug Administration Law:

It is effective since 01.12.2001, and the practice rules based on this law is effective since 15.09.2002. This law specifically rules the research and development, manufacture, sell, use and the regulation and administration of drugs. The older Drug Administration Law on which this law is based was made in 1985.

2.) Drug Manufacture Quality Control Regulation, Order number 9 of SFDA

Also called Drug GMP for short, this order was modified in 1998 and is effective since 01.08.1999. It sets out the basic regulations for drug manufacture and quality control. It applies to the entire process of drug manufacture, and to the key processes in the drug ingredient manufacture which influence the quality of the drug.

3.) Drug Manufacturing Administration Methods (trial use) – Order number 37

Effective since 01.02.2003, it is used in applications and permits to set up a drug manufacturing company, the administration of drug manufacture permit, etc.

4.) Biological Products Proof, Certification and Release Administration Methods (trial use) - Order number 36

It is effective since 15.01.2003 and deals with the rules concerning mandatory proof, control and permit for vaccine products, blood products and in vitro biological diagnostic reagents used for blood screening as well as other biological products specified by the SFDA, before they are sold on the market or imported into China.

5.) Clinical Trial Rules and Norms:

Effective since 01.09.2003 is the new “Rules and Norms for Drug Clinical Trial Quality Control” which is the Order Number 3 of the SFDA. According to this Order, all clinical trials conducted in China must comply with the Helsinki Declaration (addressing ethical issues) first passed in 1964 in Helsinki, Finland and last modified in 2000 in Edinburgh, Scotland.

What's worth keeping in mind is that China is still in the phase of updating and formulating such regulations and rules, hence, make sure you are looking at the most current ones.

China has a comprehensive set of rules and policies concerning biotechnology and biosafety already, although in a country of its size and in rapid transition, whether efficient enforcement is in place is another question.

A list of rules and regulations (Wang, ca. 2003):

1.) 1993: "rules concerning gene" by the Ministry Of Science and Technology (MOST)

2.) 1996: "rules concerning agricultural genetic engineering safety regulation and application", by the Ministry Of Agriculture (MOA)

3.) Since 1997, certification of the safety of agricultural transgenic products has been done

4.) 1998: "temporary rules for regulating human genetic resources" by the MOST and the Ministry Of Health (MOH)

5.) 2001: "rules concerning the safety regulation of agricultural transgenic products" by the congress

6.) 2002: "ways to regulate the safety assessment of agricultural transgenic products", "ways to regulate the safety of imported agricultural transgenic products" and "ways to regulate the labeling and recognition of agricultural transgenic products" by the MOA

7.) There's also a series of regulations from the National Environmental Protection Bureau (NEPB) entitled "framework of Chinese national biological safety"

8.) Since 2002, MOST, NEPB, MOA, MOH etc. have been working together on the formulation of biotechnology safety law and related law, and on the improvement of the rules, orders and ways in the regulation of biosafety

9.) Laws which also cover GM plants and its import and export include the People's Republic of China's Seed Law, which is effective since 01.12.2000 (China, 2000).

Aside from laws and regulations, ethical issues in the use of biotechnology have been discussed in China. Professor Renzong Qiu at the Chinese Academy of Social Sciences' center for Bioethics, for instance, is well-known in the field. He has served as a member to the International Bio-ethics Committee of UNESCO and to the Ethics Committee of the Human Genome Organization and to the Ethics Committee of the Ministry of Health in China, among others (Qiu, no date).

Readers interested in more detailed treatment of ethical issues in biomedical research in China may find useful. the article "Entwicklung und Ethik: die biomedizinische Spitzenforschung in China will den Kontakt zur Gesellschaft halten, die Medizinethik sucht nach passenden Regeln", listed in chapter 6.

4.2.5 Intellectual property issues

Concern over intellectual property (IP) protection has frequently been cited as a reason by foreign companies for not doing business with/in China. However, this is almost a stereotype impression of China because China has progressed fast in the past ten years in the recognition and protection of IP rights. In fact, there is a rather high awareness of the IP issues in China now, the IP related laws and regulations are in place and their enforcement is continuously being improved.

Developing countries including China (in 1993) extensively changed or substantially strengthened their patent systems to move towards compliance with their international obligations under the WTO Trade Related Agreement on Intellectual Property Rights, known as TRIPS (IFPMA, 2003). Relevant laws in China (English version) are available at the Chinese Ministry of Science and Technology web site www.most.gov.cn.

China acceded to the Convention Establishing the World Intellectual Property Organization on June 3, 1980, and is now a member state of the Paris Convention for the Protection of Industrial Property, the Patent Cooperation Treaty (PCT), the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, the Locarno Agreement Establishing an International Classification of Industrial Designs, and the Strasbourg Agreement Concerning the International Patent Classification (Wang and Liu, 2003). Further, since January 1, 1994, the State Intellectual Property Office in China has been serving as the Receiving Office of International Searching Authority and International Preliminary Examining Authority for the PCT, and the Chinese language is one of PCT’s working languages (Wang and Liu, 2003).

The Patent Law in China first came into force on April 1, 1985, and has been amended twice in 1992 and 2000, respectively (Wang and Liu, 2003). The Implementation Regulations for the Patent Law have also been issued and amended accordingly. According to the article "Patent protection in biotechnology in China" on the information network run by Biocentury Transgene (China) Co., Ltd (Biocentury, ca. 2000), from April 1, 1985 to December 31, 1992, the Chinese patent law did not grant patent rights to

drugs and substances obtained by chemical methods, nor to animals and plants. The impression from this period is perhaps still with many people in the Western countries when thinking of IP protection issues in China. However, since 1993, patent rights can be granted to drugs and substances obtained by chemical methods in China. Although currently animals and plants including those which have been genetically modified can not be patented in China, protection can be granted to new plant varieties which meet the conditions specified in the "Regulations on the Protection of New Varieties of Plants" issued in 1997 and entered into force in 1999 (Biocentury, ca. 2000). Microorganisms and genetic material can be patented (Biocentury, ca. 2000).

The World Intellectual Property Organization (WIPO)'s Intellectual property – country profile: China, also provides an overview of the field. (www.wipo.int/about-ip/en/ipworldwide/pdf/cn.pdf)

It has been pointed out that since the Chinese companies have started to see themselves as creator and owner of IP and not just the user of it, the enforcement of IP laws lies in their interest as well, and this has helped to make the enforcement move more quickly in line with international standard (Ackman, 2003). United Gene Holdings Co., Ltd (UG), which will be described in detail in the next section, has filed over 1000 patents with the PCT and over 3000 patents in China, for instance. UG is a well-known example (in China) of a Chinese company aggressively protecting its IP through patents as well as successfully cashing in on its IP.

The following events in 2003 demonstrate that IP is already regarded as a very important issue in China. First, Tianjin Intellectual Property Office officially began to accept requests for mediating patent disputes, requests for handling patent disputes, and complaints for acts of counterfeiting/passing off a patent, all through Internet (China Express Team, 2003). Second, Shanghai Intellectual Property Service Center developed and unveiled an online Patent Analysis System which allows the subscribers subject search in technology, long-term monitoring of competitors' technology, patent queries, patent knowledge training, patent distribution and patent trend analysis, etc., the first of its kind in China (China Express Team, 2003).

A MOST news release (MOST, 2003e) also reported that one of the three major strategies to be accomplished during the 2001-2005 period by the Chinese Ministry of Science and Technology concerns intellectual property. This includes the strengthening of the IP management of national science and technology projects.

4.3 A sample of Chinese Companies

4.3.1 Overview

As mentioned earlier in this report, one can say that the modern Chinese biotech industry was jump-started by the government's 863 plan, a program to fund applied research in high- and new- technology areas. The following companies (in the biopharmaceutical and the agricultural biotechnology sectors) which originated from the industrialization of 863 research achievements during its 1986 – 2001 period are among the earliest companies in the Chinese biotechnology industry, and have grown into sizable enterprises: Shenzhen Kexing Bioproducts Co. Ltd., Sunshine Pharmaceutical Co. Ltd. (Chinese name: Shenyang SanShen Pharmaceutical Co. Ltd.), Shenzhen Lupeng agricultural Hi-tech Enterprise Co. Ltd., and Shenzhen Biocentury Transgene Co. Ltd. In addition, North China Pharmaceutical Corporation (NCPC), founded in the 1950's, the largest pharmaceutical enterprise in China, also started to develop biopharmaceuticals with the 863 project on recombinant human granulocyte-macrophage colony stimulating factor (rhGM-CSF) in the early 1990's. NCPC has since established a New Drug R&D Center and NCPC GeneTech Biotechnology Co. Ltd., a joint venture with Maui Biotechnology Development Company.

In the molecular diagnostics sector, the earlier companies started by creating a branch producing PCR related reagents, such as the Sino-American Biotech Company (SABC), and the later ones entered with biochip technology such as HealthDigit and United Gene Holdings Ltd. (UG). These companies are private companies or formerly joint venture between Chinese and American companies in case of SABC.

UG is a private biotech company coming out of the genomics wave, with over 1000 patent applications (full-length gene related) filed at the Patent Cooperation Treaty (PCT). Perhaps the largest private biotech company in China, UG is much more than a biochip company. It has grown into a group of eight companies covering the whole value chain of new diagnostics and therapeutics product development.

Since biochip technology is an area that has been receiving government support since 1997, the two national biochip research centers in Beijing and Shanghai, for instance, are affiliates of two business entities – Capital Biochip Corporation and Shanghai Biochip Co., Ltd. These companies are examples of the more recent state-backed biotech companies.

Lastly, traditional Chinese medicine (TCM) is a unique resource of China. Producing pharmaceuticals out of herbs or microbes traditionally used as medicine or health food has been the business of many Chinese pharmaceutical companies. However, modernization of TCM has been a relatively recent effort. One "model" enterprise in this area is Beijing WBL Peking University Biotech Co., Ltd.

In the following a more detailed description will be provided for some of the companies mentioned above. Information concerning the companies are taken from the web sites of these companies, unless otherwise noted.

4.3.2 From Shenzhen Kexing to China Bioway Biotech Group

Shenzhen Kexing Bio-engineering Co., Ltd. originates from industrialization of 863 research achievements. Founded in 1989, it is the first modern biotech company in China. China Bioway Biotech Group Co., Ltd. (Chinese name: Weiming Group Co. Ltd.) has evolved from this enterprise into the largest biotech group company of China.

China Bioway Biotech Group Co., Ltd.

China Bioway Biotech Group Co., Ltd. (www.weiming.com.cn) is one of the four industry group companies of Beijing University (English name: Peking University – PKU), founded by Drs. Zhangliang Chen and Aihua Pan in 1992. Currently China Bioway has more than 10 wholly owned or jointly owned companies. The group focuses on research, development, industrialization and commercialization of genetically engineered pharmaceuticals, natural medicine, chemical drugs, biochemical pharmaceuticals, vaccines, diagnostics, agricultural biotechnology and healthcare products.

Wholly-owned or jointly-owned companies

1. Shandong Kexing Bioproducts Co., Ltd

2. Sinovac Biotech Co., Ltd (part of Beijing Kexing Biotech Co., Ltd)

3. Shenzhen Kexing Bio-engineering Co., Ltd

4. Xiamen Bioway Biotech Co., Ltd

5. Shenzhen PKU High-tech Investment Co., Ltd (listed on Shenzhen Stock Exchange, China)

6. PKU Weiming Diagnostics Co., Ltd

7. Beijing Pharmaceutical Group Co. Ltd

8. PKU Weiming Bioproducts Co., Ltd

9. Beijing Shidailicheng Biological Economic Research Center Co., Ltd

10. Science and Technology Industrialization Promotion Center Co., Ltd

Bioway produces more than twenty kinds of pharmaceuticals including recombinant human erythropoietin (Eposino), recombinant human granulocyte colony stimulating factor (White-C), recombinant human insulin (Sumelin), recombinant human growth hormone (Sigrow), nerve growth factor (Nobex), and hepatitis A vaccine (Healive).

Bioway has rich resources in researching and producing biopharmaceuticals, having established R&D centers with a total area of nearly 30,000 square meters in three major bases in Beijing, Shenzhen and Xiamen. Bioway has more than ten ongoing projects with proprietary intellectual property rights. It also possesses eleven production lines compliant to international GMP standards.

Portfolio company Shenzhen Kexing Bio-engineering Co., Ltd.

Kexing (www.kexing.com) originated from the industrialization of the 863 project to develop recombinant Interferon alpha 1b. Established in 1989 with the support of Peking University, Kexing is China's first modern biotechnology company (formerly named: Kexing Bioproducts Co., Ltd.). It's financing came from the Bioway Biotech Group and an American investment company, with a total initial investment of 100 million Yuan RBM (ca. 10 million Euro) (MOST, ca. 2002). The earlier top management included Drs Zhanliang Chen and Aihua Pan from Peking University (MOST, ca. 2002).

According to a talk given by Dr. Aihua Pan at the China Business Summit 2001 (Pan, 2001), although the company incurred losses of 10 to 20 million Yuan RMB in its initial years, the success of its first product Sinogen (Interferon alpha 1b) achieved profits of 60 million Yuan RMB (ca. 6 million Euro) in recent years (said in 2001) for the company. Sinogen is the top brand in the Chinese interferon market, according to the company.

Other than Sinogen, Kexing's products include also RecoSun (recombinant human Interleukin – 2), Sumelin (recombinant human insulin), and Sigrow (recombinant human growth hormone).

Portfolio company Sinovac Biotech Co., Ltd.

Sinovac Biotech Co., Ltd. (Chinese name: Beijing Kexing) was founded in 2001. At its foundation, it was jointly invested and incorporated by China Bioway Biotech Group Co., Ltd., Sino Pharmacy Co., Ltd. (Hong Kong), Tang Shan Yian Biological engineering Co., Ltd., and Beijing Keding Investment Co., Ltd.

In October 2003, approximately 51% of the issued and outstanding capital stock of Sinovac was acquired by Net Force Systems Inc., a company incorporated in Antigua in 2000. NetForce Systems Inc. subsequently changed its name to Sinovac Biotech Ltd. and its ticker symbol from NTFSF to SNVBF (listed on NASD Over-the-Counter bulletin board) in November 2003. It also acquired Tangshan Yian Biological Engineering Co., Ltd. as its wholly owned subsidiary.

Sinovac Biotech Ltd. specializes in the research, development and commercialization of human vaccines for infectious diseases such as Hepatitis A, Hepatitis A&B, influenza and SARS. In 2002, Sinovac successfully launched sales of its Hepatitis A vaccine which was developed using its own proprietary technology. It has also completed clinical trials for a combined Hepatitis A&B vaccine and the results are being evaluated. At the end of 2003, Sinovac made headline news by being the first in the world to enter phase I clinical trial with a SARS vaccine.

Interesting to note is that within China, domestic companies can achieve cost advantage by locating outside big cities. This is the case with Tangshan Yian. Tangshan Yian develops and manufactures vaccines including flu vaccines and Hepatitis A vaccines and supplies these vaccines to Sinovac Biotech Co., Ltd. The company is regarded as a low-cost R&D and manufacturing center, located in the Hi New Tech park of Tangshan, 150 km from Beijing. As compared to Beijing, Tangshan is 20% cheaper in land and 50% cheaper in labor. The company has a biosafety Level 3 laboratory, which are limited in number in China. The first 20,000 SARS vaccine doses were produced there.

The strategy of Sinovac is to develop vaccines that are as safe and efficacious as Western products but far less expensive, hence achieving a competitive advantage in marketing in China and to the Southeast Asian developing countries.

4.3.3 Sunshine Pharmaceutical Co., Ltd.

Sunshine Pharmaceutical Co., Ltd. (Chinese name: Shengyang Sanshen pharmaceutical Co. Ltd.) (www.3sbio.com) was founded in 1993. Its marketed products are EPIAO (recombinant human erythropoietin), INTEFEN

(recombinant human interferon alpha 2a), and INLEUSIN (recombinant human Interleukin-2). EPIAO commanded over 40% of market share and was regarded as the best brand in China (Xinhua Net, 2003). Sunshine has recently completed phase III clinical trials for its recombinant human thrombopoietin, rhTOP, which was listed as a 863 project in 1997. So far Sunshine is the only company in China coming up with this product. In its pipeline are products including therapeutic monoclonal antibody, recombinant peptides, DNA vaccine and molecular diagnostic products, according to the company. Sunshine has a well-established sales force and more than 80% of its over 300 employees are scientific staff, according to the company. Sunshine also received support from the MOST's Innovation Funds for SMEs.

Sunshine has established an overseas R&D center, Lifegen Inc., in Maryland USA in 1996. Lifegen plays an important role in providing the company with timely information concerning trends in the biotech field and in facilitating its international exchanges and collaborations.

4.3.4 Shenzhen Lupeng agricultural Hi-tech Enterprise Co., Ltd.

Lupeng agricultural Hi-tech Enterprise Co., Ltd. (www.863.org.cn/15year/industrial/idl-bly401.html; own web site under construction: www.lupeng.com) was founded in 1996. Its founding investors were Shenzhen City Investment Management Company, Shenzhen Special Economic Zone Newspaper Group Company, China Agricultural Technology Development Center, China Science and Technology Development Institute, Shenzhen South Oil (Group) Co. Ltd, and Shenzhen City Ronghe Investment Development Co. Ltd. Its registered capital was 40 million Yuan RMB (ca. 4 million Euro).

In 1997, the city government of Shenzhen, CNCBD of the MOST, and the Chinese Agriculture University jointly signed a collaborative research and development agreement and invested a lot of capital in the Animal Mammary Gland Bio-reactor Project. This project belongs to one of the important key projects in the 863 plan and is being undertaken by the Chinese Agriculture University and Lupeng in both R&D and commercialization. In the framework of this project, transgenic animal breeding bases have been built up in Beijing and Shenzhen. The research base of the company has the capacity for 102 transgenic cows. Embryos carrying transgenes (human albumin, interferon, etc.) have been successfully transplanted in acceptor animals such as rabbits, sheep and cows.

4.3.5 Shenzhen Biocentury Transgene Co., Ltd.

Founded in 1998, Biocentury Transgene Co., Ltd. (www.biocentury.com.cn/ckzl/syjs_2.htm) commercialized transgenic Insect-resistant cotton which is now widely planted in China. The company has exclusive rights to the related technologies and patent (inventors are from the biotechnology research institute of the Chinese Institute for Agriculture Sciences). Biocentury has carried out several product development and field trial projects which were listed as 863 plan projects. It was also supported by the Innovation Funds for SMEs from the MOST.

Shenzhen Biocentury is the core company, with 5 other Biocentury companies located in different provinces. Biocentury has had agreements with several large domestic seed companies to co-develop insect-resistant cotton. Moreover, it has discussed with countries like Australia, Argentina, Vietnam, and Philippines for collaboration (Cui and Guo, 2002). In 2001, Biocentury signed collaborative R&D and commercialization agreement with India on new varieties of insect-resistant cotton.

4.3.6 Sino-American Biotech Company

Sino-American Biotechnology Company (SABC) (www.sabc.com.cn) was founded in 1985 in Luoyang, Henan province, as a joint venture with Promega in the USA as a partner (Promega, 2003), the first joint venture in biotech in China. In 2002, Promega sold its shares in SABC to an international investment company Bona Group Ltd.

The company's over 250 kinds of products include molecular biology reagents, medical diagnostic reagents, immunohistochemical reagents, laboratory instruments and health food. SABC is known as the manufacturing base of enzymes and is one of the biggest diagnostic reagents suppliers in China, according to the company. Since 1989, it has produced a series of PCR diagnostic kits. SABC products have been sold to Germany, USA, Canada, Australia, Egypt, South Africa, etc. At the end of 1987, SABC's RNasin was exported to Promega in America (Promega, 2003).

SABC has 340 employees, and has established two manufacture and research centers with 180 staff. In 2002, SABC's "high-tech model project for the industrialization of HIV ELISA diagnostic kit" was supported by the government with a promised 6 million Yuan RMB (0.6 million Euro). The total investment for the commercialization project was supposed to be 60 million Yuan (6 million Euro). The annual manufacturing capacity of this project when it's completed is expected to be 30 million kits.

4.3.7 Shanghai HealthDigit Co., Ltd. and CASarry Co., Ltd.

Both Shanghai HealthDigit and CASarray are founded by Professor Gengxi Hu, from the Shanghai Institute of Biological Sciences, Chinese Academy of Sciences, a former leader of the Max Planck Junior Group in Shanghai.

Shanghai HealthDigit Co., Ltd. (www.health-digit.com) was founded in 2000, with an R&D center in Shanghai Caohejing High-tech Park. The company is engaged in the research and development of biotechnology and therapeutics as well as the related technical consultation. It has developed a state of the art biochip technology, including related detection devices and software. It has a well-equipped manufacturing base, and established a sales force covering Mainland China and Southeast Asia.

CASarray Co., Ltd. (www.casarray.com) was founded in 2001, and jointly held by the Chinese Academy of Science (CAS). It produces gene chips as well as engages in the R&D of related technologies and services. The core technology of the company comes from Dr. Gengxi Hu. Products include DNA arrays for expression profiling, function-related arrays (categories such as tumor and tumor-inhibitory genes, cell cycle protein related, immunity related, metabolism related, etc.), detection of GMO, as well as various kits for routine molecular biology research (PCR purification, plasmid isolation, etc.)

In the following a more detailed description will be provided for HealthDigit.

Three products are offered by HealthDigit so far:

1. Protein Chip System for Multi-tumor Marker Detection developed in 2002. It's for detection of up to 12 tumor markers in parallel and can test up to 42 patient serum samples simultaneously. This is the first product of its kind used in the clinical diagnosis in the world. It has been sold to Thailand, Philippines and Hong Kong.

2. Chip Reader for the Protein Chip System.

3. Kit for Chemosensitivity Testing of Cancers (MTT assay). The cancer diagnostic product has been approved by the State Drug Administration (SDA, now SFDA) and has completed all the clinical trials.

Products in development include a hepatitis protein chip which would cost only about half of the current price for hepatitis test in China.

Interesting sales issues regarding the Protein Chip System have been revealed by Dr. Hu in an interview with FinanceAsia.com (Slater, 2002) as follows: HealthDigit sells mainly to hospitals. The protein chip itself costs

around $40 per piece. The chip reader however cost $80,000. This seems to be a lot for the Chinese hospitals but it is actually the health insurance companies who pay for it. The major cities in China have compulsory health insurance for both state and private sector employees and hospitals are among the richest business segments in China now. HealthDigit also has no problem with the distribution system in healthcare in China which many regard as difficult because of corruption. HealthDigit appointed a single distributor per province, and if the sales target was not met, it replaced the distributor.

HealthDigit got $10 million starting capital from a Chinese investment company after speaking with venture capitalists from the USA who could not be convinced that the company would have a unique product ahead of American or European companies, according to Dr. Hu in an interview (Slater, 2002). The Chinese investor granted HealthDigit a 3-year grace period and was surprised to learn that the company was ready to market and sell the product after only six months.

During his interview with FinanceAsia.com (Slater, 2002), Dr. Hu described the patent system in China as "quite well established and getting better", although ignorance may still give rise to problems. HealthDigit does have a group of lawyers to work on potential problems, however it does not just rely on patents to stay ahead. Part of the company's strategy is that they use a combination of "difficult-to-imitate, high-tech machinery, proprietary technology and low profit margins" to keep the sector unattractive to future competitors, revealed Dr. Hu.

4.3.8 United Gene Holdings Ltd.

United Gene Holdings Ltd. (UG) (www.unitedgene.com) is perhaps the largest private biotech company engaged in gene function research, application and product development in China. It originates from a project company founded in 1997 by two professors, Yuming Mao and Yi Xue, from Fudan university in Shanghai. UG now has grown into a group of at least eight member companies.

UG member companies according to the UG Chinese web site (www.unitedgene.com):

1.) BioDoor (Chinese name: BoDao) Gene Development Limited

BioDoor is a core holding company. It aims to take the results from the exploratory research done at the research institute one step further by conducting value-added research and business activities necessary for its commercialization. Examples of its activities are direct technology transfer, or use UG's IP as equity to form companies with others.

2.) Shanghai LianZhen Gene Science & Technology Research Institute

The institute is the R&D base of UG. It is engaged in cloning novel genes, gene function research, gene-based drug screening and R&D of related products. It has 94 full- and part- time researchers, of which 25 hold Ph.D. degree. The 23 part-timers are graduate students at leading universities. Technology platforms include: HTP gene cloning, gene chip, protein analysis, drug screening, and cellular biology.

Products and services include: human full-length cDNA, human/mouse gene clones, gene database and system for its analysis, sequencing/cloning service, nucleic acid structure analysis, gene family analysis, recombinant gene service.

3.) Shanghai BioStar Biochip Ltd.

BioStar is currently the largest in scale in China in the R&D, manufacturing and marketing of gene chip products.

Early in September 1999, Shanghai Science and Technology Commission approved BioDoor as the first microarray manufacturer in China. With ScanArray microarray analysis systems purchased from Packard BioChip Technologies, LLC in the USA, BioDoor started to market its chip products in

May 2000. In September 2000, BioDoor used its microarray-related technologies as capital to form a 50-50 joint venture Shanghai BioStar Biochip Ltd. with GuangDong XingHu Biotechnology Ltd. who invested 0.25 billion Yuan RMB (ca. 25 million Euro). This has set the record for the highest market price paid to biotechnology in China.

BioStar offers gene chip products and related services for basic research, disease diagnosis, and drug screening. Products include: human/mouse/rice transcription profile chip, hepatitis series of detection chip, blood screening chip, gene chip detection kit, gene chip data processing system, and technical services related to gene chip products

According to the company, it has a big market share in the gene expression profiling market.

4.) Extrawell Pharmaceutical Enterprise Holding Company Ltd

Extrawell was founded in 1985 and went public in 1999 in Hong Kong. UG became its largest share holder in 2002. This company consists of 3 subsidiary companies in China. Its sales network covers 30 cities and regions. Extrawell serves as a base for UG in the pharmaceutical industry.

5.) Shanghai BioLink (Chinese name: Bolian) Bioinformatics Limited

Using ChinaGeneNet (www.chinagenenet.com) as platform, BioLink develops information products and service and e-business in life sciences.

6.) China Gene Database and 7.) United Gene Valley

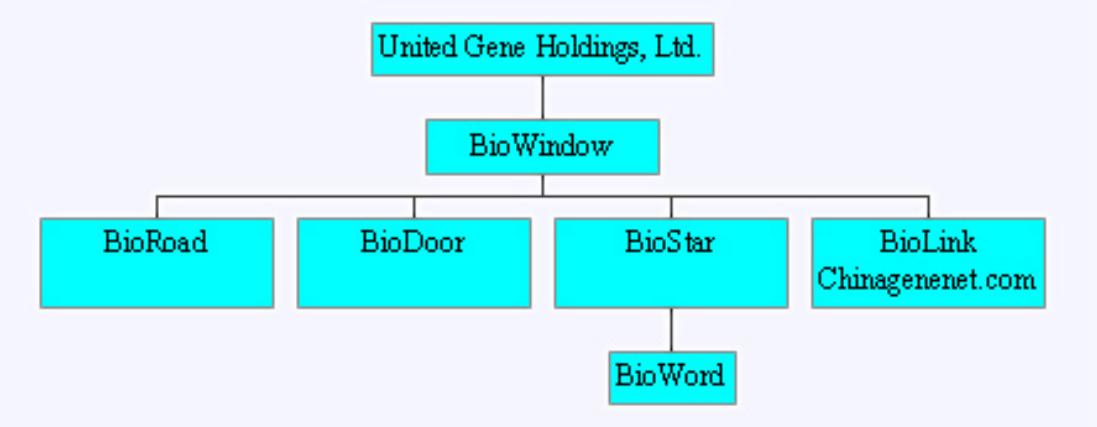
Both companies engage in venturing using gene patent and patent management.

8.) Shanghai Fudan Biological Science & Technology Limited

Its businesses include technical service in biology and biochemistry, sale of biological products, biochemical products, reagents and related raw material, and environmental products, as well as investment in high-tech companies in biotech. The company is also into research, development and sale of natural pharmaceuticals, functional foods and green foods.

BioWindow

According to personal communication with UG, the BioWindow Gene Development Inc. serves as an "international marketing window" for the UG biotechnology activities. The BioWindow web site (www.biowindow.com; both Chinese and English versions) give a less complex and slightly different UG company structure as shown in the following organigram:



Source: www.biowindow.com

According to this structure, BioWindow consists of a number of subsidiaries – BioRoad, BioDoor, BioStar and its subsidiary BioWord, and BioLink. BioRoad Gene Development Inc. is responsible for the large-scale sequencing and cloning of genes from animals and plants, as well as bioinformatics studies. BioDoor Gene Technology Inc. focuses on the study of gene function for the discovery of novel drug targets and drug candidates. BioStar Genechip Inc. is dedicated to developing and manufacturing BioDoor genechips, while its subsidiary BioWord Genechip Inc. for the production of BioDoor diagnostic genechips. BioLink Bioinformatics Inc. provides information service in biotech industry through www.chinagenenet.com. BioWindow has created BioWindows gene database and UG gene expression database.

UG – financial issues and IP

UG is a private company, and has been growing very fast. Other than having succeeded in capitalizing on its intellectual properties, the company has also encouraged investment through the following concept: According to a Nature report (Cyranoski, 2001), the founders Yumin Mao and Yi Xie stipulated that, with any investment, one-third goes towards buying stocks and two-thirds go towards a low-interest, long-term loan to the company. As there are few investment banks in China, the company borrows from individual investors. With this concept, they would show the investors that risk is lowered for them

should the company fail, because in that case, the company would still owe them two-thirds of what they invested.

Now, since UG has purchased majority shares in Extrawell which is listed on the Hong Kong stock exchange, it has also access to international investors.

UG is an interesting case to show how a Chinese company aggressively pursues intellectual property rights. According to UG, by May 2002, it has filed over 3000 patent applications (over 2700 full-length gene related) in China and over 1000 (full-length gene related) with PCT, and by June 2002, it has published 183 scientific papers, of which 44 have appeared in journals covered by the Science Citation Index.

One paper, for example, results from a research collaboration among Fudan university, Liverpool university and UG on human inosine triphosphate pyrophosphatase and the gene that encodes it (Lin et al, 2001).

A search by the author of this report (in February 2004) of the PCT database by inventor returned 967 patent applications by Xie Yi, 1146 by Yumin Mao, 899 by BioWindow, 57 by BioRoad, and 72 by BioDoor. In contrast, only 82 patent applications were filed by Fudan university.

The World Intellectual Property Organization (WIPO) statistics (WIPO, 2003) showed that BioWindow Gene Development Inc. ranked third in 2002 among developing countries as a major applicant at PCT with 136 applications, after only the Council of Scientific and Industrial Research in India and Samsung Electronics Co. Ltd. in South Korea, each with 184 applications.

As mentioned earlier, UG set the record for the highest price (ca. 25 million Euro) paid to biotechnology in China when it created a joint venture with GuangDong XingHu Biotech Ltd. In 2002, when the Extrawell Pharmaceutical enterprise acquired commercialization rights for 19 diabetes-related genes from UG, it paid 95 million HK Dollar (ca. 9.5 million Euro) for them. Hence, on average, each gene was valuated at 5 million HK Dollar (ca. 0.5 million Euro).

The founding of Shanghai BioRoad Gene Technology Inc., was supported by Shanghai Science and Technology Committee and Shanghai economy committee. During its founding and growth, it has gotten support also from China National Science and Technology Committee, the Ministry of Education, the MOST, and the Ministry of Health, according to the company.

4.3.9 Capital Biochip Corporation

Capital Biochip Corporation (www.capitalbiochip.com) and its affiliate, the National Engineering Research Center for Beijing Biochip Technology (NERCBBT) were founded in 2000. By the directives of the Chinese Vice Premier Li Lanqing, Tsinghua University Enterprise Group acted as the lead investor (holding 39.84% of shares) to found Capital and the NERCBBT, along with nine additional investors. These nine additional investors hold shares ranging from 4.25% to 8.1% and include universities, pharmaceutical companies, and investment groups. The total registered capital was 376.5 million RMB (ca. 37.65 million Euro). The company is rapidly growing, currently recruiting principal investigators in various disciplines from abroad, as well as staff from China. The number of employees is expected to increase from the current 200 to 400 by 2005. Capital Biochip aims to be a global leader in biochip technology and a key player in the medical diagnostics as well as in drug development business in China.

Research areas of Capital include microfluidic chips, active microarrays, laboratory-on-chip systems, implantable chips, bioinformatics, medical information system software, nanomaterials, bio-automation and other technologies.

So far one set of product has been brought to market, the Detection System for Early Stage SARS Virus Infection. This package System includes SARSarray Gene Chip for SARS Virus Detection, EcoScan-100 Economical Chip Reader, SARSearch Identification System and SARSinforma Clinical Information System.

Capital has already three companies in its portfolio. AVIVA Biosciences Corp. (San Diego, USA) (www.avivabio.com) and Chipscreen Biosciences Co., Ltd. (Shenzhen, China) (www.chipscreen.com) were established based on technologies transferred from Capital Biochip Corp. to develop biochips for use in disease diagnostics, pharmacogenomics and high throughput drug screening. In addition, Capital has acquired Beijing Wandong Medical Equipment Co., Ltd, (www.wandong.com.cn), listed on Shanghai Stock Exchange. According to Capital Biochip Corporation, Beijing Wandong Medical Equipment Co., Ltd is a leading player in China's medical equipment market with annual sales of 400 million RMB Yuan (40 million Euro) and a profit of 40 million RMB Yuan (4 million Euro).

Capital Biochip Corporation has attracted a lot of attention from well-known international companies in the biotechnology as well as in the banking sector. It has been featured by scientific and business magazines such as Science, Nature and Furtune. More details can be found on its web site.

4.3.10 Beijing WBL Peking University Biotech Co., Ltd.

Funded in 1994, Beijing WBL Peking University Biotech Co., Ltd (WPU) (www.wpu.com.cn) is a well-known modern Chinese medicine enterprise in China. It is a joint venture of WBL Corporation Ltd. (Singapore), Peking University (Chinese name: Beijing University) and Beijing Enterprises Holdings Ltd. (Hong Kong), with a registered capital of RMB 80 million Yuan (8 million Euro). It has developed and marketed two products, Xuezhikang Capsule and Specially Made Red Yeast Rice (Hong Qu).

Xuezhikang, a lipid-regulating medicine, contains 100% Red Yeast Rice (Hong Qu), is a natural product of fermentation of red yeast, *Monascus purpureus* Went strain, on rice. It contains a mixture of natural HMG-CoA reductase inhibitors, monacolins. Xuezhikang is specially formulated for the treatment of dyslipidaemia in a clinical setting, and extensive clinical studies have shown its safety and efficacy. The related product Specially Made Red Yeast Rice, containing also the proprietary Red Yeast Rice, is a dietary supplement used for mild to moderate hyperlipidemia. Both products have been marketed in America, Europe, Singapore, Japan, Korea, Hong Kong, Taiwan, etc., and the export turnover has reached 7 million USD since 1996. The annual sales of Xuezhikang exceeded 100 million Yuan RMB (10 million Euro).

WBL Peking University Biotech Co., Ltd. is the owner of the China Patent (ZL 97 1 16744.3), the United States Patent (No. 6,046,022) and the Hong Kong Patent (No. HK1017614) of Red Yeast Rice product. It has been issued the CPM (Chinese Proprietary Medicine) certificate by the Ministry of Health of Singapore. In addition, the clinical studies on Xuezhikang were conducted in Japan, Hong Kong, Taiwan and Canada. These efforts will change the record that TCM can't be exported as drug, according to WPU, who aims to be the pioneer in internationalizing TCM.

How was the product developed? The health enhancing qualities of this yeast have been known (recorded in the ancient Chinese pharmacopoeia Ben Cao Gan Mu) and the yeast has been used in China for over two thousand years.

In the 1970's, a Japanese scientist discovered that when selected strains of *Monascus purpureus* were fermented with rice, they produced metabolites called monacolins, which effectively inhibited HMG-CoA reductase, the enzyme responsible for cholesterol production in the liver.

In the 1980's, Professor Zhang Maoliang from Beijing University identified and patented specific strains of *Monascus purpureus* yeast. When these strains of yeats are fermented under strict control, a right mix of monacolins is produced

having an optimal effect on cholesterol reduction without the adverse effects of undesirable byproducts like citrinin.

Professor Zhang and his team subsequently carried out extensive clinical research on the cholesterol-lowering efficacy and safety of Red Yeast Rice, in collaboration with leading medical institutions in China. The invention of two proprietary Red Yeast formulations came out of these studies.

More details on the development path can be obtained on the web site of the company (http://www.wpu.com.cn/english/products/xuezhikang-m.htm). This work is regarded as having set up a framework for the standardization and assessment of TCM using modern scientific techniques, good manufacturing and clinical practice guidelines.

To help turn the pharmaceutical enterprises in China into the major body for undertaking new drug discovery and development, the Chinese government has come up with various supportive policies. Among these policies is to set up post-doctoral research stations in some pharmaceutical companies having a relatively strong technological base. WPU recently has been permitted by the government to establish a post-doc station, according to the news at the company web.

4.4 A sample of joint ventures and foreign-owned companies

4.4.1 Overview

A lot of well-established biotech companies have already been present in China and some have set up a subsidiary. These companies include Ciphergen, Bio-Rad Laboratories Inc., Chiron Corporation, Agilent Technologies Co. Ltd, and Celera Genomics Corporation, all based in the USA. Companies headquartered in Europe such as Invitrogen Corporation, Amersham Biosciences and Novo Nordisk have Chinese subsidiaries as well. Needless to say that most of the world's large pharmaceutical companies have already established subsidiaries in China for years. Roche, for instance, has been active in China for 10 years in both diagnostics and pharmaceuticals and employs about 1200 people in Hong Kong and Shanghai (Roche, 2004). In January 2004, Roche became the first global healthcare company to establish a wholly owned R&D center in Shanghai to discover and optimize active ingredients of potential new drugs. The center, expected to be in full operation by the end of the year, will be operated by Roche, with an initial staff of 40 chemists (Roche, 2004).

A all who entered the Chinese market agree that relationships (many times personal relationships) are very important for the success of establishing a presence and of operating in China. In the entry phase, finding a good Chinese partner or hiring a good Chinese manager is almost a prerequisite. However, many of the success factors for China operations are also those necessary for a successful business in a domestic market – such as doing a thorough investigation of the market before setting up the business, as pointed out by several speakers at a recent meeting focusing on doing business in China, organized by IHK Frankfurt ("China – Von der Gründung eines Untrnehmens bis zum Transport nach und in China", 19 April 2004).

As mentioned earlier in chapter 3 under 'Sources of support for collaborations between Germany and China', IHK local chapters organize meetings for information exchanges concerning doing business in China. In this recent meeting mentioned above, officers from AHK offices and German consulates in China, as well as experienced managers from German companies who have set up and have been operating businesses successfully in China shared their insight with the audience. Although not in the biotechnology field, many of the views and advice concerning doing business in China from these companies coincide with those reported by biotech companies, as portrayed by the cases below.

For the cases that follow, published material is used for the first two cases. The other two cases result from the interviews the author of this report has done with the respective companies – Debiopharm in Switzerland, and the first Sino-German biotechnology company Bicoll in Munich, Germany, and Shanghai, China.

4.4.2 Case 1: Promega

The Promega case concerns managing a joint venture and information concerning Promega in this case is summarized from a presentation by Dr. Zhang (2003).

Promega has set up three operations in China and recently sold its shares in one of them. These operations are Sino-American Biotechnology Company (Joint Venture) which is a diagnostic kit manufacturer for the Chinese market and which is not a Promega joint venture anymore; Shanghai Promega (Joint Venture), which manufactures for Promega and distributes Promega products in China; and Promega Beijing Representative Office, which manages Promega distribution, marketing and technical support in China. The first

operation, Sino-American Biotechnology Company, was set up as early as in 1985. SABC was described earlier in this chapter.

Why did Promega choose to manufacture in China? The factors include cost advantage, access to unique resources (in this case: human placenta for RNasin), alternative manufacturing to circumvent patent restrictions in the U.S. market (in this case: the enzyme M-MLV-RT), acquiring new technology, and a huge market.

Whereas the reason bypassing patent restrictions would very less likely hold true nowadays (unless the invention has not been patented in China and the product involving the use of the very patent rights is sold only in China) because of the fast progress China has been making in the intellectual property field (described earlier in this report), the other reasons do still hold and they are the same reasons given by other non-Chinese companies operating in China.

Promega credited its success in China to the following factors: early entry, technology transfer, training employees in the United States, good relationship with partners, flexibility in operations, upholding principles and having good consultants. Advice it gives to companies wanting to establish a successful business in China include: conduct a product or technology market investigation, plan step by step and act according to one's capability, establish a reliable partnership, handle well pricing and competition, and have good process administration in place such as putting in a strong chief-accountant and quality control.

Managing a joint venture is not easy. In fact, many advice against setting it up in the first place, because of not having 100% control of the business. Promega has used the following measures to manage its joint venture: board meetings in China twice a year, board representation from each partner, intermediaries as consultants (for instance, the Shanghai Promega advisory committee has seven professors), Promega-employed interpreters for all business meetings, hiring only local employees, and having a China Team in the U.S. to manage the joint venture.

Points mentioned by Promega here and also emphasized by German managers who have successfully run business operations in China include: thorough market research, hiring the right people/finding the right partner, good control mechanism, etc.

4.4.3 Case 2: Sino-Danish Pig Genome Consortium

The Sino-Danish Pig Genome Consortium case concerns international collaboration between foreign industry and a Chinese academic institute and is summarized from an article by Murphy (2001).

China offers the best cost advantage in sequencing genomes and can therefore enter into international collaborations. Aside from Europe and the U.S., who are the major collaboration partners for China in this field now, China has also attracted attention from its neighbours like Japan, Singapore and Korea.

The Sino-Danish Pig Genome project is a collaboration between Beijing Genomics Institute and the Danish Pig Producers Association, a $20 million joint venture. Most of the work is carried out in China. What has brought this collaboration into existence is the following: "outside commercial and scientific interests coincide with China's food-security concerns and thirst for scientific know-how, plus a web of personal contacts to bring these factors together", according to Murphy (2001).

Concerning the first point – interests from both sides: Denmark has a very profitable pig industry with an annual export worth over $3 billion, and is interested in improving the breeding of pig (such as reducing diseases and selecting for mild-temper – a better feature for industrial farming, etc.). Pork is the most-consumed meat in China and is preferred by the Chinese. International collaborations also bring new knowledge and ideas to Chinese institutes which are very much needed. And the second point: Dr. Yanming Huang, director of Beijing Genomics Institute at the time, obtained his Ph.D. in Denmark.

As mentioned earlier in this report, in the field of biotechnology, successful Chinese scientists trained in the USA and Europe have been playing an important role in facilitating the transfer of ideas, personnel and funding to China. For example, many of the Chinese biotech companies described earlier in this chapter have top managers and founders who have done their Ph.D. and/or postdoctoral training in the USA and Europe.

4.4.4 Case 3: Debiopharm

The Debiopharm case concerns an unique business approach. Information for this case comes from exchanges between the author and Dr. Lucienne Cicurel, Secretary General and Member of the Management Board of Debiopharm.

Debiopharm, founded in 1979 in Lausanne, Switzerland, focuses on evaluating compounds with promising *in-vivo* results in animals, to in-license them, develop them for global registration, and out-license them to marketing pharmaceutical partners. Debiopharm's major commercial successes to date are Eloxatin®, one of Sanofi-Synthelabo's leading marketed products, Decapeptyl®, the leading product of Ipsen in Southern Europe, and Trelstar®, with combined sales estimated to be in excess of $1.8 billion in 2004.

Debiopharm is part of an established group of three complementary companies, Debiopharm, Debio R.P., (Martigny, Switzerland) and Debioclinic (Paris, France), with a successful track record in developing, registering and out-licensing innovative therapeutics. Some 250 people are employed in the Debio group. In addition to its internal expertise, Debio has an extensive international network of 450 experts, to help tap into top-level scientific, development and business capabilities.

Debiopharm forms partnerships with individual researchers, research institutions, pharmaceutical as well as biotechnology companies. Debiochine, a department of Debiopharm, with offices in Paris, France and Shanghai, China, is devoted to product candidate search for in-licensing from the People's Republic of China.

The Debiochine Department, including the office in Shanghai, was set up about 10 years ago. One person works in Shanghai, liaising with 2 other persons in the Paris office, which are responsible for activities in China.

For the past ten years, once every two years, Debiopharm calls for abstracts in China for a competition for the Debiochina Award. An international jury of experts, including Chinese ones reviews the abstracts and decides for the winner. Debio has established a lot of contacts in China because it is well-known through this award. Debiochine has contributed in translation, clinical trials, etc, to registering oxaliplatin in China. For instance, Debio has conducted clinical trials for oxaliplatin for the treatment of advanced colorectal cancer in China. Recently, a group of Chinese researchers with whom

Debiopharm was in contact regarding a collaboration came to visit the company, while touring Europe.

A success story resulting from the Debiochina Award competition concerns ZT-1. ZT-1 is a patented drug for the treatment of Alzheimer's disease. It is being developed by Debiopharm, and currently in clinical trial phase II. ZT-1 was discovered by the Shanghai Institute of Materia Medica, Chinese Academy of Science. It is derived from huperzine A (hup A) which was originally isolated by the Chinese scientists from the club moss *Huperzia serrata.* Hup A is one of the most potent acetylcholine esterase inhibitors. After oral administration, ZT-1 is progressively hydrolysed into the active compound hup A.

Debiopharm's unique approach - establishing a competition for the Debiochina Award, has helped it to succeed in its business activities in China.

4.4.5 Case 4: Bicoll

The Bicoll case concerns the first Sino-German biotech company Bicoll group, located in Munich, Germany and Shanghai, China. Below, an introduction of the company, kindly provided by the Bicoll Group, is followed by an extensive interview between the author of this report (Q) and Dr. Kai Lamottke (KL), Managing Director of Bicoll and Dr. Heinrich Arnold (HA), Head of Business Affairs of Bicoll. In this interview, Bicoll tells us about its rationale behind setting up the company simultaneously in Germany and China, the scope of its business activities in China, the role of its German company, important factors in establishing the Chinese company and the key issue of building up robust personal relationships. In addition, Bicoll shares with us its experience in managing the company across continents, insight in doing business in another cultural environment, intellectual property (IP) protection issues in China, observations and thoughts of the Chinese biotech industry and Bicoll's networking activities with Chinese companies. At the end of the interview, Dr. Arnold comments on the likely upcoming trend of relocating research from the Western countries to China and what that would mean for the Chinese biotech companies as well as the Western companies.

The "Bicoll Group" is the first Sino-German biopharmaceutical enterprise. It was founded in 2001 with two legal entities: Bicoll GmbH in Munich, Germany, and Bicoll Biotechnology (Shanghai) Co. Ltd. in Zhangjiang High Tech Park, P.R. China. Technology development, cooperation management and marketing are functions in Munich, while facilities for research and development are located in Shanghai.

The company is specialized in high-tech natural product chemistry with a focus to make compounds from natural resources compatible with drug discovery systems in modern drug research.

Bicoll's primary products are optimized small molecule libraries for drug discovery in the biopharmaceutical industry. The libraries are tested and developed for fee and milestone payments in co-operations. They are customized to the target protein of the partner's indication field to provide a high success rate in screening and further development. The starting material is generated from endemic Asian plant resources.

Bicoll has two proprietary core process technologies BIFRAC N and BIPRESELECT.

BIFRAC N is a high resolution, high efficacy isolation and separation system for the delivery of biologically active compounds. The resulting compounds have physico-chemical properties - such as a certain range of polarity or molecular mass - that are required for the further development process. Bicoll claims to be the only company that can provide compounds from natural resources suited for HTS at cost comparable to combinatorial chemistry sources.

The BIPRESELECT pre-selection tool allows to narrow in on compounds with selected ADME criteria. Thus non-successful drug candidates, which would otherwise block the drug development pipeline, are supposed to be eliminated early.

Just three years after its foundation, the company already sells its research products to five strategic customers in the pharmaceutical industry and leading research institutions.

Additionally, Bicoll follows up its own in-house development projects such as diabetes type II, and is currently building up expertise with a new approach in the area of oncology.

Interview

Q: It seems quite unusual to start up a company simultaneously on two continents –especially in countries that are quite different at first sight like China and Germany. What made you decide to start up a company in these two countries?

KL: The access to bio-diverse plants plays a crucial role in our research. The core competence of Bicoll is to make natural products – a historically very successful source of new drugs – applicable for the modern drug discovery and development approach as it is followed by the modern biopharmaceutical companies and the large international pharmaceutical corporations. Bicoll's vision is to initiate a renaissance of natural product chemistry within the modern pharmaceutical research. Now this characterizes the situation Bicoll is in: On the one hand, our research partners and customers are mostly located in Europe and North America. On the other hand, we need to work with plant resources that occur in only very few places in the world, the so-called "biodiversity hot spots".

Q: So, it would not have been possible to start up Bicoll in one country alone?

KL: The founding team was Chinese and German anyway; but apart from personal preferences there are a couple of hard facts: As far as the plant resources are concerned, the Rio Convention of 1992 and the Bonn Guidelines of 2002 require among others the "equitable sharing of benefits" from using endemic plants and "sustainable use of biodiversity". Therefore it is no option to collect plants and fly them out of the country for further analysis without benefit for the originating country. The biodiversity hot spots are in places like Congo, Peru and other "jungle" places where evolution has produced a high degree of organism interaction and diversity. China is one of the few countries where you could seriously consider the set-up of some sort of advanced organization to do effective analysis and drug research. So, for us, there was no way around China to produce a significant share of Bicoll's added value. In our current structure, we do a large portion of our research and development in China.

HA: There are three important elements to our activities in China:

First, we have found good collaboration partners that do the botany part, i.e. the plant selection, for us. We train them with modern techniques for localization and documentation. One of the results is an electronic inventory of the plants we encounter. Part of this inventory is accessible for free on the

web at www.biflora.org and is especially valuable for scientists and environmental policy makers.

Second, we have our own lab in Shanghai, where we carry out the proprietary high-tech natural product chemistry processes.

Third, we are lucky with our cooperation with the Shanghai Institute of Materia Medica, where we have access to world-class talent and also large scale high end equipment in the field of natural product chemistry.

Q: What's left to do for your location in Germany?

HA: In Germany we do marketing, project management with customers, cooperation management, and technology development.

You should never underestimate the importance of marketing an innovation (Arnold, 2003). In our case it is hard enough to convince people that we are the ones that have found a way to make natural products fully compatible for HTS at costs that are even lower than dealing with synthetic substances. Of course, with every customer we add to our list this process becomes easier. After all, we speak about a substitution of so far rather unsuccessful synthetic substances by natural compounds as starting point in drug discovery. To our observation, arguments regarding credibility are received much better when they are made by a contract partner in Western Europe or the US.

Closely related is international project management. It is not enough that we send substances to our customers and leave them alone with it. We assign project managers who have excellent skills in English or German, besides their scientific education, to accompany our customers throughout their work with our products. The people that can do this are in fact very rare in China.

KL: Then there is the aspect of having access to biotech clusters where we can tap into the most advanced thinking in drug research. For this purpose we could certainly also be located in other biotech clusters like in the Boston area.

Chinese research is in many aspects very good, but when it comes to transfer experimental results into a well-documented process that runs after SOPs you require a skill which Germans are trained to produce in very good format.

And we certainly need to stay abreast with our technology lead. For example, we claim to have the technology with the best resolution and yield in place. We want that this continues to be like this. So this is one more thing we push for in Germany.

Q: For our Western – especially German – audience, let's talk about the process you had to go through to start your Chinese entity. In "Biotechnology in China - Picking new therapeutics" (Feling and Lamottke, 2002), you said that "assisted by the Delegation of German Industry and Commerce (AHK), Bicoll could deal with all the formal (and informal) problems in setting up an initial infrastructure in Shanghai." Could you elaborate a bit – what the formal and informal problems were and could you give an example of how the problem was solved with the assistance of AHK?

KL: The initial founding team consisted of three chemists from Germany and China, and we were glad to get the assistance of AHK. AHK gave us a good view of the requirements for setting up a company in Shanghai, and of the documents that need to be prepared. We worked together to get things done. The process we had to go through looks complex to non-Chinese, however, it is in fact not more complicated as compared to the equivalent process in Germany. There were some unique problems such as identifying the Chinese agency responsible for dealing with biodiversity issues. And we needed to get access to the authorized local counterparts as well. As we mentioned already earlier, this was an especially necessary aspect for our overall business concept, but I really don't know if we would have managed all the necessary steps without the involvement of our Chinese founding partner who had an established local network. We were very happy that our founding team knew each other already personally for quite a while and that we could really trust each other. Building up a robust relationship is very important in Europe as it is in China.

Q: It sounds like personal interaction is a key part in establishing successful operations?

HA: Yes, indeed. There are so many examples of how international projects fail because the partners have no open interaction or even worse, mistrust each other. In my eyes, it would not have been possible to build Bicoll in a green field approach. Without the personal relationship that had been established among the scientific founders through their joint research long before the actual initiation of the company we would have not come so far. I would even say, Bicoll is the result of some international scientific cooperation programs.

Q: Two of the founders Dr. Haug and Dr. Ye knew each other during their Ph.D./post-doc time at the University of Munich and Dr. Haug then did his post-doc research on a DAAD fellowship in Shanghai. Was Dr. Haug's stay in SHA essential for Bicoll to set up its Shanghai subsidiary?

KL: Dr. Haug is the only German postdoc in this special issued DAAD program along with 139 Chinese colleagues from all over China. He and Prof. Ye have known each other for eight years now.

HA: But Bicoll is not the result of a University spin-off. All of the team members spent several years in industry and research institutions before they took the step into starting their own venture.

KL: Before Bicoll Shanghai was officially set up, there was also a pre-phase for infrastructure building up – machinery, connections to people, etc. It takes time to build up stable long-term relationships.

HA: You can also say that Bicoll could only come into life because the personal relationships existed beforehand. I guess, if you tried to build up what Bicoll has now without this initial network you would have to spend about 10 times more resources.

Q: Managing Bicoll - a biotech company crossing continents and cultures has been described in the article entitled "Pionierarbeit – auch in der Mitarbeiterführung" (Haug and Lamottke, 2004). What would you describe as your daily challenge in managing across continents?

KL: As our company started to grow we began to hire more staff. And the new colleagues in our laboratory brought new challenges for the management of our company. The first issue we had to address was clear communication structures.

Q: One key point, which was also voiced by several companies doing business in China at an IHK Frankfurt meeting over China, is that Chinese employees need to have clear job descriptions and clear reporting structure in place. They are not yet used to teamwork.

KL: For our Chinese founding members that have international exposure and experience during their education and career this does not apply, but for some of our lab staff this is certainly true. So we put a lot of thought into establishing some tools to make our lives easier in this respect. And this is also what we talk about in the article.

Q: What is your personal experience of doing business in China – what are the unique challenges/surprises, if any?

KL: In a new environment people tend to spot first the differences. However, generally speaking there is not much difference in doing business in China, if you are dealing respectfully but firmly. People are similar in fact.

HA: I even observed some managers from the West that concentrate so much on dealing properly with some supposed differences that some of their Chinese counterparts perceive them as funny or even "fake". To avoid misunderstandings I would recommend to act like in any other business meeting in Germany.

Q: Any IP concerns?

KL: IP is always an issue and you have to try to sustain it inside the company. Patenting is a way to go, but will not help always. Establishing a unique structure, not easy to copy can also protect IP rights.

HA: It seems as Chinese authorities now really understood that protecting patent rights is inevitable to build a stronger base in high tech. There are some recent cases of radical prosecution of companies that violated patent rights. Nevertheless I feel that patenting is currently an option for large firms that have weight even on a political scale. For smaller companies it may take a while until patenting will be an effective means of IP protection.

Q: Could you say something general about the Chinese biotech industry? What are the most obvious weak points and the most positive factors there? Do you think that the biotech in China will take off? For example, the cost-intensive and time-consuming nature of biotech industry does NOT seem to fit the Chinese reality as long as people with money and connections can make profit faster elsewhere. Could you share your opinion here?

HA: For sure there is a lot going on in China. Business models are often production oriented and usually driven by the expectation of quick returns. This has to do with the investor environment. Most investors are willing to stay invested for 1-2 years, but they can hardly imagine to stay invested longer. This is certainly difficult for research-intensive companies. On the other hand I see a very active VC scene in China that is really interested in dealing with new ventures. Nevertheless, I guess, they still have to learn how to deal with the biotech industry.

KL: After all the hope for "quick money" has also its positive side: companies are forced to establish contacts to the customers early. This will help them to understand the customer requirements, relationships are being established, and maybe complete failures become less likely.

Q: I was wondering whether there are Chinese pharmaceutical companies able to absorb innovation from biotech companies?

HA: By Western standards, Chinese pharmaceutical companies are just starting to develop new drugs. Although very strong in the Traditional Medicine field, the development of "Western" medicine is still very small.

KL: For the Chinese companies it will be decisive, how well they can integrate the huge international know-how into new business models and to leverage their knowledge for a mutual beneficial growth of the whole industry. Every success for a single company will support the success also for the other biotech companies in China.

Q: Do you think that China will have a viable biotech industry in the sense that there will be established companies along the entire value chain of the industry – from research-only to sustainable product companies?

KL: There are a couple of commercially successful ventures in the Pharmaceutical industry in China, be it new ventures or privatized former state run companies. To a large extent they play on the cost advantage. The question for the future is about innovativeness. Will these companies develop the capability to discover new drugs that will find their way into the profitable international markets? How can the creative potential of the people be leveraged in dealing with new frontiers in science and open new markets? It will take time and experience - experience you currently find in the biotech business in the US and Europe.

Q: Any networking, information or experience exchange among the biotech companies in Shanghai?

KL: Bicoll has organized some networking events with local companies already. What we do is we first screen companies around and then invite them for one-to-one talks covered by confidentiality agreements. These events are in essence for business development, to discuss possible collaborations or simply to build up a local network. Bicoll also makes sure that the people who come for exchange and networking are decision-makers in the companies.

Besides that there are also activities organized by local authorities. Due to the fact, that not all of these activities rely on English as the official conference language, it is hard for all of the multinational members of the company to get integrated into the exchange process easily.

Q: What do you see as advantages for being one of the pioneering foreign biotech companies in China? Do you see unique opportunities for growth? Are these real possibilities, such as collaborating with Chinese

pharmaceutical companies, getting financed by Chinese sources – bank/VC/private?

KL: There was no serious Chinese biotech venture capital company around ready to finance an international approach when Bicoll set up its Shanghai – Munich operations in 2001. There are some now; many though are state-backed.

HA: Our big asset now as we talk about financing our further expansion is our already achieved break-even. For other biotech companies in the US or Europe that would be hard to achieve. Due to the fact, that there is currently no experience in establishing, running and selling biotech companies, the Chinese VCs are looking for exit strategies in the 1-2 years range. There are some foreign VCs, such as from Singapore, or from some corporate venture funds, who are checking out opportunities.

KL: Bicoll has an advantage being the first Sino-German biotech in China: It is English-speaking, well-connected in Europe and in China and has already built the necessary process infrastructure to perform its collaborations on a top quality level. Of course, our success will make it easier for similar international set-ups and for the just started Chinese biotech companies.

Q: Biotech companies engaged in drug development and discovery have a symbiotic relationship with the big pharmaceutical companies here in the West.

HA: Well and I would say there is even a trend to relocate research activities from the Western countries into China. This is very frightening for the Western countries but it is starting on a large scale. For start-ups in China I see a big opportunity arising from this: In several years, a few international pharmaceutical companies will realize that they have missed the trend. And they will be looking for partners or acquisition candidates in China in about 5 years very desperately. From a financial point of view this will of course drive the prices for all small and medium sized companies that are operating according to international standards in China.

4.4.6 Conclusions

There is a large potential in the Chinese biotechnology field and consequently abundant chances for international collaboration which would benefit the parties involved. Mr. Ernst-Udo Rauhe, international marketing director of Orpegen Pharma GmbH in Heidelberg, Germany, is also highly positive about the potential of China and believes in the opportunities of doing business there. During an interview with the author of the report, Mr. Rauhe described how companies from China and India are competing out others by low-priced quality products in the fast-changing chemical industry. As a matter of fact, for instance, roughly half of the exhibitors now at CphI, a leading exhibition on pharmaceutical ingredients and allied industries, are from China and India. In the biotechnology field, Western companies are starting to discover this same combination of cost-advantage and quality in doing research and development in China. In the interview above, Dr. Arnold at Bicoll even sees this as a trend as it is happening at a large scale.

For many though, China is still a foreign country and the first step in doing business with or in setting up a business there is especially difficult. Chapter 3 in this report has already shown that there is a good number of sources to turn to for support and information.

Mr. Rauhe at Orpegen Pharma who has established good contacts to some Chinese chemists and who is experienced in doing business internationally, revealed sensible approaches to how to get first connections, how to attract potential business partners as well as other issues:

- Major international scientific/business meetings and exhibitions in one's field are good places to meet potential partners/customers. Well-prepared company catalogue in Chinese, for instance, is an effective instrument to show a company's interest in China and in attracting potential Chinese partners/customers. Mr. Rauhe's experience is that even the Chinese who work in the USA and speak fluent English would always take a Chinese catalogue.

- Clear understanding of reasons for cooperation from both sides is essential for successful collaboration. Stop it if a collaboration does not work.

- Hiring a Chinese manager who knows the market well for larger collaboration, and entrust the person with responsibilities. It helps to understand the importance of this if one thinks of collaborations between the USA and Germany. The Americans are satisfied when

they find Germans here to set up subsidiaries for them in Germany and vice versa.

- Being sensible is important in doing business internationally. One needs to listen well and to know when to stop talking. Understanding the customer's needs is crucial and this involves digging behind a seemingly "wrong" inquiry sometimes.

- Advertise in well-known international journals.

5. INTERVIEWS WITH CHINESE COMPANIES

5.1 Sinovac Biotech Co. Ltd.

The following interview, between the author of this report (**Q**) and Dr. Weidong Yin (**Yin**), Managing Director of Sinovac Biotech Co., Ltd. (hereinafter referred to as: “Sinovac”) and Dr. Evelyn Wang (**Wang**), Deputy General Manager of Sinovac, was done on May 14, 2004, at Dr. Yin's office in Sinovac. Sinovac Biotech Co. Ltd. is located in the Beijing University (hereinafter referred to as: “PKU”) Biology City, home of PKU Weiming group, of which Sinovac is a member company.

Q: Dr. Yin, you have studied Hepatitis A for 20 years and are the inventor of inactivated Hepatitis A vaccine technology. May I start by asking you to explain us what an inactivated vaccine is and what the key success factors for developing a new vaccine are?

Yin: Simply stated, a vaccine simulates the effect of a pathogen in immune response to generate a rotective effect to the body, without having the adverse effect of the pathogen. To make inactivated vaccines, viruses are cultured in cells and their pathogenic effect is then eliminated by treating the viruses with chemical reagents either before or after their purification.

These two aspects are important for the success of making a new vaccine, according to my opinion:

1. One needs to have a well-established long-term study concerning both the epidemiology of the viral disease and the pathogen itself.

2. The study of vaccines is a systematic study requiring various technologies which support one another. Purification technology, for one, is important. China has reached a relatively good level in these technologies.

Sinovac has advantages in these two aspects which are crucial to successfully bringing a new vaccine onto the market. Take SARS for

instance. Repetition is crucial in the study and this would not be possible without a large sample size. The same is true for Hepatitis A disease. When the last Hepatitis A epidemic broke up in Shanghai, there was a large number of people being infected.

Q: Do you have an advantage when you have successfully established a system for the study and manufacturing of a vaccine product? In other words, can you apply the same or similar methods of study, techniques, etc, to the research and production of a new vaccine?

Yin: Definitely. That's what I meant by systematic. The study and production of one vaccine lends readily usable methods, techniques, etc, for another vaccine product. This acts as a barrier to entry in this field.

Q: How are clinical trials for a vaccine done?

Yin: First of all, in contrast to clinical trials for a new drug where volunteers are patients suffering from the particular disease, in clinical trials for vaccine products the volunteers are healthy people. The observation criteria for clinical trials for a new vaccine include:

1. Safety issues concerning side effects.

2. Reactivity issues concerning protective criteria such as antibody. For SARS vaccine, for instance, neutralization antibody level is a key criterion.

3. Protective effect which is required for the issuing of a product permit. The rotective effect is measured by the ratio of the people having the disease in the vaccinated group versus those in the control group. Protective effect can be measured only in the next epidemic when there is one.

Q: It means that only when there is another SARS epidemic can a SARS vaccine get a product permit by the State Food and Drug Administration (SFDA). We all hope that there will never be another SARS epidemic. However, what does this mean for your company commercially when you have developed the vaccine and may not sell it after all?

Yin: The vaccine has a value even if we may not sell it. For one, we are the one who has it when it is needed one day. I'd like to think of how best to formulate this value.

Q: Maybe we can see it as an option?

How long does it take to bring a vaccine product onto the market?

Yin: This varies depending on the vaccine. For Hepatitis A, the virus was isolated in 1984, but not until 1995 did we decide to go for Hepatitis A

vaccine. In 1998 we got permit for clinical trials, and one and half a year later in 1999 we have completed clinical trials for Hepatitis A vaccine.

Q: How long is the life span of a vaccine, and how long can a vaccine protect you?

Yin: This differs again depending on the virus. Hepatitis A virus strain never changes while Influenza virus changes every year. Hepatitis A vaccine can protect you up to 20 years. There is a mathematics model to predict the protective effect of a vaccine, based on the change of the antibody level in the body with time.

Q: Were there Hepatitis A vaccine products on the market before your product?

Yin: Hepatitis A vaccine produced by Sinovac is the first Chinese product of its kind. Hepatitis A vaccines from companies outside China have come into the Chinese market but their prices are high. Our vaccine offers cost advantage with high quality. As you know, we imported our manufacturing facilities from Europe to ensure international quality standards of our products. We have anticipated international competition in the Chinese market and hence have set high quality standards for our products in the very beginning. In Sinovac our expectations are to "let Chinese children use vaccine of international standards, let children in the world use vaccines made in China". Besides, we own the intellectual property rights of our vaccine products.

Yin: For vaccine products, the proprietary intellectual property rights rest with the ones who have isolated the pathogen.

Q: I can see that the vaccine field hence offers Chinese companies vast opportunities.

Yin: Yes.

Q. Can one predict the market size of a vaccine?

Yin: Easily, by population size and the rate of vaccination. In China, for instance, the Center for Disease Control (CDC) offers five free vaccinations – Hepatitis B, DTP (Diphteria, Tetanus & Pertussis), BCG (Bacillus Calmette-Guerin; protects against tuberculosis), measles, and OPV (Oral Polio Vaccine). In the USA, the children and the elderly can enjoy three more types of free vaccination. This of course is determined by the developmental stage of a country. While now (some) Chinese children can afford consuming ice

cream of top international brand, they may not have been protected by hepatitis vaccines.

Q: Dr. Wang, you mentioned yesterday at the "How to do business in biotechnology" workshop at ACHEMASIA 2004 (*note: the workshop programme is given at the end of this interview*) that there are two types of potential buyers for SARS vaccine – the state buyer CDC who would distribute the vaccine for free to people in affected areas and individuals who would pay for the vaccination on their own. Is this the same for other vaccines?

Wang: Yes, most probably. In China, CDC is a monopolized distributor for vaccines. Individuals get vaccination at CDC and need to pay for it when it falls outside the free list.

Q: When CDC decides to buy a vaccine product, how is the buying done? For instance, how does it decide to buy from a certain manufacturer?

Yin: The buying process has incorporated market mechanism, it is in fact more market oriented than the US CDC. We can bid, for instance.

Q: Are there other Chinese companies who produce inactivated Hepatitis A vaccines?

Yin: One other Chinese company recently came up with a Hepatitis A vaccine. There is administrative protection for vaccine manufacturers. Permits to set up a vaccine company are highly regulated. That limits the number of companies in this field.

Q. Is vaccination covered by health insurance?

Yin: Currently the insurance companies in China do not yet cover vaccination.

The insurance industry is said to be at an immature stage here. Due to different problems, many insurance companies are reluctant to offer health insurance as an individual product and offer it only as an additional coverage attached to other insurance. However, with the development of the Chinese society, this likely will change.

Q: May I ask you about the ownership of Sinovac? Last year the former Net Force Systems Inc. (a NASDAQ OTCBB listed company) purchased 51% of the stock of Sinovac and subsequently changed its name to Sinovac Biotech Ltd. (hereinafter referred to as: “Sinovac-U.S.”). Is it right to say that 51% of Sinovac is Sinovac-U.S.?

Yin: Correct. When Sinovac was founded, the stock holders were PKU Weiming Group, Sino Pharmacy (HK), Tangshan Yian, and Beijing Keding Investment company. Last year Sino Pharmacy (HK) and Tangshan Yian sold their combined 51% of Sinovac stocks. Now Sinovac-U.S. owns 51% of Sinovac, PKU owns 45%, and Beijing Keding Investment Group 4%.

Q: Concerning PKU Weiming Group – what is its relationship to Beijing University (in English also: Peking University – PKU for short)?

Yin: PKU Weiming Group is 100% owned by Beijing University.

Q: And Beijing University is state-owned.

Yin: Right now yes. However, this may also change in the future.

Q: Tangshan Yian seemed to be a private company when it was purchased by Sinovac-U.S. However it has biosafety level 3 laboratories. It seems a bit unusual to imagine a private company able to get permit for such laboratories.

Yin: The aim of facilitating this high level of biosafety laboratory condition is to serve the state's imperative needs. The change of ownership, from state-owned to private or vice versa, happens in order to facilitate the development of a company. This is the key issue. Take the German Railways (Deutsche Bahn - DB) for instance: privatization of DB did not change its facilities nor the purpose of the company. The same applies to Tangshan Yian.

Q: Up till now how much of the financing Sinovac has obtained came from the state and local governments?

Yin: 30% to 50% of our R&D financing is state money. At industrialization stage, our financing involves no more than 10% state money.

Q: Could you tell us how Sinovac is managed? How are important decisions made and who has the final say, for instance?

Yin: There are two aspects which I'd like to stress. Firstly, as a stock company, Sinovac is managed according to the Company Law. Stock holders participate in decision making. Secondly, I would not hesitate to say that as Managing Director I do play a very important role in decision making. This ensures that our decisions are made within a short time. For example, when SARS epidemic broke up, we reacted very fast and decided promptly to go for the SARS vaccine.

Q: I know Sinovac works closely with CDC and SFDA. Could you tell us a bit more concerning Sinovac's partnerships and ways of collaboration?

Yin: I think that the developmental stage of a company and the resources a company controls determine with whom it will collaborate as well as how to collaborate.

In the field of technology, our collaboration partners are mainly domestic partners from governmental agencies and universities. From a business point of view, we collaborate with PKU for its brand name, and with a company in Hong Kong for international access. We acquired technology using stocks. We worked together with financial companies and banks to take part of our company onto the stock markets – both the NASDAQ and Frankfurt stock exchanges. In marketing, we now have partners in Korea and we are having talks with Mexico, for instance, to introduce our vaccine to these markets.

Q: Have you collaborated with a German company?

Yin: When we needed to purchase a filling machine, we found out that products from a German manufacturer were the best, so we bought from this German company. Other than that, we have no collaboration with Germany so far.

Q: According to your experience, was there any barrier or problem caused by cultural differences in doing business with an international partner?

Yin: We have not had any barrier or problem in our business because of cultural differences. Different cultures have different value systems and this will always be so. However, in business collaboration, it suffices if the partners involved can see eye to eye the same value in the collaboration.

Q: How do you make sure that you get the best partner and how do you make your company known internationally?

Yin: We strive for the best within our abilities. In China, by being the best in our field we can attract the best partners. Internationally, we need to do more in this regard.

Q: Sinovac has an informative English web site, which is a good tool for communicating the company to the public.

Dr. Yin, you are responsible for the State High Tech Industrialization Project (see note at the end of the interview for a general description of the project). Could you tell us a bit about how a project is funded?

Yin: The state money is actually seed capital to a company. In the evaluation of a project for funding, the state looks at the capability of the project carrier, especially at how much funding the project carrier can obtain on its own. In

general, the state funding comprises about 10% of the total funding for a project, about 30% of the total funding comes from the bank, and the rest from other sources. However, getting bank loans and other investment money in turn depends largely on whether the state would fund the project. Hence there is an interesting interplay of these elements in the process of obtaining financing.

Note on the Chinese State High Tech Industrialization Project

The high-tech industrialization model project is one of the four devices for implementing the national high-tech industrialization development plan by the national planning committee and the ministry of finance in China. In biotechnology, the goal is to speed up the development of the industry through these projects so that the sales revenue from biotechnology products will increase from 20 billion RMB Yuan (ca. 2 billion Euro) in year 2000 to 200 – 300 billion RMB Yuan (ca. 20 – 30 billion Euro) in year 2005.

Source: National Development and Reform Commission (www.sdpc.gov.cn)

Programme of the ACHEMASIA 2004 Workshop
„How to do Business in Biotechnology“
Thursday, 13 May 2004, 14.30 - 16.30
Chair: R. Schmid, University of Stuttgart/D

Sustainable bioproduction. A good opportunity for cooperation
R. Schmid, University of Stuttgart/D

Accessing privileged chemical structures for novel pharmaceuticals
C. Haug, Bicoll GmbH, Munich/D

Preclinical drug discovery in Asia. A challenge and chance for small biotech companies in Asia
M. Daffertshofer, Evotec Technologies GmbH, Hamburg/D

Inactived SARS vaccine study brings the new opportunity to development of China Biotech Industry
W. Yin, Sinovac Biotech Co. Ltd., Beijing / PRC

New process for production of chitosan oligosaccharide and its applications
J. Qin, China Petrochemical Technology Company/PRC; T. Tan, Beijing University of Chemical Technology/PRC

Chinese start-up companies in biotechnology
G. Hu, Shanghai HealthDigit Co., Ltd, PRC

Biopharmaceutical industry in China
J. Lou, Shenyang Sunshine Pharmaceuticals Company/PRC

5.2 Sunshine Pharmaceutical Co. Ltd.

The following interview between the author of the report (**Q**) and Dr. J. Lou (**Lou**), CEO of Sunshine Pharmaceutical Co. Ltd. (hereinafter referred to as: Sunshine), was conducted through email exchanges in English in June 2004.

Q: Dr. Lou, could you describe briefly how Sunshine was founded, in particular, how financing and key technologies were obtained in the initial phase and how that changed with the evolution of the company?

Lou: As I mentioned in my short talk (at ACHEMASIA 2004 in Beijing), the company started from a research laboratory in a medical institute of Shenyang. Before the recombinant DNA technology was introduced into China, the bioactive protein drugs were extracted from animal organs or blood. The initial funding of Sunshine was from the technology transfer of the licenses for thymosin and nature interferon produced by founders of Sunshine using biochemical extraction methods. The founders licensed out the two technologies to other drug companies. In the later development stage, most funding was from our own profit from sales of products and bank loans.

Q: In your talk at ACHEMASIA 2004, you seemed to have defined the playing grounds for Sunshine to be in the generic drug field. Is this a long-term or short-term strategy?

Lou: This is totally wrong feeling. We did perform a lot of novel product development since the very beginning. The generic biopharmaceuticals are really an entry point for the current and future strategy for access to the world market.

We now have some novel candidates from research and development. We would have had a lot more candidates in our pipeline if there would be more funding.

Q: As compared to the West, does it actually take shorter to go through the clinical trial phase because organizing the trials would be faster, for instance, due to a larger pool of patients?

Lou: I don’t think so. We spent 10 years for our last drug.

Q: In order to come up with a new drug, pharmaceutical companies in the West rely heavily on acquiring new technologies and drug candidates from others. Does Sunshine also in-license? How much, in terms of % of total sales, does Sunshine invest in R&D currently?

Lou: Yes. We do license-in for candidates and technologies. There will be royalty deals in the future, but until now we had only one-payment deals.

We invest in R&D all the time.

Q: Sunshine has a well-established sales force. How much is its sales and marketing expenditure in terms of total sales?

Lou: Very high. ~ 33%.

Q: In your opinion, what are preferred sources of funding to grow the company?

Lou: Product sales and public offering.

Q: Could you describe LifeGen (a subsidiary of Sunshine in the USA): its purpose, how has it helped Sunshine in its business, etc.?

Lou: LifeGen has contributed a lot in terms of process development for our major products.

Q: You obtained your Ph.D. from Fordham University in New York City and did your post-doctoral training at the National Institute of Health in the USA. Did your experience in the USA bring you contacts which in turn benefited Sunshine?

Lou: This experience did help me and Sunshine a lot, as you said.

Q: How should one best describe the biopharmaceutical industry of China – what challenges do the companies face regarding competition nationwide and internationally? What unique opportunities do they have, if any?

Lou: I believe we do have opportunities as I mentioned in my presentation (at the "How to do business in biotechnology" workshop at ACHEMASIA 2004).

Q: What is the financial situation of Sunshine? Is it profitable already? Who are the major stock holders of the company?

Lou: Very profitable as compared to many other companies in the field. But not enough in terms of absolute numbers. Founders of the company are the major share holders now.

Q: Why is Sunshine doing better than other companies in the field in generating profit?

Lou: We are working harder and have a good infrastructure.

Q: Currently, there's a up to 10-fold difference in selling price between a recombinant protein drug manufactured by a Western company and a Chinese company. If one looks only at the absolute number in total sales or profit of a Chinese company against a Western company, one misses something. One should remember at the same time that the living standard and the cost of running a business in China is also proportionally lower. Perhaps a better comparison would be to look at return on investment. What do you think of this?

Lou: Not exactly.

Q: What would Sunshine be looking for in an international partner for a potential collaboration?

Lou: A strategic partner.

5.3 HealthDigit Co. Ltd.

The interview with Professor Gengxi Hu (**Hu**), CEO of HealthDigit Co., Ltd., by the author of the report (**Q**), was done on May 26, 2004, at Professor Hu's office in HealthDigit, located in the Caohejing Hi-tech park in Shanghai. Professor Hu focused his talk on the start-up companies in the Chinese biotech industry, especially on the differences between the biotech start-up companies here and in the USA or in the West at large, as well as cultural differences in doing business with international partners.

Q: Professor Hu, you planned to talk about the Chinese start-up companies at the "How to do business in biotechnology" workshop at ACHEMASIA 2004 in Beijing but unfortunately did not make it. Could you share with us your insight into the Chinese biotech start-up companies here?

Hu: Certainly. First of all, I'd like to make aware of the fact that biotech clusters in China are already comparable in size to those in the USA. Information about the biotech industry in China is often very superficial or even worse - inaccurate. It is unknown to many, for instance, that in Shanghai alone, there are more than 200 modern biotechnology companies, and in the Yangtzi Delta area (the Shanghai area), within a radius of 100 to 200 kilometres, there are over 300 biotechnology companies. In comparison, in the Boston biotechnology cluster, there are also just over 400 biotechnology companies. So the size of the biotechnology cluster here is comparable to the world's second largest. However, similar to those in the USA, most of the Chinese biotech companies do not survive long.

If the Chinese and the Western companies want to collaborate, they need to understand each other first. Differences between them are vast. I would even go so far as to say that the only similarity they share is that they both engage in a business whose products come out of biotechnology. Everything else differs, from obtaining financing to marketing.

There is very limited collaboration between China and the West in the biotechnology industry right now due to the following reasons. If you look at technology, Chinese companies do not really need "guidance" from western companies because they are founded mostly by people who studied and/or worked in the West (USA and other countries) and who are very strong in their fields. In financing, although money is sought after by companies here, investors in the West do not readily put down money in biotechnology in China. In marketing, because of different legal regulations, it is hard to collaborate also.

What is most needed, I believe, is for the Chinese and the Western companies to really know each other. Therefore, it is important that we have more direct exchanges of information.

Q: The journal Nature last November published a special issue entitled China Voices about science in China. The articles were written by overseas Chinese, mostly American-born Chinese. This issue is one of the references I used for my report on the Chinese biotechnology industry.

Hu: China is in fact efficient in doing scientific research. Unlike Western countries who can afford focusing on certain fields of research and acquire technologies from other countries in other fields for the development of their nations, because of ideological differences, China must develop its own technologies in all fields. If you look at these figures – the funding for science and technology in China is 1/30 to 1/50 of that in the USA, and both countries have about the same number of scientists in total – and consider what we have achieved so far, you'll have to conclude that China is very efficient in research activities.

New technologies are also less costly to acquire here. For instance, I am in the process of setting up a fund with European investment companies to acquire projects in the biomedical fields here and to develop them further. I have a pharmaceutical company which has already two drug candidates in clinical trials.

In the West, big companies have low yield in research activities, due mainly to their system of doing research. While it's always being told that high technology implies higher risk, I do not think this is true. I believe that high

technology does not imply higher risk per se, the role of management is crucial.

Q: The probability of failure is higher if the technology on which a product will be based is new and has to be worked out first. Research-based international companies always engage in some exploratory research.

Hu: A biotech company here would not be founded based on exploratory science. One has to be product-oriented. The US start-up company model based on the investors' view there has more of a technology focus, especially several years ago. The companies may aim to bring a new technology to the next developmental phase in two years, for instance. After two years, the investors would then evaluate the technology and decide whether to invest further. In China, in contrast, all an investor would like to hear is when he/she will get how much return on investment, so one has to make profit pretty fast.

That is one of the reasons why Chinese biotech companies are extremely healthy financially. Equally important is that, in China, according to the securities law, a founder's stock can not be traded publicly in the stock market even if the company is listed on the Stock Exchange. The founders can only sell their shares in a private way. Thus, the boards usually tend to force companies to make money instead of making a good public image in the newspapers.

This makes the Chinese biotech companies extremely healthy but also extremely difficult to survive. Because there is no exit channel here nor immediate bridge to international market, if a company does not make profit after a while, it fails totally.

I have a friend who founded a company in the stem cell research field. The road to a product is long for this company. In order to survive and to fund its research, the company started to do business in clothing as well as in feed stuff, after an initial phase of cash-burning.

Q: Why would people then bother investing in high-tech business at all if there are easier ways to make money elsewhere?

Hu: First of all, for a higher return in the long run. Secondly, we are scientists, high-tech business is our field and we have an advantage here.

Q: Concerning the exit channel, can one not list the company on the Hong Kong stock exchange?

Hu: HealthDigit is in fact listed on the Hong Kong stock exchange because it has been acquired by a Hong Kong company which is listed on the Hong Kong stock market, with the ticker number 0233.

Q: You have had contacts with business people from different countries in the biotechnology field, what impressions do you have regarding cultural differences?

Hu: American companies who operate in China are usually very practical. In comparison, my impression is that German businesses take longer to make decisions and to react, and are somewhat beaurocratic. Germans take pride in being old brands while Americans may happily claim to have established a company yesterday. It's not rare that ambiguities arise when the Germans and the Chinese communicate.

Q: What does that mean for doing business together?

Hu: First of all, it goes without saying that a collaboration works only when the interests of both/all partners have been considered, and that the collaboration benefits both/all. One has to be clear about one's purpose and make that clear to the potential partner.

According to my experience, champions are needed to bring a collaboration into existence when we do business with companies from abroad, except with the USA. The US companies make decisions on their own after direct interactions with the potential Chinese partner(s). Companies from UK are more similar to the USA in this aspect. In other cases, a champion who diligently talks to the decision-maker in the non-Chinese company about how the collaboration would benefit the company seems to be important.

I believe there are good opportunities for the Germans in doing business in China. The contacts between Germany and China are still pretty limited. The presence of German business in China, in comparison to the weight of the German economy on the world market, is underdeveloped. There is a big potential for certain German equipment manufacturers such as the biomedical equipment makers in the Chinese market, and I will be more than happy to help where I can to realize this potential.

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7. SELECTED ADDRESSES CITED

1.) Chinese Ministry Of Science & Technology (MOST):

www.most.gov.cn

2.) Chinese National Center for Biotechnology Development (CNCBD):

www.cncbd.org.cn

3.) State Food and Drug Administration of China (SFDA):

www.sda.gov.cn

4.) Ministry of Health of China (MOH):

www.moh.gov.cn

5.) The offices of German Industry and Commerce (GIC) in Beijing, Shanghai, Guangzhou and Hong Kong:

www.china.ahk.de

6.) The German Office for Foreign Trade (bfai):

www.bfai.de

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