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Department of Business Studies

China's Creation of Biopharmaceutical Drugs

Combining Political Steering, Military Research, and Transnational Networking

Åse Linné

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Abstract
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Not only the Western world is focused on creating new innovations based on scientific discoveries; this is also the case in China where discoveries in biotechnology science are aimed at creating new biopharmaceutical drugs in order to create a future biotechnology industry and in the end generate economic growth. The focus to invest in high-tech industries such as biotechnology can be traced to the "open-door policy" issued in 1978 with the aim to modernize China and transform China into a "socialistic market economy." However creating new biopharmaceutical drugs in China is challenging due to the scientific and industrial conditions in China in the late 1970s, including a weak science base due to the Cultural Revolution (1966-1976), an industrial base mainly related to the defense industry and heavy industry along with a planning tradition where interaction between science and industry was forbidden. This thesis sets out to investigate how Chinese biopharmaceutical drugs are created.

With the aim to increase the understanding of China's creation of biopharmaceutical drugs the thesis is a case study with five embedded cases, representing five new drug innovation processes spanning the whole innovation journey including the developing, producing, and using settings. The investigated innovation processes were singled out through a specific method, more specifically by using a focal resource, a biotechnology system used in the scale between lab and process scale. Through this method it became obvious that among hundreds of Chinese drug development projects there were few that reached scale-up and actual use. By analyzing the resource interfaces that the five drugs encountered while being embedded in the developing, producing, and using settings, the creation of biopharmaceutical drugs in China could be revealed. Through the case study three main components was crystallized as important in the creation of Chinese biopharmaceutical drugs, more specifically a) the active role of the Chinese government, b) the utilization of Chinese military research, and c) the utilization of transnational networking. The thesis concludes that Chinese biopharmaceutical drugs are created through something that could be characterized as a "command network economy."

Keywords: innovation, biotechnology, China, resource interfaces, commercialization, Chinese government, command network economy, biopharmaceutical drugs, military research.
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Finally the thesis journey is finished and a new research journey starts…

Åse Linné
March 2012, Uppsala

CONTENTS

ABBREVIATIONS

API: Active Pharmaceutical Ingredient
AMMS: Academy of Military Medical Sciences
CAS: Chinese Academy of Science
CNBG: China National Biotech Group
CNCBD: Chinese National Centre for Biotechnology
CDC: China Centre of Disease Control and Prevention
CMC: Central Military Commission
CNIP: Chinese National Immunization Program
CSO: Chief Science Officer
EPS: Electronic Publishing System
FDA: Food and Drug Administration
FDI: Foreign Direct Investment
FPLC: Fast Protein Liquid Chromatography
GCP: Good Clinical Practice
GLP: Good Laboratory Practice
GMO: Genetically Modified Organism
cGMP: Current Good Manufacturing Practice
HAV: Hepatitis A Virus
HUGO: Human Genome
IND: Investigational New Drug
KIP: Knowledge and Innovation Program
MOA: Ministry of Agriculture
MOFTEC: Ministry of Foreign Trade and Economic Cooperation
MOE: Ministry of Education
MOH: Ministry of Health
MOST: Ministry of Science and Technology
NDA: New Drug Application
NDI: New Drug Investigation
NKL: National Key Laboratory
NSFC: National Natural Science Foundation of China
NTE: New Technology Enterprise
PLA: Peoples Liberation Army
PRC: Peoples Republic of China
ROI: Return On Investment
SAPI: Strategic Action Plan for S&T and Innovation
SDPC: State Development Planning Commission
SEC: State Economic Commission
SEZ: Special Economic Zone

SFDA: State Food and Drug Administration
SMMU: Shanghai 2nd Military Medical University
SOE: State Owned Enterprise
SPC: State Planning Commission
SSTC: Shanghai Science and Technology Committee
STC: State Technology Commission
TCM: Traditional Chinese Medicine
TVE: Township Village Enterprise
SMSTC: Shanghai Municipality S&T Commission
WIBP: Wuhan Institute of Biological Products

LIST OF TABLES

List of Figures

CHAPTER 1: INTRODUCTION

Setting the Scene: China, from Low-tech to Biopharmaceutical Drugs

After the Cultural Revolution ended in 1976 China was an underdeveloped country with its industrial activities mainly focusing on heavy and defense industry. Just years later, China declared the ambition to invest heavily in high-tech and science-based industries and especially the use of biotechnology knowledge in medical and agricultural industries. As an attempt to reform and modernize China the Deng Xiaoping government initiated the "open-door policy" in 1978, thereby opening up to foreign trade and economic development. Along with the open-door policy the government introduced the "four modernizations", i.e. 1) science and technology, 2) industry, 3) agriculture and 4) military as the main drivers of economic development. A reconstruction of the economy followed and the transition from a planned to a "socialistic market economy" began. Investments in high-tech in general and biotechnology[1] in particular became an important task for the Chinese government. The ambition to develop biotechnology became a key issue for the Chinese government and initiated the creation of new types of drugs based on biotechnology, so-called biopharmaceutical drugs.[2] Since then and during the last decades the Chinese

[1] Not only is the biotechnology concept wide with a variety of definitions but the application areas for biotechnology are also multiple. Biotechnology and application of biological processes have been used by humans for several thousands of years, for instance fermentation techniques for the production of bread and beer are commonly used techniques and seen as part of biotechnology. However in 1953 when Watson and Crick discovered the structure of DNA, the Triple Helix, modern biotechnology was born. Living organisms consist of large-scale molecules, mainly proteins, and these building blocks consist in turn of strings of nucleotides. DNA is in charge of designing these nucleotides into proteins and therefore DNA is the clue to how living things are created and developed. Increased scientific interest in DNA resulted in another important scientific breakthrough, the discovery of recombinant DNA (rDNA). By using rDNA techniques it is possible to import/export genetic information from one organism to another. (Robbins-Roth, 2000) The discovery resulted in an increased focus on the possibilities of changing the structure of molecules to be applied in various industries such as pharmaceuticals and agricultural industries, etc.

[2] Traditional pharmaceuticals consist of small simple molecules that can be chemically synthesized in laboratories, while biopharmaceutical drugs on the other hand are based on large complex molecules (100-1000 times larger than small molecules). These large molecules are mainly proteins, which are the main building blocks of living organisms. Traditional chemical drugs are usually taken orally in the form of a pill; the pill is transported through the whole body including

government has promoted biotechnology as a future industry for economic growth or as President Hu Jintao puts it:

> "Biotechnology is the priority of high-tech industries by which China will try to catch up with the developed countries, and China will strengthen the application of biotechnology to agriculture, industry, population and health." (As cited in Chen et al., 2007: 951)

Research Question

The ambition to create world-leading biotechnological science and business applied in the pharmaceutical world has been the main aim behind several policies issued by the Chinese government in order to catch up with the Western world. The ambition is set out to develop a biotechnology industry, where biopharmaceutical drugs would be one part, resting on the idea that innovations in terms of new drugs are based on the advances in biotechnological science. Thus, innovations based on science have been pointed out as critical in reaching economic growth. However this is not limited to the Chinese government and China in particular, but is also a worldwide phenomenon. Government and policy organizations all over the world are highlighting the importance of science as fuel for new innovations and contributing to economic growth (Slaughter and Leslie, 1997; Grandin et al., 2004; Eklund, 2007; Widmalm, 2008; Waluszewski, 2012).

Relating the ambition by the Chinese government to the weak scientific and industrial conditions in China in the aftermath of the Cultural Revolution, the Chinese government's promotion of the development of biotechnology science, companies, and innovations seems both bold and challenging. Innovation in general is risky; earlier research concludes that only a limited number of all new developments result in new innovations (Cooper, 1975; Tidd et al., 2001; Håkansson and Waluszewski, 2007b). Here it is important to remember that as long as an innovation is not taken into a use, it is still regarded as an invention (Rosenberg 1982). Thus, in order to become an innovation a new

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the digestive system before it reaches its target. Along the way the drug loses its activity and also affects other organs, which may result in side effects. As a result many traditional drugs only alleviate the symptoms of the disease but not the disease itself (Robbins-Roth, 2000). In contrast, biopharmaceutical drugs are designed to attack specific infectious cells, for instance cancer cells, and are injected directly into the human body. By designing the drugs in a particular way, it is possible to reduce side effects and produce more effective drugs that actually target the disease itself (Grace, 1997). To summarize, biopharmaceutical drugs can be beneficial by resulting in more effective drugs and by reducing side effects, compared to traditional chemical drugs.

solution has to be developed but also taken into large-scale production; i.e. become embedded into a structure of related suppliers and sub-suppliers, and furthermore, be embedded into a structure of established users. However, if the innovation journey is a biopharmaceutical drug based on inventions made in biotechnology science, the innovation journey appears to be even more challenging. These challenges are related to how the new solution is developed, how it is going to be scaled up and embedded into a producer setting, including securing the activities of proteins, the sanitary of high-end production equipment as well as effects – and side-effects – when used within the healthcare system. The Chinese governments' promotion of biotechnology science and biotechnology-based innovations, and biopharmaceutical drugs in particular, thus raises several intriguing observations and questions. However, there is one overall question that appears critical if we want to understand the processes behind biopharmaceutical drug innovation in China:

How are biopharmaceutical drugs created in a country that lacks an established modern biotechnology science base, a pharmaceutical industry related to advanced biotechnology, as well as experienced users of biopharmaceutical drugs in the healthcare setting?

More specifically in order to answer this research question, we need to consider the following empirical aspects:

How are government-initiated innovation processes materialized: a) in terms of development of new biopharmaceutical drug solutions and b) in terms of embedding these into large-scale production and c) into large-scale use.

To better understand the background to this research question, let us take a closer look at the challenges associated with the innovation journey of biopharmaceutical drugs in general and in making this journey in the Chinese business landscape in particular.

The Challenge of Creating Innovation in a Biopharmaceutical Context

Biopharmaceutical drugs with their developing origin in research and experiences from the US underline that out of 5,000 compounds found only five "survive" the step from laboratory tests to clinical trials on patients (Robbins-Roth, 2000). Furthermore, in the US only one out of these five is successfully transformed to a drug to be launched. It takes approximately 15 years to develop a new drug from drug discovery to product launch, and it is estimated to cost at least around US$ 500 million for the whole development journey (Robbins-Roth, 2000: 112-115) and the cost of drug development tends to

increase year by year (Pammolli and Riccaboni, 2004). Thus, the journey from research finding to a new biopharmaceutical drug in use implies a high failure rate. From the launch of the first biopharmaceutical product, Humalin, targeting diabetes in 1982 by Eli Lily, there were another 286 new product approvals by the US Food and Drug Administration (FDA) up to 2008. It is interesting that there are more and more products in the pipeline but there are there are fewer and fewer approvals of new drugs. (Rader, 2008)

If we consider the settings where biopharmaceutical drugs are developed, where they are turned into large-scale production and where they are taken into medical use, there are some distinct characteristics and features that complicate the innovation journey further. First let us consider the using setting in a biopharmaceutical context; this setting is dependent on competent and technically advanced users, for example hospitals with medical specialists such as doctors, and nurses treating patients. Having technically advanced users enhances the possibility of surviving the innovation journey. For instance highly educated and experienced medical specialists at hospitals are of vital importance in managing clinical trials and are important when aiming for good treatment outcomes. Also, medical researchers involved in medical trials are important in that they publish papers based on the new innovation. Rajapakse et al. (2005) emphasize the need for increased knowledge of the users in finalizing drug development; especially knowledge in terms of suitable pricing of the final drug and the number of potential users is pointed out as critical. As mentioned above, the using setting is affected by products and innovations already in use. In investigating new drug innovations within the Taiwanese biopharmaceutical context Shih (2009) concludes that the Taiwanese using setting is structured around the use of generic drugs and thus inhibits the innovation of novel biopharmaceutical drugs.[3] This means that it is difficult to embed a novel drug in a setting where the main products in use are generic ones. In supporting the use of novel drugs, investments are required, for instance investments in new high-end equipment along with the employment of personnel with "novel" experience; however this imposes a major change to the existing using setting of the Taiwanese biopharmaceutical context.

One main difference with the innovation of biopharmaceutical drugs compared to other types of innovation is the fact that drugs are produced to be inserted in the human body, which can have both positive and negative effects. Therefore the producing setting of new drug solutions is strictly directed by high regulatory demands on how to produce a "safe" drug, which increases the complexity and uncertainty of finalizing the innovation journey (Pisano, 2006). Hence producing biopharmaceutical drugs is strictly regulated by the US FDA

[3] Generic drugs refer to drugs that are comparable to an already existing drug in terms of features and intended use.

or other country-specific regulative agency,[4] and in order to get a drug accepted for sale biopharmaceutical companies need to produce according to high sanitary requirements set up by the FDA. Sanitary requirements increase for each phase from clinical one, two, and three to final drug approval, and due to increased sanitary pressure many drugs fail during late clinical trials (Robbins-Roth, 2000). Along with this the production facility in charge of producing a new drug need to correspond to current Good Manufacturing Practice (cGMP) set up by the FDA in order to get a new drug approval. Establishing production of a new drug is not only related to strict regulatory demands but also requires large investments in physical equipment and production facilities. In order to produce according to regulations, production facilities consisting of high-end production equipment are required along with highly experienced personnel in charge of setting up the production. Production equipment is expensive and therefore the producing company needs to invest large sums of money in production equipment, resulting in large fixed costs over a long period of time. Because large investments are needed in producing biopharmaceutical drugs, venture capital has been pointed out as crucial, especially in financially supporting small biotechnology firms (Powell et al., 2002). However venture capital not only provides financing for new biotechnology ventures but is also an important factor in providing contacts between other companies, affecting recruitments, etc. (Ibid). The companies involved in producing biopharmaceutical drugs experience economic pressure to produce as efficiently as possible and to keep investment cost as low as possible; thus one key issue is to produce using equipment in place. Shih (2009) show in his research that in order to establish a biopharmaceutical drug industry in Taiwan production facilities needed to be re-built, and finding personnel with the experience from use of high-end equipment was demanding. Certifying the production facilities according to international regulation standards turned out to be difficult due to the lack of experience from biopharmaceutical drug production. Thus in order to produce new innovative drugs, technically advanced companies with high-end equipment and production facilities are a must, which is also supported by Waxell (2005) and Waxell and Malmberg (2007), who conclude that industrial excellence including technologically advanced companies both as supporting but also as competing with other biopharmaceutical companies is supposed to enhance the innovating capability and facilitate the development of biotechnology companies and innovations within a region. However, one critical aspect of producing a biopharmaceutical drug is the step from small-scale research to large-scale production. Without reaching large-scale production it will be impossible to reach economies of scale and pay for investments made. Therefore if the producing company fails to scale up the new drug, the producing com-

[4] Other countries use the FDA as a role model when setting up pharmaceutical guidelines, thus the FDA can be seen as the international regulatory agency for biopharmaceutical development and production.

pany will face major financial difficulties. Scaling-up a biopharmaceutical drug is difficult because the proteins that act as the basis of the drug are produced by living organisms. Thus the active substance may be altered when scaling up. Since much is still unknown about the proteins, many unforeseen things can happen when scaling up. For instance the activity or the function of the molecules can easily be altered, or some molecules may even be so complex that it is impossible to produce them in large scale (Pisano, 2006). However, in order to facilitate the step from lab-scale to production-scale, interaction between the developing and producing setting is required.

Biotechnology science is ascribed a central role in shaping the biopharmaceutical drug innovation process in particular, since discoveries in science are the main source of innovation in a biopharmaceutical context. Thus, biopharmaceutical drugs are dependent on new science discoveries and new developments in the science world. What does this mean for the creation of new drugs? Due to the dependence of new science discoveries, "knowledge units," such as research institutes and universities, play a significant role in providing new discoveries in the biopharmaceutical world. The importance of science and connections to knowledge units when developing biopharmaceutical drugs also emphasizes the need for highly trained and educated personnel, and many researchers highlight the connection with producers of science as crucial when developing biopharmaceutical drugs. Owen-Smith et al. (2002) see universities and research institutes as important building blocks in developing biopharmaceutical business, where the science producers are seen as "seeds" for new biotechnology innovations. Especially basic research is viewed as the key to develop biotechnology within a certain region (Zucker et al., 1998). Zucker et al. (2002a: 139) also mention "…the strong effects of academic science on the success of the firms" and excellence in science or "star scientists" (Zucker et al., 2002b: 653) as key ingredients in diffusing scientific discoveries into new biotechnology innovations. Research not only highlights the fact that a science base is a prerequisite in order to be able to develop biotechnology and biopharmaceutical drugs in particular, but also the importance of strong interaction between technically advanced biotechnology companies and these knowledge units (Powell and Koput, 1996; Zucker et al., 1998; Mckelvey et al., 2003). This also reflects the fact that the developing, producing, and using settings need to be interrelated and connected during the innovation journey (Håkansson and Waluszewski, 2007a). In the drug development process, scientists focus on finding proteins or "target molecules" in stopping specific diseases. However, this is a highly uncertain activity since the drug development process consists of many other activities in verifying the target molecules' effect on a certain disease, including activities such as target validation, pre-clinical and clinical trials, along with regulatory approval. Due to the complex and long development process many things can go wrong in developing new scientific discoveries and transforming them into functioning drugs. For instance, a chosen protein may not have the desired effect, the molecule can break up when inside the human body faster or more slowly than assumed, the dosage of the drug can be wrong,

resulting in no effect or too great an effect on the disease in focus, etc. Thus there is high uncertainty regarding how the human body will respond to new drug innovations. The development of biopharmaceutical drugs is as Pisano (2006:57) describes it: "…fundamentally about successively reducing uncertainty through the acquisition and interpretation of information." As a consequence, the development of new drugs is time-consuming; especially in verifying if the discovery really can be used to stop certain diseases during all development steps, and basic science need to be supported by industrial R&D activities. Moreover data in early development are hard to evaluate and interpret, much due to the fact that much is "unknown" about the human biological system. (Pisano 2006)

To summarize the innovation journey of biopharmaceutical drugs is probably a more complex and difficult journey than that in most other areas. The using setting is affected by the fact that the use of any new drug requires a certain medical expertise and experience along with users wanting to pay for the new drugs. It is also important how it works and interacts with existing product systems. The producing setting is very much concerned with technically advanced company's ability to produce according to regulations set up by the FDA or other regulating agency. However, in order to establish production of drugs large financial investments are required, and the producing companies need to consider how to establish an effective production process. The developing setting is dependent on experienced and well-trained knowledge units, such as scientific research institutes and university labs, to provide new scientific discoveries. Due to these characteristics of the using, producing, and developing setting in the biopharmaceutical context, it is not surprising that a majority of all biopharmaceutical drug innovation processes fail, have long lead-times, and are costly.

The Chinese Challenge: Creating Biopharmaceutical Drugs

The above discussion on innovation in the biopharmaceutical context reflects the drug innovation process as a winding and uncertain path, including the development of the new drug along with embedding the new drug in large-scale production and use. Thus the innovation process of biopharmaceutical drugs is assumed to require a using setting with technically advanced users and a producing setting with technically and economically advanced companies to produce new drugs in large scale according to sanitary requirements set up by the FDA along with a developing setting with highly experienced scientists at research institutes and universities. If we then consider the scientific and industrial conditions in China to support and facilitate innovation of biopharmaceutical drugs, what picture do we get?

There is little information about the use of biopharmaceutical drugs in China, but China has an established pharmaceutical industry where approximately 90% consists of generic drugs, and Chinese pharmaceutical companies can be characterized as "numerous, small, scattered, disordered, and of poor quality" (Feng, 2002: 69).[5] However China has developed a strong position in the production of Active Pharmaceutical Ingredients (API), i.e. crude materials used for chemical pharmaceuticals, and China is the second largest supplier of API in the world (Weiss and Forrester, 2004). In line with the production of chemical drugs, biopharmaceutical drug production in China mainly consists of generic drugs, estimated to be up to 99% (Feng, 2002). Thus the producing setting in the biopharmaceutical context is structured around generic drugs, not novel drugs. Moreover China not only lacks technically advanced companies in producing novel drugs but also lack technically advanced users such as highly experienced medical expertise or hospitals used to treat patients with biopharmaceutical drugs (Chen, 1998).

The command economy directed by a central plan has colored the conditions for industrial development and business exchange in China. Before the transition (starting in 1978) private businesses were forbidden, and all companies were state-owned enterprises (SOEs) and business exchanges between suppliers and customers were handled indirectly through government planning authorities. Opening up and allowing a transition from a command economy to a "socialistic market economy" has resulted in an increasing number of private or non-state owned companies such as Township Village Enterprises (TVEs) or New Technology Enterprises (NTEs) but the tradition of having a plan to govern the Chinese companies has left imprints on contemporary China; for instance, almost all large companies are still SOEs, and many still suffering from deficits (Suttmeier, 1997). The Chinese government is still the main financier of business ventures in China, and high-tech businesses, in particular. The venture capital industry is weak, immature, and small, mainly consisting of government departments and agencies (Kenney et al., 2002). Having a tradition of a plan economy where the production was directed by quotas set up by the government, innovation and product development issues ended up in the shade. Thus, as a result, China has been forced to import new technology and copy products from abroad, just as in the case of pharmaceutical and biopharmaceutical drug production, where Chinese companies mainly focus on generic or "me-too" drugs. By being part of an old command economy there are weak links between universities or research institutes and companies, because direct interaction between science and industry was prohibited and only handled by government authorities. (Suttmeier, 1997) When the "open-door policy" was issued in 1978, there were no production structures to support high-tech in-

[5] The Chinese State Food and Drug Administration (SFDA) controlling pharmaceutical production has traditionally been rather weak in implementing regulations and has received international complaints for being too easy-going in approving New Drug Applications (NDA) compared to the US FDA.

dustries, because China had been focused on production in heavy industry and the defense industry. During the 1980s and 1990s China became known as the "manufacturer of the world," reflecting labor-intensive production with a low level of technology, such as garments and toys, etc., a suitable production structure for a country with a large population.

Chinese history has had a great impact on scientific development in China at large. Looking back, starting with the announcement of the People's Republic of China (PRC) in 1949, the Chinese communist leadership has been focusing on developing both science and technology. Not all types of science and technology were supported, only those types that the Chinese government considered important. A similar system as the socialistic Soviet was introduced in line with centralized plans directed by the government, where all research institutes were organized under the Chinese Academy of Science (CAS). Thus, both research and technology development became an issue directed by the Chinese government. Scientific discoveries were connected to military application and industrial investments mainly focused on developing heavy industry and the defense industry (Handberg and Xinming, 1992; Jian, 1997). Due to the planning system, the relation between science and industry was managed through government authorities and planning units; thus there was no direct interaction between the two. Technology development between the 1950s to the 1970s was mainly a result of a technology import strategy, where China bought turn-key projects from other socialist countries and China also used foreign "socialist" scientists or engineers to solve technological issues (Cheung, 2009). Thus building the science and technology base in China was in many ways a result of support from other socialist countries. With the new organization of science and technology, approximately 18 million engineers and scientists were educated by 1970 (Jian, 1997: 282) and scientific progress, such as the successful launch of "two bombs and a satellite" (Simon, 1989a) along with the production of synthesized insulin in 1965, was a fact (Chervenak, 2005; Simon and Cao, 2009). However, the situation had an abrupt end due to the "decade of destruction," i.e. the Cultural Revolution between 1966 and 1976, where the science base built up during the whole 20th century was destroyed. Scientists were sent to the countryside for reformation by hard labor, and universities and research institutes collapsed. As a result of the hostile environment for scientists and academics, China suffered from a "brain-drain," starting from the late 1970s and still ongoing. The Cultural Revolution destroyed a whole generation of scientists and affected the following science development in a negative way; due to the "decade of destruction" science is considered to be rather weak in China.

To summarize, China seems to lack technically advanced users of biopharmaceutical drugs, and the using setting is mainly structured around generic drugs. China also lacks technically advanced companies to produce biopharmaceutical drugs, and the producing setting is still colored by the planning system, where interaction between science and industry was forbidden. Moreover China also evinces a weak science base, still marked by the Cultural Revolution.

How Have Biopharmaceutical Drugs Been Promoted in China?

In catching up with the Western world the Chinese government has been concerned with the creation of economic growth as the main driving force to transform China into a modern market economy surpassing the Western world. One main issue in reaching economic growth has been the creation of innovations, and here high-tech and science-based industries have played a significant role. As the Ministry of Science and Technology (MOST) put it:

> "…to boost innovation capacity in the high-tech sectors, particularly in strategic high-tech fields, in order to gain a foothold in the world arena; to strive to achieve breakthroughs in key technical fields that concern the national economic lifeline and national security; and to achieve 'leap-frog' development in key high-tech fields in which China enjoys relative advantages or should take strategic positions in order to provide high-tech support to fulfill strategic objectives in the implementation of the third step of our modernization process." (MOST, 2006)

Hence, the Chinese government sees innovation as driving economic growth and supporting the transformation from a developing country into a modern industrialized country. The Chinese government has engaged in steering the promotion of biotechnology innovation, where achieving the innovation of biopharmaceutical drugs has been one main ambition.

What has the Chinese government done in order to support the processes that will lead to innovation of new biopharmaceutical drugs? Basically, the government has tried to establish a suitable milieu to facilitate biopharmaceutical drug innovations by issuing different policies both on central and regional level which aims to; a) stimulate the development of biotechnology knowledge and b) stimulate the transfer of this knowledge to commercial actors. Thus, the Chinese government has applied an innovation system approach where two main components are crystallized. Firstly, the Chinese government has focused on supporting a system where biotechnology knowledge can be developed. Here the Chinese government has focused on establishing research institutes responsible for developing new scientific discoveries as seeds for new innovative biopharmaceutical drugs. Also, investments in establishing and strengthen Chinese universities have been important since the universities have the main responsibility for educating future employees at Chinese biopharmaceutical companies in charge of commercializing these new innovative drugs. Secondly, the Chinese government has also promoted the establishment of a system in charge of commercializing new innovative drugs. Here the focus has been on the growth of technically advanced biotechnology companies responsible for commercializing new drugs. Policies such as tax relaxation for high-tech companies or the creation of science parks have been supporting this commercial producing system. To support these two main components of the

innovation system, the Chinese government infuses financial capital through public funds or programs but also through state-owned venture capital firms. (CAS, 2003)

Summing Up and Outline of the Thesis

The aim of the study is to gain a deeper understanding of China's creation of biopharmaceutical drugs. As mentioned, the Chinese government has singled out the biotechnology industry and the creation of biopharmaceutical drugs in particular, as drivers of economic growth. China hopes to become a biotechnology superpower and decrease the gap with the industrialized Western world. As a consequence, the Chinese government has issued a number of policies to stimulate the establishment of biotechnology science along with the establishment of companies to commercialize biotechnology science over the last few decades. However the creation of biopharmaceutical drugs in China seems rather challenging, since innovations of biopharmaceutical drugs are dependent on both on the development of new discoveries in science along with technically advanced companies and technically advanced users in the healthcare setting. The basic conditions to support the development, the production, and the use of biopharmaceutical drugs seem to be weak in China. Bearing this in mind, the research question is repeated once again:

How are new biopharmaceutical drugs created in a country that lacks an established modern biotechnology science base, a pharmaceutical industry related to advanced biotechnology, as well as experienced users of biopharmaceutical drugs in the healthcare setting?

More specifically in answering the research question, we need to consider the following empirical aspects:

How are government-initiated innovation processes materialized: a) in terms of development of new biopharmaceutical drug solutions and b) in terms of embedding these into large-scale production and c) into large-scale use.

The topic of the thesis is challenging for many reasons: firstly, due to the political system of China, where the tradition of allowing a foreign researcher to carry out investigations concerning the interfaces among companies and organizations and the relation to the political level is far from established. Secondly, due to the size of the country and of its biopharmaceutical activities, where official numbers indicate that there are several hundreds of research institutes and companies engaged in the development and production of biopharmaceutical drugs. This in turn requires a theoretical and methodological approach that can capture what is going on in the interface among organizations responsible for the development of new biopharmaceutical substances, companies engaged

in turning biopharmaceutical substances into drugs, and healthcare organizations responsible for the use of such drugs in medical treatment.

Suitable analytical tools are further discussed and elaborated on in the coming theoretical chapter, Chapter 2, where an interactive view of innovation processes is presented along with the main research tool for the thesis, the four resources model (4R model), developed by Håkansson and Waluszewski (2002). Then the method and a methodological discussion are presented in Chapter 3. Especially the issue of delimiting the study to five drug innovation processes is thoroughly discussed. The empirical part of the thesis starts with Chapter 4, where the Chinese business landscape is sketched during three phases; before 1978, 1978-1992, and 1993 and onwards. This chapter is followed by an introduction to the development and production of drugs in China in Chapter 5. The following Chapter 6 discusses the evolution of Chinese biotechnology, and the characteristics of the developing, producing, and using settings of Chinese biotechnology are revealed. Chapters 7 to 11 are dedicated to presentations of five innovation processes related to five Chinese new drug solutions, including an analysis of each innovation process. In the last chapter, Chapter 12, a concluding discussion related to the creation of Chinese biopharmaceutical drug innovations is presented and elaborated on along with suggestions of future research.

CHAPTER 2: THEORETICAL DISCUSSION

The following chapter is dedicated to a theoretical discussion, which is strongly colored by an interactive view on innovation in general, and by the research carried out within the Industrial Marketing and Purchasing (IMP) group in particular.

Innovation as the Result of Combining Resources across Organizational Borders

In order to investigate innovation processes we need to know what innovation really is about. What is typical for innovation processes? How can innovation be characterized? As mentioned in the introductory chapter, innovation is about a new solution being developed and produced, but also used. Thus innovation is related not only to the development of a new solution but also very much to the interface between the producing and using of new solutions. Due to the fact that innovation is related to the development of a new solution, to the production of a new solution along with the use of a new solution innovation is always stretching organizational borders (Rosenberg, 1982; Kline and Rosenberg, 1986; Basalla, 1988; Rosenberg, 1994; Håkansson and Waluszewski, 2002). This implies that it is impossible for one single company to internally have all the resources needed to develop, and transform it into a new solution and create a widespread use of the innovation. Instead interactions with other organizations and companies are required in order to understand the other side of an interface between resources, it is only through interaction with others that a resources' potential and characteristics are revealed. Hence interaction is a necessity in understanding how companies' resources are working together with other companies' resources both on the producing and using side of a new solution (Penrose, 1959; Alchian and Demsetz, 1972; Håkansson and Waluszewski, 2002; Håkansson et al., 2009). Innovations are therefore not an isolated phenomenon; instead any new solution is related to other technologies, products, companies, individuals etc., which means that any new solution needs to be seen as being "…deeply embedded in the structure of industrial societies" (Rosenberg, 1982: ix) and part of an interrelated network of technologies, artifacts, humans etc., which Rosenberg refers to as the "system nature" (Rosenberg, 1982: 59) of innovations. Thus any new solution is a result of

combining both technical resources (such as equipment, products, technologies etc.) and organizational resources (such as humans, organizations, knowledge etc.) across organizational borders (Rosenberg, 1982; Kline and Rosenberg, 1986; Basalla, 1988; Bijker et al., 1989; Hughes, 1989; Rosenberg, 1994; Håkansson and Waluszewski, 2002; Håkansson and Waluszewski, 2007b). As a result one key process of innovation is interaction and it is through interaction that an innovation gains its features (Latour, 1984; Rosenberg, 1994). By combining resources over time and space resources "rub off" on each other and give the new solution specific features. The innovation process is therefore a collective activity or as Hughes (1989: 64) put it:

> "Innovation clearly reveals technologically complex systems. The inventor-entrepreneur, along with the associated engineers, industrial scientists, and other inventors who help to bring the product into use, often combines the invented and developed physical components into a complex system of manufacturing, sales, and service facilities"

Innovation involves a wide number of interacting actors therefore: "… the activities of engineers and inventors are best described as heterogeneous system- or network-building, rather that as straightforward technical invention" (Bijker, 1995: 273). Gudeman (2001) also highlights the notion that companies and individuals representing innovations are interdependent and linked together and influencing each other. In the innovation process the entrepreneur is forced to link to others to create a use of the new solution at hand. Since an innovation is a result of a larger system of combinations of technical and organizational resources any new innovation is a product of its context (Rosenberg, 1982; Kline and Rosenberg, 1986; Rosenberg, 1994; Bijker, 1995). An innovation can be characterized as a "mobilisation process" (Håkansson, 1987: 5) where resources are exchanged, adapted, and combined across organizational borders. Thus, the innovation process takes place between companies and organizations where interaction is the glue. By using others' resources when innovating "…new ideas can emerge" (Håkansson, 1987: 4) but also because "…new products are often based on the combination of several technologies" (Ibid). Due to the fact that innovations are the result of an intricate network of interrelated resources between and across organizations it is interesting not only to investigate what is happening within the organizations but to what is happening between the organizations and what effects this "betweeness" has on the innovation process. Håkansson (1987: 3) summaries it as:

> "An important part of the development process, we suggest, take place in the form of a technical exchange between different 'actors' such as individuals or companies. Accordingly, interest should be focused as much on the interaction between different actors as on what happens within the actors. An innovation, therefore, should not be seen as the product of only one actor but as the result of an interplay between two or more actors; in other words as a product of a 'network' of actors"

In line with Håkansson (1987) Mowery and Rosenberg (1979: 146) also promotes "interfirm relationships" as the unit of analysis when understanding development processes such as innovation processes. Having the notion that innovations come into being through combining technical and organizational resources across organizational borders, how does it affect the innovation process per se?

First of all due to the fact that innovation is a result of interaction between numbers of resources, it is impossible to get a total understanding of the innovation process, since many resource interactions are hidden or indirect. Therefore the potential gains, usefulness and features of any innovation are difficult to predict and the innovation process is highly uncertain (Rosenberg, 1982; Dosi et al., 1988). Since partly hidden resource interaction processes precedes a new solution, its characteristics and features are not entirely revealed until extensive use has been made of the new solution (Rosenberg, 1982). Due to the large amount of interrelated resources an innovation process can in many ways be characterized as a "trial-and-error process" where the actual use of the new solution is blurred and may change during its development and production (Basalla, 1988: 141). Innovation can be seen as a cumulative process between organizations, where past experiences are used in new types of constellations (Hägg and Johanson, 1982). Van de Ven et al. (1999: 181) define the innovation journey "...as a sequence of events in which new ideas are developed and implemented by people who engage in relationships with others and make the adjustments needed to achieve desired outcomes within an institutional and organizational context" and also see the innovation as part of a "nonlinear dynamic system" (Van de Ven et al., 1999: 5). Thus empirical-oriented innovation researchers have characterized the innovation as a non-linear process that is hard to predict and manage. The non-linear characteristics of an innovation process mean that it is a both risky and costly endeavor. Empirical studies of innovation have pointed out the difficulties in surviving the innovation journey, and it is estimated that a majority of all innovation ventures are failures (Tidd et al., 2001). Thus, the innovation journey is highly uncertain and there are many studies highlighting the problem of reaching economic and commercial success of new innovations (Cooper, 1975; Pavitt, 1991; Cooper and Edgett, 2003). A common estimation is that only one out of ten development projects are commercial viable (Pavitt, 1991), thus the majority of all innovations do not reach

commercial success and have disappointing sales figures (Cooper and Edgett, 2003) or many never even reach the launching stage. Calculating the cost and revenue of the innovation journey is difficult, due to the fact that an innovation is not limited to one company but instead is the result of many participating companies and organizations (Håkansson, 1989; Håkansson and Snehota, 1989; Waluszewski, 1989; Håkansson and Waluszewski, 2002). An innovation may be initiated by one company but developed in cooperation with many companies; therefore the costs for each participating company are hard to evaluate. One main issue of the innovation journey is the fact that the cost always occurs before the revenue, and since the innovation is spread across company borders, cost and revenues are not always spread equally among the participating companies. Therefore the company investing the most does not necessarily get the highest revenue.

Secondly, any resource has a history that will affect the innovation process, in particular. As a result the innovation is part of "long sequence of path-dependent activities" (Rosenberg, 1994: 15) or as Gudeman (2001: 147) points out, the innovation has a "historical trajectory" developed over time. Therefore the innovation process is dependent on what already exists, i.e. the new is affected by the old and the other way around (Lundgren, 1991). Basalla (1988) highlights this as he argues: "Any new thing that appears in the made world is based on some object already in existence" (Basalla, 1988: 45) and "…each new technological system emerges from an antecedent system, just as each new secrete artefact emerges from antecedent artefacts" (Basalla, 1988: 49). Innovation processes are path-dependent and in order to grasp them we need to investigate the "history" of the new solution, i.e. track the origin of the innovation and reveal the development process over time and understand the innovation as part of a historical process.

The above discussion reveals that innovations are the result of combining technical and organizational resources where interaction across organizational borders is crucial. As a result innovations become context dependent and dependent on a larger whole of interrelated resources. Since the innovation process is the result of resource combining across organizational borders the innovation process can be characterized as multidirectional and non-linear in its character, resulting in a highly uncertain and unpredictable process. Moreover innovation processes are to a high degree based on the past, such as old knowledge used and combined in new ways, meaning that history matters during an innovation process. Therefore in gaining understanding of the innovation process of Chinese biopharmaceutical drugs I need a suitable theoretical tool to investigate the larger "interrelated clustering of innovations" (Rosenberg, 1982: 59), more specifically a tool to reveal both the hidden resource-combining process across organizational borders and the resource-combining process over time.

Innovation in Three Different Settings Imbued by Different Economic Logics

As indicated the innovation journey of a new solution is not only a matter of combining resources within and between a number of different organizations but the combining processes also stretches across three different settings: the using, producing and developing settings (Rosenberg, 1982; Pavitt, 2005; Håkansson and Waluszewski, 2007a; Ingemansson, 2010). Thus, any new solution needs to find its place in three different but related empirical settings during an innovation process and every new solution needs to be part of an economic structure where it can be used, produced and developed. Much simplified, it is the using, producing and developing settings that shapes and molds the new solution during its innovation journey. The new solution needs to be developed but also produced and used in order to be referred to as an innovation (Rosenberg, 1982). However in finalizing the innovation journey a new solution needs to be embedded into all three settings. Embedding a new solution means to connect and adjust the new solution to already activated resources or as Akrich et al. (2002b: 210) say: "adopt is to adapt." Thus any new solution needs to be connected to other companies, products, technologies, individuals, etc. in each of these settings. However, seeing an innovation as part of the using, producing and developing settings also reveals one problematic issue of an innovation coming into being: the fact that each setting has its own economic logic that will affect the new solution in different ways. More specifically what is rewarded and viewed as being economically beneficial varies between the settings. The following sections will be dedicated to a discussion on the characteristics of the using, producing and developing setting and how a new solution can come to life in each setting with its own economic logic. The economic logic is discussed by reflecting on the "return on investment" (ROI) of each setting and how this is related to the embedding of a new solution. It is important to realize that I do not use return on investment as an exact measure (ROI=revenue of investment-cost of investment/cost of investment), since it entails many "soft" measures such as routines, knowledge, etc., but more of a way to reveal the economic logic in each setting. For instance any company needs to show profit in order to survive; thus the estimated revenue of a new solution must exceed the estimated costs and investments of a new solution in order to be economically viable.

Embedding a New Solution in the Using Setting

The use of a new solution is crucial when transforming the solution into an innovation, since as long as an innovation is not used it is still regarded as an invention (Rosenberg 1982). However trying to embed and introduce a new solution to an established using setting is problematic due to the "products already in use," which are in turn interrelated to other resources such as users,

end-users, companies, organizations, technologies, products, etc. The products in use with their activated resource structures constitute the product system. *Therefore, when introducing a new solution in a using setting already existing product systems will be affected.* In order to use a new solution there have to be users ready to pay for a new solution; however since a new solution is dependent on the product system already in use, the new solution needs to create benefits for the using setting at large. If we discuss the estimated "return on investment" of a new solution, it needs to create positive economic benefits such as increased revenue due to larger sales volumes, decrease of costs due to a more efficiently distribution system or reduction of required investments in order to be embedded into a using setting.

Let us discuss the using setting further by empirically illustrating the embedding of a new solution within the biopharmaceutical context. In a biopharmaceutical context users and end-users of the healthcare system play a significant role when embedding a new drug solution in use. Users are mainly hospitals and healthcare clinics including medical staff, while end-users are patients in need of medical treatment. However imagine that these users are connected to a product system based on the use of generic drugs, i.e. copies of already existing drugs. Generic drugs require less training and experience than treatment using novel drugs. Therefore when introducing a novel drug to such a using setting it requires major changes in the using setting, such as training of doctors in treating patients with novel drugs and new distribution system due to other requirements of transportation etc. Any change affects the already activated resources within the using setting, and it inherits a cost. One important activity in relation to the using setting is the marketing and sales activities performed by the companies developing and producing these drugs. Companies need to convince doctors to prescribe novel drugs to patients. Usually novel drugs are set at a higher price due to their uniqueness, lead-time and high development costs. As a consequence not only users such as doctors need to be convinced to use the drugs but also the end-users, the patients, need to be convinced to pay for the new drug. However the end-users willingness to agree to use new drugs is very much related to the healthcare insurance system and payments of the drugs. Depending on their health insurance individuals are required to pay more or less for drugs; the more the individual patients need to pay for themselves, the more reluctant they will be to use a specific drug, i.e. the harder it will be to create a widespread use of the new drug.

The empirical example reveals the importance of having an active dialogue with the users when embedding a new solution. By having connections to potential users, the new solution can be suitable priced, and special features of the new solution can be enhanced etc. Connecting to users enhances the possibilities of attaining widespread use of the innovation (von Hippel, 1988; Oudshoorn and Pinch, 2003). It is important to consider both direct users but also end-users and resources indirectly affected by introducing a new solution to the using setting (Ingemansson and Waluszewski, 2009; Baraldi et al., 2011). The illustration also reveals that an introduction of a novel drug will likely in-

crease the costs and/or also the investments, and in order to embed the novel drug the estimated future revenue needs to exceed the increased cost or investment of the new solution. However, it is always difficult to estimate "return on investment" beforehand, much due to the fact that the features of the new solution that may affect positively or negatively are partly hidden and appear only through use (Rosenberg, 1994). The introduction of a new solution entails effects and changes on the existing product system; however, the new solution is also changed and adjusted in order to fit the established using setting (Latour, 1984; Van de Ven et al., 1999; Oudshoorn and Pinch, 2003; Yates, 2009). As mentioned any change of the existing using setting has a cost, and the organizations affected by the introduction of a new solution want to keep the cost and investment as low as possible. A new solution with minor differences compared with existing product system in use it will be easier to embed, than an innovation with large differences in relation to existing products in use (Håkansson and Waluszewski, 2007a; Ingemansson and Waluszewski, 2009). For instance embedding a generic biopharmaceutical drug will be easier than embedding a novel drug since it requires fewer changes of the existing using setting. However, the embedding of a new solution is also related to a learning curve: in the beginning the cost of treatment with new solutions are high but diminishes by use over time (Håkansson and Waluszewski, 2007a). One main issue when embedding a new solution in a using setting is therefore the economic effects it creates on the already activated resources. Therefore in reaching widespread use of a new solution, the interdependent users and related resources needs to be aware of the positive economic benefits of the new solution (Utterback and Abernathy, 1975; Håkansson and Waluszewski, 2007a). If "powerful" organizations within the using setting estimate the "return on investment" to increase with the new solution, it is more likely that the new solution will be accepted and embedded within the using setting. On the other hand, if "powerful" organizations estimate the "return on investment" to decrease with the introduction of the new solution, it is more likely that it will not be embedded in a using setting, and thus the innovation will remain an invention and fail to reach economic success. This highlights the fact that embedding a new solution is very much a matter of mobilizing others to support an introduction of a new solution and thereby create widespread use (Håkansson and Waluszewski, 2007a). This is also emphasized by Akrich et al. (2002a: 203f): "Innovation is perpetually in search of allies. It must integrate itself into a network of actors who take it up, support it, diffuse it." The less radical the innovation is in comparison with products already in use, the cheaper it will be embedded into a using setting due to fewer changes in the existing structure, while the more radical and novel innovation is the more costly it will be to embed due to major changes in the existing system (Håkansson and Waluszewski, 2007a; Ingemansson, 2010). Any new solution that can increase the revenue through increased sales volume, or reduce the cost through less in-put materials, or reduce investments such as using already existing production equipment and thereby have a positive economic benefits on the using setting and the existing product system at large will

more easily be embedded within the using system than a new solution creating negative economic effects such as increased costs due to changing routines or additional investment in production equipment, etc.

Embedding a New Solution in the Producing Setting

The producing setting sets the conditions to scale up the new solution and transform it into an actual artifact. It is within the producing setting that the manufacturing of solutions takes place, and the setting is very much directed by the already established producing structures consisting not only of the producing company itself but also the interrelated web of resources, such as suppliers, sub-suppliers, production equipment, production facilities, technologies, raw materials, etc. (Piore and Sable, 1984; Håkansson and Waluszewski, 2007a; Håkansson et al., 2009; Ingemansson and Waluszewski, 2009; Ingemansson, 2010; Baraldi et al., 2011). To able to produce a new solution large financial investments are necessary, for instance investments in production equipment, in new technologies, in new suppliers, and in training of personnel, etc. (Håkansson and Waluszewski, 2007a; Håkansson et al., 2009). However investments in establishing production result in major costs and loans over a long period of time. Companies need to show profit in order to survive and a main part of a company's expenses are related to production activities, and therefore one main issue of producing a new solution is to keep the production costs as low as possible and thereby keeping its estimated "return on investment" under control. Thus the economic pressure increases within the producing setting, and already made investments in physical facilities and equipment play a main role within the producing setting (Pisano, 2000; Ingemansson and Waluszewski, 2009; Ingemansson, 2010). *As a consequence when introducing a new solution within the producing setting the existing production system will be affected and "investments in place" need to be considered.*

To illustrate this further let us go back to the biopharmaceutical context and discuss the producing setting and the challenges associated with the production of biopharmaceutical drugs once again. In setting up production for biopharmaceutical drugs there are some issues to keep in mind. Any production of pharmaceutical drugs requires resources: first of all, a production facility is a must, a factory, where the actual production will take place. Secondly, the production facility must contain interlinked production equipment to perform the actual production of the drug. Thirdly, there has to be personnel to set up the production process and supervise the production process. Fourthly, there have to be in-put goods such as proteins, media, chemicals, solvents, etc. to be transformed into a drug during the production process. All these four main categories of resources are in turn related to other resources, for instance the production facility is dependent on a building entrepreneur, the production personnel needed are related to theoretical and practical experience and the in-put goods are represented by suppliers and indirectly also represented by the suppliers'

suppliers. However, the creation of biopharmaceutical drugs is more complicated since the production needs to correspond to the strict sanitary regulations put up by the US FDA or other country-specific agency. Under these specific biopharmaceutical conditions, imagine a producing company with an established production of a generic drug wanting to direct its business to include a novel biopharmaceutical drug. In such a situation major changes in the established production system are required, such as investment in new production equipment along with changes of the relationships with suppliers and sub-suppliers and training of personnel etc.

The example reveals that the production setting is very much related to large financial investments in physical resources such as production facilities, production equipment and in-put goods. It is therefore easy to understand that the producing setting is strongly affected by already made investments, i.e. what is sometimes referred to as "heavy business processes" (Håkansson and Waluszewski, 2007a: 147f). Setting up production is about creating efficient production by using production equipment and production personnel in the best possible way, for instance reducing the number of interruptions during the production process or minimizing waste by adjusting production equipment. By creating efficient production the company can reach economies of scale and thereby decrease the cost for each unit produced. However the high regulatory demands on biopharmaceutical drug production result in large financial investments such as expensive high-end sanitary production equipment. The example also reveals that the producing setting is not only an internal issue of the producing company but also to a large extent an external issue, where other companies and organizations affect the production structure by supplying equipment, facilities, personnel, knowledge, regulations, etc. As a consequence actors other than the producing company have major effects on the producing setting due to the fact that there are a wide range of interdependencies between a variety of organizations (Ingemansson and Waluszewski, 2009). A new solution that creates minor changes in the established production structure is more easily embedded in a producing setting then a solution creating major changes (Gadde and Håkansson, 1998; Håkansson and Waluszewski, 2007a; Håkansson et al., 2009). One way to control the estimated "return on investment" when starting production of a new solution, already made investments, "investments-in place" (Utterback and Abernathy, 1975: 21) need to be used to the fullest extent. Introducing a new generic drug instead of a novel drug would entail only minor changes to the production structure in terms of additional costs of the new solution (for instance the necessity of new production equipment or training of the production personnel, etc.); thus the estimated "return on investment" would be controlled. However, even though novel drugs may result in increased costs and investment, these can create higher revenue compared to generic drugs due to higher margins or great demand from users of a certain drug. Therefore if the estimated revenue of a new novel drug exceeds the investment needed to produce a novel drug, it is more likely that the new drug will be embedded into a producing setting. Thus when embedding a new solu-

tion in the producing setting, already existing production structures need to be considered since any new solution entails changes. Any change will create a cost, whether it is the establishment of a new supplier relationship or the need to train employees. However, this cost needs to be considered in relation to the estimated revenue from the new solution.

Embedding a New Solution in the Developing Setting

Being able to use and produce a new solution also requires a development of the actual solution. It is in the developing setting that the development takes place, where new solutions are discovered, developed and brought forward. When developing a new solution, resources are combined and re-combined, and the aim is to find "seeds" to new solutions that can be transformed to functioning artifacts to be used in one way or the other (Håkansson and Waluszewski, 2007a; Ingemansson and Waluszewski, 2009; Ingemansson, 2010; Baraldi et al., 2011). *In developing new solutions the aim is to find new combinations and to transform these new combinations and knowledge into something more, into a functioning solution that can be further combined and used with other resources.*

In discussing the developing setting let us once again illustrate it with empirical examples from the biopharmaceutical context. In developing biopharmaceutical drugs university departments, research institutes or R&D departments plays a significant role. They are in charge of discovering new combinations of molecules to be transformed into drugs. Developing biopharmaceutical drugs is highly uncertain due to the fact that the drugs are based on living organisms along with the fact that much of the human body is still unknown. Finding new target molecules is a difficult and uncertain process; however earlier research acts as a guideline regarding what targets to search for. The search for new molecules and further development of the molecule structure into a new solution entail several developing activities: from identifying new drug targets, selecting specific drugs targets to be further developed, validating safety and activity of the drug to setting up clinical trials of the new drug. These developing activities are mainly about gaining more knowledge and reducing the uncertainty associated with the drug. Since the developing of new drugs involves a number of activities it also includes a wide range of resources such as scientist from different disciplines (biologists, biochemists, computer analysts, etc.) and a variety of equipment (screening equipment, purification equipment, computers, etc.). (Pisano, 2006)

As the empirical illustration shows, the developing of new drugs takes place in close connection to internal and external "knowledge units." These units consist of personnel with experience in combining resources in new ways and thereby creating new solutions. However, the knowledge units are dependent both on the education system, where theoretical skills related to the developing of new drugs are provided but also on the business climate, where practical experiences are provided. Even in the biopharmaceutical context the devel-

opment departs from old knowledge when searching for new knowledge and new solutions. However the concentration of "newness" within the new solution compared to earlier developments varies, from very strong concentration of the new to very weak concentration of the new. Radical solutions are more uncertain both in terms of estimating the future "return on investment" and in terms of producing and using it, while incremental solutions are easier to estimate along with relating it to production and use (Ingemansson and Waluszewski, 2009; Ingemansson, 2010).

However, knowledge units in driving the development of new solutions can vary in their characteristics: for instance, a large majority of academic knowledge units are focusing on developing activities related to basic research, while others are focusing on developing activities for applied research, developing solutions for a specific industry with a specific purpose. Depending on the type of development activities the knowledge units are closer to or further away from the producing and using of the new solution that affects the innovation journey at large. Basic academic knowledge units put main emphasize on creating new knowledge, not the possibilities of transforming the knowledge into a commercial solution. In a scientific context new radical scientific discoveries are appreciated and rewarded and radical discoveries enhance the possibilities of getting published, which is the main evaluation criterion for obtaining future grants. If the developing setting is science, it is the scientific community that decides the value of the new solution and if the new solution can be of scientific significance. (Ingemansson and Waluszewski, 2009; Ingemansson, 2010) Through publications others can use and spread the discovery and thereby enhance funding for future research. A common problematic issue with developing a new solution is vague ideas of what already exists, for instance in terms of existing production and products systems; thus there are problems in relating the new solution both to a producing and a using setting. However it is important to emphasize that the developing process is not only limited to the academic world but also stretches to the industrial world. One main source of new solutions and new innovations are supplier-customer relationships (Lundvall, 1985; von Hippel, 1988; Håkansson, 1989), where R&D departments play a significant role in finding new functionality of new solutions.

Innovation a Process of Handling the Differences between the Using, Producing and Developing Settings

It becomes evident that any new solution is greatly affected by what already exists; thus each setting (the using, producing and developing) is part of an activated resource structure set up by companies, organizations, products, technologies, etc. (Utterback and Abernathy, 1975; Rosenberg, 1994; Håkansson and Waluszewski, 2007a). As a consequence, one main aspect of embedding a new solution is relating it and adapting it to already activated resources. How-

ever, the above discussion also reveals that the settings differ in their character and that using a new solution may be very far from producing or developing it. Since the three settings vary in their economic logic and it is impossible to have a "total fit" between the settings, these differences are evident in any innovation journey, and it is in fact a matter of learning how to handle these differences in the best possible way. The new solution needs to be developed in close relation to knowledge units such as research institutes, R&D departments including experiences personnel and scientists, and the new solution needs to be transformed into an artifact in a producing setting affected by an established producing system including production equipment, suppliers, production personnel, etc. The new solution also needs to be embedded in a using setting structured around an activated product system related to companies, equipment, etc. However the innovation process is not linear but rather stretches between and across the developing, producing and using setting. To diminish the tension between the different settings, interaction between the settings is a key issue. Pisano (1996; 2000) highlights the importance of the developing and producing settings and pleads for increased and further interaction between these to facilitate the innovation process, especially in novel environments. Imagine a producing company establishing a new production process for a new solution, by employing a scientist involved in earlier development of the new solution; connections and interaction between the developing and producing setting are thus created. However, interaction between organizations in different settings is handled rather differently depending on the surrounding business landscape. Therefore the next section will discuss different business landscapes and their effect on business exchange and the innovation journey in particular.

Innovation in Different Business Landscapes

As I have discussed innovation is about combining resources across organizational borders. However, any new solution is developed, produced and used within a certain business landscape. By the business landscape I mean the surrounding context that sets the conditions for any business exchange and thus affects the development of any new solution and its possibilities of being produced and used. A main characteristic of any business landscape is that it is imbued by *interdependence*; all companies are dependent on other organizations on the supplier and user side in order to perform business (Rosenberg, 1982; Håkansson, 1987; Hughes, 1989; Rosenberg, 1994; Ford et al., 1998; Gadde and Håkansson, 2001; Gudeman, 2001; Håkansson and Waluszewski, 2002; Håkansson and Snehota, 2006; Waluszewski and Håkansson, 2007; Håkansson et al., 2009). By connecting to others, companies can combine resources, such as certain equipment, knowledge or capital. In order handle this interdependency, companies need to *interact* with other organizations; thus through interaction interdependencies can be used in order to create benefits. Therefore all

business exchanges within any business landscape are related to these interdependencies and handled through interaction. Or as Ford and Håkansson (2006a: 12) conclude: "A key aspect of business interaction is the building, managing and exploitation of interdependencies over time."

If we look closely at the innovation literature, a majority of it is based on investigations in western countries where a relatively free market system exists and decentralized interaction is allowed. This kind of business landscape can be referred to as the "market-based" business landscape. The market-based landscape is very different compared with the empirical setting of this thesis, the Chinese business landscape, where a plan economy dominated and directed business exchange during a main part of the 20th century. Thus in the following sections I discuss how resources are combined in a market-based business landscape and compare it to how resources are combined in a business landscape within a transition economy like China. Even though the business landscape may differ "…there only exists one general mean in an economic world characterised by different rationalities and that is interaction" (Waluszewski and Johanson, 2008: 16). Thus, interdependency between organizations are important in any business landscape, although these interdependencies are handled through interaction rather differently depending on the specific conditions of each business landscape (Gudeman, 2001).

The "Market-based" Business Landscape

The main characteristics of innovation in a market-based business landscape can be characterized as "decentralized," where innovation are the result of interaction on a company level (Håkansson and Waluszewski, 2007b; Waluszewski and Johanson, 2008; Håkansson et al., 2009). In such a landscape companies can interact with each other relatively freely without restrictions from organizations on the central level, such as government authorities. By interacting with other companies, resources can be combined and re-combined over organizational borders. Through interaction companies gain access to and learn more about the resources within the business landscape. For instance through interaction with others, companies can generate information on how a producing company can use customized production equipment or information on what features end-users want from a certain product etc. In a market-based landscape decentralized interaction is taken for granted based on the basic assumption that it is the companies themselves that can combine resources in the best possible way. Thus free and direct interaction is the basis for business exchange in a market-based business landscape, and through interaction companies can make the most of the resources at hand. Of course companies can be more or less hierarchically organized but the companies themselves (top-management or not) are responsible for initiating contacts and establishing cooperation with their customers and suppliers. During interaction processes,

resources such as products, components, knowledge, employees, equipment, etc., are combined and new solutions are developed, produced and used.

As a result of interaction concerning how to utilize and adapt resources across company borders, long-term relationships tend to emerge. Thus in a market-based business landscape relationships constitute a main part of companies revenue, and established relationships can be viewed as a company's main asset (Håkansson, 1982). Due to the interdependency with others' resources, "thick" interaction processes are a main ingredient of the business landscape (Håkansson et al., 2009). These interdependencies can be of varying kind such as technological interdependency that can for instance intervene in any attempt to change components already in use; social interdependence can for example influence how the customers' customer is using a new solution; and economic interdependency may be obvious when one important supplier is closing down (Johanson, 2001). On the one hand, these interdependencies create stability, but on the other hand the ongoing adaptations between organizations also create a constant change and motion within the business landscape. Thus, the content of relationships between established suppliers and customers is always changing and in motion, although this motion and change are directed by the existing interdependencies, and thus the established stability of the business landscape sets the rules for and acts as the framework of any change. (Håkansson et al., 2009) Interdependencies within the market-based business landscape create restrictions on what types of resource combining are possible; for instance using certain equipment for R&D purposes may direct the future use of certain production equipment, although it can also creates possibilities in creating new solutions when hidden features of a resource are revealed through interaction (Håkansson and Waluszewski, 2002; Håkansson and Waluszewski, 2007a).

To summarize, the market-based business landscape is imbued by interdependence that is handled through decentralized interaction and new solutions often emerge as a result of a problems-solving process between established counterparts, but the new solution needs to be embedded into producing and using setting characterized by a number of material and immaterial resources that are adapted to each other. (Håkansson and Waluszewski, 2007b) Thus innovation in a market-based business landscape is often initiated by a specific set of companies, but in order to successfully scale up a production and spread the use of any new solution it is necessary to adjust to what already exists in terms of already activated resource structures.

Between Plan and Market: The "Transition" Business Landscape

Due to the fact that the Chinese business landscape has been directed by a plan economy over a long period of time, it is rather different in terms of basic conditions for business exchange and innovation, particularly in relation to the market-based landscape characterized above. Although both landscapes are

imbued by interdependence between organizations, the interaction processes where these interdependencies are handled can be characterized quite differently. In a business landscape directed by a plan, interaction processes are steered by a central government planning apparatus; thus interaction processes can be characterized as "centralized" and handled from top-down (Nee, 1992; Johanson, 2001; Lu and Lazonick, 2001; Waluszewski and Johanson, 2007; Waluszewski and Johanson, 2008). The planning units are in charge of handling and allocating resources between organizations such as suppliers and customers. All business is directed by quotas set up by the government and administrated through the planning units that supply the production companies with resources such as raw materials from "unidentified" suppliers; the planning units are also in charge of delivery of the products to unidentified customers. Thus business exchange is allocated through the government planning apparatus from pricing of the products, to delivery, to quantities, etc. Since interaction is handled through the planning authorities, interaction between companies such as suppliers and customers is always indirect. Interaction across organizational borders is therefore limited and restricted and is always steered by the government. As a result companies have very little knowledge and information outside of company borders (Johanson, 2001; Waluszewski and Johanson, 2008); thus the need of the users in terms of quality, quantity and prices, etc., are "unknown" to the supplying companies. The planning units play a key role in providing information between suppliers and customers, and the planning units "mediate" between companies, although the companies have very limited knowledge of their counterparts. As a result companies within a planning system rely on the planning units for getting as much information about their counterparts as possible (Waluszewski and Johanson, 2008). The companies in a plan economy could be characterized as "passive" in relation to external organizations, in the sense that they can only react to the information and directions supplied by the planning units (Liu and White, 2001). The companies can only actively adjust and combine resources that are internal to the company (Waluszewski and Johanson, 2008). Thus, the business landscape in a plan economy can be described as a "well-defined hierarchy" (Johanson, 2001: 81) where "…the redistributive firm (weather a collective or a state-owned enterprise) operates as an appendage of the state, responding to commands sent down from the central ministry, provincial bureau or local government" (Nee, 1992: 7). Since all business exchange is decided and controlled by the government, so is the issue of innovation. Therefore innovation in a business landscape directed by a plan economy is never an initiative of the individual companies or the end-users but instead a decision from above to be implemented and performed step-wise on lower levels of society (Fischer, 1984; Fischer, 1989; Liu and White, 2001; Lu and Lazonick, 2001; Waluszewski and Johanson, 2007; Waluszewski and Johanson, 2008). Under a plan economy the central government is seen as the best provider and allocator of the resources at hand, not the companies and organizations themselves.

These typical characteristics of business exchange in a business landscape under a planned economy have been a reality in China and become obvious in the study by Lu and Lazonick (2001) investigating the innovation of Chinese Electronic Printing System (EPS) from the 1970s to the 1990s. During the planning era, the innovation process was a top-down activity, initiated by top bureaucrats within the central government, further connected to lower levels of the government, the fourth Ministry of Machine Industry, where a coordinating office, Office 748 was set up to coordinate the innovation project. The ministry appointed Beijing University to conduct basic research for the new solution, along with appointing the largest press agency, Xinhua News agency, as the testing site for the new solution; to provide the new laser system along with soft- and hardware a large SOEs was contracted. According to Lu and Lazonick (2001: 56) this could be described as a typical large-scale innovation project during the planning era with characteristics such as: "…financial commitment from the state, direct government involved in organization and coordination, and cooperation among research institutions and industrial enterprises—both producers and users—across organizational boundaries." Thus this innovation process was a result of a hierarchical system where each company and organization was allocated specific assignments from the government. Business exchange and innovation in particular is characterized by "limited and restricted" interaction processes under the planning era in China. Direct interaction between research institutes and companies were rare. Research units (under the Chinese Academy of Science (CAS)) and companies only interacted directly with the government units appointing the research units certain research projects and companies production assignments of new solutions (Lu, 2001). The companies themselves were not allowed to initiate the development of new solutions; moreover the research units were not allowed to participate in the production of any new solution (Fischer, 1989; Liu and White, 2001; Lu, 2001). Thus it was a clear division of labor between developing a new solution, producing and using it. Liu and White (2001) emphasize that it was the government that had main control of both the internal resource-combining activities within research units and companies but also the external resource-combining activities between these units. Thus companies and organizations "… depended on top-down allocations for necessary inputs, whether personnel, technology, capital, intermediary inputs, or other resources. As a result, they had to excel linking activities with central government bodies" (Liu and White, 2001: 1098). This reflects that companies and organizations could not be "proactive" but instead "passive" recipients of directions from the government along with the fact that no direct interaction existed between organizations; instead the developing and producing organizations could only interact indirectly through the government planning authorities. Due to the lack of interaction between research units and companies China relied a great deal on imported technology when innovating during the planning era (Liu and White, 2001).

With the introduction of the "open-door policy" in 1978 the planning system has been successively dismantled and a Chinese version of market system, a "socialistic market system" has been introduced, which combines a strong government involvement in business with free market influences. Along with the transition from a plan economy to a socialistic market system conditions for business exchange and innovation changed in China. The main change from the planning era is the changed role of the Chinese government during the transition. Business exchange changed from being a top-down centralized activity to a more decentralized activity where companies and organizations themselves took charge of resources and the combining of resources across organizational borders (Liu and White, 2001). During the transition organizations were encouraged and allowed to interact directly with their counterparts, and thereby companies became accountable for their business (Ibid). As a result companies and organizations did not depend on government approval for activities such as development of new solutions or investment issues (Lu, 2001). Thus the dependence on the government for business exchange gradually diminished (Nee, 1992). As a result companies could interact directly with their suppliers and customers and resources could be combined at decentralized levels, i.e. the company level. However, the Chinese government still plays a significant role in Chinese business, but the role of directly controlling and allocating resources between companies has changed and instead the government has a more indirect role in affecting business exchange. Indirectly the government affects business by issuing policies, programs, funds, establishing institutions, adjusting taxes, etc. (Lu, 2001; Lu and Lazonick, 2001). But the government still has a direct role in business since many companies are under government control, such as venture-capital firms, SOEs etc. Especially important for spurring science-based innovation is the increased government attention towards the establishment of an innovation system, where companies, research institutes and universities are main components and fueled by governmental funds (CAS, 2003). Within the "transition" business landscape the Chinese government is also steering Chinese business towards novel innovation, where the new innovations should be innovations originally developed in China, not merely incremental innovations, imitations and technology transfer common during the command era (von Hippel and Jin, 2008).

As the above discussion reveals the Chinese business landscape is rather different than the market-based landscape that is constituted by thick, decentralized and unrestricted interaction processes. China is instead a transitional economy, both imbued by planning and market elements affecting business exchange. Still the Chinese business landscape is affected by "limited" interaction processes due to the planning tradition; also the Chinese government intervenes in business exchange, though more indirectly than before.

In order to capture innovation processes in China I need to be aware of these specific conditions of the Chinese business landscape, and this requires a theoretical tool that can capture the special characteristics of the Chinese business landscape. I need a suitable tool that can reveal the resource-combining

processes that are not always direct and decentralized but also indirect, informal, centralized and hidden across organizational borders within and between the using, producing and developing settings. Also due to the strong influence from the Chinese government I also need a tool to reveal how government units are involved in the innovation processes, whether these government units are at the centralized level, setting up policies and institutions, or government units directly involved in business exchange on a company level. In the following section I will go deeper into a discussion of suitable theoretical tools in revealing the innovation processes in a Chinese context by arguing the usefulness of using the IMP research tradition along with the 4R model as a basic theoretical tool for answering the research question.

The IMP Research Tradition as Theoretical Base of the Thesis

Business exchange and business development has been discussed by researchers within the IMP research stream since the mid 1970s.[6] Based on empirical research findings, the researchers opposed the prevailing economic thinking, where suppliers were seen as active and customers as passive, where business exchange only were determined by lowest price, where business exchange was only related to homogeneous products and independent business exchange (Ford and Håkansson, 2006b). Instead IMP researchers discovered through empirical studies that the business landscape was imbued by interdependence across organizational borders (Hägg and Johanson, 1982; Håkansson et al., 2009).

A first development of an equivalent analytical tool was *the Interaction Model* (Håkansson and Östberg, 1975; Håkansson, 1982), which was based on the assumption that the business landscape was characterized by a limited number of stable relationships between companies. The main contribution of the interaction model was its ability to analyze dyadic long-term relationships between two companies. Four elements could be analyzed as affecting the focal dyadic relationship: the environment surrounding the relationship for instance market structure and social systems, the atmosphere reflecting the power and dependence between the companies, the interacting parties which are the companies at the fore of the relationships both reflecting the organizations itself along with the individuals representing these, and finally the interaction process

[6] IMP researchers have been influenced by researchers in inter-organizational studies emphasizing the interdependency between actors and organizations such as March and Simon (1958) and Levitt and March (1988). For an overview see Håkansson and Waluszewski (2002) and Johanson and Mattson (2006).

itself where both short-term business exchange and long-term relationship could be analyzed (Håkansson, 1982). Along with the interaction model came one important insight, the fact that interaction between the parties not only shaped the interacting companies themselves but also the products exchanged. Thus a product's features and characteristics are dependent on the relationship between the two companies (Håkansson and Waluszewski, 2002). By using the interaction model it was possible to analyze the "in-betweenness" of business exchange, more specifically how resources could be combined between two companies. Due to the fact that companies establish long-term relationships and become more dependent on each other over time Håkansson (1982: 394) conclude that: "Instead of free moving units within a market we have companies with very little freedom to move."

IMP researchers continued investigating business exchange and business development and found empirical evidence that companies are not only linked dyadically but also through an even wider network of relationships, for instance the resource combining process can be affected by other companies than the focal buyer and supplier such as the buyers' buyer or suppliers' supplier. As a consequence of these findings IMP researchers presented a new model, *the Network Model or the ARA-model*, where the larger network of business relationships could be analyzed (Håkansson, 1987). The model constituted of three interdependent parts of a relationship; actors, resources and activities, thereby the abbreviation ARA, which can be identified as:

> "Actors are defined as those who perform activities and/or control resources. In activities actors use certain resources to change other resources in various ways. Resources are means used by actor when they perform activities. Through these circular definitions a network of actors, a network of activities and a network of resources are related to each other." (Håkansson, 1992: 1)

More specifically actors refer to companies involved in business exchange that control resources such as money, knowledge, equipment, etc., both individually and in cooperation with others. The companies perform activities by using resources; for instance in production resources are changed and combined through activities performed by the companies. The model could capture relationships on three levels, the individual company, the dyad and the network (Håkansson and Snehota, 1995). However, the model only accounted for already established relationships, which called for the development of a model with the capacity to investigate business exchange between companies having no established relationships (Håkansson et al., 2009). As a way to analyze business exchange without having a focus on established relationships, Håkansson and Waluszewski (2002) presented a new analytical model, *the Four Resources Model* (4R model). The model puts emphasize on one of the elements in the ARA-model, the resource element, since multifaceted resources are seen as the cornerstones of all business exchange (Håkansson et al., 2009). The 4R model is further discussed in the next section along with a deeper discussion on the im-

portance of resources when investigating change processes such as innovation processes.

The 4R Model as Main Theoretical Tool

The model was developed to go a step further, from investigating established business relationships as the main unit of analysis as in the case of the interaction and ARA-models. Nevertheless, business relationships are not ignored in the 4R model but rather treated as one of companies' most valuable resources. Just as the name of the model suggests there are four resource elements in the fore. Two types are technical in their character, products and facilities, while two are more social in their character, organizational units and organizational relationships (Håkansson and Waluszewski, 2002). The product element refers to any artifacts exchanged between organizational units (Wedin, 2001; Håkansson and Waluszewski, 2002; Baraldi, 2003). Products can be very different in character, such as raw materials, components, etc. The features of any product are determined by the interaction with other resources; thus the organizational units exchange products through organizational relationships which leave imprints on the products exchanged. Facilities are resources referring to any physical artifact (equipment and good) used in transforming products; thus facilities are related to activities such as production, distribution and logistics (Wedin, 2001; Håkansson and Waluszewski, 2002; Baraldi, 2003). For instance, factories with production equipment are important facilities in assembling and putting together several components into a final product. A product is therefore produced in a production facility set up by interlinked equipment, and thereafter the product may be further processed in the customers' production facilities. Organizational units can be described as a part of an organization or company (Wedin, 2001; Håkansson and Waluszewski, 2002; Baraldi, 2003). Compared to facilities, organizational units are intangible in their character inheriting social elements such as knowledge, routines, experiences, etc. Organizational units are represented by individuals and personnel, and, since the unit is developed over time, it gains experiences and expands its knowledge in interaction with other organizational units through organizational relationships. Thereby organizational relationships are used by organizational units to achieve certain activities (Wedin, 2001; Håkansson and Waluszewski, 2002; Baraldi, 2003). Also, organizational relationships are social in character, and the relationships are the result of interaction between two units or more. Over time the interacting units adapt to each other, and routines are established between the units. As the discussion show the four types of resources are affecting each other in numerous ways and development takes place as a result of the resource interactions between the four resource elements.

Since 2001 several studies have used the 4R model in analyzing how resources stretches across organizational borders, how resources are developed over time and space, along with how resources play significant roles during

change processes; see, for instance, Wedin (2001), Håkansson and Waluszewski (2002), Baraldi (2003), Gressevold (2004), Jahre (2006), Baraldi and Strömsten (2008), Hoholm (2009), Ingemansson and Waluszewski (2009), Shih (2009), Wagrell and Waluszewski (2009), Waluszewski et al. (2009), Håkansson et al (2009), Ingemansson (2010), Ciabuschi et al. (2012). For an overview see Baraldi et al. (2012). Having the 4R model in mind, let us go deeper into the characteristics of resources through important concepts such as *resource heterogeneity, resource embeddedness, and resource interfaces* and their connections in analyzing the innovation process.

The Importance of Resources When Investigating the Innovation Process

Resources have been pointed out as important for business exchange in the IMP research community for a long period of time. Snehota (1990: 173) defines a resource as: "A resource is an element, material or immaterial, that can be used for some purpose. It is the purpose that makes an element become a resource and no element, material or not, is a resource without a known purpose." Thus in order to be considered as a resource it has to have a "use" or "known purpose." Another main feature of resources is the fact that they are viewed as being heterogeneous in their character. The notion of *resource heterogeneity* originates from Penrose (1959) but also Alderson (1965) refers to heterogeneity and "the perfect heterogeneous market." A company is viewed as a bundle of heterogeneous resources to be activated to perform business (Penrose, 1959). Johanson (2001) points out three main characteristics of why and how resources are heterogeneous: First of all, resources differ due to their nature, for instance, raw materials such as wood differ fiber by fiber; also, resources differ due to the use of these raw materials, different actors use the fibers differently, so the final product will therefore differ. Finally, resources differ due to changes both in time and space, when the raw material is processed by one unit within a saw mill then transported to another unit for further processing of the raw material, the resources changes but also its use. The main contribution of Penrose (1959) is the insight that resources themselves are useless and have no value until they are combined with other resources. It is in the resource-combining process that the value and features of the resources at hand are revealed. Thus, a bundle of heterogeneous resources is linked to an "infinite" bundle of possibilities. Due to the possibility of combining resources, a resource's features are hidden and never fully exposed; thus it is impossible to have full knowledge and information about the resources at hand, which reflects that the business landscape is not fully controllable and thus imperfect. In combining resources the value is more than the sum of its individual resources. One main activity for companies is to combine resources in the best possible way or as Alchian and Dementz (1972: 793) put it: "Efficient production with

heterogeneous resources is a result of not having better resources but in knowing more accurately the relative productive performance of those resources." However, the more technically complex the resources are, the greater is the need for resource-specific knowledge to use and combine them in an efficient way (Hägg and Johanson, 1982). Due to the fact that resources are combined over time, resources always bear the mark of history or earlier resource combinations. Thus, the longer the "history" of a resource, the more embedded the resource is to other resources, i.e. the more dependent it is on other resources, such as companies, products, equipment etc. (Håkansson et al., 2009).

Embeddedness is a common term especially among empirically based researchers in describing economic organization. It reflects the fact that any resource (company, product, facility, knowledge, etc.) is embedded with others in different ways due to the interdependency of the business landscape. We can divide *resource embeddedness* into three different types: social, technical and economic embeddedness. Social embeddedness refers to the fact that any resource is not only part of an economic context but also embedded in a social context that affects business exchange (Granovetter, 1985). Thus, companies that interact and are engaged in business exchange are also embedded in a social context shaping the business exchange and shaping the features of the resources at hand. For instance, biopharmaceutical drugs are socially embedded in a strict regulator environment consisting of regulations that lend certain features to the drug. A type of social embeddedness important in the case of biopharmaceutical drugs is therefore political embeddedness (Sun et al., 2010), where government units play a significant role in setting up regulations. Resources are also technically embedded in each other (Ford et al., 1998); for instance in order to produce a new drug the producing company needs to invest in a variety of production equipment supplied by several suppliers and the production equipment needs to be adjusted and interlinked in order to set up an efficient production process. Moreover, resources are also embedded economically: companies interact and combine resources and over time become economically dependent on each other; usually a limited number of customers account for the majority of a company's' revenue (Håkansson, 1989). Thus resources are socially, technically and economically embedded in each other, but it is important to remember that all these three types can affect each other in all possible directions (Baraldi, 2003), i.e. the economic embeddedness affects the social and the technical, and the other way around.

As mentioned an innovation process can be seen as a process where a new solution is embedded in three different settings: the developing, producing and using settings, each setting is part of an already activated resource structure. Therefore a new solution cannot be analyzed in isolation but has to be considered as the result of many interacting resources. In revealing resource embeddedness the concept of *resource interfaces* can be used. It is through resource interfaces that resources gain features, characteristics and values (Wedin, 2001; Håkansson and Waluszewski, 2002; Baraldi, 2003; Baraldi and Strömsten, 2006; Baraldi and Strömsten, 2008). Thus it is through resource interfaces that re-

sources "rub off" on each other. Interface can be described as: "…the specific contact points between two resources, defined along relevant technical (shapes, weights, materials etc.), economic (cost, prices, etc.) and social (skills, preferences, power, etc.) dimensions" (Baraldi, 2003: 18). Due to the fact that resources interact and are combined, resources also affect each other technically, economically and socially. Resource interfaces are results of resource-combining across organizational borders. For instance, a specific component is affected by the technical resource interface between the company producing the component and the equipment used at the customers.' In order to fit the production equipment at the customer the component needs to be adjusted to the customers' production equipment; thus the components design is decided by the technical resource interface between the producing company and the customers' production equipment. Therefore when studying innovation processes resource interfaces will not only include the interaction between companies and products but also the effects they have on each other. Resource interfaces can be of different characteristics, some more weak relating simple resources to each other, while others can be more profound, when two uniquely-designed resources are dependent on each other and co-developed (Baraldi and Waluszewski, 2007). Resource interfaces can also be direct and indirect: direct when connecting two resource elements and indirect when connecting two resource elements to a third one (Baraldi and Strömsten, 2006). Thus by focusing on resource interfaces, it is possible to capture the resource-combining process of both technical (products and facilities) and social (organizational relationships and organizational units) resources between organizations. Moreover through resource interfaces it is possible to capture the embedding of a new solution in the developing, producing and using settings.

Summing Up: Resource Interfaces to Capture the Embedding of a New Solution in the Using, Producing, and Developing Settings

The thesis investigates how Chinese biopharmaceutical drugs are created. As suggested, any new solution needs to be embedded in three very different settings: the using, producing and developing settings, in order to be called an innovation. The innovation itself can be seen as a resource spanning all three settings. Since the innovation process can be seen as a process where resources are combined and re-combined in three different settings across organizational borders, I need to investigate how resources are combined and connected between companies and organizations. Since the Chinese business landscape differs compared to other western business landscape, I need to take this into account when approaching drug innovation processes in China. Typical characteristics are centralized, limited and restricted interaction processes along with

strong government involvement. Thus my theoretical tool needs to be able to grasp resource combining processes that are not only direct and decentralized but also limited, indirect and hidden, whether these stem from centralized government units or government units at decentralized levels. By using the 4R model as a main theoretical tool, it is possible for me to capture how these resources are combined. The four resource elements – products, facilities, organizational units and organizational relationships – are brought to the surface through the concept of resource interfaces, revealing what other resources the new solution encounters when embedded within the using, producing and developing setting. Thus, I use the 4R model as a research tool to explicate/extricate the complexity of embedding a new solution by looking at the new solutions' relation to other resources through specific resource interfaces spread within and between the using, producing and developing settings.

CHAPTER 3: METHOD AND METHODOLOGICAL CONSIDERATIONS

This thesis focuses on gaining understanding of biopharmaceutical drug innovations in China. But how is it even possible to investigate drug innovation processes in such a large country as China? How is it possible to catch innovation processes in a country with such a complex business structure, where the political dimension always is present, albeit not always in an outspoken way. And last but not least, how is it possible for a foreign researcher to investigate what is going on in the interface between companies and organizations in a country like China. The following chapter is devoted to describing how I made the research question "researchable," i.e. the research journey and its connection to method and methodology issues. Although the presentation of this research journey is described as somewhat linear, it is important to remember that the collection, presentation and analysis of data have been a simultaneous process.

Background and Starting Point of the Thesis Project

After years of studying Chinese in both China and Sweden along with working in China I returned to the university with the ambition to get a deeper understanding of the changing Chinese business landscape due to the abandonment of a plan economy in favor of a "socialistic market economy." It was a conscious decision to get in contact with my former supervisor from the undergraduate level, Alexandra Waluszewski, and her research group, when returning to the academic world, for several reasons. First of all this research group, since 2004 located to the Science & Technology Studies (STS) Centre at Uppsala University, was working within the industrial network tradition, the so-called IMP tradition, where development processes, such as technology and product development processes along with innovation processes have been a central theme for a long period of time. Within the IMP tradition business activities, including innovation processes, are viewed as interaction processes between companies and organizations where resources are exchanged. Already as an undergraduate I was interested in technology development and industrial networks, and my master thesis evolved around the reinvestment in a paper machine and its implications on new product development. Thus I was already

familiar with the IMP research tradition and its basic and underlying assumptions. Secondly, when analyzing technology development in the paper industry I was introduced to the 4R model developed by Håkansson and Waluszewski (2002), which also is the main theoretical research tool used for this thesis. However at that time, in 1999/2000, the model was still under development and not yet published. Thus, before starting this thesis project I already knew the basis of the model and how it could be used and what advantages it had. Finally, the theoretical approach also corresponded to my own empirical experience. In my practical work, first working as a purchaser in a large research institute in Sweden, followed by working in a purchasing office in Shanghai on behalf on a Swedish department store, along with establishing new lingerie brands in Chinese department stores, I was constantly engaged trying to understand how to utilize resources in the best possible way, something that meant that I had been developing relationships within and across the organizations I was working in. To conclude, I approached my current research group because I knew that the research themes within the group would fit my interest for investigating development processes in line with the IMP tradition.

Thus, I started this doctoral thesis with a view of innovation processes very much colored by experiences from the IMP and related research traditions such as large technological systems (LTS), lead-user research approach along with history of technology represented by researchers such as Hughes, von Hippel, van de Ven and Rosenberg. These researchers view innovation as a non-linear process, part of a large system of interactions between companies and organizations across time and space (for more information see Chapter 2). Thus, the whole thesis, i.e. delimiting the research questions, collection of empirical data, penetration and presentation of empirical data and the analysis, is directed and affected by this way of framing innovation. Or as Waluszewski (2004: 97) puts it: "…the outcome of any investigation is the result of the interaction between certain empirical phenomena and the tools used to investigate them" and continuing "…the only aspects we can see are those that our research tools allow us to capture" (Waluszewski, 2004: 97). Through my research group I got involved in a larger research project concerning the development of the biotechnology industry in Uppsala and during my first months as a doctoral student I did a follow-up study on the development of biotechnology companies in the Uppsala region. This first biotechnology study gave me some basic insights concerning the development of biotechnology in general but also detailed information about the biotechnology industry in the Uppsala region. More importantly, due to my participation in the research project I also became aware of how the largest biotechnology equipment supplier in Uppsala, GE Healthcare, was related to the biotechnology industry in other regions than Uppsala. GE Healthcare is world leading in supplying biotechnology instruments to the biotechnology industry worldwide, including my country of interest, China. I realized that through my contact with GE Healthcare, I could learn more about the Chinese biotechnology industry in general – and also gain access to Chinese biotechnology companies involved in creating new biopharma-

ceutical drugs. I learned more about the historical evolution of the biotechnology industry in China, mainly through secondary sources, and realized that the Chinese government has invested a lot in both Chinese biotechnology science and business over the last decades as the Chinese government considers the biotechnology industry a future high-tech industry important to create economic growth. Therefore the Chinese biotechnology context would be an interesting empirical setting in which to investigate not only drug innovation processes per se but also the connection between the government promotion of biotechnology and its imprints on biopharmaceutical drug innovation on a company level. As a result I decided to focus on studying innovation processes within the Chinese biopharmaceutical context.[7]

In order to be able to capture innovation processes in a Chinese biopharmaceutical context I needed a suitable methodological approach to somehow delimit the study. Thus, a key question was how to make such a large research question concerning the creation of biopharmaceutical drug innovations in China "researchable." The basic point of departure for finding a suiting methodology was the 4R model. More specifically I choose a focal product, a specific instrument that is used in the phase where biopharmaceutical development projects are reaching the pilot scale; i.e. when it is going to be transformed from a development project to be embedded into large-scale production and use. The product, labeled ÄKTApilot™ is supplied by the world-leading biotechnology equipment supplier, GE Healthcare. Thus, through this methodological approach it became possible to identify innovation processes that have gone through the greater part of the innovation journey. By using the ÄKTA system in general and ÄKTApilot in particular as point of departure it was revealed that among the hundreds of drug development projects going on within the Chinese biopharmaceutical context, there were few projects that actually had reached the scaling-up stage. More specifically I found six drug development projects where ÄKTApilot was used, all supported by the Chinese government in one way or the other. I approached all companies responsible for these six projects and got access to five of them. As a result, the main part of the empirical data is an in-depth case study of five drug innovation processes, with the ÄKTApilot and the companies' utilizing this instrument, as point of departure. The largest investigation of the biopharmaceutical drug industry in China performed by Louët (2004) supports the finding that few drug development projects have reached the scaling-up stage. It was estimated that 13 drug development projects were in late development, i.e. phase three, in 2004. Of the five drug development projects that I found through the use of the focal product, ÄKTApilot, four were in late stage drug development in

[7] I was also accompanied by two other researchers, one doctoral candidate focusing on investigating the biotechnology industry in a Taiwanese context and one post doctoral research fellow focusing on investigating the biotechnology industry in the US. For more information see Shih (2009) and Waluszewski et al. (2009).

2004.[8] Thus, besides giving an indication of the total size of biopharmaceutical drug projects close to scaling-up in China, the study also provides more detailed insight into a significant part of these.[9]

Developing and Delimiting the Research Question

As mentioned earlier I started with investigating the historical roots of the biotechnology industry in China, mainly through secondary data. Through this historical review I realized that the Chinese government has invested a lot in both biotechnology science and business during the last three decades, and the Chinese government has high expectations on biotechnology in creating economic growth. Moreover it was evident that China would have difficulty in succeeding in creating new biotechnology drugs due to its historical background. First of all, the Cultural Revolution (1966-1976) destroyed the main part of science development and scientific organizations during the 20th century, which would affect the emergence of a "science-based" industry like the biotechnology industry. Secondly, the Chinese industrial activities during the 20th century had mainly been centered on the defense industry and heavy industry, not traditionally characterized as either "high-tech" or "science-based." Thirdly, the communist tradition with centralized plans as directing the Chinese economy also affected the creation of new solutions in the biotechnology industry; especially the limited interaction between science and industry probably complicated the creation of new biotechnology solutions in China. These three main points gave me an indication that creating new solutions based on biotechnology in China and biopharmaceutical drugs in particular would be a great challenge.

During my first research trip to China my research was focused on utilizing the focal product, the ÄKTApilot, that led me to biopharmaceutical drug developing projects that had reached the state of being scaled up, i.e. to a stage where producer-user interfaces was under creation. Another important function of choosing the ÄKTA system was the role that the supplier of this instrument, GE Healthcare, played as a "door- opener" to the drug development projects. It was through the introduction by GE Healthcare that I actually managed to get access to five out of six drugs where ÄKTApilot was utilized.[10] In the next stage my research focus became more directed toward the whole innovation process, in which the ÄKTApilot constituted only one of many interlinked resources. Thus, the focal product became something of a method in accessing and capturing biopharmaceutical drug innovation processes. From the begin-

[8] One of the four drugs finished clinical three trials in late 2003 or the beginning of 2004.
[9] A deeper discussion on this methodology will come later in the chapter.
[10] The access issue will be further discussed below.

ning I was aware of the challenges in creating use of new solutions. However, after my first fieldwork in China this became even more evident. It seemed especially difficult to link the producing of new drugs to the using of the same. Therefore a critical issue in investigating the innovation process was to study the relationship and connection between the producing and using of a new solution. However the biotechnology industry further added difficulties to the innovation journey due to the strong interdependence on academic research. Therefore it became natural to include the role of research both in the development of new drugs – and in the creation of a medical use of these.

But the focus on three distinct settings and its relation to new drug innovations was not a fact until I encountered a study stressing the different economic logics of the using, producing and developing settings, and how crucial these differences are for any innovation journey, presented in Håkansson and Waluszewski (2007a). This specified my research further, especially in terms of defining research questions and how I could interpret the collected data. It made me direct the research focus to the embeddedness of new drugs in these three very different settings in order to understand drug innovations in China. More specifically the overall question became: *How are new biopharmaceutical drugs created in a country that lacks an established modern biotechnology science base, a pharmaceutical industry related to advanced biotechnology, as well as experienced users of biopharmaceutical drugs in the healthcare setting?* In answering the research question I needed to consider the following: How are government-initiated innovation processes materialized; a) in terms of development of new biopharmaceutical drug solutions and b) in terms of embedding these into large-scale production and c) into large-scale use. By pinpointing the research question I also found a specific way to use the 4R model. By focusing on a limited number of resource interfaces, reflecting the four resource elements, it would be possible for me to map the main resources involved during an innovation process, and how a new drug was embedded in other resources within and between the using, producing and developing settings.

A Qualitative Case Study

This thesis is concerned with investigating how biopharmaceutical drug innovations are created in China. Capturing the embedding and understanding the innovation process are very much concerned with revealing what resources a new solution is encountering and affecting while being embedded in three different settings; the using, producing and developing setting. But revealing the resource interfaces within and between different companies and organizations requires a suitable methodological approach. I use a qualitative approach, arguing that searching and revealing resource embeddedness through resource interfaces would be impossible using only quantitative methods, due to the fact that resource interfaces are partly hidden, indirect and combined across organiza-

tional borders. Since the resources themselves are "mute" I needed to find the people that could represent them, i.e. find respondents that can reveal the resources for me, mainly through interviews. In able to answer the research questions I needed to approach the phenomenon using a qualitative method. As Silverman (2005) points out, it is important to choose a suitable method based on what research questions you have and what kind of model you are using. When I started the investigation concerning biopharmaceutical drug innovations in China, I already assumed the innovation process to be a complex interactive process involving many different companies, organizations, individuals, equipment, products, etc., due to my background within the IMP research tradition. In order to capture complex innovation processes in a Chinese biotechnology context I chose to do a case study, also suggested by Yin (1994) when studying complex and unique situations. When answering "how" and "when" questions Yin (1994) also promotes a case study approach. A multidimensional view on the studied phenomenon and its context can be provided by using a case study, and Eisenhardt (1989) stresses the advantage in revealing and describing development and change processes through a case study. Moreover a case study can provide a "thick" description of the dynamic and complex character of a network. Easton (1995) also emphasize the possibility for deep understanding of the studied phenomenon when using case study, and Dubois and Araujo (2007) point out the use of case study as a possibility to investigate interconnectedness and interdependencies over time. As argued in the theoretical chapter, innovation processes are results of interlinked resources and interdependencies between resources. Also within the IMP research tradition, where the research focus has been on complex industrial networks characterized by stability and change, qualitative research methods and case studies have been proven to be useful (Dubois and Gadde, 2002; Halinen and Törnroos, 2005; Dubois and Araujo, 2007).

I characterize this study as a one large case study consisting of five embedded cases where I investigate five innovation processes of biopharmaceutical drugs in China. One advantage in having five embedded cases is the possibility of pointing out both unique situations for one embedded case and the similarities between them (Eisenhardt, 1989).

A Methodological Challenge: From 500 Companies to Five Drug Innovation Processes

Above I have already given an account of how the choice of a specific biotechnology instrument guided me to five biopharmaceutical drug innovation processes and also how it gave me an understanding of the total amount of such drug projects in China. Below I will give a deeper account of this process. The first impression I got of Chinese biotechnology was that it is huge. In the litera-

ture it was estimated that the Chinese biotechnology industry consisted of around 500 companies spread around the whole country in early 2000, although concentrated in the areas around Beijing, Shanghai and Guangzhou (Chen et al., 2007). However, a focus on the biopharmaceutical drugs already produced and utilized in the Chinese healthcare system revealed dramatically lower figures – around 35 biopharmaceutical drugs had been launched until 2006 (Chen et al., 2007). Another 140 biopharmaceutical drugs were claimed to be in the "product pipeline," which refers to substances that have been identified and are being tested as potential drug solutions (Louët, 2004). According to the latter numbers there were still a wide number of biopharmaceutical drug innovation processes to be studied.

First of all in being able to capture the main part of the innovation process, with its resource interactions, I needed to find innovation processes as close to production and use as possible. Out of all these new drugs mentioned above I needed to sort out the ones that actually were or had been in an industrialized stage. As mentioned earlier, a specific instrument supplied by GE Healthcare[11] along with its personnel became important in sorting and delimiting these hundreds of development projects into a handful of drugs close to industrialization. GE Healthcare's life sciences division has its roots in the Uppsala region and is one of the worlds' largest biotechnology companies and is market leading in supplying protein separation equipment to biotechnology companies all over the world.[12] ÄKTApilot is based on so-called fast protein liquid chromatography (FPLC) and the basic technique was developed in Uppsala, Sweden, in the 1920s/1930s (Janson, 1987; Andersson, 1996; Waluszewski, 2004). Chromatography or protein separation provides a technique where the main active component in biopharmaceutical drugs, proteins, is separated from contaminants and other waste substances using liquid solvents. Thus, equipment for protein separation is necessary at all companies and organizations involved in drug development (Grace, 1997).

GE Healthcare is not only world leading in supplying protein separation equipment to western biopharmaceutical companies but also market leading in supplying protein separation equipment to Chinese biopharmaceutical companies. GE Healthcare supplies more than approximately 80% of the Chinese biotechnology companies and organizations with protein separation equipment along with protein separation consumables (internal material GE Healthcare, 2004).[13] Being market leading in supplying Chinese companies with protein

[11] GE Healthcare is spread around the globe with more than 40 000 employees and an annual turnover of around US$ 17 billion (for more information see: www.gehealthcare.com).

[12] GE Healthcare life science division was formerly named Amersham Biosciences and even earlier, Amersham Pharmacia Biotech, from now on when I use GE Healthcare I only refer to the life science division within GE Healthcare.

[13] GE Healthcare has been present in China since the late 1960s and has developed business with Chinese biotechnology companies and organizations during the last four decades. The company was one of the first international companies allowed to have a wholly-owned subsidiary in China, even before international companies were officially allowed to be wholly-foreign-owned.

separation equipment meant that GE Healthcare had business relationships with a majority of all Chinese biotechnology companies. When GE Healthcare (at that time still Amersham Biosciences) was approached by me and my research group and asked to act as a "door-opener" for the investigation of biopharmaceutical drug innovations in China, Taiwan and the US, the response was positive.[14] GE Healthcare approved of the investigation in early 2004 and already at an early stage in the discussions the relatively newly launched chromatography system, the ÄKTApilot, appeared as a suitable point of departure. Since ÄKTApilot was developed to be used as a scale between lab and process scale, it could be used for both research and production purposes. Moreover, it is certified by the American FDA to be used as production equipment, and the product is mainly used to fine-tune the separation technique for production in small scale, and then apply it to larger production machines. By using ÄKTApilot it is possible to link development and production closer together and to facilitate the industrialization of the new drug. From GE Healthcare it is argued that no other company worldwide can supply a system like the ÄKTApilot. Due to the fact that ÄKTApilot is mainly used in linking and scaling up new drugs, I could use it as a "probe" to sort out innovation processes being industrialized, and thereby reveal innovation processes not only developed but also close to production and use. Thus ÄKTApilot can be seen as the point of departure and a way for me to get access to the empirical world of Chinese biopharmaceutical drug innovations. Furthermore, through the supplier of the ÄKTA system I also got an understanding of the total amount of processes close to scale-up, and realized that I through utilizing ÄKTApilot could capture a significant part of them.

Since the launch of ÄKTApilot in late 2002 GE Healthcare has sold more than 300 machines worldwide, with the majority (around 200) in the US. In spite of the Chinese government's promotion of biotechnology, GE Healthcare has only sold 10 systems to six Chinese companies and organizations. Five customers are based in the Shanghai area, while one customer, a military research institute involved in developing a vaccine for SARS, is based in Chongqing (the western part of China). During my fieldwork in China (October-November 2004, May 2005, March 2007) I met five of these six organizations using ÄKTApilot; unfortunately I could not get access to the military research institute in Chongqing. The following table summarizes and identifies the Chinese companies using ÄKTApilot in the Shanghai area, the year of purchasing the product, the number of products bought, and where in the drug development process ÄKTApilot is used at the five companies.

[14] For more information, see Waluzsewski et al. (2009).

Company[15]	Year of purchase	# of ÄKTApilots	The use of ÄKTApilot
Cardio Pharmaceutical	2004	5	Production
Xin Pharmaceutical	2003	1	Pre-clinical
Vitamin Biotech	2003	1	Production
MAB Pharmaceutical	2005	1	Production
Wison Bioengineering	2005	1	Production

Table 1. Summary of the five ÄKTApilot users.

The finding that ÄKTApilot has only been sold to six companies indicates the fact that few drugs are being industrialized and have survived the development stage of the innovation journey in China. Official numbers also illustrate that few Chinese biotechnology companies have reached an industrialized stage, for instance of all the 140 drugs in the product pipeline, 96 are found in pre-clinical phase, while only 13 are in later stages of development, i.e. clinical phase three, up to 2004 (Louët, 2004). Connecting these official numbers of late drug developments with the drugs found by using ÄKTApilot as a probe yields an interesting picture. Four out of five drug developments where ÄKTApilot is used were in late development in 2004. Therefore I argue that my study can provide a general picture of biopharmaceutical drug innovations in China.

Data Collection

When discussing data collection in China it is important to remember that China has been a closed country; thus before the introduction of the "open-door policy" in 1978, China restricted not only business and foreign trade but also the presence of foreign researchers in China. With the introduction of opening up to the west, the conditions for performing fieldwork and data collection in China gradually changed for the better. Nevertheless, there is still a rather complicated procedure to officially apply for permission to collect data in China as a researcher (Halskov Hansen, 2006). Without official permission there are restrictions on gathering documents and official data, making the possibility of accessing official documents limited (Thøgersen, 2006). However, since I had already been granted access by GE Healthcare to their Chinese customers I did not need official permission, which, on the other hand, resulted in limited access to written Chinese official documents and records. Still the thesis is based on both primary and secondary sources. However, there is a bias towards the primary data collected through interviews, much due to the empiri-

[15] The companies are renamed due for reasons of anonymity, except for Wison Bioengineering.

cal setting of the thesis. Moreover Chinese biotechnology is a rather new phenomenon, with increased investment and promotion during the last two decades; therefore there are limited written sources, such as articles, reports and analyses related to Chinese biotechnology. However, I have tried to collect as much secondary data as possible during the research process, and I have also used some internal material supplied by GE Healthcare.

As mentioned, the main part of the collected empirical data has been primary, mainly through interviews. Håkansson and Waluszewski (2002) emphasizes the importance of interviews as the main source of data when performing research with an interactive approach; thus in order to reveal resources involved in an innovation process we need to discuss directly with those involved representing these resources. When collecting empirical data the 4R model developed by Håkansson and Waluszewski (2002) has acted as a guideline. As a consequence, when approaching drug innovations in the Chinese biopharmaceutical context, I searched for resources such as products, facilities, organizational units and organizational relationships that the new drug has encountered while being embedded in the using, producing and developing setting. The following section mainly discusses the collection of primary sources during the research process.

Interviews in Sweden

I started my data collection in Sweden in the autumn of 2003. Even though I had experience and knowledge from Chinese business life, I had no knowledge of the development of the biotechnology industry in China; thus I first searched for written reports, articles, books related to the development of the biotechnology. I did my first interview in Sweden with Jan-Christer Janson, Professor Emeritus at the Department of Surface Biotechnology at Uppsala University. Professor Jansson has also been partly employed by GE Healthcare since the late 1960s. Jan-Christer Jansson is considered to be the one Swedish expert on Chinese biotechnology with extensive experience in working with Chinese science and business since the mid 1970s. Also, he has been a frequent China visitor, as a representative from Uppsala University and GE Healthcare but also as employed and connected to several Chinese universities involved in developing biotechnology science and business. Jan-Christer Janson opened the door to a complementary background to the secondary sources concerning how Chinese biotechnology had evolved since the late 1970s. Since the start of my thesis research project I have continuously searched for new written material concerning the biotechnology development in China, in order to keep up with the development.

After getting access to GE Healthcare and the focal product, ÄKTApilot, in early 2004 I needed to understand the basis of protein separation and detailed information about the development of the focal product. This resulted in seven interviews with people employed at GE Healthcare in Uppsala

that have been involved in the development of the ÄKTApilot. For instance, I interviewed the product manager and the product leader for product development process. Also, to further understand the development of ÄKTApilot I interviewed GE Healthcare's first customer, Biovitrum in Stockholm, Sweden, and focused on the company's role in evaluating and fine-tuning the ÄKTApilot during its development.

To widen my understanding of GE Healthcare's business in China, I also did four interviews at GE Healthcare in Uppsala with people experienced in working with Chinese biotechnology customers. These respondents gave me a picture on the presence of GE Healthcare in China, both the history background and GE Healthcare's present situation in China. Since one of the respondents was Chinese and had worked for GE Healthcare in China for several years, she also gave me a more detailed introduction to GE Healthcare's business activities in China, for instance, which customers are considered important, how GE Healthcare approaches and develops customer relationships, etc.

Interviews in China Related to Five Drug Innovation Processes and GE Healthcare

During my doctoral thesis project I visited China three times to collect empirical data. The first research visit was in October-November 2004, followed by a second visit in May 2005 and a third and last visit in March 2007. These trips have lasted an average of three weeks with the main focus on the five Chinese biopharmaceutical companies using ÄKTApilot in the Shanghai area. I met and interviewed some of the companies during each visit, while other companies I met during only one or two visits. The reason behind this is twofold, but both are related to time. First, not all companies had time to spare for me during each visit; second, it also depended on when the companies bought ÄKTApilot. During my first visit in 2004 only two of the companies had bought the ÄKTApilot system and therefore there were only two customers I could actually meet. By the following, second, visit another two companies had bought the system, while during the last trip there was another fifth company using the system. Due to the matter of access in each company I sometimes met the same person several times during my visits, while in other cases I met people with different functions and roles within the companies. In total I performed 22 interviews with the Chinese companies using ÄKTApilot. The background and function of the respondents have been different, but all of them have been in a managerial position, for example, general managers, production managers, pilot managers, purification managers, chief scientist, etc.

Due to the fact that Chinese respondents are not used to the interview situation, along with the fact that China historically has been an "informer society," none of the Chinese interviews were recorded. I wanted the respondents to feel as comfortable as possible in during the interviews. This approach was

also adopted by Polsa (2002) when investigating distribution networks in China. In retrospect I realized that being a young foreign researcher was an advantage during the interviews; I think the respondents did not find me intimidating, which also facilitated the asking of straightforward questions. Even though I can speak Chinese, it was difficult for me to discuss biotechnology issues in Chinese, so my contact person at GE Healthcare, the technical supervisor, was also acting as an interpreter during the interviews. One positive effect of it was the fact that I had the time to take detailed notes during the interviews. Also, I have had the possibility of returning to my contact person at GE Healthcare to discuss unclear issues with him. But this can also have affected the result in a negative way: for instance, the person from GE Healthcare might have misunderstood me and thus the respondent might have misunderstood the question. Also, the representative from the Chinese company could have felt the pressure to describe GE Healthcare in a positive way with the technical supervisor present. Nevertheless, a handful of interviews were in English with no representatives from GE Healthcare present. The interviews lasted between 1.5 to 2.5 hours and were usually followed by a guided tour and introduction to the research and production facility of the company; this gave be a better understanding of the physical environment of R&D and production at the Chinese companies. After the interviews I reviewed my written notes as soon as possible in order find missing pieces or unclear issues and as a way not to lose important material and data from the actual interview.

As a way to understand how GE Healthcare organizes, develops and maintains business in China, I have interviewed nine representatives from GE Healthcare, including the head of Asia Pacific and several interviews with marketing and sales personnel in China. In addition to the interviews with the five Chinese biotechnology companies using ÄKTApilot I have interviewed GE personnel involved with the sales and marketing of ÄKTApilot. By interviewing these people I have gained a better understanding of the innovation processes, because GE Healthcare's personnel, especially technical supervisors and sales managers are well informed about the situation at their customers'. They have detailed information of the background of the customers' project and how it has evolved over time, for instance, what actors have been involved in the process and what products have been used in the process, etc. Of course, personnel at GE Healthcare also have a general knowledge of the biotechnology industry in China; for instance, the technical supervisor has extensive knowledge about the development of biotechnology in China after working more than ten years for GE Healthcare in China and also several years at a domestic Chinese biotechnology company. In addition to the interviews I also participated in a one-day seminar held by GE Healthcare where industrial customers were invited to be informed about new biotechnology developments such as: the latest products, interesting new research and commercialization's, new regulatory aspects to be considered when developing biopharmaceutical drugs etc. This observation gave me an insight into the status of new drug developments

in China along with more information about the interaction between GE Healthcare and their Chinese customers.

As mentioned earlier the 4R model by Håkansson and Waluszewski (2002) guided me during the research process. During the interviews with the Chinese biopharmaceutical companies I did have a general interview guide where the search for resources was a central issue. First, the company where ÄKTApilot is based and used was discussed, including the general background and development of the company in focus. This discussion was followed by the company's contacts and relations with other products, facilities, organizational relationships and organizational units related to the focal drug. Secondly, the up-stream activities were in focus, for instance, where does the drug originate from, supplier units and financing units and their contacts and relations with other products, facilities, organizational relationships and organizational units related to the focal drug. Thirdly, the down-stream units were discussed, for instance, clinical hospitals performing clinical trials or final customers, and their relations with other products, facilities, organizational relationships and organizational units related to the focal drug. To clarify the interview guide was just a point of departure for directing the interviews with a main focus on capturing the resources involved in the innovation process from science discovery to actual use. After the first interviews it became easier for me to be more open in the interview situation, asking follow-up questions, asking the respondents to clarify unclear situations, etc. Thus the more interviews I did, the easier it was to elicit the information I wanted from the respondents.

Interviews in China on a General Level

Along with the collection of data with direct focus on the Chinese biopharmaceutical companies connected to GE Healthcare and ÄKTApilot, I also performed interviews with other respondents representing other organizations in Chinese biotechnology. These interviews gave me a better understanding of the Chinese government's promotion of the development of biotechnology and the development of the Chinese biotechnology industry in general. These respondents have been representatives from both science and business, altogether eight interviews. The interviews have had different focuses depending of the respondent's role: for instance, when interviewing a prominent scientist at Chinese University I focused on science and the role of the government in promoting and financing science. While talking with representatives from the Chinese Academy of Science (CAS) and the Swedish Technical Counselor in Beijing, the interviews focused on the government's role in promoting biotechnology through policies, plans and programs. During the interview with a consulting company providing services such as contract manufacturing and services for regulative aspects within biotechnology, the focus was on the business environment for Chinese biotechnology companies. In an interview with an American consulting company focusing on analyzing the Chinese biotechnology in-

dustry as a whole, the focus was on the general development of the Chinese biotechnology industry. Also, the interview with the Director of Shanghai Biotech Association revolved around the issue of biotechnology science and business in Shanghai. However, one disadvantage in collecting data is the fact that I am only a PhD student, having the possibility to meet policy makers such as Ministry of Science and Technology (MOST) requires not only better contacts with important people working with policy issues but also at least a PhD title. The following table summarizes the interviews that compose the primary data of the thesis.[16]

Type of Interview	**# of Interviews**
Interviews in Sweden	13
Interviews in China related to companies	31
Interviews in China on general level	8
Total # interviews	52

Table 2. Summary of interviews.

Structure and Presentation of Empirical Data

The empirical data are presented in eight different chapters. Chapter 4, following, is mainly based on secondary sources and is intended as an introduction and background to understanding business exchange and the Chinese business landscape in transition. Chapter 5 is a short chapter with the aim to describe the drug development process in China. The chapter is an introduction to the drug development processes and its relation to the regulative aspects along with a delineation of the main production steps of drugs in China. This chapter is necessary since it gives the reader a background to understand the coming empirical chapters. Chapter 6 is a presentation of how Chinese biotechnology has evolved over time, from the 1970s and onwards in particular. More specifically the chapter presents the general features of the developing, producing and using setting within Chinese biotechnology mainly using secondary sources.

My main empirical chapters are concentrated in Chapters 7 to 11, where I present the five innovation processes that I discovered through the "probe," ÄKTApilot. These chapters are mainly based on interviews but also complemented with secondary sources such as journal articles, magazine articles and Internet sources, etc., although usually not referred to for confidentiality reasons regarding the participating companies. Since my data collection along with the analysis of the data has been imbued by the 4R model (Håkansson and

[16] For a detail table of the interviews see Appendix.

Waluszewski, 2002), I have approach my empirical data by searching for the resources involved in each drug innovation process. Each chapter from 7 to 11 represents one embedded case. The logical sequence of the cases is based on the degree of embeddedness of the drugs in the developing, producing and using settings; therefore the first case (chapter 7) is the least embedded drug within the three settings, while the last (chapter 11), fifth, case evinces the most embedded drug in the three settings. The actual presentation of each case is structured in a similar way to facilitate the process of finding similarities and differences between the drug innovation processes. The descriptions of the innovation processes are written to reveal both the time and space, and each embedded case ends with a timeline summarizing main points of the innovation process. Each case is followed by an in-depth analysis, however the analysis is further discussed in the following section. Even though the empirical presentations, especially in Chapters 7 to 11, are presented as a description of empirical data, I adhere to those researchers that view the empirical description itself as a first analysis of the empirical data (Easton, 1995; Håkansson and Waluszewski, 2002).

Analysis of Empirical Data

As mentioned above, the embedded cases are presented in Chapters 7 to 11. Each case is followed by a detailed analysis of each drug innovation process, using the 4R model developed by Håkansson and Waluszewski (2002). The analysis of each embedded case starts with an illustrative map where the main resource interfaces related to the focal drug in the developing, producing and using settings are pointed out. To clarify I focus on what resources the new drug solution has interfaces with while being embedded in the developing, producing and using settings. The analysis is concentrated in two main types of resource interfaces, social and technical resource interfaces. These interfaces are reflecting the four resource elements, more specifically the analysis is focused on interfaces between the focal drug solution and *a) organizational units, b) organizational relationships, c) facilities, and d) products*. Moreover, this analysis is performed in relation to each of the three settings: the developing, producing and using settings. The 4R model allows me to investigate what resource interfaces have been created across organizational borders and developed over time and space, but it also reveals what organizations are behind these interfaces. An advantage of using resource interfaces is that it is possible to reveal the resources within a setting but also the connection between the three settings important for the whole innovation process.

CHAPTER 4: AN INTRODUCTION TO THE CHINESE BUSINESS LANDSCAPE

The Chinese business landscape has been widely discussed and debated, much due to the transition from a command economy to a market economy. The Chinese business landscape is particularly interesting since China is on the one hand characterized by political dictatorship and on the other hand characterized by economic freedom. Thus the Chinese society as such is not an open society. Despite these special conditions, China is viewed as a future economic superpower with annual growth rates around 10%. Since 1978, when the Chinese government issued the "open-door policy" the centrally planned economic system started to gradually break down and a "socialistic market economy" has been established during the last decades. The following chapter is intended to introduce the basic conditions for business exchange in China by describing the evolution of the Chinese business landscape, during three different stages: before 1978, from 1978 to 1992 and after 1993. The first stage is related to the conditions during the command economy, while the two following stages related to the transition from a command economy to a "socialistic market economy." The chapter will provide the reader with a background to understand the economic conditions for a country like China to create an emerging Chinese biotechnology industry, and biopharmaceutical drugs in particular.

Before the Transition (–1978)

If we look back in time, before the introduction of the "open-door policy" in 1978, China was a centrally planned economic system. Several main characteristics can be pointed out as important during the age of the command economy. First of all China was a closed society including a closed economic system where foreign trade were strictly controlled and supervised. Also during the Cultural Revolution (1966-1976) there was widespread skepticism towards foreign goods and foreign trade in general. There were regulations and trade barriers for foreign companies to do business in China, and the main part of foreign companies were doing business with Chinese counterparts indirectly through foreign trade corporations. In many ways, foreign companies were doing business with unidentifiable Chinese business actors (Perkins, 1994). Secondly, industrial and business actors were owned and directed by the Chinese gov-

ernment, and private businesses did not exist. Thirdly, and perhaps most importantly, Chinese companies were heavily directed and affected by an institutional framework, a central state planning system, obeying the State Council and several state commissions. Government planning authorities was established in the mid 1950s, with the State Planning Commission (SPC) in charge of long-term planning and the State Economic Commission (SEC) in charge of annual planning, along with the General Bureau for the Supply of Raw Materials, and the State Technology Commission (STC) in charge of technology development as the most important units in developing and planning the Chinese industry before 1978 (Lu, 1996). In addition to these authorities there were other industrial ministries handling the regulations within certain areas and product categories. Also, as a complement to the central state planning authorities there were regional and local governments and planning authorities controlling and directing the economic activities on regional and local levels.

What role did the planning system have in developing Chinese business activities, and how did it affect the business landscape at large? It was actually the planning authorities that directed and controlled the business activities in China during the command economy, not the companies themselves. The planning authorities were in charge of allocating resources between business actors such as suppliers and customers; thus the main issue for Chinese companies was to obey the planning authorities and implement the plans and produce and sell according to state quotas. Due to the central planning system Chinese companies had little ability to affect business activities; the companies did not have direct contact and interaction with their suppliers or customers and thus could only adjust internal routines in line with the plan. With the centrally planned tradition, Chinese companies acted according to the central planning authorities. Suppliers to be used were assigned by the authorities to the companies as well as what customers to sell to; thus the business exchange was organized with no direct relationships and interaction between companies and their suppliers or customers. All interaction was handled indirectly through the planning authorities and annual production plans directed companies' production and sales. In addition the authorities also handled the distribution between the companies, and an important issue was that the prices were set by the government, both what prices to pay to suppliers for input material but also the prices for the output sold to customers, which meant that the companies had no ability to affect the price themselves (Lu, 1996). Hence, Chinese companies were in the hands of the planning authorities both for the allocation of input goods and production quantities. The central planning system resulted in the lack or shortages of consumer products demanded by the Chinese people, much due to the impossible task of including all products in different production plans. This resulted in shortages of products that the Chinese people needed and inefficient use of resources (Lu, 1996). Moreover, companies did not have any incentive to innovate other than by decree from the Chinese government. Economic business activities were thus organized hierarchically, i.e.

top-down, and vertically with the planning authorities as main nodes organizing and controlling Chinese business exchange.

The Chinese business landscape was very much in line with the Russian system under the age of the command economy: all business exchange according traditional market exchange and market relationships were forbidden. Thus business actors were only allowed to work according to the existing central plan. Waluszewski and Johanson (2008) point out the difficulties in handling all business exchange indirectly through planning authorities, utilizing indirect resource interfaces but in a Russian business context. The authors emphasize the problem of companies not having direct interaction with their suppliers, which resulted in difficulty adjusting production, for instance companies having trouble with both shortages and excess goods in stock. Also when suppliers delivered low quality input goods through the planning authorities, the companies had little ability to affect changes and adjustments at "unidentified" suppliers. Thus the companies had to produce and continue the production according to quota with the result of low-quality output to be delivered to customers indirectly through the planning authorities. Companies were in the hands of the planning authorities, and it was only the authorities that could make the changes in combining different resources in the developing, the producing and the using setting.

Another characteristic along with the central planning authorities' power over the Chinese economy before 1978 was the role of the Communist Party and its direct impact on Chinese business activities, especially in business management. Party representatives held leading positions in companies where business professionals were put aside and politics were in command; thus Chinese companies were in many cases controlled and directed by political principles not business principles per se (Lu, 1996).

Beginning the Transition (1978–1992)

With the introduction of the open-door-policy in 1978 the Chinese government started the modernization and reformation of China, including a transition from the centrally planned economy to a market economy. From now on China opened up not only domestically but also internationally. Foreign companies were allowed to act more freely in China; the earlier strict regulations concerning foreign companies' presence in a Chinese business setting were relaxed for instance by allowing foreign companies to create joint ventures with Chinese companies (Chen et al., 1995). In order to gain access to foreign capital and technologies and as a way to handle increased foreign trade, Special Economic Zones (SEZs) were established in different parts of China during the 1980s. In these zones foreign companies could do business with Chinese companies more freely and under privileged conditions (Chen et al., 1995), and in the early 1990s foreign companies could interact directly with their Chinese counterparts

without involving trade corporations (Perkins, 1994). As a result of relaxed regulations on foreign trade, foreign direct investment (FDI) increased significantly during this first phase of the economic transition. An example of opening up to foreign trade is the large State-Owned Enterprise (SOE), the Second Automobile Corporation, focusing on the production of vehicles. As early as the early 1980s the corporation initiated business activities with foreign companies followed by direct export to foreign counterparts. Thus the corporation could interact directly with both suppliers and customers. Since then the corporation has increased its involvement in foreign trade, and in 1988 the corporation was transformed to a joint venture with the American company Thomson International. (Hannan, 1998)

Economic reforms related to domestic Chinese companies started in small scale in the countryside within the agriculture sector when the Chinese government opened up for cultivating the government-owned area through new business formations such as collectives and Township Village Enterprises (TVEs) (Naugthon, 1996). Positive results such as increased harvest spurred the Chinese government to open up for more economic reforms also in sectors other than agriculture. The economic reforms issued resulted in an increased autonomy of Chinese companies through more freedom for the companies to develop and plan their own production and sales (Lu, 1996). A dual-track system was introduced, i.e., where both a traditional plan and a market worked side by side. Companies still had to produce according to the central plans but the surplus could be sold according to an open market system in competition with other companies. Hence, two main pricing systems were introduced: a lower fixed state price and a higher market price set by supply and demand. (Naugthon, 1996) As a result companies were given the opportunity to affect the market price for input goods from suppliers but also the market price for the output goods to final customers. Being a part of the dual-track system, the Second Automobile Corporation had to sell vehicles according to the state plan, where around 30% of the company's total production capacity were sold at fixed price of US$6500 to the military, the remaining 70% were sold at a higher state price set also set by the government, around US$7000-7800, to other SOEs within the annual plan. Any excess production could be sold to private customers at as much as the double state price. Thus the Second Automobile Corporation tried to keep the estimated production capacity as low as possible to be able to sell more vehicles on a private market with a higher turnover. (Hannan, 1998) Several other polices were launched in order to decentralize resources from central to local government; for instance, local government could directly receive local revenues without the interference of the central government. Through these policies local governments gained the possibility of developing their own local economy, and regional experiments were introduced (Qian, 1999). Also, government policies were introduced to encourage companies to directly cooperate and interact with each other (Naugthon, 1996).

The major change during this period was the fact that the planning authorities' power over Chinese business activities was gradually reduced and com-

panies were granted the possibility of interacting directly with their counterparts, such as suppliers and customers, not only indirectly through the planning authorities. During the transition to a market economy fewer and fewer products were included in the central production plans: in 1988 the production plan consisted of only 29 strategic materials, such as petroleum and certain chemicals (Lu, 1996: 42). The Chinese government emphasized the importance of further reforming Chinese companies from the mid 1980s, followed by increased autonomy for Chinese companies. At the same time the concept of market was introduced but business activities were still tightly linked to the government since: "The state guides the market, the market directs enterprises" (Lu, 1996: 19). In order to further strengthen the environment for economic activities, the Chinese government wanted to separate companies from the government as much as possible, and the reformation of SOEs was initiated. However, few SOEs were closed down and workers were still enjoying "the iron rice bowl," i.e. they were life-times employees (Naugthon, 1996; Qian, 1999). As a result of reforming the SOEs along with the shortage of raw materials, smaller SOEs encountered problems and tried to connect to larger SOEs, for instance, by offering shares in the company. In the case of the Second Automobile Corporation this became a reality, and the corporation became share holders in a variety of businesses. Thus large SOEs became even larger and more influential. During the time of raw-material shortage the Second Automobile Corporation also invested in steel mills and other raw-material units to secure future production. Due to shortages of raw materials the corporation got involved in barter, where payments consisted of raw materials instead of money. As a result of investing in raw materials and merging with smaller SOE units, the corporation consisted of more than 300 production sites in 1988. (Hannan, 1998) Also, at the same time the Chinese government initiated activities to defuse the Communist Party's role in the management of Chinese companies, where top management would consist of more business-experienced and business-oriented people, not only of politically and administratively experienced people (Lu, 1996).

This first transition phase resulted in the breaking up of the long-term institutional framework associated with the planning system, and the relationship between companies and planning authorities was gradually dissolved in the Chinese business landscape. But with the acceptance of allowing companies to have direct interactions with their counterparts such as suppliers and customers other problems arose. Just as Waluszewski and Johanson (2008) point out there is a learning process involved in handling direct interactions. It takes time to develop knowledge of handling issues directly in comparison to the indirect interactions that were the traditional principles. This transformation will not adjust overnight; a new situation where business interactions are developed requires reciprocity between internal and external interactions, which takes time to establish. However it is important to point out that the transition from plan to market in China is different from the Russian transition in two major respects. First of all, the transition in China was gradual, with a plan and a market

developing side by side, while in Russia the shift from plan to market was a distinct and radical break with the traditional plan. Secondly, the Chinese transition was taking place within the communist tradition; thus the Chinese did not open up the whole society but continued as a dictatorship and as a communist nation. In contrast the transition in Russia was characterized as more "revolutionary" in breaking totally with the communist tradition. (Naugthon, 1996)

Nevertheless, in the late 1980s and beginning of 1990s the Chinese government along with the Communist party still had extensive power over Chinese business activities, where supply and network structures in many cases were controlled by central plans. Also, private companies were not a reality since the non-state companies were indirectly controlled by other government units, such as local authorities along with lack of institutions based on a market view and no rule of law to direct the economy (Qian and Wu, 2000). Hence, more reforms were needed, and these were initiated with the "southern tour" by Deng Xiaoping in 1992. During the trip Deng visited the economic zones in southern China and proclaimed the acceptance of private entrepreneurs and encouraged the Chinese people "making money" by themselves; thus another round of economic reforms followed, with an emphasis on "opening up" the Chinese business landscape further. (Naugthon, 2008)

Continuing the Transition (1993–)

When the transition was continued, the Chinese economy was further opened up to the Western world through a relaxation of the trade regulations. Much of the trade regulations were a result of the Chinese governments' intention to be accepted as a member of the World Trade Organization (WTO), which became a reality in 2001. One main characteristic during this period was the intention to further divide and separate the government from business and its influence on Chinese business exchange. As a way to decrease the Chinese government involvement in the business landscape, privatization was introduced as a new type of ownership in 1997. Thus, privatization became a reality among Chinese companies and was accepted as an "important component of the economy" (Qian, 2000: 16); the government promoted a variety of company ownership categories such as "privately owned, individually owned and foreign-invested" companies (Tenev et al., 2002: 16).

Along with the introduction of privatization came the pressure to further transform the SOEs. The Chinese government issued policies to decrease the number of SOEs, and government initiated a pressure for them to show profits (Naugthon, 1996). In 1995 the government launched the policy of "zhuangda fangxiao," or keeping the big and letting the small go, where large SOEs were kept under state ownership and control, while the smaller were sold out through privatization or other types of ownership (Yueh, 2011). The Second Automobile Corporation stayed under state ownership as the corporation was

considered to be one of "three big" SOEs in the production of vehicles for the Chinese market. However, the Second Automobile Corporation was also affected by the increased pressure on SOEs: for instance, the corporation had problems with payment from SOE customers, so the corporation focused even more on sales to private customers. An increased pressure on SOEs and the transformation of ownership structures among SOEs forced many of these to declare bankruptcy, and the earlier life-time employment system was destroyed. The Second Automobile Corporation held on to the life-time employment for a long time and tried to adjust to the new system gradually by employing people on long-term contracts up to eight years. In addition the company still offered favorable working conditions to their employees such as providing housing allowances. Being considered a large and important SOE, the corporation could still enjoy favorable interest rates at banks, etc. (Hannan, 1998) During the transition period in the 1990s, corporate reforms and shareholder ownership became a reality, and different ownership structures along with stricter control of state-owned companies resulted in a mix of hybrid companies, such as state/public, private, collective, pervading the whole Chinese business landscape (Tenev et al., 2002).

From 1993 and onwards the dual track system was abandoned, and the Chinese economy further approached a market economy regarding business exchange, with only one pricing system, the market price (Naugthon, 1996). In the case of the Second Automobile Corporation the majority of the customers were already private, with prices set according to a market system, although a minority of the sales still went to the military with a set, lower, "government price." When the transition moved forward from 1993 and onwards, the Chinese companies received increased individual freedom and built up a knowledge of handling relations and interactions with counterparts; thus at this time the Second Automobile Corporation interacted directly with all their suppliers and customers. (Hannan, 1998) Even though the Chinese government relaxed their control of business activities, for example, allowing private companies and selling out SOEs, a great deal of Chinese business exchange was still affected by the Chinese government. In an attempt to limit the government's control of business activities government bureaucracy was downsized and international best practice market institutions were introduced, such as a uniform fiscal and tax system (Qian, 1999). However, the Chinese government still has a large impact on Chinese business exchange, since the majority of large companies in China are SOEs and thus under state control, along with the fact that the Chinese government constitutes the main part of venture capital firms in China (Kenney et al., 2002).

CHAPTER 5: AN INTRODUCTION TO THE DEVELOPMENT AND PRODUCTION OF DRUGS IN CHINA

To understand the coming empirical chapters concerning new drug innovation processes in China, the reader needs to have a basic understanding of the drug development process in China along with some insight concerning the production process of drugs. Therefore the following chapter is devoted to an introduction to the development and production of drugs in China.

Introducing the SFDA, the Chinese Regulative Agency

It is the Chinese State Food and Drug Administration (SFDA)[17] that is in charge of the inspection and control of safety related to both food and health products in China. Moreover, the department is in charge of drug regulation including R&D, manufacturing, registration, and distribution of drugs. SFDA was established in 1998 as the result of the joining of the Ministry of Health's (MOH) Department of Drug Administration and the State Pharmaceutical Administration of China (SPAC). The SFDA (before 2003 named State Drug Administration (SDA)) was created due to an increased demand for better regulation and control of drug development in China and also due to international pressure to conform to international standards of drug regulation.[18] To outline suitable regulations concerning pharmaceutical and bio-pharmaceutical production processes, the SFDA has used the American FDA as a role model. As a result the Chinese biotechnology regulations are becoming more and more comparable to international standards. Modification of existing procedures and practices has resulted in better quality and manufacturing practices; for instance, the Chinese government decided that all manufacturers of pharmaceutical or bio-pharmaceutical drugs should have current Good Manufacturing Practice (cGMP)-certified facilities by June 2004 (Louët, 2004).[19] Nevertheless, in 2006 a bribe scandal within the SFDA was exposed when it was discovered that

[17] SFDA is a department directly under the State Council.
[18] For more information see SFDAs homepage: <www.sfda.gov.cn/eng/>.
[19] cGMP, an international standard for the control of food and pharmaceutical production.

the head of the SFDA, Zheng Xiaoyu, had accepted bribes in exchange for NDA-approvals. Zheng Xiaoyu was executed in July 2007 as a result of the scandal. Also, another two high officials within the SFDA were sentenced to jail for corruption. Due to the scandal the SFDA was forced to review the applications and the NDA-approvals for more the 170 000 drugs between 2002 and 2006 and stricter regulations on drug development issues were put in place. (Cyranoski, 2007)

The Drug Development Process

The drug development process can be divided in several main steps: first the drug discovery phase, followed by the pre-clinical phase, thereafter the Investigational New Drug (IND) phase to approve the subsequent clinical trials one, two and three. After clinical trials the New Drug Application (NDA) is filed for the final drug approval followed by a final clinical phase four. The following table summarizes the main phases along with its estimated time, test group and the purpose of each phase.

	Drug discov-ery	Pre-clini-cal	IND	Clinical I	Clinical II	Clinical III	NDA	Clini-cal IV
Time[20]	At least 5 years	1 year	9 month - 1 year	1-2 years	1-2 years	1-2 years	9 month - 1 year	After 2 years of sales
Test Group[21]		Ani-mals		Humans # varies, min. around 20, (20-80)	Humans # varies, min. around 100, (100-300)	Humans # varies, min. around 300, (1000-3000)		Hu-mans # varies, min. 1000
Pur-pose	Find molecule structure for specific disease	Safety and activ-ity	Ap-proval of clinical trials by the SFDA	Deter-mine safety and dosage	Evaluate effec-tiveness and toxic effects	Confirm effec-tiveness and long-term side-effects	Evalu-ate safety and effec-tive-ness by the SFDA	Evalu ation of long-term side-ef-fects by the SFDA

Table 3. Illustration of the drug development process in China. Modification by the author of Box 1 in Hu et al. (2006: 1218) and Table 15.1 in Robbins-Roth (2000: 117).

First, in the initial drug discovery phase, specific molecules are identified and targeted for specific use. It is in this phase where new drugs are discovered and designed. Different molecule structures are studied to see if they can react to a certain disease. In the following pre-clinical phase the targeted molecules are tested on animals with the main purpose of evaluate if the drug is safe and has a sufficient activity on animals to be further developed in clinical trials and tested on humans. Thereafter the IND is sent in to the SFDA for approval in order to continue with clinical trials. The clinical trials are divided into three separate clinical phases: clinical phase one, clinical phase two and clinical phase three. One main difference between the clinical one, two and three is the number of participants in testing the drugs, with more participants during later clinical phases, but there is also a difference in the purpose of each phase. In clinical phase one there are a low number of healthy test participants with the main purpose of evaluating the drug's safety and its suitable dosage for humans. The

[20] The time is an estimate based on the information gained through interviews with the Chinese biopharmaceutical companies and GE Healthcare.
[21] Numbers in brackets refers to the average test population in the US, just as a comparison.

results of the first clinical trials direct clinical phase two, where the number of test participants rises to a minimum of 100 participants and include people with the disease. The main purpose is to evaluate the effectiveness of the drug and possible toxic side effects on humans. In the final clinical phase three trials, the test is focused on a larger population (minimum of 300) to confirm the drug's efficacy and also to look at potential side effects of the drug. After the clinical trials a New Drug Application (NDA) is sent to the SFDA where the scientific documentation is evaluated with a focus on safety and effectiveness of the new drug. (Hu et al., 2006) In order to be able to sell a drug, companies need NDA approval from the SFDA. These drug approvals are divided into five different classes. A class one drug is a totally new drug with no similar drug world-wide, while a class five is an already existing drug, a generic drug, with only a small difference in the formulation of the drug compared to existing drugs (Gross, 1998). Traditionally Chinese companies has been focused on developing class three to five drugs; thus several firms are producing the same or similar drugs, which has resulted in a fierce competition between these biopharmaceutical drug producers (Chervenak, 2005). When the drug has been NDA-approved by the SFDA, the drugs production process, including production equipment and the factory, needs to be cGMP-approved by the SFDA. After the drug has been on the market for two years of sales, the drug needs to pass the final clinical phase four, also referred to as clinical production, evaluated by the SFDA. This phase aims at evaluating and controlling the new drug's long-term side effects on a larger population (minimum of 1000).

If we compare the drug development process in China with the process in the US, it is similar. There are differences, however: for instance, the Chinese drug development process includes a final fourth clinical trial phase, and each phase takes a shorter time in China partly due to easy access to a large population to be used for clinical trials along with lower regulatory requirements concerning the number of participants in the clinical trials in China compared to the US (Robbins-Roth, 2000). However, it is important to point out that the number of participants in clinical trials differs in China depending on the disease in focus; specific types of cancers along with advance diseases require a lower number of participants in clinical trials. Thus a "fast track" exists for specific drugs (Hu et al., 2006; Yin, 2006).

The Production Process of Drugs

Before supplying the biopharmaceutical drug to customers, the actual production process of the drug need be performed by a company. If we look more closely at the production process, it is divided into three main steps: first the fermentation step, followed by the purification step and finally the formulation step.

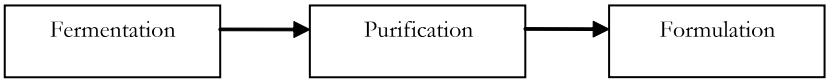

Figure 1. The main production steps of drugs.

As mentioned earlier, biopharmaceutical drugs are based on large-scale molecules, mainly proteins, which cannot be produced synthetically like traditional small-molecule drugs. But how then is protein produced and extracted? Proteins are complex and exist in all living organisms, but for the production of biopharmaceuticals, animals and sometimes humans are the source of proteins. First the DNA is altered by recombinant techniques to produce a certain protein. Then the protein compound's so-called "cell cultures" are extracted. It is these cell cultures that constitute the "living" basis for the drug. During the first production step, the fermentation step, these cell cultures or proteins are grown and increased in number with the aid of fermentation equipment such as bioreactors or fermentation tanks. Thereafter the cell cultures are gathered and extracted. During the growth of cell cultures, unwanted particles, molecules and contaminants are also developed and increased in number; hence in the purification phase unwanted waste substances are separated from the wanted active substance such as the protein in focus. This purification is a necessity because in order to be approved NDA of the new drug solution the company needs to show a "clean" active substance as a basis for the drug. The protein or virus in focus is cleaned and concentrated using specific purification equipment. In the final formulation step the drug is transformed to a drug, by mixing the drug with chemical liquids to get an injectable substance.[22]

[22] The production of substances for clinical trials is also set up according to this three-step process, although pre-clinical production is limited to the two first steps, the fermentation and the purification phase. It is important to remember that biopharmaceutical drugs are injection substances.

CHAPTER 6: THE EVOLUTION OF CHINESE BIOTECHNOLOGY

The following chapter aims to describe the promotion of biotechnology science and business in China from the late 1970s onwards. Through this description I will provide an overall characteristic of the using, producing and developing setting of Chinese biotechnology and thereby give an overview of the basic conditions for creating biopharmaceutical drugs in China.

A Challenge to Develop Biotechnology in China

When studying the creation of biopharmaceutical drugs it is important to remember that this is characterized by research-intensive activities, long development times, large financial investments, and high regulatory issues just to mention a few critical aspects when entering the biotechnology arena (Grace, 1997; Robbins-Roth, 2000). Thus, the development of biotechnology business as such is a highly risky and uncertain journey. In the early 1980s when the Chinese government decided to develop biotechnology science and business, there were more issues than these to keep in mind. First of all science and technology, i.e. the "first productive force," (Chang, 1996: 387) was weak. As in many other countries, Chinese development of science and technology has been closely linked to the military. Due to the threat of an invasion by the Japanese the development of Chinese science and technology from the 1920s and onwards needed to co-develop with the military force according to the Chinese government; thus investments and development of science and technology were made in line with strategic defense decisions. In 1949 China became a centrally planned economy with the announcement of the People's Republic of China (PCR), and along came a centralized planning system, where all research institutes were organized under the Chinese Academy of Science (CAS) (Simon and Goldman, 1989; Yan, 2004).[23] The central planning system included a clear division between science and business, mainly represented by the defense sector, where science would be applied. Technological innovation was initiated due

[23] CAS is a department directly under the Chinese State Council with the purpose of leading science development in China.

to administrative decisions included in the central plan (Nee, 1992; Liu and White, 2001; Lu and Lazonick, 2001). Nevertheless, in the 1960s some scientific results had been achieved, for instance "two bombs and one satellite" (Simon, 1989a) not to mention progress in the chemical industry through the success of Shanghai Institute of Biochemistry in producing chemically synthesized insulin in 1965 (Chervenak, 2005; Chen et al., 2007).

But the Cultural Revolution (1966-1976) affected both science and technology in a negative way. Mao Zedong decided that "the masses", i.e. the farmers, would direct and control the future development of China. Hence, professionals and experts in science and technology were pushed aside for representatives of the farmers. The farmers would act as role model for the Chinese people, and therefore scientists were sent to the countryside to be reformed through practical farming or through factory work. As a consequence not one person was enrolled in Chinese universities between 1966-1969, and scientists lost their permission to pursue science and teach (Simon and Cao, 2009). As a consequence the Chinese universities collapsed, and the science and technology base and the progress in science that had been built up during the 1920s to the mid 1960s was severely eroded (Simon, 1989a). The universities opened again in 1970 but "politics was in command" (Simon and Cao, 2009: 27), meaning that before students could be enrolled at the universities they needed to participate in hard labor, doing farming or factory work. For instance at Qinghua University 80% of the time were allocated to hard labor in factories along with other "practical" work, while 15% of the time focusing on the study of communistic thinking, and 5% of the time was allocated to farming and activities related to the People's Liberation Army (PLA) (Simon and Cao, 2009). Moreover students were enrolled to the universities based on the "practical" experience from hard labor, not academic records per se. As a result a large proportion of the student did not have sufficient knowledge to assimilate university education; for instance, few even had a high-school diploma. This resulted in that the Chinese university education was eroded. It is important to remember that the Cultural Revolution happened at the same time as most western countries made a breakthrough in their science and technology development. As a consequence the Cultural Revolution resulted in an even wider gap between Chinese and Western development. (Simon and Goldman, 1989) In the late 1970s and early 1980s China did not have a science base; the universities and research institutes were destroyed, and a whole generation of scientists were ruined due to the Cultural Revolution. Also, in the late 1970s the main part of new technology was imported from other socialist counties as a result of an import technology strategy declared in the 1960s (Liu and White, 2001; Cheung, 2009). Due to the Cultural Revolution and a general negative view on scientists resulted in the starting point of a major "brain–drain" from China to other industrialized countries, mainly to the US. Around 1.2 million Chinese students and researchers left China between 1978-2007, while around 300,000 of these have returned (Simon and Cao, 2009: 31). Since then China has suffered from a lack of highly professional managers and scientists, combined with a shortage

of managerially experienced professionals with commercial training (Simon and Cao, 2009). In the early 1980s not only science and technology was weak but also the industry was underdeveloped and mainly concentrated to the defense industry and heavy industry. Also due to the planning system, there was no natural link between science and business. Moreover, the Chinese had little experience in commercializing science, and Chinese companies were at the time strictly controlled and directed by the central planning authorities and were state-owned.

The Chinese Government Directs Attention to High-tech and Biotechnology

Thus, in the aftermath of the Cultural Revolution the Chinese government faced the problem of catching up with the Western world, and the country had to be rebuilt from scratch. To summarize, in the late 1970s and early 1980s, after the Cultural Revolution, the production of science had been put on hold and the scientific infrastructure had been heavily damaged, and universities and research institutions had been undermined. However, the military organization has been held relatively intact in order to maintain national security.[24] Thus, the military organization sustained their work but with limited resources at hand. By the end of the 1970s the Chinese military was the best developed organization in China, and Deng Xiaoping saw the potential in using the military as a means to lead the transformation towards a market economy (Lee, 2006: 440-449). When issuing the four modernizations the military played a central role, and Deng opened up for a "marknadization" of the Chinese military. The military was encouraged to engage in business activities as a way to drive economic development but also as a way to be self-supporting (Karmel, 1997). The military budget was cut radically, and the military was encouraged to strengthen its finances by getting involved in business. Since the late 1970s the People's Liberation Army (PLA) has cut half of its work force, from 4.5 million to 2.25 million (Scobell, 2005).[25] The underlying assumptions was that the civil society and the military would support each other and fuel the transformation from central planning system to a market system or as the slogan says: "Combine the military and civil/combine peace and war/give priority to military products/let the civil support the military" (Bitzinger, 2007: 110). This became the introduction of transferring military technologies to commercial solutions with the

[24] During Mao Zedong's leadership the military was allowed to established "third-line" factories in remotes areas in China to supply goods to the military such as arms and electronics. (Welker, 1997)

[25] The PLA is directed by the Central Military Commission (CMC) elected by the National People's Congress. (Scobell, 2005)

hopes of jump-starting the economy and the creation of new business activities (Bitzinger, 2007). The encouragement resulted in military engagement in a variety of industries, from electronics and medical products to retail and department stores (Karmel, 1997). In the early 1990s more than 10 000 companies were under military control with a workforce of more than 700,000 (Lee, 2006).[26] With an increased focus on investing in new high-tech industries for future development, especially military-civil collaborations has been encouraged (Scobell, 2005; Bitzinger, 2007).

As mentioned, biotechnology is characterized as a research-intensive industry; thus research and science are considered main components for developing biotechnology. The importance of biotechnology research is reflected in how the Chinese government started promoting biotechnology as a future industry for China in the early 1980s, where the main focus initially was on establishing a research base within biotechnology. The intention behind the focus on research and science as the starting point has been the underlying assumption that a biotechnology science base is essential when developing biotechnology, and investment in science would result in scientific breakthroughs that can be transferred and applied by biotechnology companies in industry and result in commercial solutions and ultimately in economic growth (Bartholomew, 1997). The basic idea is that investments in science would be transferred and applied by companies and result in commercial success. Also, since the 1990s the Chinese government has put an increased emphasis on developing a suitable innovation system for the production of new high-tech ventures such as biotechnology, where the main components would consist of research institutes and universities along with "high-tech" companies. The injection of government capital would support and develop these two main components. (CAS, 2003)

To establish biotechnology in China the Chinese government has relied greatly on issuing national high-tech policies, programs and plans in order to promote and develop biotechnology science and business.[27] A first step to highlight the importance of biotechnology in China was the announcement of the first high-tech policy in China, the Key Technologies R&D Program, in 1982 by the Ministry of Science and Technology (MOST) (before 1998 named State Science and Technology Commission (SSTC)).[28] The main purpose of the policy was to restructure traditional industries and promote the development of new high-tech industries, one of which was biotechnology (MOST, 1998a). The

[26] In 1998 the Chinese government restricted the Chinese military involvement in business and gradually the military companies were transformed to SOEs. (Lee, 2006; Shambaugh, 2004)

[27] The Chinese government has been influenced by the launch and implementation of other Western and Japanese policies, for instance the American Strategic Defense Initiative in 1983 and the Policies for the Promotion of Science and Technology in the Next Ten Years of Japan. (MOST, 1998a)

[28] MOST is a government department organized directly under the Sate Council in charge of issuing policies, plans, programs and regulation related to the development of science and technology in China.

following timeline highlights important central government programs and critical events to promote the development of biotechnology in China.

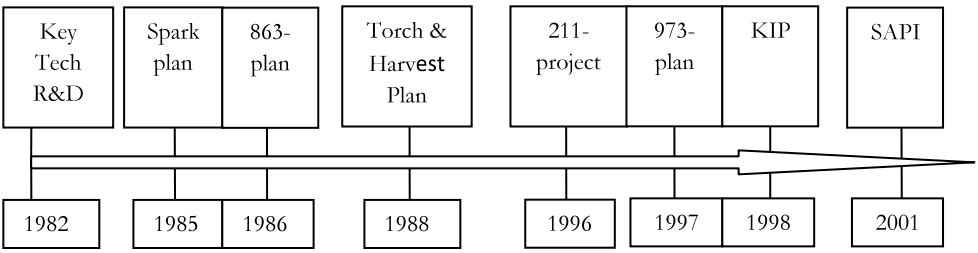

Figure 2. Timeline of Chinese national biotechnology policies and programs.

In addition to the timeline illustrated above the following figure summarizes the main central government units involved in promoting Chinese biotechnology science and business.

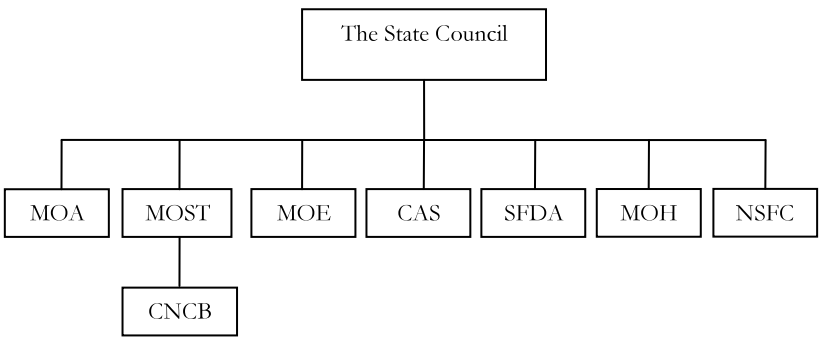

Figure 3. Central Chinese government units promoting biotechnology.

It is important to bear in mind that China is a large country with a population of more than a billion and that the country consists of more than 20 different provinces with different conditions for economic growth and industrial development. Along with this there is great diversity within in the Chinese population, with more than 50 minorities. As a consequence China can be looked upon as several coexisting economies; however the industrial development has come furthest in the coastal regions with Beijing, Shanghai and Guangzhou as the metropolises. We also need to consider that the regional governments also shape and direct both biotechnology science and business through regional policies, programs and investments, although these are usually very much in line with policies and programs issued by central government units referred to above. In the following sections I will give an overall description of the evolution of Chinese biotechnology science and business by discussing the national

programs issued by the government units mentioned above. Through this description, features of the developing, producing and using setting of Chinese biotechnology will be revealed.

The Chinese Biotechnology Developing Setting

Establishing a National Biotechnology Science Base

Many of the biotechnology investments during the 1980s and 1990s have been on the establishment of a biotechnology science base, and a first attempt to establish and develop a biotechnology science base was the launch of the National Hi-Tech R&D Program, also called the 863 plan, by MOST in 1986. The plan was issued to catch up with the western economies and create a sustainable scientific infrastructure (Simon, 1989a; Qin, 1992). With the plan came a shift in the Chinese tradition that science would be linked to the military; instead science would also be exploited for industrial purposes and thus not only limited to military applications (Zhao, 2003). The plan focused on developing seven new high-tech industries: information technology, space technology, laser technology, automation technology, energy technology, advanced materials and biotechnology (Simon, 1989a). The plan financed both basic and applied research projects in the seven sectors during three five-year plans, totaling RMB 10 billion (US$ 1.25 billion). Seven institutions were created to support each industry, with the Chinese National Center for Biotechnology Development (CNCBD) supporting biotechnology.[29] Around RMB 1.3 billion (US$ 162 million) was allocated to biotechnology between 1986 to 2000 (Huang and Wang, 2003). The plan is still today one of the main funding sources for biotechnology research in China and is allocated every fifth year. To further strengthen basic research within the 863 plan, MOST issued a second important program to support biotechnology development, the National Program on Key Basic Research project, the so-called 973 plan. The plan was launched in 1997 only to focus on basic research with the main argument that: "Basic research is a driving force for the progress of human civilisation, a source and backbone of S/T and economic development, a precursor of inventions and new technology, and a cradle of S&T talents." (MOST, 1998b) During 1997-2002 RMB 2.5 billion (US$ 312 million) was invested in basic research within the program (Huang and Wang, 2003). When applying for funds from the 863 and the 973 plan,

[29] The CNCBD was established in 1983 with the aim to: "…strengthen our innovation ability and improve our international competitive capability, to strive to keep pace with international fast moving frontiers and to make the new bio-industry one of pillar industries in China". (CNCBD, 2005)

MOST has specified certain research demands; however, MOST has been criticized for overly narrow research specifications since these favors certain research groups in China (Interview respondent J, 20070312).

Along with the launch of the 863 and 973 plans, the Chinese Academy of Sciences (CAS) has been pushing for Chinese biotechnology research development. CAS biotechnology work is mainly focused on two main issues; one is pharmaceutical research and new drug development, where platforms for drug development are supported. The second issue concerns energy sources, such as biogas and bio-ethanol. (Interview respondent J, 20070312) CAS launched the Knowledge Innovation Program (KIP) in 1998 to support technical development in prioritized high-tech areas such as biotechnology and to support the establishment of a national innovation system (CAS, 2003). Within the KIP program, 80 research institutes will be restored and act as science bases for high-tech innovation, where 6,000 employees at 24 different institutes are handling biotechnology research issues (Chen et al., 2007). Due to the large brain-drain of Chinese scientists from the early 1970s onwards, much of CAS work is to provide training for young scientist but also to actively convince foreign-trained and experienced Chinese scientists to move back to China. Within the KIP program, one aim is to invest RMB 600 million (US$ 70 million) to attract young Chinese scholars from abroad back to the mainland in order to develop Chinese biotechnology. Researchers are offered highly professional laboratories, part-time work at universities and higher salaries compared to their Chinese colleagues. Thus the Chinese government is using foreign-trained scientists as a base for the future development of biotechnology in China, and hoping for a reverse brain-drain effect. (Stipp, 2002) Investments in the high-tech programs mentioned have also resulted in the establishment of thirty new special National Key Laboratories (NKL) involved in biotechnology research and development. To further support the KIP program CAS issued the Strategic Action Plan for S&T Innovation (SAPI) in 2001, with the main task to create "original innovation," referring to the policy that science discoveries should be made within China to a larger degree, which is viewed as a necessity for China to become a future biotechnology superpower (CAS, 2003).

Apart from research institutes represented by CAS, there are also universities focusing on developing biotechnology science and focusing on educating China's future biotechnology scientists and engineers. In order to create and establish a science base for the future in biotechnology science, the Ministry of Education (MOE) has reformed the Chinese universities from the 1990s and onwards.[30] One of the most important reforms is the implementation of the National 211 project (1996-2000), where around US$ 100 million has been allocated with the aim to merge several universities and appoint key universities

[30] MOE is a department directly under the Chinese State Council in charge of restoring and developing university education in China. (for more information see MOEs homepage at: <www.moe.edu.cn >)

and laboratories for future research (CERNET, 2001). Along with CAS, MOE has issued several rewards program for promising scholars in order to strengthen the status of scientists and ensure the future science base. One example is the "Education Revitalization Plan Toward 21st Century," comprising the Cheung Kong Scholar Program. In addition to this, the "baiqianwan" program, the 100, 1,000 and 10,000 program, was launched in 1997. The purpose for the program was to create 100 international top researchers from China doing state-of-the-art research, 1,000 internationally leading Chinese scientists in their field and another 10,000 Chinese researchers at the basic international level by the year 2000 (Suttmeier and Cao, 1999). The Chinese government is also promoting international relations and technology transfer as a mean to develop biotechnology in China. As a result China has scientific exchange programs with more than 150 countries and research agreements with more than 100 countries (Jin, 2001).

Much of the funding of biotechnology research originates from the National high-tech programs issued by the Chinese government, for instance the 863 and 973 programs, but a large part of the biotechnology research funding comes from the National Natural Science Foundation of China (NSFC).[31] The NSFC allocates and manages the National Science Fund, and since the establishment of the foundation there has been a steady increase in funds: in 1986 there was RMB 80 million (US$ 1 million) allocated to research, while in 2005 more than RMB 3 billion (US$ 375 million) was distributed by the NSFC (NSFC Annual Report 2005). Inspired by the American National Science Foundation, the NSFC is organized by type of science, and biotechnology is a part of the Department of Life Sciences consisting of three main areas: biology, agricultural and medical sciences. In turn the actual financial support and funds are divided into different categories such as general programs with funds between RMB 200,000 and 300, 000 (US$ 24,000–36,000), key programs with funds between RMB 1 and 1.5 million (US$ 120,000–180,000) and major programs with funds up to RMB 24 million (US$ 3 million). (NSFC, 2006)

Progress within Chinese Biotechnology Science

Even though the Chinese government started the development of biotechnology more or less from scratch in the late 1970s and early 1980s, there has been some development in the area during the last decades. First of all, there are an increased number of Chinese universities and research institutes focusing on developing biotechnology. The majority of the biotechnology science is produced at public universities and research institutes, some in partnership with

[31] NSFC was established in 1986 by the State Council aiming to "…support basic and applied researchers of excellence and direct them to the national goals … of revitalizing China through science and education". (NSFC, 2006)

international actors. Also the number of students, undergraduates, graduates and PhDs in biotechnology has increased: for instance, around 2,000 PhDs in biotechnology graduate each year from Chinese universities (Chen et al., 2007) and between 1997-2003 the number of graduates in biosciences has doubled (Kermani and Zhou, 2007). In early 2000 there were around 400 universities, research institutes and institutions involved in developing biotechnology in China, with more than 20,000 researchers working with biotechnology issues (Stipp, 2002; Pefile et al., 2005). A few years later in 2005 there had been an increase in the number of researchers working with biotechnology-related issues, to more than 30,000 (Chen et al., 2007). During the first 15 years of the 863 program, around 6,500 Chinese biotechnology scientists were supported by the program and around 10,000 scientific papers were published (Pefile et al., 2005: 54). Also, more Chinese scientist are publishing in international and highly ranked journals compared to before, although the publications and citations are still low compared to the overall pool of Chinese scientists and compared to other Western and industrialized countries (Suttmeier, 1997; Suttmeier and Cao, 1999). On the other hand, many of the successful scientists in the US are originally from China but have been trained and educated in the US, and it is these researchers that the Chinese government is trying to attract back to the mainland to develop a science base for developing future biotechnology (Simon and Cao, 2009).

Not only has the amount of producers of biotechnology science increased during the last decades, but Chinese biotechnology research has also gained increased domestic interest along with international recognition. For instance China's involvement in the Human Genome (HUGO) project since 1994 received worldwide attention when Beijing Genomics Institute (BGI) traced the human genome at top-speed. The institute is one of the worlds' best institutions for gene decoding with modern facilities with over 100 sequencing machines and a highly competent work force. Also, the Chinese scientists succeeded in tracing the genome of rice in only four months. For the coming years BGI is expected to be one of the leading genetic research institutes in the world. (Stipp, 2002) A good research base in genetics with a large population including many different minorities, detailed family records and disease samples will enhance the possibilities for further discoveries in Chinese genetics (Chen et al., 2007). Other Chinese biotechnology research that has also been noticed is the progress in stem cell research and agricultural biotechnology research, for instance the successful research on hybrid rice (Chen et al., 2007). The development of Chinese biotechnology research has not happened in isolation. In many cases, Chinese scientists are cooperating with scientist from other countries. For instance a number of international research projects to integrate western and Chinese medicine are carried out through cooperation between Chinese and foreign research groups (Economist, 2002). Development in Chinese biotechnology science is also demonstrated by the fact that the world's largest biotechnology and pharmaceutical companies, for example Novo Nordisk, Eli

Lilly, Roche, Novartis have not only sales and marketing units but have also established R&D facilities in China (Pefile et al., 2005).

The Chinese Biotechnology Producing Setting

Establishing a National Biotechnology Business Base

The main investments in Chinese biotechnology have been on the science side, especially during the 1980s and 1990s, although there are also some attempts by the Chinese government to promote the development of biotechnology businesses and companies. In mid 1980s MOST issued the Spark plan to decrease the development gap between the coastal and the western part of China. The focus was to support the development of the agricultural sector and this resulted in a concentration on developing industrial enzymes and grain production in agricultural biotechnology. As a result of good results from the Spark Plan, a Harvest Plan to promote agricultural technology was launched in 1988 by the Ministry of Agriculture (MOA) (Simon, 1989a; Simon, 1989b).[32]

Nevertheless, a program with a distinct business focus was not launched until 1988, the Torch program, with the main purpose of commercializing high-tech research. Projects that had a sufficient technical level, usefulness and economic potential would receive government funds to realize the projects (Chen, 1995). The creation of innovative milieus in restricted areas was the main focus, and thereby 52 special hi-tech zones were established all over China. The intention was to create a suitable milieu within the zones in which research could be transformed into commercial products. The Chinese government's way to attract companies to locate their business in these zones was by providing relief such as tax relaxation and duty-free import of materials (Simon, 1989a; Simon, 1989b; Sigurdson, 2004). Also supporting service centers for high-tech development and R&D activities within companies was encouraged in the program, and as a result service centers and supporting agencies were concentrated in these new economic zones (Sigurdson, 2004). In 1990 over 2,500 high-tech companies were based in these zones (Chen, 1995), and the Chinese government further developed the special economic high-tech zones to transform them into 52 national science parks supported by 31 regional innovation centers in the late 1980s.[33] In line with the national Torch plan, Shanghai government established the Shanghai Zhangjiang High-Tech Park in 1992 with the aim to further promote and spur the development of high-tech within the

[32] MOA is the department under the State council in charge of organizing the development of the agricultural sector, where agricultural biotechnology is an important part.
[33] Zhongguancun in Beijing was the first science park in China established in 1988.

Shanghai region. In 1996 Shanghai Municipality in collaboration with MOST, MOH, CAS and SFDA decided to establish the Shanghai National Biomedical Industry Base within the park. In 2002 around 300 companies were established in the park, some 130 of which were biotechnology or pharmaceutical organizations. (Zhangjiang High-tech Park, 2006a) The park is often referred to as "medical valley" and world leading companies such as Roche, Novartis and Glaxo SmithKline have manufacturing and R&D facilities in the park. Altogether there are more than 65,000 employees in the park, 12,000 of them in biomedicine (Zhangjiang High-tech Park, 2006b). Similar to the central governments' intention behind establishing science parks, the Shanghai government also emphasizes the hope to increase commercialization of biotechnology research as a main reason for establishing the park. Not only multinational companies are established in the park but also a majority of Shanghai biotechnology companies. The American Silicon Valley has been the role model for the Chinese government when investing and establishing science parks all over China (Macdonald and Deng, 2004). Thus, by concentrating science, business, capital and special high-tech services within a limited area, an innovative milieu would be created to support the interaction within the park and strengthen the high-tech firms so as to: "…attract high tech manufacturing firms for the purpose of jump-starting economic development" (Walcott and Xiao, 2000: 176). Also, in accordance with the Torch plan and the development of national science parks, university-based science parks have been encouraged by the government (China Daily, 2003).

As mentioned, the Chinese government has had a great impact on funding biotechnology science development but the government has also had an important role in financing biotechnology business. Approximately 80% of the capital invested in China has government origin (Kenney et al., 2002). A general assumption is that a working venture capital is a necessity for the development of a research-intensive industry like biotechnology (Bartholomew, 1997; Powell et al., 2002). The venture capital industry in China is still under construction, and the Chinese government is the main driving force. As a means to promote and support the venture capital industry, the Ministry of Foreign Trade and Economic Cooperation (MOFTEC) founded the first Chinese public venture-capital investment company in 1986: China New Technology Venture Investment Corporation (White et al., 2005). Thereafter several public or semi-public venture capital investments firms have been established, such as the Shanghai Science and Technology Invest Corporation established in 1992 by the Shanghai municipality along with the Regional Shanghai Fund with around RMB 100 million (US$ 12 million) to be spent on biotechnology issues (Interview Yani Liu, 20050511). In 1998 the first private venture capital firm was established in China, China Beijing High-tech Venture Capital Ltd. Despite the fact that private venture capital firms are privately owned, they display strong linkages to financial support from the government. Thus, the government also supports private businesses as a means to create a venture capital industry to facilitate the development of high-tech industries such as biotechnology. (White et al., 2005)

In total it is estimated that around RMB 6 billion (US$ 750 million) in venture capital have been invested in biotechnology ventures in China (Louët, 2004).

Progress within Chinese Biotechnology Business

The business side of Chinese biotechnology China has received a lot of international attention for developments in agricultural biotechnology. In 1988 China was the first country to commercialize bio-engineered crops, tobacco resistant to virus attack. However, genetically modified (GM) cotton has received the most attention. In 1997 the first use of GM cotton was approved. Until today China's government has agreed to commercialize six Gene Modified Organisms (GMOs). (Huang and Wang, 2003) To use old traditional Chinese techniques together with new Western techniques is hoped to result in new drugs and pharmaceuticals, and several products integrating Chinese Traditional Medicine (TCM)[34] and biotechnology are under development (Pefile et al., 2005).

Efforts to boost biotechnology have not only resulted in scientific results but also as a visible imprint in the number of biotechnology firms in China: there were around 500 biotechnology firms in early 2000 (Chervenak, 2005; Chen et al., 2007), even though the definition is wide and also includes brewery and food products, such as soy sauce. The first biotechnology company in China, Kexing Biopharmaceuticals, was founded in 1989 and is considered to be China's largest biotechnology company, with earnings around RMB 1 billion (US$ 125 million) annually. The company was the first firm to get an approval of a generic drug in China (Stipp, 2002). It is estimated that around 50,000 are working in the biotechnology industry in China (Chen et al., 2007). Traditionally China has a working pharmaceutical industry with a focus on the manufacturing of drugs, and more than 60% of the worlds' production of Active Pharmaceutical Ingredients (API), raw materials for pharmaceuticals, takes place in China (Weiss and Forrester, 2004). In order to commercialize science and reduce governmental funding, the Chinese government has encouraged universities and academic institutions to establish and create spin-off companies of their own. For instance CAS established more than 500 new spin-offs companies in high-tech industries, including all high-tech industries, one of which is biotechnology (Suttmeier and Cao, 1999; Suttmeier, 2002). However, few of these biotechnology spin-offs have succeeded in developing a durable business (Interview respondent J, 20070312).

If we only look at the biopharmaceutical part of the biotechnology industry, there has been an increase in the number of biopharmaceutical companies from 240 to 350 between 1998 and 2002 (Pefile et al., 2005), and in 2005 there were around 500 biopharmaceutical companies in China (Chen et al., 2007). Until 2006, SFDA had approved around 35 biopharmaceutical drugs for

[34] TCM refers to a holistic medical system including herbs, meditation, acupuncture, etc.

sales on the Chinese market (Hu et al., 2006; Chen et al., 2007) and a steady increase in sales revenue is revealed in the following table.

Year	Revenue (billion US$)
2001	1.85
2002	2.01
2003	2.80
2004	3.12
2005	3.80

Table 4. Sales revenue of biopharmaceutical drugs in China 2001-2005 (Zhou, 2006).

Along with the existence of many Chinese biotechnology companies and some products, there are also around 140 drugs in the development pipeline, but only 13 are a later phase, i.e. clinical phase three (Louët, 2004). However, the main part of new drugs in late clinical phases will get a NDA-approval. For instance the SFDA approves around 10,000 NDAs each year compared to the American FDA, which approves approximately 100 new drugs each year (Chenoweth, 2005). This indicates that the Chinese drug regulations are still more relaxed than FDA regulations.

A Summary of the Chinese Government's Attempts to Promote the Biotechnology Science and Business

The following table summarizes the discussion above on what the Chinese government has done in order to spur the development of Chinese biotechnology science and business. The table reveals the government unit involved, along with its function, its performed activities and its aim/purpose.

Government unit	Function/role	Activities	Aim/purpose
MOST	-Development of National S&T, High-tech and biotech	-Key Technologies R&D Program -863 plan -The Spark plan -Torch plan -973 plan	-New areas and restore of old ones -Develop research a base in new areas -Regional balance (enzymes and grain prod.) -Establish HT-zones and Science Parks -Develop basic research for original innovation
CNCBD	-Implement and develop S&T biotech plans	-Promote biotech -International biotech exchange	-Establish biotech as a future industry
CAS	-Public research institute	-KIP -SAPI	-Technical dev. in high-tech -Establish NKL -Restore institutes -Interact within the innovation system -Original innovation and technology transfer
MOE	-Develop higher education through universities	-211 project -"baiqiwan" program -University SP	-Merge universities -Creation of Chinese top scientist -Commercialize research
NSFC	-Funding of national science	-Manage the National Natural Science Fund	-Finance research according to national goals
SFDA	-Regulation of drug dev and drug production	-Drug licensing	-Control manufacturing of drugs

Table 5. Illustration of the Chinese governments' promotion of biotechnology science and business.

The Chinese Biotechnology Using Setting

In the following section I will discuss the Chinese healthcare system, which is closely related to the use of new biopharmaceutical drugs, as it is the healthcare system that sets the conditions for spreading the use of any new drug (Torsteinsdóttir, 2007). To facilitate an understanding of the Chinese healthcare system of today, I will give a short backdrop to the healthcare system before the transition started.

An Introduction to the Chinese Healthcare System

Before the transition of the Chinese economy the Chinese government provided free healthcare, either from the public health insurance, including all government employees and military staff or through the labor insurance (financed by the SOEs themselves), including all employees within the SOEs (Guo, 2003). The farmers on the countryside were included in the Cooperative Medical System, where barefoot doctors constituted the main physicians (Blumenthal and Hsiao, 2005; Zhao, 2006). Thus the Chinese government financed all healthcare services, including treatments, drugs, facilities all over China (Guo, 2003; Zhao, 2006). A healthcare system including a large population providing free healthcare resulted in large and increasing expenditures for the Chinese government. In such a healthcare system there were no motives for users such as hospitals, doctors or patients to lower the spending on healthcare, and this created an untenable situation (Guo, 2003).

With the introduction of the "open-door policy" the healthcare system also changed. In line with the transition, the Chinese government decentralized the economic responsibility of the healthcare sector to local and regional governments. Thus the Chinese central government decided not to continue with the generous financial support of the healthcare system; instead regional and local governments became responsible to sustain and finance a large part of the healthcare system. To be able to pay for increased healthcare expenditures, local governments were forced to make changes such as increased taxes, which especially had negative effects on rural areas with poor populations. (Blumenthal and Hsiao, 2005) Along with the transition came the gradual reformation of the SOEs including pressure on the SOEs to cover their own costs resulting in a large part of SOEs going out of business. As a consequence many Chinese workers were left outside of any healthcare insurance, since the labor insurance was connected to the work unit within the SOEs and did not cover unemployment (Guo, 2003). Along with the reformation came the dissolution of the commune system of the farmers, as a result around 900 million people ended up without any medical care (Blumenthal and Hsiao, 2005). Thus with the transition to a "socialistic market economy" a majority of the Chinese ended up with no healthcare benefits at all. It is estimated that individual payments for healthcare increased from 20% in 1978 to 58% in 2002 (Ibid). At the same time the Chinese Central government reduced its national expenditures on healthcare radically from 32% in 1978 to 15 % in 1999 (Blumenthal and Hsiao, 2005).

As the reimbursement of healthcare shifted from being fully covered to being only partially covered by the Central government so did the pricing of healthcare including services and drugs. The earlier governmentally fixed prices for healthcare set up by the State Development Planning Commission (SDPC) were relaxed, and providers of healthcare and drugs such as hospitals and clinical units could adjust prices of healthcare services and drugs by themselves within certain limits. Basic healthcare services remained tightly controlled by the central government and were offered to the patients at a low price; how-

ever, the reimbursement from the central government usually did not cover the cost of this basic care (Eggleston and Yip, 2004; Blumenthal and Hsiao, 2005). To balance the reduced reimbursement from the government, higher prices on new technology treatments were allowed, including higher margins on drugs. Thus to fill the gap between the cost of basic services it was possible for hospitals to get higher revenues from specialized care, high-tech services, and drugs (Eggleston et al., 2008). Since Chinese hospitals are the main owners of Chinese drug stores, the hospitals could attain revenues from drug sales. With the relaxed pricing system hospitals could sell pharmaceutical drugs with a mark-up of 15% on the wholesale price for generic chemical drugs (Eggleston and Yip, 2004; Blumenthal and Hsiao, 2005) and a 20% margin on the TMC drugs, along with a mark up at 25-30% on novel or biopharmaceutical drugs (Gross, 1998). As a consequence there was an "over-prescription" of drugs along with an increased use of specialized healthcare services in China (Eggleston and Yip, 2004; Blumenthal and Hsiao, 2005). The increased prescription of drugs and of expensive treatments was spurred by the fact that hospitals introduced bonus systems based on the revenue of each doctor. Thus the increased costs for drugs have been paid for by the individual Chinese. It is estimated that around 60% of Chinese hospitals' total income comes from drugs sales (Guo, 2003; Blumenthal and Hsiao, 2005). The increased use and sales of drugs are evident in the expenditure of total healthcare in China, where between 50-60% is related to payments for drugs. This differs a lot from the US, where only 10% is related to drug expenditures, and the EU, where 18-25% is related to drug expenditures (Chen and Schweitzer, 2008).

In trying to establish a new healthcare system, the Chinese government introduced the New Health Insurance system in 1998, including all employees in companies and government in urban areas. Both the individual employee and his/her employer pay for the insurance system, 2% of wages from the employee and 6% of the salary from the employer (Guo, 2003). Still the insurance only includes basic healthcare services; thus the new healthcare system still requires a lot of individual payments from the insured. It is estimated that more than 60% of total healthcare expenditures are paid by the individual Chinese patients themselves, with insurance paying around 30%, where the main insurance service is related to basic care along with basic chemical drugs and TCM drugs, i.e., no biopharmaceutical drugs are included in any healthcare insurance at this stage (Blumenthal and Hsiao, 2005; Zhou, 2006).

The main providers of healthcare and thus the main users of drugs but also prescribers of drugs are the Chinese hospitals. Around 90% of all hospitals are owned by the government, while the remaining 10% are private (Eggleston and Yip, 2004). These hospitals treat end-users, i.e., patients, but these hospitals also perform clinical trials of new drugs. However, to be a clinical unit the hospital needs to be certified by the SFDA as a Clinical Pharmaceutical Research Base adhering to Good Clinical Practice (GCP). In spreading the use of drugs and handling the treatment of patients and clinical trials, medical expertise is a necessity, including doctors, nurses, and clinical personnel. With the transition,

hospitals began to compete for patients, and around 80% of all healthcare expenditures were related to large urban hospitals in spite of the fact that 70% of the Chinese population still lives in rural areas (Hew, 2006). This indicates that urban Chinese can afford to pay for the increasing healthcare services, while poorer rural Chinese cannot. Thus there are major inequalities between Chinese rural and urban areas when it comes to healthcare. The education of Chinese medical expertise can be questioned: for instance, 70% of village doctors have no more than high-school diplomas along with 20 months of medical training (Eggleston et al., 2008). The drugs that mainly circulate in the healthcare system are generic chemical drugs and TCM drugs. Looking specifically at biopharmaceutical drugs there are around 35 biopharmaceutical drugs on the Chinese market, although these biopharmaceutical drugs are mainly generic drugs (Zhou, 2006). It is estimated that more than 90% are generic drugs and 3-7% consists of novel biopharmaceutical drugs (Kermani and Zhou, 2007; Frew et al., 2008). As a consequence, hospitals and the medical expertise are used to use generic chemical and TCM drugs in medical treatment, while the treatment using biopharmaceutical drugs is less common; however, a majority of these "scarce" drugs are generic ones.

In the coming Chapters 7 to 11, five cases are presented. These cases are descriptions of five new drug innovation processes in China. As mentioned the sequence of the cases is decided by the degree of embeddedness of each new drug within the three settings, the developing, producing and using settings. This means that the least embedded new drug is presented in Chapter 7 and the most embedded new drug is presented in Chapter 11. Each case is followed by an analysis of the innovation process, and each chapter ends with a short summary of the main findings of the case. While reading the cases, it is important to bear in mind that the thesis purpose is to gain a greater understanding of the creation of government-initiated biopharmaceutical drugs in China.

CHAPTER 7: TECHNOLOGY TRANSFER — THE CASE OF AN ANTI-CANCER DRUG ORIGINATING FROM KOREA

In the mid 1990s a Chinese company, Xin Pharmaceutical,[35] decided to enter the field of biotechnology by establishing a research department focusing on the development of biopharmaceutical drugs. Some years later a Korean company attained a patent related to a molecular structure inhibiting the growth of cancer cells. These two companies are interconnected in the following case, where the innovation process of an anti-cancer drug is presented.

Xin Pharmaceutical: a Pharmaceutical Company with a Long History

Xin Pharmaceutical is a large state-owned pharmaceutical company with a long history. The company can be traced back to the early 1920s and the establishment of several pharmaceutical laboratories that was developed into separate pharmaceutical companies, one of which was Xin Pharmaceutical. The company was actually established in partnership with a foreign doctor, but he sold his share at an early stage in the company's history. The company is based in Shanghai and during its development has focused on developing chemical drugs for various uses. Today the company consists of more than 6,000 employees and around 17 subsidiaries all over China with the production of more than 1200 pharmaceutical drugs. During Xin Pharmaceutical's long history in China the main headquarters have been located in the central parts of Shanghai, but due to worn out facilities Xin Pharmaceutical moved to new facilities to the Shanghai Jinqiao Export Zone close to the Zhangjiang High-tech Park in 2005. As of 1996 Xin Pharmaceutical is a subsidiary to the large state-owned conglomerate, Shanghai Pharmaceutical Group. The pharmaceutical group concentrates on three main business areas: TCM, chemical medicine and antibiotics, Over the Counter drugs (OTC). A majority of all pharmaceutical SOEs in the

[35] Re-named for anonymity reasons.

Shanghai area are part of the Shanghai Pharmaceutical Group. In total there are around 60,000 people working within the group.

Starting Off by Establishing a Biotechnology Research Department

In the mid 1990s when the Chinese government emphasized the promotion of biotechnology as a future high-tech industry for China, Xin Pharmaceutical was encouraged to widen its portfolio to also include biopharmaceutical drugs. Hence Xin Pharmaceutical's existing research department, Xin Pharmaceutical Drug Research Institute,[36] was developed to also include research on biopharmaceutical drugs. As a result the research institute was divided in four main research departments: formulation of drugs, synchronized medicine, TCM, and a biotechnology department. In total around 40 people are working at the research institute. However, when Xin Pharmaceutical decided to develop biopharmaceutical drugs there were few people working at the company with knowledge of and experience from biotechnology research and development. Therefore Xin Pharmaceutical employed a scientist with a doctoral degree in biochemistry from a prominent Chinese university as chief scientist of the new biotechnology department in the late 1990s. The Chinese scientist had more than 15 years' experience from biotechnology research at both universities and research institutes in China. Another ten researchers were also employed to be based in the biotechnology department, most of them just graduating from university but all of them with at least bachelor's university degree in biotechnology and engineering, two of them holding a master's degree in biochemistry. To establish the new biotechnology department investments were necessary not only in personnel but also in new equipment. With the new biotechnology department and some equipment in place, Xin Pharmaceutical only lacked a biopharmaceutical drug project to be further processed into a new drug.

Finding a Korean Research Project with a Little Help from a Chinese Intermediary Agency

Xin Pharmaceutical had an established relationship with a Chinese intermediary agency that provides suitable research projects on a regular basis. The Chinese intermediary agency started out as a state-owned company focusing on research in pharmaceuticals but has been transformed to an agency only focusing on

[36] From now on referred to simply as the research institute.

connecting pharmaceutical and biopharmaceutical research organizations and companies. There are around 50 employees working at the agency, which is now a semi-public company with an established subsidiary in the US with the main mission to establish contacts between American and Chinese companies or research organizations. When Xin Pharmaceutical was looking for a first biopharmaceutical drug project to exploit, the agency became an important company once again.

At the same time as Xin Pharmaceutical directed attention to biopharmaceutical drugs in the mid 1990s, a research team at a South Korean university discovered a new compound for cancer treatment. A spin-off company was established around the patent that was achieved in 1997, which included the molecular structure, the function and the potential usage of the invention. The professor of the research department at the Korean university in charge of the basic research also became the president of the new company. After doing basic research for several years (estimated 5-8 years) at the university and the establishment of the new Korean company, a search started for an external collaborative partner to commercialize the discovery. At an earlier stage, in the early 1990s, the Korean professor was doing research in the US. During his stay in US the Korean professor met representatives from the Chinese intermediary agency arranging cooperation between foreign and Chinese research organizations and companies. Thus a few years later when the Korean professor was searching for an external partner for the new Korean company, he contacted the Chinese intermediary agency with the request to find a suitable Chinese partner to develop the Korean research into a commercial product.

To summarize, both Xin Pharmaceutical and the Korean company were searching for suitable collaborative partners and both already had established relations with the Chinese intermediary agency. Thus the Chinese intermediary agency approached Xin Pharmaceutical and asked if they were interested in commercializing an anti-cancer drug project with a Korean research partner.

Signing a Research Agreement and Transferring the Project to China

In 2001 Xin Pharmaceutical and the Korean company were introduced to each other by the Chinese intermediary agency. An expert group within Xin Pharmaceutical was formed in order to evaluate the potential biotechnology drug project. The chief scientist of the biotechnology department became the head of the project group, which also consisted of experts in engineering, clinical and pre-clinical research, purchasing, and financing from other departments within Xin Pharmaceutical. As a point of departure in evaluating the Korean drug project the Korean professor did a presentation of the basic research for the expert group at Xin Pharmaceutical, where the experts could ask questions and

discuss certain part of the process in detail. In order to ensure the research quality Xin Pharmaceutical and the biotechnology department in particular studied the basic research results and the animal samples, which looked promising for further development in China. The expert group proposed to continue and further develop the Korean drug project to the top management, emphasizing the potential in developing a drug for cancer treatment. Also the fact that the Korean drug relied on a patent facilitated the decision to team up with the Korean company, along with the fact that the drug project had passed the critical basic research phase.

Two years after the Chinese intermediary agency contacted Xin Pharmaceutical, in early 2003, a research agreement was signed between the two parties. At this stage the Korean company had finished basic research. According to the agreement Xin Pharmaceutical was supposed to further develop the research project in China, i.e., take the project through pre-clinical phases along with clinical one, two, and three trials. Xin Pharmaceutical would pay altogether US$ 500,000 to the Korean company for the licensing of the patent and the technology transfer of the drug project from Korea to China. As a first payment Xin Pharmaceutical paid US$ 15,000 to be able to perform pre-clinical trials in China. According to the agreement the Korean company owned the original patent and would get 30% of the sales of the final product during the first five years of sales and thereafter Xin Pharmaceutical would get full ownership of the product.

In spring 2004 the actual transfer of the drug project from the Korean company to Xin Pharmaceutical started. The Korean professor in charge of the discovery handled the transfer along with some doctoral students. Both parties, the Korean company team and the research team from the biotechnology department, collectively performed the whole research process from fermentation to purification of the substance.[37] As it turned out the drug discovery in Korea had been performed by using manual laboratory systems. During a two-month period the two research teams repeated the development process together until the research team at Xin Pharmaceutical had enough background information about the development process. From then on, Xin Pharmaceutical, more specifically the biotechnology department, was supposed to proceed with the development by themselves, though with some support from the Korean company.

[37] It is interesting to keep in mind that the both parties used English to communicate although both parties speak English very poorly.

Investing in New Separation Equipment

When Xin Pharmaceutical entered the research agreement with the Korean company in early 2003 the need for investment in equipment became obvious. In order to handle the production of substances for the coming pre-clinical and clinical 1-3 trials, equipment that could handle larger scale production, especially for the clinical trials, was a necessity. Since the purchasing policy at Xin Pharmaceutical is to buy equipment in connection to new large development projects, the expert group set up to evaluate the Korean drug project also proposed suitable investments in separation equipment in order to further process the Korean research into a new drug. When the chief scientist was employed, he invested in one ÄKTAexplorer™[38] supplied by GE Healthcare[39] as main lab separation equipment. The chief scientist was a longtime user of ÄKTA systems, and since the introduction of ÄKTA equipment at the biotechnology department, there were close contacts between the biotechnology department and GE. For instance, investments in new separation media have taken place on a regular basis, and GEs' sales representatives and technical supervisor have introduced new products to the department. When investing in separation equipment for the future development of the Korean drug, the expert group suggested the purchase of ÄKTApilot™[40] supplied by GE. The chief scientist's being an experienced user of ÄKTAexplorer and having experience from ÄKTA systems facilitated the decision to scale up using a similar system, the ÄKTApilot. As a complement to ÄKTApilot, ÄKTApurifier™ was suggested as a second investment for process optimization and standard improvement of the purified substances. The chief scientist presented the expert group's evaluation of suitable new separation equipment to the top management. A week later a final purchasing decision was made by top management to proceed with the investments and purchase of separation equipment from GE.[41] Within six months the planning and evaluation of the system were completed, and an actual purchase agreement was signed. In December 2003 the new purchase agreement was signed including one ÄKTApilot and one ÄKTApurifier along with suitable columns and media. The following spring in May, the systems were installed at the biotechnology department by GE's technical supervisor. By arguing that Xin Pharmaceutical is involved in high-tech development with

[38] ÄKTAexplorer is a separation system specially designed for small-scale lab research. The system is the most common separation system in China.
[39] From now on only referred to as GE.
[40] ÄKTApilot is a system developed as a link between lab and production scale. The system is suitable for operating on a scale between lab and production for small-scale production, complying with sanitary requirements put up by the American FDA and cGMP. ÄKTApilot can handle around four times larger scale compared to the ÄKTAexplorer.
[41] According to the chief scientist at the biotechnology department it is easy to get an approval by top management as long as you can present a detailed evaluation.

the need for high-quality equipment, the company received a tax reduction on the imported equipment from the Chinese government.[42]

When evaluating the investments in new equipment, the chief scientist has been the main driving force. As mentioned he has extensive experience working with separation issues, both in theory and practice, and 15 years' experience in using ÄKTA systems. Nonetheless, the rest of the research team at the biotechnology department was lacking practical experience with protein separation, since most of the ten researchers are young and newly graduated. The lack of practical experience is reflected in the Chinese education system, where theoretical instead of practical issues are emphasized. Also, there is a lack of high-quality equipment at the Chinese universities, thus when graduating from university the students do not have the practical experience of actually using automated chromatography systems. As a result when employing newly graduates the chief scientist has been forced to teach protein separation in practice including the use of specialized high-quality separation equipment. Furthermore, the main equipment supplier, GE, has played an important role in training and supporting the personnel at the biotechnology department by providing ÄKTA training to the employees.

The Pre-clinical Process of the Anti-cancer Drug

The pre-clinical production process is as a two-step process, starting with the fermentation phase, using bioreactors supplied by domestic Chinese suppliers for growing the cells. Then the proteins are gathered and concentrated into a sample using a centrifuge and ultra filtration system also supplied by domestic suppliers. The whole fermentation phase will take around five days. In the following purification phase ÄKTAexplorer was used as the main purification equipment to start with but replaced by ÄKTApilot due to the need of larger scale production for the pre-clinical samples.[43] The main separation equipment, ÄKTApilot, can only be used by three senior staff members at the biotechnology department including the chief scientist, according to company policy. After running the ÄKTApilot the sample needs to be further concentrated by using a filtration system from American supplier PALL. The last step is to

[42] Chinese government policy prioritizes the support of the domestic equipment suppliers. There are some Chinese suppliers providing separation equipment, but it is of very low-quality. However by negotiating with the government a tax reduction is possible. Purchasing and using imported and high-quality systems also reflects the intention to produce new drugs and research according to existing requirements, not only copying existing drugs.

[43] The biotechnology department has had some contacts with GE for technical consultation setting up the pre-clinical production. The chief scientist mainly uses the technical support from GE to verify suitable solutions when having problems, which reflects the chief scientist's extensive working experience from chromatography.

freeze-dry the sample and prepare it to be used for the pre-clinical trials. Altogether the purification of the pre-clinical production takes approximately two days. The final formulation step is not needed in the pre-clinical phase; it is just a matter of dissolving the freeze-dried powder into a liquid substance before using it for the pre-clinical trials. The pre-clinical phase is developed in accordance with Good Laboratory Practice (GLP) certified by the SFDA.

The chief scientist is in charge of the whole development process of the Korean drug. Nevertheless, it is the first time he is in charge of directing a whole development process to final production. During earlier experiences he has been managing one step of the development process, for instance developing and producing pre-clinical substances for one project and clinical substances for another. The chief scientist reports to the vice president what the research team has done on a daily basis and these daily reports are the basis of monthly meetings between the chief scientist and the vice president.

Problems with the Pre-clinical Preparation, Back to Basic Research

After transferring the drug project to Xin Pharmaceutical the Korean researchers would continue with finding new areas of use for the discovery and the compound in focus, while the research team at the Xin Pharmaceutical biotechnology department started out their own development and refinery of the process developed by the Korean company. Already during the technology transfer period the research team at the biotechnology department realized that the development process could be further improved, much due to the use of manual systems in basic research. The biotechnology department started out by repeating the earlier development process in order to find more efficient development methods that could lay the groundwork for the pre-clinical trials. After the Korean company left Xin Pharmaceutical, the research team at Xin Pharmaceutical worked intensively for a two-month period to produce the right substance for the pre-clinical trials.

After two months the research team encountered problems with the substances. A protein-based drug needs two main components: first of all, a satisfactory level of purity for the actual protein substance[44] but also a satisfactory level of activity[45] for the protein in order to act effectively as a drug. The research team reached a satisfactory protein level easily, but the activity level was not as easy. Something happened with the activity level in the development process. Was the problem related to the fermentation phase or the purification phase or perhaps even further upstream? In order to proceed with the devel-

[44] Purity refers to a clean protein without contaminants.
[45] Activity refers to the efficiency of the purified protein related to a certain disease.

opment process Xin Pharmaceutical needed to present both sufficient purity and activity levels. To locate and solve the activity problems interactions between the biotechnology department at Xin Pharmaceutical and the Korean company followed, where the Koreans focused on the basic structure and function of the molecules, i.e. the basic research, while the biotechnology department concentrated on the pre-clinical process including fermentation and purification. After six months the activity problems were not yet solved, and after checking the whole process in detail over and over again, the biotechnology department did something unexpected and checked the gene sequence provided by the Korean company with the original patent from 1997, which was published in a gene bank on the Internet. Then in the early spring of 2005 Xin Pharmaceutical discovered the root of the activity problem, the protein in focus was expressed in the gene sequence provided by the Korean company, and the biotechnology department realized that the Korean company had provided the wrong gene sequence. There was a difference with the nucleotides in the gene sequence from the Korean company compared with the original patent, one of the four main components, ACTG, had been changed somewhere along the way. Thus Xin Pharmaceutical blamed the Korean company for the delays of the development and claimed an alteration of the signed research agreement and the payments of the patent licensing. According to Xin Pharmaceutical the Korean company would need to pay back some of the US$ 15,000 patent licensing already paid. Before the discovery of the gene sequence mismatch the Korean company and the biotechnology department communicated on a weekly base, both trying to solve the activity problem. When Xin Pharmaceutical suggested a reimbursement from the Korean partner and a change in the research agreement, the Korean company decided to keep a low profile and did not get back to the biotechnology department at Xin Pharmaceutical for more than six months.

Due to the non-response of the Korean company, the biotechnology department continued with the development without help from the Korean company. Because of the wrong gene sequence the biotechnology department was forced to go backward in the development process, back to do the basic research and drug discovery phase based on the right gene sequence.[46] Nevertheless, the research team in the biotechnology department did not have much earlier experience from basic research; instead the chief scientists' main experience was from pre-clinical and clinical research. Basic research is more difficult to interpret, and one argument in buying the Korean project was the opportunity to focus on clinical development phases rather than on unpredictable basic research. However, due to the delays and the investments already made in the project, Xin Pharmaceutical decided to proceed with the basic research. One result of the alteration of the research focus from pre-clinical phase back to

[46] In China it is possible to reverse the development process as long as it is fully documented and filed according to SFDA regulations.

basic research is the scale of substances. In basic research the scale is small and thus the biotechnology department changed its main equipment and started to work with lab equipment once again, i.e. ÄKTAexplorer. After six months of basic research Xin Pharmaceutical was contacted by the Korean company in order to settle the disagreement. The company did not get any of the patent payments back, but the Korean company agreed on a deduction of the percentage of the final drug sales, thereby leaving Xin Pharmaceutical with more of the sales turnover for the final product. However, due to the activity problem, the development process of the biotechnology project had been delayed by more than a year. Altogether the biotechnology department at Xin Pharmaceuticals spent around one year to finish the basic research in China based on the right sequence.

Developing the Anti-cancer Drug with Support from the Chinese Government

Investing in biotechnology has not been a cheap task for Xin Pharmaceutical. In order to pay for the development of the new biopharmaceutical drug project, Xin Pharmaceutical needed financial support; for instance, Xin Pharmaceutical needed to pay for the patent licensing and new equipment when developing the biotechnology department. How has Xin Pharmaceutical been able to pay for these investments? There are different financiers in the background, all of them public, not surprisingly because Xin Pharmaceutical is a large public company. Since 1996 Xin Pharmaceutical is a part of the large Shanghai Pharmaceutical Group, one of China's largest Pharmaceutical companies with several subsidiaries in the Shanghai region. The group is owned by the Chinese government through three state-owned companies, Shanghai Invest 1 (30%), China Invest (40%), and Shanghai Invest 2 (30%). Xin Pharmaceutical also has a long history in developing chemical drugs, many of which have been sales successes and have generated a lot of money for Xin Pharmaceutical. Furthermore, Fazhan gaige (the New Technology Development Fund), a national governmental fund, has granted around RMB 5 million (US$ 625 000) in financial support for the development of the anti-cancer drug. The drug project also has government support status, which in initial stages provides advantages such as tax deductions on imported material. Further downstream in the production phase, Xin Pharmaceutical can get some reimbursements of the development costs of the anti-cancer drug from the government.

Looking Ahead — The Future of Xin Pharmaceutical

Xin Pharmaceutical was aiming to finish the pre-clinical studies of the anti-cancer product during 2008. The users of the future drug are hospitals and doctors and the anti-cancer drug is an injection substance to be supervised by doctors and medical staff. The end-user, the patient, will need approximately 20 injections doses during the whole treatment period.

Due to the fact that Xin Pharmaceutical is a large company with many subsidiaries and an established sales and distribution structure, the actual distribution of the future product to the hospitals will be managed by Xin Pharmaceutical sales companies. The company is aiming for class-one NDA for the anti-cancer drug and aspires to export the future drug and thus produce according to existing regulations. One main determinant of choosing to proceed with the Korean drug project was the fact that the research was based on a patent. Xin Pharmaceutical bought a production facility in 2001 from an old chemical producer in Shanghai. At this point around 200 relatively low-quality drugs are produced in the production facility, and this cGMP-approved facility is supposed to handle all biopharmaceutical drug production. Nevertheless, in order to be able to produce biopharmaceutical drugs the company needs to invest in new high-quality equipment in the production facility.

The biotechnology department at Xin Pharmaceutical started out by developing the anti-cancer project as first drug project for the newly formed department. However, since then two other biopharmaceutical drug projects have been bought and developed in parallel with the first anti-cancer drug. These drugs are also being developed with an external partner. Xin Pharmaceutical bought them in later stages of development in order to skip the uncertain drug discovery phase. One of the two new projects has come further downstream than the anti-cancer drug, partly due to delays in the development of the latter along with the fact that the new drug project was bought in a later stage of development. This new project is a skin treatment, an alfa B Growth factor product, and it is used for repairing and restoring human skin. In late 2006 the skin product was approved NDA from the SFDA. Xin Pharmaceutical has a central clinical department in charge of handling all contacts with the SFDA along with the clinical hospitals involved in the clinical trials. However the actual start of production of the skin product has been delayed due to problems with a new contractual agreement with the biochemistry research institute developing the basic research for the skin treatment. The production of the skin product has been set up in the new research facilities in Jinqiao Export Zone but on a very small scale, which is reflected by the fact that ÄKTAexplorer is used as main purification system in the production process.[47] ÄKTAexplorer has mainly been used for developing the anti-cancer drug, but over time the use

[47] In China it is accepted to use ÄKTAexplorer in production, in Western countries ÄKTAexplorer is not a production system complying with sanitary requirement according to the FDA but it is only used in a research setting.

of ÄKTAexplorer has changed to also be included in the production process of the skin treatment product. Xin Pharmaceutical hopes to scale up the production when sales begin to increase.

A Timeline of the Innovation Journey of the Anti-cancer Drug

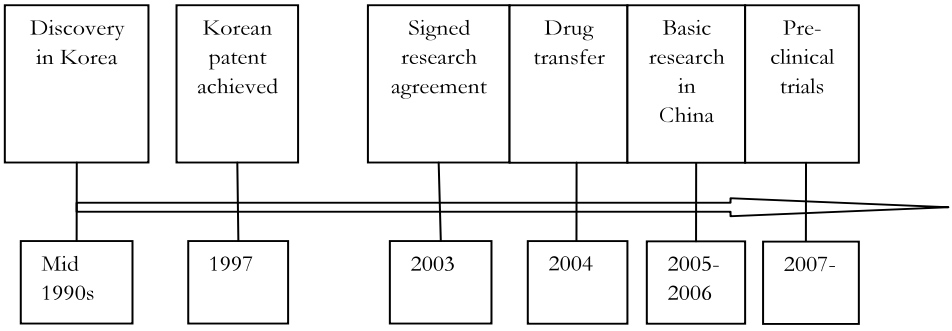

Figure 4. Timeline of the anti-cancer drugs innovation journey.

Analyzing the Embedding of the Anti-cancer Drug

When analyzing the anti-cancer drug case, we will focus on what resources the new solution has interfaces with, in a developing, producing, and using setting. The interfaces reflect the four resources elements of the 4R model, and thus the interfaces are of two main types: the anti-cancer drug and interfaces involving social resources and the anti-cancer drug and interfaces involving technical resources. The following figure summarizes the resource interfaces related to the new drug solution in the developing, producing, and using setting.[48] In this case it is evident that there is no embedding of the anti-cancer drug within the producing and using stetting, instead the anti-cancer drug is limited to interfaces within the developing setting. The following sections will thus analyze the resource interfaces that the anti-cancer drug encountered while being developed.

[48] Organizational relationships are not included in the figure.

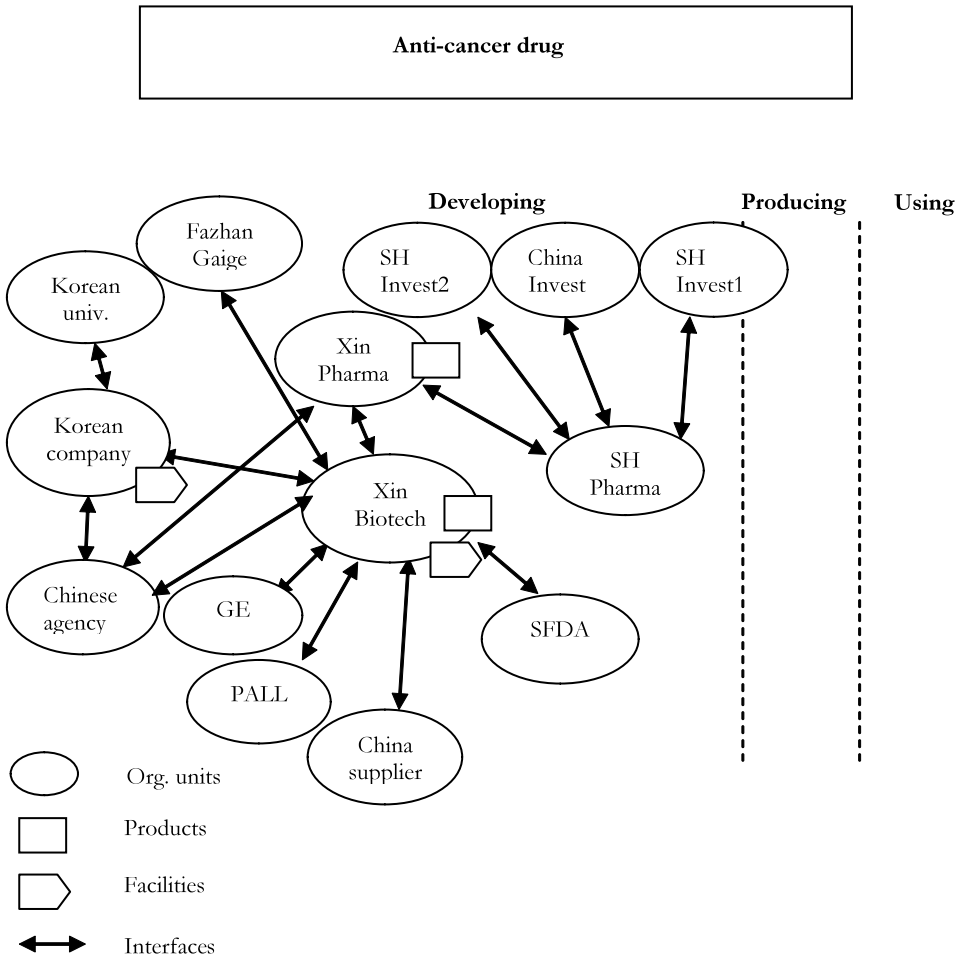

Figure 5. The embedding of the anti-cancer drug.

The Anti-cancer Drug and Interfaces in the Developing Setting

If we investigate the interfaces between the anti-cancer drug and *a) organizational units* in the developing setting we can identify strong interfaces to knowledge units in both Korea and China. The original drug discovery was made by a *research team at the Korean university*, which resulted in an approved patent belonging to *the Korean company*. Thus it was these knowledge units that were in charge of the initial discovery and the reason for starting further development of the new drug. As the case points out the Korean professor played a significant role in the drug discovery but also in establishing the Korean company as an organizational unit. In transferring the anti-cancer drug to a Chinese developing set-

ting, the *Chinese intermediary agency* became an important unit in providing contact between the Korean company/university and Xin Pharmaceutical. The unit had through government support and ownership established contacts with Chinese research groups and scientists. Along with the presence in the US the agency established contacts to research groups and pharmaceutical companies and organizations interested in opportunities in China. Within the developing setting in China *Xin Pharmaceutical* became the main unit responsible for developing the anti-cancer drug. Xin Pharmaceutical is an established company with long experience of developing and producing pharmaceutical drugs in China. Thus the anti-cancer drug could take advantage of the established resources within Xin Pharmaceutical while being developed. Nevertheless, the unit did not have the knowledge needed to pursue biopharmaceutical drug development. Instead, Xin Pharmaceutical established an internal knowledge unit, *Xin Biotechnology department*, managed by a chief scientist in charge of the development of the new drug. However, the knowledge unit still lacked experience from drug development projects and needed to connect to other units to get access to more knowledge. As a result the main supplier unit, *GE Healthcare*, played an important role not only in supplying equipment but also in training the researchers. Also, other supplier units such as the *American PALL* along with *Chinese supplier units* have been realizing the development of the new drug in China. To be able to start to develop the anti-cancer drug in a Chinese setting, including establishing the internal knowledge unit with both personnel and equipment, Xin Pharmaceutical needed contacts to financing units. Here the anti-cancer drug displays strong interfaces to financing units belonging to the Chinese government: the state-owned *Xin Pharmaceutical*, and *the Shanghai Pharmaceutical Group* owned by the Shanghai government and the central government, along with *Fazhan gaige*. The regulatory unit, *SFDA*, is affecting the development of the anti-cancer drug in that the research team at the knowledge unit within Xin Pharmaceutical needs to develop the new drug in accordance to good laboratory practice (GLP) along with technical guidelines related to preclinical trials set up by the SFDA.

In analyzing the interface between the anti-cancer drug and *b) organizational relationships* there are two relationships crucial in development of the new drug: *the relationship between Xin Pharmaceutical and the Chinese intermediary agency along with the relationship between the Korean company/univ and the Chinese intermediary agency*. Both Xin Pharmaceutical and the Koreans had an established relationship with the Chinese agency. Through these established relationships the Chinese agency became an important unit in establishing a *new relationship, between Xin Pharmaceutical and the Korean company*. If we look closely into this relationship there is a clear division of labor between the units. I would characterize the relationship as rather weak, lacking both long-term interaction and commitment. It was due to the weakness of the relationship that solving the activity problems related to the anti-cancer drug took time. On the other hand, there is an interactive relationship between the main supplier unit*, GE,* and the knowledge unit*, Xin biotechnology department*. As mentioned the supplier unit not only

supplies equipment but also knowledge and training of the researchers to be able to continue with the development of the drug. It is evident that the anti-cancer drug has strong interfaces with *established relationships with financing units originating from the Chinese government*.

The anti-cancer drug is strongly dependent on *c) facilities* for its development. For instance, the drug discovery in Korea was possible using *manual lab equipment*, which creates difficulties in ensuring the quality of drug substances used for further development. The knowledge unit in China refined the development process by using automated lab systems such as *ÄKTA systems*. Thus using lab equipment such as *ÄKTAexplorer* and *ultra filtration systems* could refine the development technique along with the quality of the pre-clinical substance. Also, there is an important interface between *ÄKTAexplorer*, *ÄKTApilot, and ÄKTApurifier* in taking the anti-cancer drug from drug discovery to pre-clinical trials, using similar system will facilitate further development of the drug. After transferring the drug to China ÄKTAexplorer was used as main separation equipment, however, ÄKTApilot was used in pre-clinical, where larger scale was necessary. Other fermentation equipment such as the *Bioreactors, centrifuge and ultra filtration systems* has been important for the development of the anti-cancer drug in China.

There are weak interfaces to other *d) products*. Nevertheless, the anti-cancer drug has indirect interfaces to *other products belonging to Xin Pharmaceutical.* Thus sales of other products realize the investments in new drug developments such as the anti-cancer drug. Moreover, other products can be used to attract new investors. Also, through other products the anti-cancer drug has connections to the producing and using setting by an established system of sales offices all over China. In 2006 Xin Pharmaceutical was approved an NDA for a product to restore skin, though on a very small scale. Due to the experiences from developing the first anti-cancer drug, Xin Pharmaceutical bought the development project in later development stages in order to avoid drug discovery and the problems associated with it. Knowledge gained through the development of the new skin product can help when the anti-cancer drug enters later clinical stages.

Summing Up

To summarize the case reveals that the anti-cancer drug is very far from actual production and use. In the development of the new drug Korean knowledge units have played a significant role. A government-supported Chinese intermediary agency with established relationships with both Xin Pharmaceutical and the Korean knowledge units were important when establishing a relationship between Xin Pharmaceutical and the Korean counterpart. An interesting point is that Xin Pharmaceutical decided to enter the biopharmaceutical drug world without having experience from biopharmaceutical drugs; thus the company lacked the knowledge necessary to develop a biopharmaceutical drug. As a

consequence the company established an internal knowledge unit that became responsible for the development of biopharmaceutical drugs, then a search for suitable drug projects could start. In retrospect buying a first drug project and taking it through pre-clinical and clinical trials is a difficult journey for many companies, even harder for a company like Xin Pharmaceutical with no earlier experience in biopharmaceutical drugs. Also, the weak relationship between the knowledge unit belonging to Xin Pharmaceutical and the Korean knowledge units delayed the development of the drug further by not being able to solve the "activity issue" together. Instead, the internal knowledge unit reversed the innovation journey and became engaged in drug discovery and basic research. The anti-cancer drug case also display the dependence on government financing units in realizing the development of the new drugs in a Chinese setting. However, as a consequence of the difficulties associated with the anti-cancer drug, Xin Pharmaceutical has decided to buy new drug projects in later stages to enhance the possibility of being able to launch a product in time.

The following table summarizes the interfaces of the new drug and the table emphasize that the new drug is only embedded into the developing setting, while there are no interfaces between the new drug and resources within the producing and using setting. Hence the anti-cancer drug should still be regarded as an invention, and is very far from being regarded as a new drug innovation.

Anti-cancer drug	**Developing**	**Producing**	**Using**
Org. Units	Strong interfaces	None	None
Org. Relationships	Strong interfaces	None	None
Facilities	Strong interfaces	None	None
Products	Weak interfaces	None	None

Table 6. Summary of resource interfaces related to the anti-cancer drug.

CHAPTER 8: COMMERCIALIZING CHINESE MILITARY SCIENCE — THE CASE OF PRO-UK

In August 2005 the clinical phase three trials of a cardiovascular drug for treatment of acute heart attack named Pro-UK[49] was completed by Shanghai Cardio Pharmaceutical.[50] In 2006, Cardio sent in a class-one NDA to the SFDA for the drug. The following case is a description of the innovation journey of Pro-UK.

Cardio as Part of a Large Pharmaceutical Group

Cardio is a subsidiary to the large private-owned pharmaceutical group, the Cardio Group, with only one main private owner. The main owner is also the founder of the Cardio Group, and he is a scientist with long experience in research on Traditional Chinese Medicine (TCM). Before setting up the company he was chief scientist at a military research hospital that focused on TCM research. Due to his experience from TCM research, including the investigation of more than 2000 herbal mixtures, he established the Cardio Group in 1994 with the main purpose of developing and producing drugs based on TCM. Thus the Cardio Group started out focusing only on developing drugs based on TCM, and their first drug, the X[51] drug for treatment of cardiovascular problems, has reached annual sales of more than RMB 1 billion (US$ 140 million). Since the establishment of the group other business areas have evolved, including chemical medicine, healthcare, and functional food and biological medicine. The Chinese government has paid a lot of attention to the group, first of all, appointing the group as a "key scientific and technological industry." But the Cardio Group is also based in an industry park in north China with strong government support. The TCM products have made investments in new ventures and business areas possible, such as the establishment of more than 15 subsidiaries covering the four business areas. All subsidiaries are connected to each other through joint departments for the whole group such as a financial center,

[49] Pro-UK is a compound of molecules that make the blood flow faster.
[50] Shanghai Cardio Pharmaceutical is not the actual name of the company. The name has been altered due to anonymity requirements from the company. From now on Shanghai Cardio Pharmaceutical will be referred to only as Cardio.
[51] Product re-named for anonymity reasons.

a human resource center, an information center but also through the Cardio R&D Institute, where all new drug projects are developed. The R&D Institute consists of more than 100 employees working supporting the development of each business area. A clinical department is also connected to the institute, where all clinical trials performed within the group are managed and controlled, including handling contacts with clinical hospitals and the SFDA.

The actual background of Cardio's biopharmaceutical drug project can be traced to the end of 1999 when the Cardio Group decided to diversify their product portfolio and also include these types of drugs in their production. Nevertheless, the Cardio Group needed to find a suitable biotechnology project that could be transformed into an actual drug. A necessity would be that the project would somehow be connected to cardiovascular use since the drugs already under development were targeting patients with cardiovascular problems. The goal for the Cardio Group is to be market leading in producing cardiovascular drugs, covering all drugs based on a variety of TCM, chemical and biological substances.

Starting Off by Employing a New Director to Develop a Biomedicine Department

How could the Cardio Group find a biopharmaceutical project suitable to be transformed into a drug? A first step to find a suitable drug project was the employment of a manager of the new biomedicine department within the Cardio R&D Institute in 2000.[52] Thus the main argument behind employing a new manager was to find a particular drug project to be exploited and act as the base for a future biotechnology company. Establishing a new department within the R&D Institute as a starting point was a conscious choice, since the actual development of future biopharmaceutical drugs would take place within the biomedicine department. As a result, people working at the biomedicine department would be involved in the development of the new drug from the beginning but also involved in setting up the new department. How did the Cardio Group find a manager for the new biomedicine department? Since biotechnology was a totally new business area for the Cardio Group the group needed a manager with extensive experience from the biotechnology field, both from science and business. Also the Cardio Group was searching for someone with international experience and international contacts. The Cardio Group found what they were searching for in the UK, a Chinese professor working for more than 10 years with experience including both biotechnology research and industry development. Before working in the UK, she had been employed as a pro-

[52] The Cardio R&D Institute is co-located with the Cardio Group at the science park in the north of China.

fessor at a prominent Chinese university. With the new manager in place in 2000, an intensive search for a suitable biopharmaceutical drug project was initiated, along with the establishment of the biomedicine department, which included employing new staff and investing in equipment. Twenty-eight potential drug projects were reviewed and evaluated, and in the end only one project remained interesting, a project originating from a military research institute in Beijing. The Cardio Group bought the project from the military research institute in 2001. Shortly thereafter Cardio was officially established as the first biotechnology company within the Cardio Group. Along with the establishment of the new company, the manager of Cardios' biomedicine department became the managing director of the new biotechnology company, Shanghai Cardio Pharmaceutical.

Finding a Biotechnology Project Originating from the Chinese Military

Cardio bought the project from the military research institute in late 2001. The project is based on urokinase, which can be described as a discovery to make the blood flow faster, which is helpful for patients with cardiovascular problems. The military research institute has a long research history in China and is divided into different departments with a wide range of research activities ranging from basic research to industrial application.[53] The Pro-UK project that Cardio bought was developed within a department focusing on blood research. The department consists of experts in blood-related research with one main scientist and his research team. The start of the Pro-UK project can be traced back to the early 1990s when the military research team discovered a certain compound that inhibits the formation of clots in the blood. From then on the military research team had further developed the project, and when Cardio bought the project, the military research institute had finished the basic research, pre-clinical trials, along with the first clinical trials.

The two parties were introduced to each other during an ÄKTAclub meeting in Bejing arranged by the common equipment supplier, GE Healthcare.[54] At ÄKTAclub meetings GE invites users of ÄKTA equipment to talk about the latest findings using ÄKTA equipment. During this meeting the military research institute presented their latest findings concerning treatment of cardiovascular diseases, the Pro-UK project. Cardio realized that this was the

[53] Before 1978 Chinese military research focused only on military application. However, with the "four modernizations" the military also had to be reformed; for instance, the government invested less in the military and encouraged the military to find financial support elsewhere, thus the military directed its attention to civil society and industrial applications.
[54] From now on only referred to as GE.

project they had been searching for, and the company saw an opportunity in developing the research into a final product. After the initial ÄKTAclub meeting, Cardio bought the project from the institute in 2001, just when the military research institute finished the first clinical phase trials. A signed formal agreement between the two parties exists, and since signing the contract the military research institute has been an important partner in setting up and developing the subsequent development steps, such as clinical phases two and three along with the final production phase. Cardio and the military research institute were already customers to the same supplier, GE. As it happens the military research institute was one of GEs' oldest customers in China, their business relationship dating back to the early 1970s. Four of the nine departments at the military research institute use GE separation equipment, and the separation of the Pro-UK project had been performed by using ÄKTAexplorer. Moreover, the Cardio Group had already invested in both a ÄKTAprime™[55] and an ÄKTAexplorer to be based at the biomedicine department in northern China. Further, the new managing director of Cardio, also director of the biomedicine department, had extensive experience from using GE products for the last 20 years. For instance, she has visited GE's production site in Uppsala twice.

When Cardio was searching for suitable drug projects and attended the seminar held by GE, they already knew about the good research reputation that the military research institute had, especially in blood-related research. But teaming up with the military research institute was not only a question of the best possible drug project but also a matter of access to information. Cardio saw a major advantage in working with a military research institute compared to other research institutes or departments. In a university department there is high employee turnover, with PhDs and researchers coming and going. Thus, in a non-military research institute the basic research knowledge is scattered among many people. By contrast, in a military research institute the employment turnover is low due to the secret nature of the institute's research. Once you are employed by the Chinese military, you are supposed to stay in the military. When developing biopharmaceutical drugs it is important to have detailed information about the basic research and easy access to the people working with the project from the start. By collaborating with the military research institute, Cardio had easy access to the original source and to detailed information. The company is still working closely with the research team at the military research institute. Much information and know-how is not written down or documented but exists merely in the heads of the scientists. Cardio's managing director emphasizes the need for: "Face-to face interaction in an early stage between industry and academia." The intention for Cardio has been to buy a research project externally but to try to gain the best possible knowledge of upstream activities, such as basic science, as possible. By learning more about

[55] ÄKTAprime is a separation system specially designed for the simplest purification in a lab environment.

the upstream activities, the development of the drug in later stages downstream will be facilitated.

Developing the Project Further and Setting Up the New Company in Shanghai

After Cardio bought the Pro-UK project from the military research institute Cardio transferred the project to the biomedicine department within the Cardio R&D Institute. The Pro-UK project was therefore further developed at the biomedicine department at the same time as Cardio was established in Shanghai; thus the Pro-UK project was developed in parallel with setting up the new company. In the first stage it was mainly a matter of finding a suitable location for the company and the future factory in Shanghai. After some consideration it was decided that Cardio would be based in the Shanghai Zhangjiang Hi-tech Park. Being close to the world-leading companies in biotechnology would be a good environment for biopharmaceutical development and production. By locating the new company in the high-tech park Cardio wanted to create an image of state-of-the-art technology and quality or as the managing director of Cardio said: "If you are going to establish a high-level company you also have to be located in an attractive location."

At the biomedicine department the development of Pro-UK continued in close collaboration with the military research institute. There were 23 people working with the Pro-UK at the biomedicine department including the managing director. All employees have university degrees from prominent Chinese universities, with a major in biochemical engineering or the like. The majority of the 22 employees were newly graduated from the university; thus in many cases the managing director has been forced to practically teach and instruct the employees herself with help from the military research institute. When transferring the drug project to the Cardio biomedicine department, the military research institute had just finished first clinical trials in 2001. At the biomedicine department the Pro-UK team began to produce samples for coming clinical trials using GE's equipment, ÄKTAexplorer and ÄKTAprime. The Pro-UK team worked closely with the clinical department (with approximately 15 employees), within the Cardio Group, that handled all clinical trials and contact with the SFDA and clinical hospitals.[56] Clinical trials two and three for the Pro-UK were performed between 2002 and 2005. Around 25 different clinical hospitals were used in different parts of China for clinical phases two and three and

[56] In order to be a clinical hospital you need an approval to be a Clinical Pharmaceutical Research Base by the SFDA. This means for instance that the hospital needs to be certified as adhering to Good Clinical Practice (GCP). Chinese companies can choose by themselves which clinical hospitals to use for the clinical trials as long as these are approved by the SFDA.

all together 600 patients were involved in the trials. Cardio could choose which hospital to use for the clinical trials, as long as they were approved by the SFDA, and the company tried to use hospitals where doctors with good scientific reputations worked, in order to enhance the future drugs' quality and the possibility of publications based on the Pro-UK project.

Investing in Equipment

In late 2002 the Pro-UK research team at the biomedicine department within Cardio R&D Institute moves from the science park in the north of China to Cardio in Shanghai Zhangjiang High-Tech Park. Cardio consists at this stage mainly of the people originating from the biomedicine department in the north of China. They form together an R&D department at the new company. The R&D department is focused on producing samples for the clinical trials. Parallel to the production of clinical samples is the development of the future production process, thus the clinical trials direct the following production process. In order to succeed in developing the Pro-UK, production equipment was a necessity. At this stage GE, which played an important role in connecting Cardio and the military research institute, once more became an important part of the development of the Pro-UK. Since the ÄKTAclub meeting in Beijing GE had been in contact with both Cardio and the military research institute on a regular basis to get information about the development process and the need for equipment. By getting detailed information on the development process GE could understand the need for separation equipment in coming production phases. In late 2002 GE suggested Cardio to buy three 3mm bio-process systems[57] for the new factory and subsidiary in Shanghai. Nevertheless, when ÄKTApilot was launched in early 2003, GE changed the specification to include several ÄKTApilot systems as a complement to the bio-process systems. Cardio was and still is an important customer to GE, much due to the fact that the company is an industrial customer in need of a whole production system where the production will run over and over again with a constant need for consumables. Hence, extra effort was made by GE in handling the sales process. Normally regular sales representatives are in charge of different customers but in Cardio's case the business manager of North China, and the business manager of Asia-Pacific had been involved in the actual sales process. Last but not least the technical supervisor of GE North China has been heavily involved in the sales process, assisting Cardio with technical details. In the technical specifica-

[57] A bio-process system is a large production system for protein separation that can handle large volumes of purification substances. The systems comply with sanitary requirements put up by the American FDA and standards such as cGMP. Since it is a large production system the price is much higher than ordinary lab equipment.

tions it was emphasized that the system must be able to handle high pressure and flow rate along with the capacity to scale up and down, in line with the special benefits of ÄKTApilot. Cardio's managing director was handling the sales and negotiating contact with GE since she also was in charge of the development of the production process where ÄKTApilot and the other separation equipment from GE would be used. The managing director got an approval of the purchase from the president of Cardio Group, and a purchasing agreement was signed in April/May 2004 after negotiations between GE and Cardio. The agreement consisted of the purchase of five ÄKTApilot systems and two 3 mm bio-process systems, along with suitable columns and media. In order to find suitable systems for Cardio, frequent interaction between GE and Cardio was vital. Hence, GE acted as hardware experts, while Cardio focused on setting up the production process guided by the clinical production.

Setting Up the Production Process

The production of Pro-UK will take place at the Cardio factory in Shanghai Zhangjiang High-tech Park. One main issue for Cardio has been to build up a suitable production process. In pharmaceutical production clinical trials direct downstream production; thus much of the actual production process was developed in earlier clinical phases at the military research institute and the biomedicine department. If the technique behind the drug is simple and the research easy to qualify, it will be easy to develop a suitable production process but in Cardio's case the technique is rather complex and has been developed during a long period of time (more than 10 years). Cardio has been developing the production process since they bought the Pro-UK from the military research institute in 2001, where the Cardio biomedicine department and the R&D department at Cardio in Shanghai have been main drivers in setting up the production process. However, the process was developed in close cooperation with the military research institute due to the fact that the first clinical trials were performed by the military research institute.

The production process is divided into the three main steps: fermentation, purification, and formulation. In order to further ensure quality, one employee has the main responsibility for one step. In the fermentation phase, the company uses the newest fermentation technique connected to a special production system, the Cellmate,[58] a tool supplied by a UK firm, The Automatic Partnership (TAP). By using the Cellmate it is possible to harvest larger volumes of cells, although the new technique takes more time, approximately two weeks more, compared to traditional techniques. The Cellmate is an automatic

[58] Up to 2007 only two systems had been sold in Asia, one to Cardio and one to a Korean company.

system with a robot, which has resulted in fewer people being involved in the fermentation step. By using the Cellmate Cardio has cut down the number of people working with the production of cell cultures from ten to two. The company did not buy the Cellmate directly from TAP; GE acted as an agent between Cardio and TAP in supplying the Cellmate. Cellmate is an automated system and therefore rather expensive, costing approximately US$ 600 000. In addition to the Cellmate Cardio has eight fermentation tanks of 300 liters each, which are supplied by a domestic Chinese supplier. As mentioned, two employees are managing the fermentation phase. The following purification phase is divided into five separate steps using one purification system for each step. By using one system for each purification step, Cardio can easily control the quality of the purification. In the first purification step the company uses bio-process system supplied by GE, in the following four purification steps ÄKTApilot is used, one ÄKTApilot for each step; thus four ÄKTApilot systems are used during the last four purification steps. By using a combination of bio-process and ÄKTApilot systems a higher efficiency of the production is achieved: in the initial purification step the scale is large and therefore bio-process systems are suitable; in the following steps the scale diminishes, and thus ÄKTApilot is suitable because it is designed for smaller scale purification. Using bio-processors at later stages would be a waste due to the small scale. Due to larger scale, compared to earlier clinical production, there is higher pressure on the systems in the production process; thus there is need for systems like bio-process and ÄKTApilot that can handle higher pressure. At this moment four employees manage the purification step in the production of Pro-UK. The substance is transformed into an actual injection in the formulation step by using stirs and centrifuges supplied by domestic Chinese suppliers. Total lead time of the whole production process of the drug is approximately two months.

By looking at the use of the systems supplied by GE, ÄKTApilot is a good complementary system to the bio-processors, so the main argument for buying ÄKTApilot was the suitable scale for separation in later purification steps. The military research institute also promoted GE as a supplier for the systems, because of the basic research and the first clinical trials at the institute had been performed using ÄKTAexplorer. Also, the fact that clinical production at the biomedicine department and the production set up at the R&D department at Cardio in Shanghai used ÄKTAexplorer in developing the Pro-UK further facilitated the choice to invest in production equipment from GE. Another important factor was that both the bio-processors and ÄKTApilot support sanitary requirements for production, such as cGMP and legal requirements set up by the American FDA. Using systems that comply with biopharmaceutical regulations will facilitate any future export of the new drug to Europe or the US.

The production team at Cardio did not have any earlier experience from production, but they have been involved in developing Pro-UK by producing substances for clinical trials at the biomedicine department and at Cardio in Shanghai. As they were relatively recent graduates the managing director pro-

vided them with training, with assistance from the military research institute. The managing director emphasizes the importance of both science and business by saying: "We need to train employees to know both worlds [read science and industry]." To summarize, the team has developed the clinical trials at the biomedicine department along with clinical production and production set up at Cardio in Shanghai with extensive help from the military research institute. All of the production employees have also attended ÄKTA system training at GE.

Equipment and Factory Set Up and Problems on the Way…

In parallel with the development of the production process of Pro-UK there was the physical set up of the production facility, the Cardio factory, in Shanghai. Investing in production equipment from domestic suppliers used in the fermentation and formulation step was a relative easy task and did not cause any particular delays or problems. However, in relation to the investment of purification equipment from GE Cardio did encounter some problems. Cardio wanted to import equipment for high-tech production, but the Chinese customs required Cardio to pay full taxes on imported material. The government policy states that as long as you can find similar equipment in China, this is what you should buy; otherwise you have to pay taxes of 17% on imported equipment. By issuing a policy on imported equipment the Chinese government want to promote and support domestic Chinese equipment suppliers. Nevertheless, the definition of *similar* equipment is broad, as it actually refers to any standard protein separation system.[59] There are some Chinese suppliers of purification equipment but these systems do not comply with sanitary requirements set up by the American FDA. According to GE no other company offers a purification system with the particular scale and use of the ÄKTApilot. Cardio initiated negotiations with the government to get a reduction of the tax rate; meanwhile, the GE systems were held at the Chinese customs. Intensive negotiations between Cardio and the Chinese government followed, and Cardio emphasized that the future Pro-UK product would be good for the Chinese people and the development of Chinese high-tech and biotechnology in particular. After negotiations Cardio and the government came to an understanding by reducing the actual tax from 17% to 10%, and Cardio obtained "government status,"[60] and actually in the end Cardio got the imported systems tax-free. Due to the negotiation process with the Chinese government, Cardio did

[59] There are a wide variety of protein separation systems between lab and process scale.

[60] The government status refers to that the company receives government support; for instance, the company will receive benefits such as reduced taxes but also some reimbursement of developing costs when getting the final approval of the new drug.

not receive the purification systems until late December 2004, a delay of four months. When developing business in China government contacts are essential; good relations with the government can facilitate the development process. This is emphasized by the managing director of Cardio: "Relations with government are very important, you definitely need it" or as the production manager at Cardio put it: "Good relations [read with government] will result in more government support."

Along with the delay of the equipment for production there were delays in the building of the factory where the equipment would be set up and used. Since Cardio would produce biopharmaceutical drugs, it was of great importance that the factory comply with existing sanitary regulatory requirements. First the entire factory needed to comply with cGMP.[61] However, the entrepreneur building the factory did not comply with the detailed sanitary requirements put up by Cardio. For instance, Cardio emphasized the importance of an even floor to facilitate sanitary control. Thus Cardio gave instructions that the entrepreneur should first build the working floor of the whole factory then divide the factory into working areas. The entrepreneurs did it the other way around, first dividing into working areas then building the floor; as a result the floor was uneven. As a consequence the factory had to be re-built, with a delay of half a year. The building of the factory started in 2002, and in late 2005 all production equipment was installed in the factory.

Applying for the NDA and Contacts with the SFDA

As the Pro-UK project has been developed, the SFDA has been closely involved in the development process from the beginning. SFDA manages the approval of clinical trials, which is a time-consuming and complex process. First of all, the military research institute sent in an investigational New Drug (IND) in the late 1990s where the SFDA evaluated the pre-clinical trials and validation of the drug's safety in order to be able to proceed with clinical trials. The SFDA approved the IND, and clinical phase one trials of the new drug could start in 2000. Subsequent to this Cardio bought the project and transferred the project to the biomedicine department. When entering the clinical phase two Cardio needed to pass the clinical phase two application from the SFDA along with the following clinical phase three trials based on a validation of the drugs efficiency and the purpose of the drug. Within the Cardio Group the clinical department handled contacts both with the clinical hospitals (around 25 all over China) and the SFDA. Before Cardio could start full-scale production the NDA needed to be approved by the SFDA; also the SFDA

[61] All pharmaceutical production sites in China need to comply with cGMP requirements as of July 2004.

needed to inspect the factory in terms of cGMP. In early 2006 Cardio sent in the NDA application for class one to the SFDA, including three batches of production samples.[62] Due to the fact that SFDA was part of a bribe scandal in 2006, there were delays in the application process for Cardio. Reviewing approved licenses resulted in heavy delays in handling incoming applications on time. The final NDA sent in by Cardio has passed some of the analysis steps; for instance, there is a sufficient activity level of the drug. On the other hand, other aspects remain: for instance, the SFDA has forced Cardio to re-submit documentation on the protein concentration level of the drug. Due to the SFDA scandal, regulations have become stricter; for instance, more testing of the protein concentration level of the final Pro-UK drug is required, which was not a standard when starting the clinical trials in 2002. In total the final NDA approval will take at least one year and the cGMP approval of the production facilities will take at least another three-four months. Moreover, further delays of the final approval are due to the purchase of Cellmate for the fermentation phase. In the application to SFDA Cellmate was not used as part of the production process; thus Cardio needs to validate the Cellmate as new fermentation equipment for the production of the Pro-UK, which will further delay the final approval of the new drug.

The Use of Pro-UK and Other Products in the Pipeline

Pro-UK is the first drug under development for Cardio. The actual drug is to be used in emergency situations and has to be supervised by a doctor at a hospital. During the clinical trials of the Pro-UK, one aspect was to find the right dosage of the drug. The trials started out with 30mg per patient, then increased to 40mg, and in the end the suitable amount would be fully 50mg per patient per heart attack. The amount would be supplied in two doses, first when the patient arrives he/she will get 20mg directly into the vein followed by another 30mg via drip. Cardio estimates a future production of approximately 10 000 50mg doses per month. The sales will be managed through the Cardio Group via wholly-owned sales companies all over China. When Cardio receives the NDA approval along with cGMP, the first step is to supply the new drug to the 25 clinical hospitals used when developing the Pro-UK. In China there are three other companies developing a similar drug, although these companies are not close to finishing the development journey but are still in early development phases. If we look worldwide there is an American company, Abbott, which has a similar product as Cardio aiming to be used by patients with stroke, and the drug was in phase three clinical trials in mid 2007.

[62] Class one refers to a totally new product worldwide.

Apart from helping Cardio to finalize the Pro-UK drug, the military research institute is also trying to find other clinical using areas for the Pro-UK, for instance PE (ing) for stroke and also for Deep Vein Thrombus (DVT) targeting old people. Earlier Cardio also developed another drug in parallel to the Pro-UK project. This was focusing on an anti-cancer drug; however, Cardio discovered that around eight other Chinese companies applied to the SFDA for a similar type of drug. Hence, after finishing the clinical phase one trials Cardio decided to abandon this development project because many other companies were targeting the same drug. If we look at the Cardio Group as a whole, the group has another ten drug projects in the pipeline, although the majority will not be further developed or produced by Cardio. Several of the drug projects are vaccines and TCM products. It is still too early to know which project will be further processed and transformed into a final drug.

Money Invested in Cardio and the Pressure to Deliver

From the beginning Cardio has been sponsored by the privately owned parent company, the Cardio Group, with one main owner, the original founder. The group owns many subsidiaries, and has several products, for instance, the X drug, one of Chinas best selling TCM drug, used for treating cardiovascular problems. Being part of a larger group enables Cardio to be financially sponsored by other companies within the group; thus other products support the development of Pro-UK. Along with support from the Cardio Group the Pro-UK drug project have also received governmental support, for instance the Ministry of Science and Technology (MOST) have granted financial support from the 863 program. Moreover, the drug also got some funding from the "fazhan gaige" (the New Technology Development Fund), a special national governmental fund targeting high-tech ventures. In total Cardio has received approximately RMB 10 million (US$ 1.3 million) from national governmental funds when developing Pro-UK. In early development of Pro-UK at the military research institute there was other government support. Being a military research institute means that the Chinese government partly supports the research performed at the institute but also that the research is partly financed through selling research projects externally to be further commercialized. Thus Pro-UK was initially supported by the government but also other research projects. To sum up, government support has been important for Cardio but not just as a way to get money but also as a means to attract other investors or public attention. Thus getting governmental support enhances the image of a successful company with high-quality products. The majority of the government support was received in the beginning of developing Cardio as a company and the Pro-UK project in particular. Being granted financial support from large national research programs enhances the chances of receiving other financial support (Nilsson et al., 2006).

When the Cardio Group decided to develop biopharmaceutical drugs in the late 1990s the ambition was to create a new business area with approved drugs in just a few years, but since finishing the clinical trials three in 2005, Cardio has felt increased pressure from the Cardio Group to deliver and finalize the development of Pro-UK. The development of Cardio and its products has suffered from delays that the Cardio Group did not count on; hence the Cardio Group let the managing director go from Cardio in April 2006. A new managing director was appointed, the vice president of the Cardio Group. At that time around 80 people were working at Cardio in Shanghai, mainly with R&D and production issues. The main goal for the new managing director was to finalize the development of the Pro-UK drug but also to find other investors. A new investor was a fact in 2006 when Cardio announced the sale of 50% of Cardio shares to an UK investment company.

Epilogue

In 2011, Pro-UK has still not received a class one NDA approval…

A Timeline of the Innovation Journey of Pro-UK

The following figure is a timeline where the drug development process of Pro-UK is summarized.

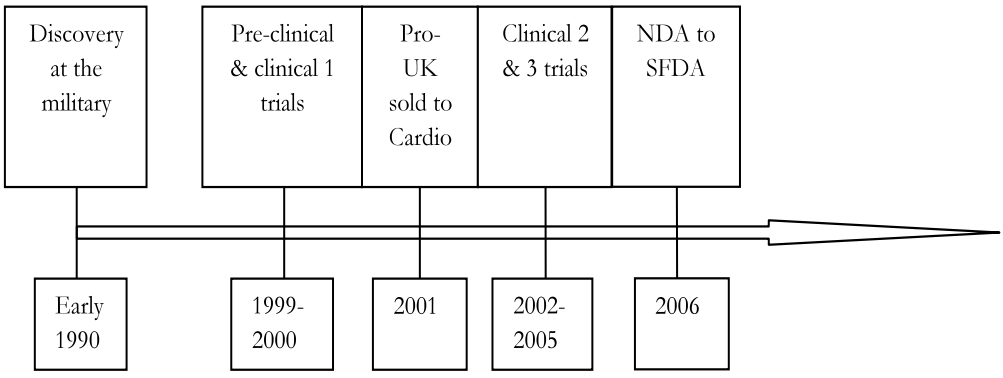

Figure 6. Timeline of Pro-UK's innovation journey.

Analyzing the Embedding of Pro-UK

When analyzing the Pro-UK case, we will focus on what resources the new solution has interfaces with, in a developing, producing, and using setting. The interfaces reflect the four resources elements of the 4R model and thus the interfaces are two main types: Pro-UK and interfaces involving social resources and Pro-UK and interfaces involving technical resources. A first impression of the Pro-UK case is the that interfaces mainly emerged within and across the developing and producing setting, while interfaces to resources in the user setting are weakly represented. The following figure summarizes the resource embeddedness of Pro-UK in these settings[63] and the next sections will discuss the resource interfaces that Pro-UK encountered while being developed, produced, and used.

[63] Organizational relationships are not included in the figure.

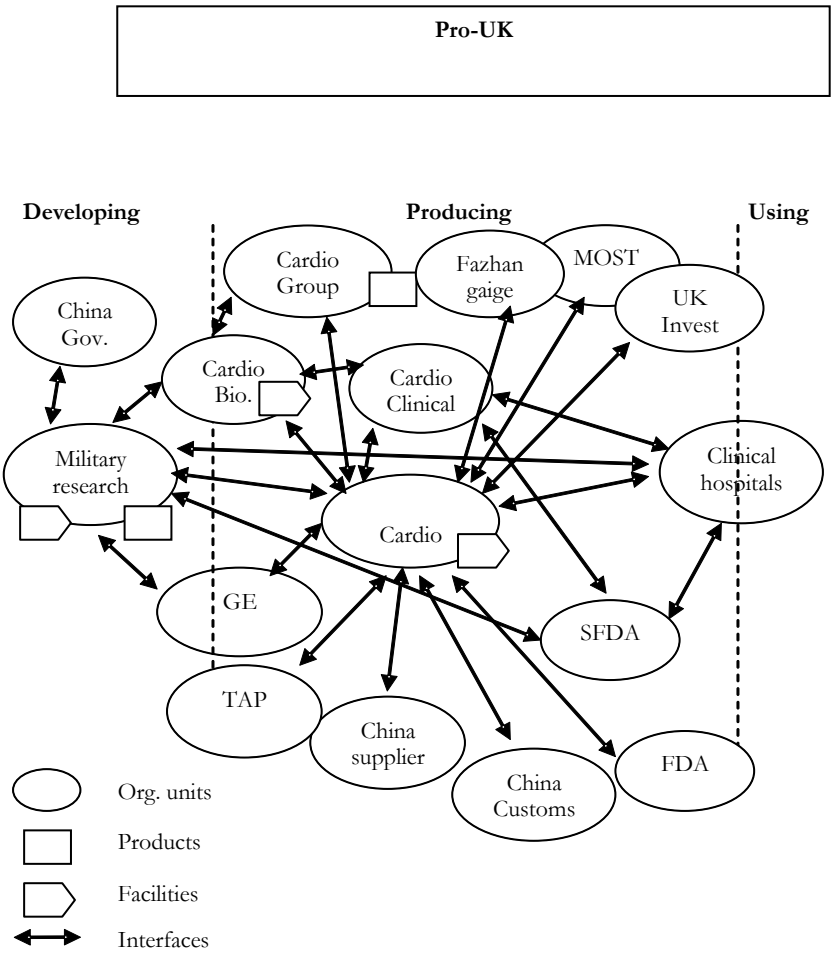

Figure 7. The embedding of Pro-UK.

Pro-UK and Interfaces in the Developing Setting

There is a strong interface between Pro-UK and one *a) organizational unit* in the developing setting, more specifically the knowledge unit responsible for the discovery of Pro-UK, *the military research institute*, the unit in which the new drug solution emerged. It is evident that the features of the military knowledge unit have played an important role in shaping Pro-UK. Thus when Cardio was searching for a potential cardiovascular drug, the company needed to connect to a knowledge unit that had been engaged in advanced scientific knowledge development over a long period of time, and that also had the ability to create a stable and skilled group of researchers engaged in this issue. In aftermath of the

Cultural Revolution, it was probably only a military knowledge unit that had the ability to fulfill these requirements. Moreover in being able to discover the new drug, the military knowledge unit had been depending on financial support, thus in developing Pro-UK there are strong interfaces to *the Chinese government* being the main financing unit. Also, units related to the main producing unit, *Cardio*, such as *Cardio Biomedicine* and *Cardio clinical department*, have been involved in developing Pro-UK. All these units have been involved in setting up and carrying out clinical trials of the new drug.

If we continue with the strong interface between Pro-UK and b) *organizational relationships,* these also appear of be of great importance. It was through the changed *relationship between the military knowledge unit and the Chinese government* that Pro-UK could be further commercialized. The military knowledge unit was partly financed through the government, although the government emphasized the importance of military research to be developed for civil use. The founder of Cardio Group was important since *the relationship between his military unit and the government facilitated the establishment of Cardio Group*, owners of the main producing unit. Thus the discovery and the development of Pro-UK can be seen as a result of the changing conditions for the Chinese military and the changing relationship between the military and the Chinese government. Moreover *the relationship between the military knowledge unit and the main supplier unit, GE Healthcare*, was important in linking the main producing unit and the military knowledge unit together. Also, in being able to carry out clinical trials of Pro-UK there is a *strong relationship between the military knowledge unit and the main producing unit including Cardio Biomedicine and Cardio Clinical department*. Since the military knowledge unit already finished clinical one trials, the unit had already established relationships to clinical hospital units in carrying out these trials. The interfaces to relationships in the developing setting can be summarized as the military knowledge unit's relationship to the government and the military knowledge unit's relationship to GE along with the military knowledge unit's relationship to the main producing unit. These relationships have been determinant for both the discovery and development of Pro-UK and also for the emergence of the main producing unit responsible for the further industrialization and commercialization of the drug Cardio in Shanghai.

Also, the interface between Pro-UK and c) *facilities* in the developing setting has been crucial in developing Pro-UK. Here strong interfaces to lab equipment such as *ÄKTAexplorer,* supplied by GE Healthcare, made the discovery of Pro-UK and its molecular structure possible, which was a necessity in further commercialization and the stabilization of the new drug.

Interfaces between Pro-UK and other d) *products* are not directly apparent, but since the military knowledge unit has been involved in developing new drugs for a long period of time, earlier drug development projects indirectly affect Pro-UK. Thus *strong indirect interfaces to earlier drug developments* have been crucial and necessary in developing a new drug like Pro-UK. Through earlier drug developments the scientists at the military knowledge unit have gained experience and knowledge of discovering and developing new drugs.

Pro-UK and Interfaces in the Producing Setting

If we continue by looking at the interface between Pro-UK and a) *organizational units* in the producing setting, there are strong interfaces to the main producing unit*, Cardio,* along with the *Cardio biomedicine department* and *Cardio Clinical department*. These units have been important in shaping the new drug. However, a common feature of these units is the lack of experienced production personnel, and the units can be characterized as having a "pioneering spirit." These units were engaged both in establishing the units themselves, such as personnel and equipment, etc., and at the same time trying to focus on establishing and developing production of Pro-UK. As a result the embedding of the new drug in production highlights the lack of knowledge related to production activities. Moreover, the dependence on *the military knowledge unit* for training and setting up production also reflects the lack of drug development and drug production experience within the units. *The Cardio Group* is also a central unit in embedding Pro-UK in production. Through a strong interface with the Cardio Group the new drug was connected to a set of established resources, such as, *the Cardio clinical department, sales organizations*, etc. One can say that the "investments-in-place" within the Cardio Group have been promoting the embedding of Pro-UK in production. The group has also acted as main financing unit of the new drug within the production setting. Hence, it was money from the Cardio Group that realized the purchase of Pro-UK and the establishment of Cardio, Cardio Biomedicine department, including investments in production equipment and employment of personnel, etc. Although the Cardio Group is the main financing unit, there are also other financing units originating from the Chinese government affecting the production of Pro-UK. For instance *MOST* and *Fazhan Gaige* are visible in financing the new drug. Also a foreign unit, *a UK investment firm* became an important financing unit to support the embedding of the new drug in production. Moreover, the main supplier unit, *GE Healthcare*, has supplied equipment and knowledge to realize the production of Pro-UK. It was through GE that the new drug solution could be embedded into production to start with; moreover, GE connected the new drug to another supplier unit, *TAP*. *Chinese supplier units* are visible in embedding Pro-UK in production, although these units supply rather "simple" equipment. There are also regulatory units affecting the production of the new drug. The Chinese *SFDA* is crucial in embedding the Pro-UK in to production, and the new drug is dependent on the NDA and cGMP-approvals by the SFDA. Delays in the NDA approval of the new drug reflect the immature Chinese biopharmaceutical context. Firstly regulations are still under development; secondly the producing unit lack employees with experience from and knowledge of large-scale production in compliance with high-sanitary regulations. Also Pro-UK has indirect interfaces to the American regulatory unit, *the FDA*; in order to export the new drug the production needs to comply with not only SFDA but also FDA regulations.

This creates demands on using production equipment approved by the FDA; thus equipment needed to be imported. When importing production equipment *the Chinese customs* first acted as a hindrance due to policy concerning import of equipment but later on decided to support the Pro-UK drug by offering tax-free import.

In investigating the interface between Pro-UK and b) *organizational relationships* in the producing setting, once again the strong relation between *the military knowledge unit and the main supplier unit, GE,* becomes important for building production, especially in relation to the producing unit. GE has helped with embedding Pro-UK and mobilizing resources to support the embedding of the new drug in a producing setting. It is evident that GE has combining capabilities, and GE has established relationships to both industrial customers and academic customers in China, by bringing these together not only production equipment but more importantly consumables for the running production can be sold. Thus GE's established relationships are one of the company's most valuable resources. GE has an interactive relationship to both the producing unit and the military knowledge unit in embedding Pro-UK in production. Moreover the relationship between *the main producing unit and the military knowledge unit* has been necessary in establishing Pro-UK in production, where the military unit supplies scientific knowledge for production of the new drug. *The relationships within the Cardio Group*, relationships involving the Cardio biomedicine department, Cardio clinical department, and Cardio in Shanghai have been important in producing clinical samples for clinical trials along with establishing the production process of the drug. Also, the relationship between *the producing unit and the Chinese customs* has been important in embedding Pro-UK in production. The dependence on imported equipment for the production of Pro-UK required a lot of negotiation and interaction between Cardio and the customs office in order to settle the difficulties. One conclusion of this is that Chinese government policies and regulations are not static; instead, it is possible to negotiate with government units to mobilize resources to embed a new drug.

When analyzing the interfaces between Pro-UK and c) *facilities* in the producing setting we first have to consider the fact that the new drug was developed using ÄKTA lab equipment. As a result the facilities embedding Pro-UK in production are clearly dependent on the facilities used in the developing setting. Using *ÄKTAexplorer* in the developing setting affected investments in production facilities related to Cardio in Shanghai and the Cardio biomedicine department. Thus there is a strong interface between the ÄKTAexplorer in the developing setting and GE equipment – *ÄKTAexplorer, ÄKTApilot, ÄKTAprime, bioprocess* – used in the production of Pro-UK. Using similar equipment for scale-up diminishes the failure rate in setting up the production process. The *Pro-UK production facility* belonging to Cardio is based at the Zhangjiang High-tech Park, offering government support such as tax and rent reductions, etc. Due to the location, the import of production equipment was facilitated, and Cardio could invest in FDA- and cGMP-approved equipment. Also, by connecting to international supplier units, Cardio could set up production using

sanitary and high-end equipment. Looking at the production process and its interlinked production equipment, the production process has both "sanitary" and "efficient" characteristics. The investment in production equipment is a large one-time investment. However, in keeping the cost of production under control, there has to be a resource fit with the production equipment. More specifically by using *the Cellmate*, it is possible to harvest larger volumes of the cells along with using fewer employees; this will affect the cost of running production. The purchase of Cellmate reveals the producing unit's personnel's lack experience from production of high sanitary drugs, since any change of production equipment needs to be reported to the SFDA and thus result in delays of NDA approval. Also, by using *bioprocess systems* in combination with *ÄKTApilot* in the purification step, Pro-UK can be produced with only minor waste, which will affect the cost of the production. Moreover, by using several ÄKTApilots for purification, it is easier to control the sanitary environment of Pro-UK. Thus by using GE equipment Cardio could connect to the production expertise that GE has while supplying a majority of international biotechnology companies. There are also domestic Chinese facilities, but these involve relatively simple production equipment such as *bioreactors, centrifuges, stirs* etc.

There are strong interfaces between Pro-UK and other d) *products* in the producing setting. Pro-UK is the producing unit only product, but there are *indirect interfaces to other products belonging to the Cardio Group*. Thus, indirectly sales of TCM products made the establishment of Pro-UK production possible, along with the fact that Pro-UK can use the established *sales and distribution system related to other products* belonging to the Cardio Group.

Pro-UK and Interfaces in the Using Setting

There are weak interfaces between Pro-UK and its users. When investigating the interfaces between Pro-UK and the using setting, we find there are visible *a) organizational units* in the using setting in the shape of 25 *clinical hospital units* spread all over China. These units are government hospitals that have been involved in the clinical trials of Pro-UK, and thus the medical expertise including doctors and nurses within the units has gained knowledge of how to use the new drug in treatment and therefore understand its benefits. Due to the experience within the clinical hospital units it is possible to facilitate the spread and use of Pro-UK by connecting to these units.

There are strong established *b) organizational relationships* between *the producing unit, the clinical hospital units, and the Cardio Clinical unit*. The relationships were established through the clinical trials performed at the clinical hospitals. However, it was actually through the established relationship between *the military knowledge unit and clinical hospital units* that the producing unit, could establish the relationships to clinical hospital units.

No interfaces between Pro-UK to *c) facilities and d) products* are visible in the using setting.

Summing Up

To summarize the Pro-UK is a class one drug for treatment of acute heart attack and it still awaits the NDA approval by the SFDA. The case reveals that the creation of biopharmaceutical drugs is a new phenomenon in China, especially in commercializing new drug discoveries. The new drug was developed by a military knowledge unit financially supported by the government, with an established organization and experienced scientists. It seems like the changing relationship between the military and the government directed the attention to commercialize Pro-UK. However, embedding the new drug in production was not an easy task, largely due to the fact that the main producing unit, Cardio, lacked experience from biopharmaceutical drugs. Here it is interesting to point out that Cardio was first physically established as a company without having a drug to commercialize. Thus as a consequence the company needed to connect to others to gain lacking knowledge. Due to the lack of biopharmaceutical experience the military knowledge unit became an important partner and a strong relationship between Cardio and the military knowledge unit was necessary in bridging the developing and producing settings. Another way to gain lacking biopharmaceutical knowledge was the strong interface to the main supplying unit, GE, in supplying practical training. Thus both the military knowledge unit and the producing unit had an established relationship to the supplying unit, and it was through the supplying unit that the two could establish the strong relationship necessary to embed Pro-UK in production. In order to realize production of Pro-UK the private financing unit, Cardio Group, was important for investment in personnel, facilities, and equipment. Moreover, a foreign investment firm bought 50 % of Cardio's stock in 2006. Also, the regulating unit, the SFDA, spans all three settings; thus relationships to the SFDA have been important during the whole innovation journey of Pro-UK. Nevertheless, the creation of Pro-UK was affected by the SFDA bribing scandal, which created delays in the application process. Also the Chinese customs authorities are present in first hindering the import of production equipment related to the new drug but, following negotiations, later supporting the purchase. There are weak interfaces to the using setting, although Pro-UK display links to government clinical hospital units.

The following table summarized the interfaces between Pro-UK and the four investigated resources in the developing, producing and using settings. As the table implies Pro-UK is embedded into the developing and producing setting, while is not embedded into the using setting. Thus Pro-UK cannot be considered an innovation: it is still to be regarded as an invention.

Pro-UK	**Developing**	**Producing**	**Using**
Org. Units	Strong interfaces	Strong interfaces	Weak interfaces
Org. Relationships	Strong interfaces	Strong interfaces	Weak interfaces
Facilities	Strong interfaces	Strong interfaces	No interfaces
Products	Strong interfaces	Strong interfaces	No interfaces

Table 7. Summary of resource interfaces related to Pro-UK.

CHAPTER 9: IMITATION OF FOREIGN RESEARCH — THE CASE OF VB2

In 2006 Shanghai Vitamin Biotech[64] became one of few companies worldwide to launch a gene therapy[65] drug, the VB2, targeting head and neck cancer. The following case is a story that reveals the innovation journey of VB2.

Starting Off by Buying Military Science to Commercialize Fast

Vitamin Biotech was developed as a subsidiary to Shanghai Vitamin Pharmaceutical Company, which is part of the big Vitamin Group. The Group has over 50 years of experience of producing pharmaceutical drugs, though the group is most famous for its production of vitamins through a joint venture with Suisse Roche. Thus the background of the Vitamin Group is mainly in traditional pharmaceuticals along with the production of vitamins. Nevertheless, in the mid 1990s Vitamin Group decided to enter the biotechnology field. As a result Vitamin Biotech was established in late 1995. Having no experience from developing biopharmaceutical drugs Vitamin Biotech started by buying an anti-cancer drug project developed by the Academy of Military Medical Sciences (AMMS) based on recombinant protein. This first project was not a unique project, but was aiming for a class two NDA.[66] The project was suitable for Vitamin Biotech because the military research institute had already finished pre-clinical trials and entered clinical phases, so Vitamin Biotech hoped for fast commercialization to earn money, but more importantly also to learn about biopharmaceutical drug techniques.[67] After buying the drug project in early

[64] Company name re-named for anonymity reasons. Shanghai Vitamin Biotech will be only referred to as Vitamin Biotech from now on.

[65] Gene therapy is a technique to cure a disease due to gene deficiencies, for instance by replacing the defective gene with a healthy one. A vector is used to deliver the healthy gene into the unhealthy one; usually the vector is a virus. (HGP, 2011)

[66] Class two product refers to a product that is similar to an already existing product on the market.

[67] I do not know exactly where in the development process AMMS was when Vitamin Biotech bought the project, but since the project was bought in early 1996 I make a rough estimation that

1996 from the military research institute, it was further developed through co-operation between Vitamin Biotech and the AMMS. As a result the development of Vitamin Biotech's first drug did not take place in isolation but was developed by Vitamin Biotech in collaboration with the original source, the military research institute. Vitamin Biotech was granted a class two NDA for VB1[68] in late 1998. The product is used for cancer treatment and is injected directly into the muscle of the patients to help cancer patients increase the amount of white blood cells after chemotherapy. VB1 is a relatively cheap product in the price range between RMB 50 to 100 (US$ 6-12) per dose. In 2006 Vitamin Biotech produced between 200,000 and 300,000 injections of VB1,[69] and there are around 20 other companies producing a similar drug. Since the purchase of VB1, Vitamin Biotech developed the company by establishing a clinical department handling clinical trials, an R&D department, a quality control department along with a sales and marketing department. These departments are all located at a Technology Park in Jinqiao Export Zone. To produce VB1, Vitamin Biotech has established a production facility with 12 employees. The production facility was re-evaluated and cGMP-approved in 2004 by the SFDA due to new regulations put up by the Chinese government that all pharmaceutical manufacturers need to have cGMP-approved production facilities. Vitamin Biotech has been sponsored by MOST and the 863 program to develop VB1, and the product has also received other government attention, such as the "high-tech achievement award" from the Shanghai government in 1998 along with "new product reward" after the launch of VB1.

Developing Vitamin Biotech into a Unique Company — Finding an International Patent to Exploit

In late 1996, at the same time as Vitamin Biotech developed VB1, an American firm, Tex Pharmaceutical,[70] published a paper in a top-tier international journal

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the project was in late clinical trials, based on the fact that the drug was NDA-approved in 1998. Normally each clinical step takes approximately one year (maybe at that time less than a year) with a following NDA of around a year, thus altogether at least four years for the clinical trials and NDA.

[68] Product renamed for anonymity reasons.

[69] Since I do not know about the sales figures of VB1 I can just speculate a bit. Fixing the price at the maximum RMB 100 and estimating all 300,000 doses being sold results in sales of RMB 30 million (US$ 4 million) in 2006 for VB1. However, if the price is set at the minimum RMB 50 and only 200,000 doses are sold, this results in sales around RMB 10 million (US$ 1.3 million) for the year 2006. Thus revenue of VB1 in 2006 can be estimated at somewhere between US$ 1.5-4 million.

[70] Renamed for anonymity reasons.

in biotechnology. The paper presented the latest research on gene therapy,[71] more specifically on how to make a specific virus to attack and replace cancer cells. The discovery was unique, and Tex Pharmaceutical research received a lot of international attention. Along with the discovery the company gained a patent in the US. Inspired by the promising cancer treatment results and the need for other drug projects, Vitamin Biotech applied for the same patent in China since Tex Pharmaceutical had not applied for patent protection in China. In line with Vitamin Biotech first project, VB1, this project also targeted cancer patients. Unlike VB1, this project was not based on recombinant protein but on virus. When the patent was obtained in China, Vitamin Biotech started a development of their own new product named, VB2[72] based on the research findings of Tex Pharmaceutical in 1999.[73] At this point no gene therapy product had been launched worldwide.

Developing the New Drug in a Chinese Setting

Vitamin Biotech used the published paper as a point of departure for the development of VB2, and the company started out by replicating the research performed by Tex Pharmaceutical. During the development process Vitamin Biotech has made changes, adjustments and improvements to the drug; thus it is not a direct copy of the actual project developed by Tex Pharmaceutical but a modification of it based on the published paper. Vitamin Biotech decided which cell-line should be used for growing the virus, and the following development process of the VB2 drug including pre-clinical and clinical 1-3 trials was performed by Vitamin Biotech in China without any contact with the original source.

Vitamin Biotech's internal R&D department and clinical department with 10 employees has been working closely in developing the VB2 drug.[74] The departments have been in charge of the pre-clinical studies and the following clinical trials. At the clinical department ÄKTAexplorer, supplied by GE Healthcare,[75] is used for the production of samples for clinical trials. The clinical department has close and intensive contact with the clinical hospitals, for

[71] Gene therapy research has been popular in the US since the early 1990s but due to the death of one patient in clinical trials in 1999 gene therapy has been questioned in the US and Europe, and the gene therapy hype has ceased.

[72] Renamed for anonymity reasons.

[73] Vitamin Biotech is somewhat reluctant to admit the background of the gene therapy drug, i.e. the replication of Tex Pharmaceutical research.

[74] Vitamin Biotech also rents lab space at the Shanghai Second Medical Hospital, but it was not used in the development of VB2 but rather in the development of the coming products VB3 and VB4. Moreover, the CEO of Vitamin Biotech has a doctoral degree from the Shanghai Second Medical Hospital.

[75] From now on only referred to as GE.

instance China's largest university hospital at Zhejiang University in Hangzhou. Also, the clinical department has been important in handling the contacts with the SFDA. First clinical trials were finished in 2001, the following clinical two trials in 2003 and the third clinical trials in mid 2004. In clinical phase three trials, around 140 patients were enrolled. Several articles have been published in international journals based on the clinical trials of VB2.[76] Vitamin Biotech sent in the class one NDA after finishing clinical phase three and received an approval after a year and a half. Due to the circumstances that there had been international complaints after the first approval of a gene therapy drug in China and that the SFDA had little experience in evaluating gene therapy drugs, there were delays in the approval and evaluation process from the SFDA. Thus the SFDA was cautious in approving the NDA for VB2, and the SFDA demanded additional detailed technical documentation in the autumn of 2005 from Vitamin Biotech. After sending in the final application Vitamin Biotech has been in contact with the SFDA on a weekly basis, and after Vitamin Biotech presented good documentation and clinical research, the NDA was approved in November 2005. The following year, in mid 2006, Vitamin Biotech's second production facility, where VB2 would be produced, was cGMP-approved by the SFDA. This was followed in October 2006 by a product launch of VB2, and Vitamin Biotech became one of few companies worldwide to offer a gene therapy product.[77] The company has another ten patent applications in process, mainly using viruses for cancer treatment. Nevertheless, the VB2 drug was not developed in accordance with the FDA but only in accordance with the SFDA. For instance, ÄKTAexplorer were used for the clinical production, along with the fact that the CEO of Vitamin Biotech followed up the clinical trials on site, at the clinical hospitals, and adjusted the treatment along the way, and, finally, the low number of patients in clinical trials is not sufficient according to FDA regulations.

Establishing the Production Process

Vitamin Biotech has two production facilities in Shanghai, one producing the first protein-based drug, VB1, and the other one is the virus facility, producing the new gene therapy drug, VB2. As mentioned, the pre-clinical and clinical trials were performed by employees at Vitamin Biotech in close cooperation between the R&D department, the clinical department, and the clinical hospitals. This cooperation was necessary since the planning for the future produc-

[76] The first paper was published in 2002 and followed by a handful of papers between 2002 and 2007. (Vitamin Biotech's homepage)

[77] In 2003 a Chinese company was the first company worldwide to be granted NDA-approval for a gene therapy product; however international complaints were raised due to the small number of patients in the clinical trials: in total 135 patients were used during clinical trials (1-3).

tion facility and the production process was affected and guided by the clinical trials. When VB2 was in late clinical trials, Vitamin Biotech formed a production project group to plan the establishment of the production process, including the purchase of production equipment. The project group consisted of four managers, one pilot plant manager in charge of the whole production process along with three other managers responsible for one production step each, i.e. fermentation, purification, and formulation. The pilot plant manager was employed by Vitamin Biotech in 1999 when the development of VB2 started, and he had some years' working experience from Chinese biotechnology business, while the majority of the other production employees were newly graduated from the university. The production project group reported to the Chief Science Officer (CSO) through the pilot plant manager. The CSO has international experience from both science and business and has the main responsibility for the overall development process.

The project group needed an approval from Vitamin Biotech's top management to purchase equipment for the second production facility, the VB2 facility. In late 2003 the production process was established along with the production facility, including production equipment. However, at that time clinical trials were not yet finished. When waiting for completion of clinical trials and the final NDA approval, the production team got orders from top management to use the production equipment as little as possible due to the risk of maintenance problems and additional costs for support and service provided by the equipment supplier. Hence, between 2003 and 2005 the production equipment was used infrequently, and the production team focused on validating the production process and optimizing the production equipment used. The whole production process has only been run a handful of times along with the pre-manufacturing of production batches for the final application sent to the SFDA. After the NDA was approved in late 2005 and the product was launched in autumn 2006, Vitamin Biotech produced around 10,000 injection doses during the first six months after the product launch.

The Production Process along with Production Equipment

An American firm, New Bioreactor Systems (NBS) supplies the bioreactors used for growing the virus in the fermentation phase. After the growth of the virus, a centrifuge is used, and an ultra filtration system extracts and gathers the virus, which is supplied by Chinese suppliers. In total the fermentation phase will take approximately 20 days and a fermentation manager, along with two assistants, is in charge of the fermentation. In the purification phase ÄKTApi-

lot supplied by GE Healthcare[78] is used to purify the virus. Only the purification manager is allowed to run the purifying system according to company policy. Two other employees assist the purification manager and do the preparation and supplementary work of the system. As a complement to ÄKTApilot, Vitamin Biotech uses ÄKTAbasic,™ also supplied by GE. The system is used before and after the purification of the virus in order to monitor the purity and concentration level of the virus substance. The purification step is estimated to take no longer than two days. In the formulation phase the substance is transformed into an injection by mixing the substance with chemicals using an American system attached to accessories such as a temperature detector, media, and stir equipment. No more than one day is required for the last formulation step, where the formulation manager and his two assistants perform the final formulation of the drug. The activity level of the final drug is checked only before distributing the final product, which takes approximately 15 days. The whole production process is estimated to take around 25 days, adding another 15 days for activity analysis. To be able to adjust the production to the demand, Vitamin Biotech can produce in parallel as the different production steps have different lead times. However, if the production scale is larger, the lead time of the production process will be affected, and the production will take longer than the estimated 25 days.

If we look more closely into the purification phase, a foreign equipment supplier, GE, has been important in supplying the main purifying system, the ÄKTApilot. Vitamin Biotech and GE already had an established relationship with the purchase of ÄKTAexplorer to be based in the clinical department in late 1990s. During the development of VB2, ÄKTAexplorer has been the main research equipment. Hence, the experience of using ÄKTAexplorer as the main equipment for the production of clinical samples facilitated the decision to use similar equipment in production scale. Choosing ÄKTApilot as the main purification system for the production scale (in combination with ÄKTAbasic) was a relatively easy task; no other system has the capacity to produce according to existing sanitary requirements at this scale between lab and process scale. When deciding to invest in more GE products, ÄKTApilot and ÄKTAbasic, top management accepted the purchasing agreement between Vitamin Biotech and GE in 2003 of a total of US$ 200,000, including attached columns and media. To evaluate suitable production systems took around six months, excluding the delivery time of another three months. The systems were delivered in April 2003 and installed by GE's technical supervisor in one day. Using equipment from GE has resulted in frequent interactions between Vitamin Biotech and GE. It was the sales representative and the technical supervisor that suggested that Vitamin Biotech invest in the new ÄKTApilot system. GE continuously updates Vitamin Biotech about new products and upgrades of software, while

[78] From now on only referred to as GE.

the company has been in contact with both the support and service department at GE from time to time.

Financing Vitamin Biotech with Government Capital

In order to develop the new unique drug, VB2, Vitamin Biotech needed financial investments. At the same time as Vitamin Biotech received a patent for VB2 in China and the development of the new product started in 1999, the company got new main owners. As a consequence the company has three owners: the majority owner A, an investment firm mainly focusing on IT and real estate and majority-owned by the Shanghai Government, and minority owners B and C, which are also investment firms owned by the Shanghai Government. It is estimated that the investment firm C has alone invested around RMB 100 million (US$ 13 million) in Vitamin Biotech.

Along with investments from different state-owned investment firms, Vitamin Biotech has had financial connections to other government agencies and departments, both nationally and regionally when developing VB2. The fact that Vitamin Biotech already received government support for the development of the first product, VB1, facilitated receiving more government support for developing VB2. The drug project is partly financed through MOST and the 863 program. Altogether the company has applied for funds from the 863 program 3-4 times and received around RMB 1 million (US$ 130,000) each time. Also, government agencies like the Shanghai Science and Technology Committee (SSTC) have given rewards such as "Key Science & Technology Development Projects of Shanghai" and the "National '10th-five-year-plan' Key Science and Technology Projects" to Vitamin Biotech. Receiving governmental funds and support can also attract other financiers to invest. Without the support from the Chinese government Vitamin Biotech would not be able to get very far. The main part of the development budget for VB2 has been capital originating from the Chinese government; a rough estimation is that around US$ 30 million is government support.[79]

What Happened with the American Technical Source?

After publishing the research on gene therapy in 1996 Tex Pharmaceutical continued their drug development process in the US and succeeded in taking the drug through clinical phases one and two. In 2003 when the third clinical trials

[79] Another Chinese company with a gene therapy product on the market also received extensive funding from the Chinese government, estimated at around RMB 50 million (US$ 6.5 million).

were about to start the company encountered problems in further financing the development since the main financier did not support further clinical trials; hence the drug development was dropped. Instead they started a partnership with a German company in developing another cancer treatment drug. After the groundbreaking publication by Tex Pharmaceutical in 1996 the company did not know that Vitamin Biotech had applied for a patent in China and started its own development of the drug. When Vitamin Biotech finished the clinical phase three trials of VB2 with satisfying results, Vitamin Biotech approached Tex Pharmaceutical in order to get exclusive global rights for the patent and asked for a global license. When Tex Pharmaceutical realized that Vitamin Biotech had refined and developed their research into an approved new drug the company was first somewhat surprised. Nevertheless, in 2005 Vitamin Biotech paid US$ 1 million for the global intellectual property (IP) rights to the drug patent to Tex Pharmaceutical. By licensing the global IP to Vitamin Biotech, the company saw the opportunity to get some refund on the money already invested. Future approval in the US and Europe and global sales will result in more payments from Vitamin Biotech to Tex Pharmaceutical of approximately another US$ 10 million. To summarize, Vitamin Biotech started with something that to some extent can be characterized as a patent infringement but in the end resulted in a licensee agreement between Vitamin Biotech and Tex Pharmaceutical.

Having an Unique Product and Finding Customers

VB2 targets head and neck cancer, a type of cancer that affects approximately 300,000 Chinese annually. The drug is an injection substance to be injected directly into the tumor; thus treatment with VB2 needs to be supervised by trained medical expertise, such as doctors and nurses. One benefit of using VB2 instead the traditional way of treatment, surgery followed by chemotherapy, is that VB2 does not have side effects such as nausea, hair-loss, etc. Thus VB2 is intended to be used instead of traditional treatment methods such as surgery and chemotherapy.

In investigating the market for VB2, Vitamin Biotech appointed a consultancy company to do marketing research on the future prospects the new drug. Since the launch of the first product VB1 in late 1990s the firm already had an established sales department along with established relationships with 2-3 main sales agents for the distribution of VB1 in China. As a first step Vitamin Biotech has approached clinical hospitals used for the clinical trials in distributing VB2 to end-users, i.e., patients. In mid 2007 five clinical hospitals in China were using the new drug in treatment of patients with head and neck cancer.

Being one of few companies selling a gene therapy product worldwide would naturally imply good sales; however, so far sales have not been as good as expected for any of the Chinese companies offering a gene therapy product.

Since I did not have exact numbers of Vitamin Biotech's sales, I looked at another Chinese company selling a gene therapy drug, the Xgene.[80] The company was the first company worldwide to launch a gene therapy product, GX, in 2003, also targeting cancer patients. Up to mid 2007 around 6,000 patients have been treated with GX, which is far fewer than Xgene expected. Vitamin Biotech has faced similar disappointing sales figures so far. However, the weak sales results can be related to the high prices of the drugs. An injection of VB2 is around RMB 3700 (US$ 460), and each patient needs five injections,[81] which results in a total payment of RMB 18,500 (US$ 2,300) for the whole treatment, which is not covered by any medical insurance in China. Meanwhile, an average monthly salary in China was around RMB 1500 (US$ 187) in 2005 (China statistical yearbook, 2006). Thus only a small part of the population might be able to buy the treatment. Yet, Xgene points to the large proportion of foreigners coming to China for treatment (around 800 out of 6,000), which might be a future customer group for Chinese gene therapy companies. The CEO of Vitamin Biotech explains the disappointing sales figures as owing to the lack of expertise regarding gene therapy drugs at the Chinese hospitals. In many cases the doctors has just injected the drug in the vein, not directly into the tumor, resulting in weak effects of the drugs. Thus hospitals still rely on traditional treatments such as surgery and chemotherapy in treating head and neck cancer.

Future Development of Vitamin Biotech

Vitamin Biotech has also started the development of two other gene therapy drug projects, VB3 and VB4, in parallel with the development of VB2. VB4 finished clinical phase one in spring 2007 while VB3 was still in the pre-clinical stage. In line with the focus of Vitamin Biotech both projects also target cancer patients, though different types of cancer than VB2. In the VB3 project Vitamin Biotech is cooperating with an American university, and in the VB4 project, Vitamin Biotech are also working with an American research group. These future drugs are also planned to be produced in Vitamin Biotech's virus facility, the same production facility as for VB2. In late 2007 Vitamin Biotech announced new cooperation with an American company, one of the largest biotechnology companies in the world, also involved in developing gene therapy, though not yet in possession of any approved gene therapy drug. The company approached Vitamin Biotech with the hope of performing pre-clinical and clinical trials of a gene therapy drug in China. The drug project developed by the American company was already in clinical two trials in the US and Europe. Vitamin Biotech agreed to financially support and perform the first two clinical

[80] Company name re-named for anonymity reasons.
[81] Xgene's product GX is also around RMB 3500 for one injection.

trials in China, and if Vitamin Biotech succeeds in taking the drug through clinical one and two trials, the American company will partly sponsor the clinical phase three in China. The product targets people with blood circulation problems and focuses on the growth of new vessels. Vitamin Biotech's future plan is to team up with international companies or research institutions in order to develop and produce drugs in a Chinese setting, with the focus on gene therapy. Eventually Vitamin Biotech hopes to export the approved gene therapy drug to the Western world.

Epilogue

Due to disappointing sales figures of VB2, the CEO of Vitamin Biotech was forced to leave his position in 2008; however the development of VB3 and VB4 continues.

A Timeline of the Innovation Journey of VB2

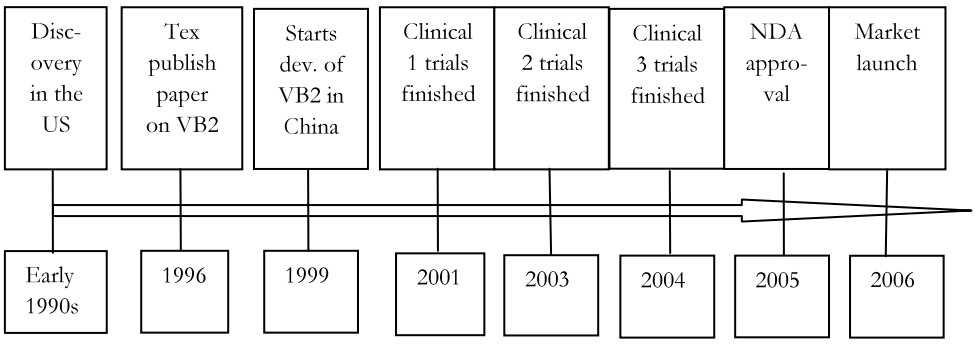

Figure 8. Timeline of VB2's innovation journey.

Analyzing the Embedding of VB2

When analyzing the VB2 case, we will focus on what resources the new solution has interfaces with, in a developing, producing, and using setting. The interfaces reflect the four resources elements of the 4R model and thus the inter-

faces are two main types: VB2 and interfaces involving social resources and VB2 and interfaces involving technical resources. The following figure summarizes the resource interfaces related to VB2 in the developing, producing, and using setting and the following sections will discuss in detail the resource interfaces that VB2 encountered while being developed, produced, and used.[82]

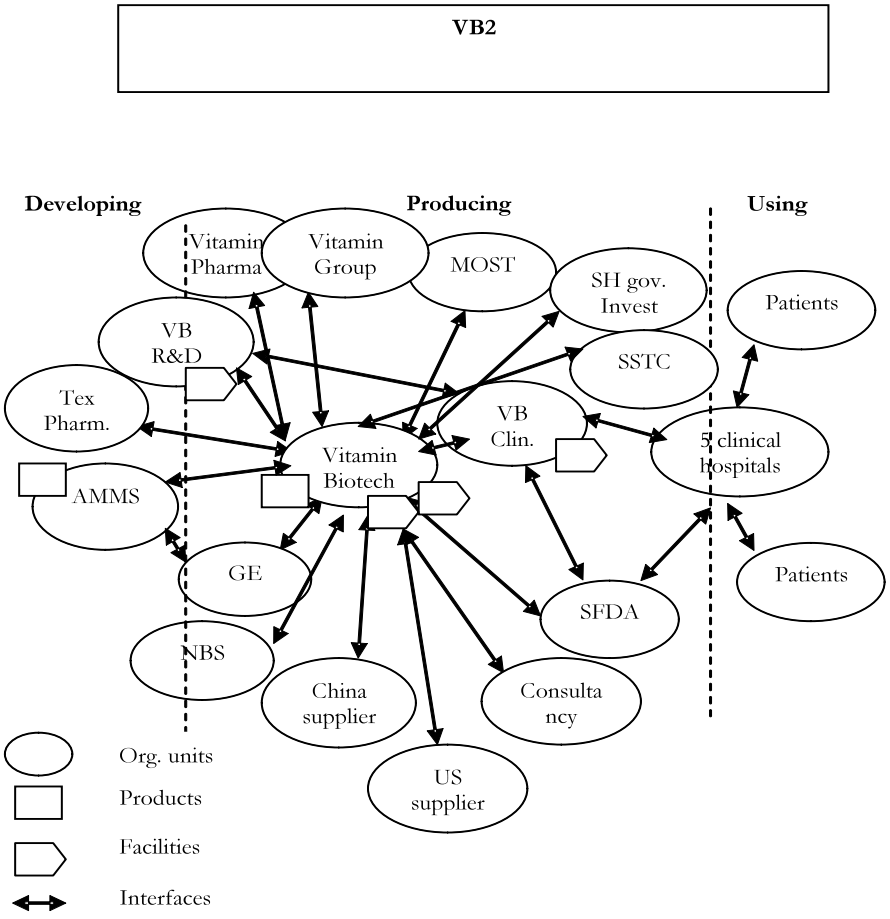

Figure 9. The embedding of VB2.

[82] Organizational relationships are not included in the figure.

VB2 and Interfaces in the Developing Setting

If we start by investigating the interfaces between VB2 and *a) organizational units* involved in the developing setting, the main knowledge unit, *Tex Pharmaceutical*, plays a significant role in shaping the new drug. It was Tex Pharmaceutical that were responsible for the new drug discovery; thus the unit found the specific molecular structure to kill off cancer cells. The knowledge unit published the new drug discovery in one of the worlds' most highly-ranked journals which clearly reflects the scientific excellence of the unit. Another important unit that affected the VB2 drug is the strong indirect interface *to a military knowledge unit, the AMMS*, in charge of developing Vitamin Biotech's first product, VB1. Here Chinese military medical science and its researchers are important in discovering new drugs, but the unit is also important in commercializing these new drug discoveries. Through the discovery of VB1 at the military knowledge unit, the main producing unit, *Vitamin Biotech*, could be further established and developed. However, the features of the producing unit, lacking experience from biopharmaceutical drug development projects, directed the unit to connect to already developed drug projects. Thus the producing unit wanted to connect to already established drugs and focus on establishing production activities related to these drugs, thus knowledge units such as AMMS and Tex Pharmaceuticals became crucial. Moreover, the producing unit was involved in developing the new drug by engaging in pre-clinical and clinical trials through the established units, *Vitamin Clinical department and the Vitamin R&D department.*

Looking at the interfaces between VB2 and *b) organizational relationships* it is important to highlight the absence of relationship between the main knowledge unit, Tex Pharmaceutical, and the main producing unit, Vitamin Biotech, when developing VB2 in China. *The establishment of the organizational relationship between the two units was not a reality until 2005*, with the payment of Global IP on the patent concerning the molecular structure. Nevertheless, the relationship seems to be more of a "transactional" character, where the producing unit merely pays for the license agreement. Thus the relationship can be characterized as weak, with the units are simply exchanging money; no adaptations between the units are made. Nevertheless, the relationship is very important for the future sales of VB2. When developing the new drug in a Chinese setting the producing unit needed to perform pre-clinical and clinical trials, in which there is a strong *relationship involving the Vitamin Clinical department and the Vitamin R&D department and clinical hospital units.*

There are is one interface between VB2 and *c) facilities* in the developing setting. More specifically, *ÄKTAexplorer* was used as main lab equipment for the production of clinical substances used in clinical trials.

There is a strong interface between VB2 and another *d) product* in the developing setting. These interfaces are related to Vitamin Biotech's first product *VB1*. Through VB1 and the military knowledge unit Vitamin Biotech gained biopharmaceutical development experience and knowledge, especially concen-

trated in the Vitamin Clinical department and the Vitamin R&D department, this experience was used in developing the new drug, VB2.

VB2 and Interfaces in the Producing Setting

There are several important interfaces between VB2 and *a) organizational units* in the producing setting. First of all the main producing unit, *Vitamin Biotech*, has been crucial in embedding VB2 in production. As mentioned, the features of the unit shaped the creation of VB2: for instance, the unit lacked biopharmaceutical drug experience both in development but also in production. However the company policy seems to hinder the development of new biopharmaceutical knowledge and experience by restricting the use of equipment due to fear of additional costs such as maintenance service. Under these conditions the producing personnel were discouraged from gaining more experience in production, which was a necessity because a majority of the employees were recent graduates. These restrictions clearly reflect a general lack of biopharmaceutical knowledge among top management. In order to set up a suitable production process and more importantly, gain production experiences, production equipment needs to be used on a regular basis. The establishment of Vitamin Biotech as a producing unit was realized through financing units, *The Vitamin Group and Vitamin Pharma* were important in financing the initial establishment of the unit, including physical facilities, internal departments, personnel, etc. (in 1995). Thus through these investments, Vitamin Biotech established an internal resource structure important not only for the production of VB1 but also related to VB2. Therefore the VB2 could benefit from already established internal units, for instance *the Vitamin Clinical Department and the Vitamin R&D Department*; we could refer to these as "investments in place." Nevertheless, establishing production of the new drug required large investments such as a new production facility, production equipment, production personnel, etc. Hence, new financing units needed to be convinced of the future economic benefits of the drug. *The Shanghai government* became main financing unit through three investments firms, and altogether these invested around US$ 30 million. Moreover, other financing units such as *MOST* and *SSTC*, also originating from central and regional government, financially supported the embedding of VB2. Through new investments it was possible for Vitamin Biotech to set up production of the new drug. As a consequence VB2 has strong interfaces with supplier units; without equipment for R&D and production the new drug would not have been a reality. The main supplier units, *GE and NBS* supply imported high-end production equipment, while *Chinese suppliers* supply "simple" production equipment. The new drug also displays strong interfaces to the regulatory unit, *the SFDA*. Although the new drug is dependent on the approval from the SFDA, the VB2 case reveals how it is possible to take advantage of the "slack" regulations put up by the SFDA. For instance, the main producing unit was actively taking part in the clinical trials at *the clinical hospital units*, result-

ing in adjustments of dosage and reverse documentation, all in accordance with SFDA regulations. The *Chinese consultant firm* doing market analysis on behalf of Vitamin Biotech is also a visible organizational unit in the production of VB2. The presence of the unit especially reveals the lack of knowledge regarding potential users of the new drug.

When investigating the interfaces between VB2 and *b) organizational relationships*, there are some relationships important for embedding VB2 in production. To start with the relationship between the producing unit, *Vitamin Biotech,* through *Vitamin Clinical Department*, and the *clinical hospital units* seems to be strong and interactive in handling and performing clinical trials, though all according to SFDA regulations. Also, the already *established relationship with the producing unit and GE* is important in setting up the production process and providing training of the employees involved in the production of the new drug.

The interfaces between VB2 and *c) facilities* are strong. Nevertheless, as I understand the interface between the *two production facilities* is weak. Instead the production facilities are separate, with separate employees and separate equipment; the production facilities are connected only indirectly through Vitamin R&D and Vitamin Clinical departments. The VB2 has strong interfaces with the virus production facility where the new drug is produced. The interlinked production equipment includes: *bioreactors*, *centrifuges*, and *ultra filtration systems* for fermentation, followed by *ÄKTApilot and ÄKTAbasic* in purification along with a *mixing system* in formulation. An interface between developing and producing facilities exists: *ÄKTAexplorer* is used when producing clinical substances and thus *ÄKTApilot* is used for purification in the production stage. When investigating the production facilities, it is evident that the production of VB2 is on a very small scale; for instance ÄKTApilot is used as the main purification equipment suitable for small scale production.

VB2 has strong interfaces with another *d) product* in the producing setting, namely *VB1*. The initial thought was that VB1 would pay for new drug development for Vitamin Biotech; however, it seems like the sales are not covering a large part of the development costs for VB2. Nevertheless, the drug does provide financing for the new drug. By having one product for sales Vitamin Biotech could attract other investments; thus VB1 can be seen as an important in attracting new government support. VB1 is also important in establishing the main producing unit, Vitamin Biotech, the established Vitamin clinical and Vitamin R&D departments have been important for the production of VB2. Here it is evident that earlier drug projects create new knowledge and experience to be used when embedding a new drug.

VB2 and Interfaces in the Using Setting

Looking at the use of VB2, there are weak interfaces to users. More specifically altogether there are five *a) organizational units* using the new drug. These five using units are *government clinical hospital units* involved in the clinical trials of the

new drug. As the case points out, the lack of use can be explained by the lack of experience from technically advanced drugs among the medical expertise at the using units. Thus in order to use the new drug in treatment the doctors need training, which is something that Vitamin Biotech have not yet been providing. In convincing more hospitals to use VB2, the producing unit needs to inform users about the benefits of the drug to the medical expertise and provide them with training. Since only five using units provide VB2 to patients the sales have so far been disappointing, thus there are weak interfaces to *end-users, patients*. One reason for lack of use is related to the price of the VB2. Treatment with VB2 is expensive and not covered by any medical insurance; therefore the end-users, the Chinese patients, need to pay for the treatment themselves. As a consequence individual Chinese patients are the main financing units of VB2 in the using setting. Thus a combination of the high price along with a weak healthcare system acts as a barrier to embedding the new drug in a using setting.

There are strong interfaces between VB2 and b) *organizational relationships*, involving the main producing unit, *Vitamin Biotech*, *the Vitamin Clinical Department* and *clinical hospital units*. The fact that the CEO of Vitamin Biotech has been personally involved in the clinical trials at the clinical hospitals reflects the close relationships between the units in embedding VB2 in use.

There are no visible interfaces between VB2 and *c) facilities* in the using setting.

Investigating the interfaces between VB2 and other *d) products*, there are weak interfaces with the first product VB1. The drugs both target cancer patients, although the benefit of VB2 is to exclude chemotherapy totally while VB1 is intended to be used together with chemotherapy. Due to the low sales of VB2 it is evident that the new drug has strong competing products and methods in treating head and neck cancer. Traditional products and methods such as surgery and chemotherapy are still the most common treatment methods.

Summing Up

One main point of the case is that the class one drug, VB2, is based on "imitated" research originating from the US. However, the development of the new drug has taken place without interaction with the original US knowledge unit. The new drug was first a patent infringement that in the end resulted in a relationship with the original US knowledge unit, Tex Pharmaceutical, and the main producing unit, Vitamin Biotech. Another distinct point of the case is VB2's indirect interface to a military knowledge unit and another generic drug. The VB2 case reveals a lack of biopharmaceutical drug knowledge and experience; for instance, the main producing unit was established as a company first and then suitable drug projects were evaluated. Through the interface with the military knowledge unit and VB1, the producing unit was able to gain access to biotechnology knowledge. As a result VB2 could be developed and embedded

into production. Also, the VB2 case evinces a strong interface with the Chinese government; the producing unit is a state-owned company and thus a large part of the financial support originates from the Chinese government. Due to the lack of biopharmaceutical drugs, the producing unit also had little knowledge about potential users of the new drug. This has impeded the spread of the new drug in the using setting. Also, the fact that the new drug is a technically advanced drug has created difficulties for the medical expertise at the government clinical hospital units. Moreover, the high price of the drug in combination of lack of healthcare insurance, along with the existence of established cancer treatment methods, also makes the spread of the new drug more difficult. Still the new drug is approved and launched on the Chinese market and is used by five clinical hospital units. One interesting aspect is the future possibility of attracting foreign patients to use the new drug. Also, through the launch of VB2 the producing unit has attracted international attention and thereby come into contact with a large American MNC for the development of new drugs in China.

The following table summarizes the resource interfaces within the three settings related to the new drug, VB2. As we can see the new drug is embedded both in a developing and producing setting, while the using setting is less developed. As a consequence VB2 is not yet to be regarded as a new innovation but is still to be regarded as an invention.

VB2	**Developing**	**Producing**	**Using**
Org. Units	Strong interfaces	Strong interfaces	Weak interfaces
Org. Relationships	Strong interfaces	Strong interfaces	Weak interfaces
Facilities	Weak interfaces	Strong interfaces	No interfaces
Products	Strong interfaces	Strong interfaces	Weak interfaces

Table 8. Summary of resource interfaces related to VB2.

CHAPTER 10: THE NEED FOR ONE CUSTOMER — THE CASE OF A HEPATITIS A VACCINE

Wison Bioengineering[83] was established in 2003 and by 2007 the company was approved an NDA for their first biopharmaceutical drug, a Hepatitis A vaccine. The following case is to illustrate the innovation process of the vaccine.

A Big Step — From Petroleum to Vaccine Development

Wison Group Holding Ltd is a privately owned group that has been in the petro-chemical business since 1997 and the group is listed on the Hong Kong stock exchange. During the last eight years the group has expanded its business to include high-tech businesses such as telecommunication and biotechnology (for more information see: www.wison.com). Wison was established in 2003 as a wholly owned subsidiary to Wison Group in an attempt to penetrate the new biotechnology field in China. When the company started out, Wison did not have a project to be developed into a drug, not even an idea what to produce and what the basis of the newly founded company would be. In 2003 Wison only consisted of a physical environment including a large building based in the Shanghai Zhangjiang High-tech Park. Thus, the search for a suitable project to actually transform into a drug began. In addition to finding suitable drug projects Wison also needed to fill the existing building with staff, equipment, and facilities in order to succeed in the biopharmaceutical drug industry.

In order to find suitable employees with experience from biotechnology, Wison could overcome some of the problems associated with being a new start-up company in a new area of business. Wison needed a knowledge base of the newly established company. Therefore Wison searched for suitable employees, and in the early 2004 after several months with just a physical environment Wison hired a deputy general manager with more than 20 years of working experience from the biopharmaceutical context. More specifically for the last 10 years he had been working for Wuhan Institute of Biological Products (WIBP),[84] which belongs to the large SOE, China National Biotech Group

[83] From now on only referred to as Wison.
[84] WIBP is one of Chinas oldest research institutes, established in the 1950s.

(CNBG),[85] mainly focusing on developing vaccines for the Chinese market. Due to the background of the deputy general manager it was no coincidence that Wison decided to develop a vaccine as its first product.

Finding a Focal Product — A Vaccine Targeting Hepatitis A Virus

In order to understand the background of the vaccine belonging to Wison we need to take a closer look at the vaccine industry in China. First of all China is the largest vaccine producer worldwide with an annual production of approximately one billion doses (Han, 2009). Vaccines in China are divided into two types, one type focusing on planned immunizations within the China National Immunization Program (CNIP).[86] These vaccines are provided for free, thus the prices of the vaccines are set by the government at a low profit margin. Due to low profit margins mainly Chinese manufacturers supply vaccines of this first type. The other type of vaccine is outside of the CNIP programs, where the Chinese themselves pay for the vaccine; as a consequence the profit margin is set at a higher level, between 30-50%, and both MNCs and domestic companies supplies these vaccines (Zhou, 2007). In general the total quantity of the vaccines produced within the CNIP such as Diphtheria-Tetanus-acellular-Pertussis (DTaP) vaccine, hepatitis A vaccines, Japanese Encephalitis vaccines is not sufficient, so the demand is larger than the supply. Until the mid 1990s China National Biotech Group (CNBG) had a monopoly position in supplying vaccines to the public health bureau China Centre of Disease Control and Prevention (CDC). The health bureau is a department under the Ministry of Health (MOH), in charge of public health issues such as immunization (Xia and Chen, 2009).[87] Along with the deconstruction of the vaccine monopoly in the mid 1990s, new Chinese vaccine producers emerged, and today around 50 Chinese companies are involved in vaccine production (Zhou, 2007). However, CNBG still supplies 90% of all vaccines included in the CNIP, estimated at around 300 million doses (Ibid).

As mentioned above with the new deputy general manager in place, Wison decided to focus on developing a vaccine, more specifically a vaccine targeting hepatitis A virus (HAV). Hepatitis A is an inflammation of the liver due to a virus found in unsanitary environments and is spread through contaminated food and drinks. The symptoms are among others nausea, fever,

[85] In 2009 CNBG was merged with another of China's largest pharmaceutical SOEs, Sinopharm.
[86] The CNIP was introduced in 1978 along with the "open-door policy."
[87] There are 19 different research institutes and institutions connected to CDC, for instance the National Centre for AIDS/STD Control and Prevention and also the China National Immunization Programs. (CDC, 2012)

diarrhea, etc. In 1992 the first Chinese Hepatitis A vaccine was introduced to the Chinese market, and in 2002 other HAV vaccines were introduced (Cui et al., 2009). However, it was not until 2008 that HAV vaccines were introduced within the CNIP;[88] earlier the vaccines could be bought by the patients themselves. Approximately 60,000 new hepatitis A cases are reported each year in China, although a large part of all cases are not reported at all. It is also estimated that there are around 17 million newborns each year in China in need of vaccines;[89] thus many doses of HAV vaccines need to be produced in order to immunize Chinese children. With this in mind, it is easy to understand the reason behind developing a HAV vaccine.

The HAV vaccine that Wison was interested in was developed by a semi-public research institute, although the original discovery of the vaccine can be traced to a university department in 1996. Some of the scientists involved in the original discovery created a research institute to continue vaccine development outside of the university lab, and the HAV vaccine was one main project that lay the foundation for the new research institute. The clinical trials were performed by the research institute by connecting to CDC clinical hospitals, and the clinical phase three trials were finalized somewhere in late 2003 to beginning of 2004. As it seems, particularly the Wison deputy general manager had direct insight in the development of the vaccine at the research institute. Moreover, Wison had many contacts with vaccine researchers and developers mainly through the deputy general manager. Since the HAV vaccine had already passed clinical phases, and only the NDA remained; Wison could focus on setting up manufacturing of the new HAV vaccine to begin with. Wison approached the research institute and suggested that Wison would build up the production capacity to commercialize the HAV vaccine into a final vaccine. The negotiations between the parties were a few months, and a cooperation agreement was signed as early as the second quarter of 2004. Wison bought the project and the vaccine patent along with it, but the research institute was to act as a partner in order to assist and support further commercialization of the vaccine. Many of the contacts between the parties since then on have been about technical issues, such as the detailed information needed for the NDA application to the SFDA. The research institute has also been helpful in setting up the production process. To sum up, when Wison bought the vaccine in 2004, the vaccine had already been in development for the last eight years, first at the university lab for two-three years and later on at the research institute for another four-five years. Through the purchase Wison got access to a new vaccine. Wison would establish production and thereby learn more about the biopharmaceutical world or as the general manager says: "...we will adopt the path from me-too to innovation" (Wang, 2007: 8).

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[88] Altogether 15 diseases are targeted within the CNIP. (Hendriks et al. 2010)

[89] The largest worldwide outbreak of hepatitis A was in Shanghai in 1988; more than 300,000 people were infected. (Cui et al 2009)

Setting up the Production Process and Investing in Equipment

When Wison bought the vaccine in 2004 there were only a few employees at Wison with the main objective to develop the vaccine into a salable product. In order to further develop the project, more employees were needed, especially in the R&D department, where the actual set up of the production process would take place on a small scale. Over time, people with production experience were employed in order to take the HAV vaccine from research into actual production. From 2004 Wison has employed more people with experience from pharmaceutical production and R&D, and in 2007 Wison consisted of a hundred employees, mainly focusing on R&D and production activities. The production process has not only been a matter for Wison but also for the research institute, since it helped with setting up the production process. Thus scientists from the research institute have worked at Wison. Also, the research institute has been important when applying to the SFDA for the NDA. If we look closely in the R&D department at Wison, the work is small-scale, i.e. small amounts of vaccine solution are in focus, where the development of the production is performed using laboratory systems. The main purifying system for the production at lab scale is the ÄKTAexplorer supplied by GE Healthcare,[90] and Wison has two ÄKTAexplorers in use at the R&D department. Since Wison bought the vaccine, they have developed the production process, and during the spring of 2007 there were around 30 people working at the production department. Between 2003 and 2007 Wison's building in Zhangjiang Hightech Park has been filled with content; the building hosts not only an R&D department but also a production facility, along with a small clinical department.

The production process of the HAV vaccine can be summarized as follows: in the fermentation phase rolling bottles[91] are used as the main equipment, supplied by a domestic Chinese supplier. Wison is using between 1000-2000 bottles for producing the cell-culture, and each bottle can hold up to two liters of substance. ÄKTApilot, supplied by GE, is the main purification system in the purification phase. The main argument behind buying ÄKTApilot has been that no other purification system can be used for both research and production purposes.[92] ÄKTApilot is suitable for small-scale production, such as

[90] From now on referred to only as GE.

[91] Traditional equipment for fermentation of cell cultures.

[92] Also, the flow-rate is flexible and two columns could be added to the system, along with the fact that the system complies with sanitary requirements put up by the American FDA and cGMP standards.

vaccine in China.[93] The vaccine is transformed to a final product in the formulation stage using equipment supplied by domestic Chinese suppliers.

Being a new start-up company Wison invested in the production equipment mentioned above, and the actual purification systems both for R&D and production were supplied by GE. The staff working with R&D and production at Wison are all experienced users of ÄKTA systems and knew the basic ÄKTA platform and the benefits of using ÄKTA systems. For instance, the production manager has been working for Vitamin Biotech while the fermentation and purification managers have been recruited internally from the Wison Group. Using the same system platform at lab and process scale would facilitate the scale-up. Wison could choose to use ÄKTAexplorer for the production of the vaccine since a lab system like ÄKTAexplorer is accepted for production purposes in China. However, in Europe and the US, ÄKTAexplorer is a lab system that is not allowed for production, because it does not support the high sanitary requirements set up by the American FDA. Wison, on the other hand, decided to use sanitary systems because Wison has an international agenda and wants to develop their business outside China, where stricter regulations direct the development and production processes. Hence, investments in equipment that supports international standards will facilitate future export and application processes outside of China.

The whole process, from deciding what equipment and system to use for production to actually signing a purchasing agreement with the main equipment supplier, GE, took just under one year. The agreement was signed by the parties in late 2005, and the systems were delivered three months later. Nevertheless, Wison encountered problems with the customs clearance: Wison wanted "tax-free" import of high-tech equipment. To get this Wison needed to define the specific use of the equipment and argue that the equipment was needed for developing a high-tech product. Wison points out the importance of describing the systems in the right way to the Chinese customs. By knowing the manual of the documents put up by the Chinese customs, it is easier to write the proper and acceptable description. However, the tax-free issue was solved after negotiations with the government, and Wison got the systems "tax-free" but had to pay a small penalty fee to the customs. This caused some weeks of delay with the equipment stuck in the customs, and this in turn affected the set-up of the production process.

[93] In general Chinese vaccine companies produce in small scale, only two out of 50 producers have bioreactors for fermentation; however, these are also small in scale (<100 l). (Xia and Chen, 2009)

Approval of NDA

The SFDA has been involved in regulating the whole development process for the HAV vaccine. For instance the SFDA approved the clinical trials performed by the research institute. Wison applied for class one NDA to the SFDA through the clinical department and the final approval was granted in the spring of 2007. It took a long time for Wison to get the final production license, largely due to the bribing scandal exposed at the SFDA in 2005/2006. According to Wison the main obstacle for the first HAV vaccine was not the production development per se but actually receiving approval from the SFDA. Normally a drug is approved within 9-12 months after submission. Wison suffered from delays in production and even when NDA was approved by the SFDA, the cGMP approval of the Wison production facility by the SFDA still remained. When discussing the development of biopharmaceutical drugs in China, many have pointed out the problems in handling cGMP approvals on time and the problems of products reaching the market (Jia, 2007). The cGMP approval of the Wison production facility encountered similar problems, and the approval was not granted until 2009.

The Need for One Customer

In March 2007 Wison had not yet developed a specific sales or marketing organization. The ambition was to set up sales and marketing departments in late 2007 or early 2008. Nevertheless, important pre-marketing activities have been taking place concerning the HAV vaccine. Since the CDC is the main purchaser of vaccines in China, the pre-marketing activities have been aimed at one main customer, the CDC. Moreover during the clinical trials CDC clinical hospitals have been involved, and Wison points out the importance of the CDC in reaching patients. There are 54 provincial CDC centers all over China; these in turn are responsible for regional CDC clinics and hospitals.[94] Altogether there are around 140 CDC clinical hospitals approved by the SFDA to perform clinical trials. In 2007 after contacts and negotiations between Wison and CDC, Wison was approved as a supplier of HAV vaccines to the CDC included in the CNIP from 2008. Wison would only need to provide the HAV vaccine to CDC centers and these centers would handle further distribution to CDC hospitals, where the immunization takes place. Thus by connecting to CDC, Wison has the possibility of reaching millions of Chinese customers. However, since Wison distributes its vaccine through CDC as a part of CNIP, the margin is set

[94] Since 2005 Chinese vaccine producers can contact hospitals and clinics directly without connecting to CDC centers, however this is only related to the vaccines outside of the CNIP. (Zhou 2007; Xia and Chen, 2009)

on a lower level; nonetheless, the price is set at around US$ 4.5 incl. VAT per dose, which is relatively high compared to the cheapest vaccines such as Diphtheria at US$ 0.04 incl. VAT within the CNIP (PRLOG, 2009). In order to get full protection of the vaccine, every patient needs two doses of the HAV vaccine. Besides Wison there are another five companies supplying HAV vaccines to the CDC and the CNIP. Two of these are injection vaccines similar to the HAV vaccine produced by Wison (the three other vaccines are nose spray vaccines). The two injection vaccines belong to SinoVac and Kunming Institute of Medical Biology (KIMB).

Investments in Wison and Future Development

In order to finance the establishment of Wison – the physical environment, the building, the equipment, the facilities and the staff – Wison has received financial support from the Wison Group. When the company is under construction Wison does not have the pressure to deliver any profit. So far the Wison Group have invested around RMB 1 billion (US$ 128million) in Wison and between 2007 and 2012 Wison Group will invest another RMB 1 billion (US$ 128 million) in order to develop a manufacturing platform for vaccine production (Wang, 2007). Wison is focusing on the manufacturing of biopharmaceutical drugs, which means that they want to attract other organizations or research institutes that want to commercialize their research by providing good manufacturing skills. The approach is first to learn the manufacturing part of biopharmaceutical drugs and later on start to develop products by themselves (Wang, 2007).

Wison has not received any direct financial support of the HAV vaccine from the Chinese government due to the fact that Wison bought a finished project and patent from the research institute. However, the company has received government awards such as "New Technology Enterprise" by the Shanghai government. But the HAV vaccine received governmental support from the national 863 program through MOST when it was developed at the research institute. Moreover, since the vaccine originates from a university department, it is partly financially supported by the government. However, Wison points out the need for good relations with the government for government approvals and future financial support. Since the purchase of the vaccine, Wison has identified other drug projects; two other recombinant vaccines originating from the same research institute as the HAV vaccine along with an antibody drug developed by another technical source, although these projects are still in early phases of development. As a result of developing more than one product Wison has developed into three separate companies, but all are under the same roof, the first company focusing on the HAV vaccine and the other vaccines under development, the second company focusing on the devel-

opment of monoclonal antibody drugs, and the third company being a joint venture with a Canadian firm focusing on therapeutic vaccine development.

Epilogue

The cGMP approval of the production facility of the HAV vaccine was granted in 2009, and along with it came a market launch in 2010. In 2009 Wison also signed an agreement with an Indian company to supply the HAV vaccine the coming ten years after international approval of the vaccine.

A Timeline of the Innovation Journey of the HAV Vaccine

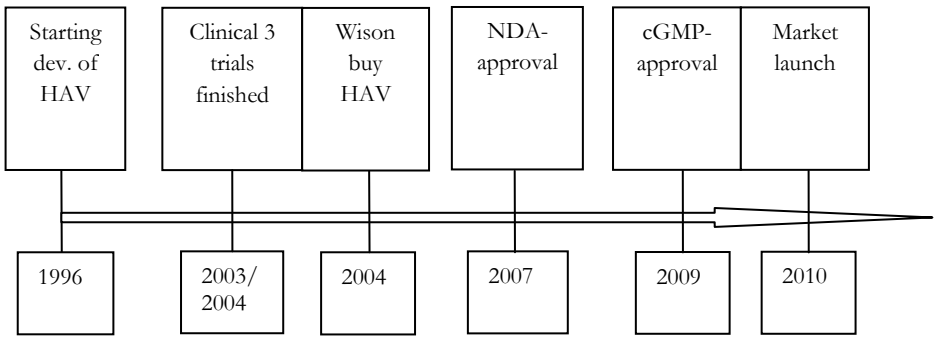

Figure 10. Timeline of the HAV vaccines innovation journey.

Analyzing the Embedding of the HAV Vaccine

When analyzing the HAV vaccine case, we will once again focus on what resources the new solution has interfaces with, in a developing, producing, and using setting. The four resources elements of the 4R model are used as point of departure, and the focus is on two main types of interfaces: HAV vaccine and interfaces involving social resources and HAV vaccine and interfaces involving technical resources. The following figure summarizes the resource interfaces

related to the HAV vaccine in the developing, producing, and using setting.[95] In this case resource interfaces are present in all three settings and the following sections will analyze the resource interfaces that the vaccine has encountered while being developed, produced, and used.

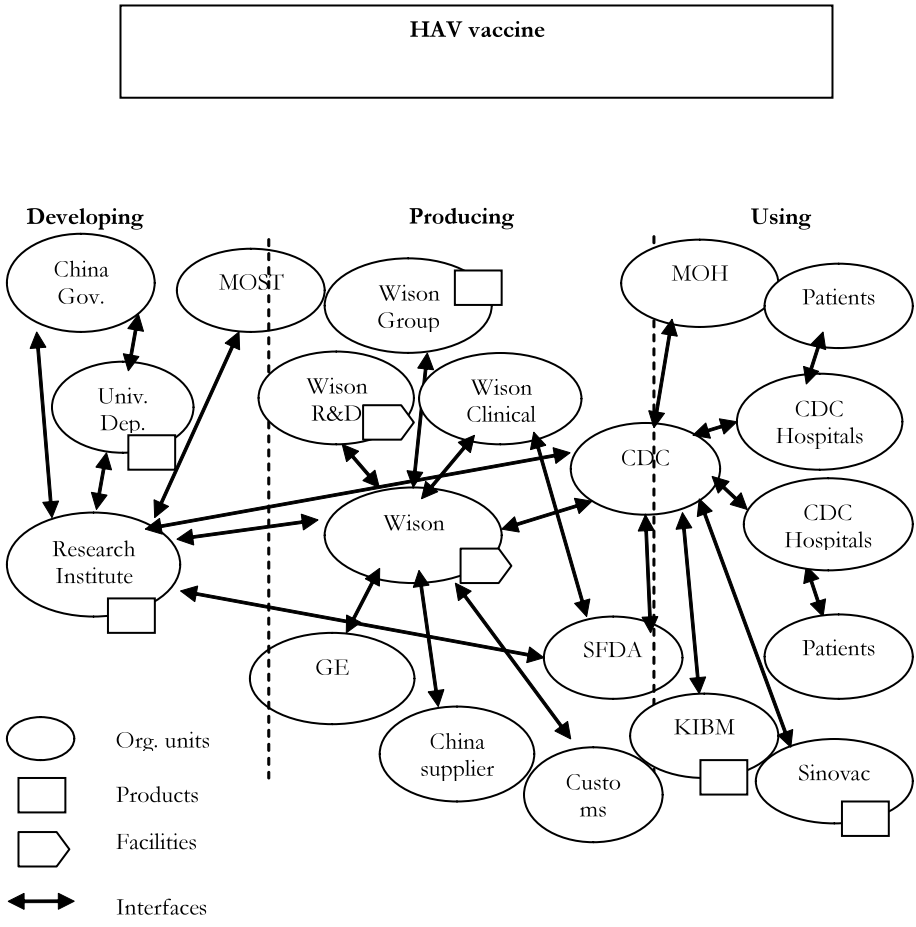

Figure 11. The embedding of the HAV vaccine.

HAV Vaccine and Interfaces in the Developing Setting

There are strong interfaces between the HAV vaccine and *a) organizational units* in the developing setting. There are two main knowledge units in charge of the

[95] Organizational resources are not included in the figure.

development of the vaccine. These units are the *university department and the research institute*. The same scientists are involved in the discovery at the university unit along with the further development at the research institute, as it seems these scientists have experience in the discovery of new vaccine substances. Being able to discover and develop the vaccine to begin with required not only connections to knowledge units but also to financing units. Both the university lab and the research institute were partly financed through *the Chinese government*. Also, *MOST* was important in financing further development of the vaccine at the research institute. Thus there are strong interfaces between the HAV vaccine and financing units originating from the government in developing the vaccine. In being able to perform clinical trials at the research institute the vaccine has strong interfaces to *CDC clinical hospital units*, which handled the clinical trials. Also, there is strong interface with the regulating unit, *the SFDA*, in further development of the new vaccine. The vaccine is dependent on the SFDA for approving pre-clinical and clinical trials along the innovation journey.

In being able to develop the HAV vaccine there has been one strong important *b) organizational relationship*. In handling and performing clinical trials *the relationship between the main knowledge unit, the research institute, and the CDC* became critical. Through the relationship the developing and using setting was interconnected, and, as a result, from the beginning the HAV vaccine has been developed in cooperation with the main using units of the new vaccine.

There are no visible interfaces between HAV vaccine and *c) facilities*.

In being able to discover the vaccine and transform it to a functioning vaccine there are strong indirect interfaces to other *d) products* in the developing setting. The main knowledge units, the university lab and the research institute have been involved in developing vaccines for a long time, thus through *earlier drug development projects* the scientists within the knowledge units have gained experience of developing vaccines necessary for the development of the HAV vaccine.

HAV Vaccine and Interfaces in the Producing Setting

There are strong interfaces with *a) organizational units,* when embedding the vaccine into production. First of all, the producing unit, *Wison*, along with the internal units, *Wison R&D and Wison Clinical*, has been crucial when embedding the vaccine in production. However, in realizing the establishing of the producing unit *Wison Group* has acted as main financing unit. It was through this financing unit that Wison could buy the HAV vaccine in the first place, along with realizing the establishment of the company and its internal units. The main knowledge unit, *the research institute*, once again is important in embedding the HAV vaccine in production. Initially it was through this unit that Wison got access to the HAV vaccine. Since the producing unit did not have earlier experience with biotechnology or biopharmaceuticals in particular, the unit was dependent on connecting to others with the right experience, in this case the

research institute. Through this knowledge unit Wison could gain access to lacking biotechnology knowledge. Moreover, in establishing the producing unit Wison was dependent on employing other employees with experiences from biotechnology. The Deputy General Manager provided the contacts with the research institute and its scientists. The producing unit aimed at focusing on establishing a producing platform and leaving the development of the new solution to vaccine experts at the knowledge unit. In producing the HAV vaccine the regulating unit, *the SFDA*, once again becomes important. It was the SFDA that approved both the final NDA along with the cGMP approval of the production facility. Supplier units, such as *GE Healthcare and other Chinese suppliers*, have been important in providing R&D and production equipment. Finally the *Chinese customs* is an important government unit when supplying the production equipment "tax-free," however after some negotiations.

In establishing the HAV vaccine in production, there are important *b) organizational relationships* present. First of all there are strong interfaces to *the relationship between the producing unit, Wison, and the main knowledge unit, the research institute*. The relationship is important in linking the development and the production of the vaccine. Through the relationship the producing unit could tap into the knowledge unit's knowledge base and launch a product fast, at a lower price by using already activated resources related to the knowledge unit. Through an interactive relationship the knowledge unit and the producing unit together set up R&D and production related to the new HAV vaccine. The interactive relationship provides necessary knowledge from development to the production setting (such as technical details, regulations, clinical information, etc.). *The relationship involving the knowledge unit, the producing unit, and CDC clinical hospital units* is important in realizing the production of the new vaccine. Choosing CDC hospitals for clinical trials with long experience of vaccine development facilitates the embedding of the new vaccine in production along with the NDA-approval. *The relationship between the main supplier unit, GE, and the main producing unit* has been important in finding suitable production equipment to embed the HAV vaccine in production.

There are strong interfaces with *c) facilities* in embedding the HAV vaccine in a producing setting. The production process consists of interlinked equipment supplied by supplier units and the choice of production equipment reflects the small scale of vaccine production. *Rolling bottles* are small in scale and also referred to as traditional fermentation equipment. Moreover, the main purification system, *the ÄKTApilot*, is also suitable for small-scale production. There is also a link between R&D and the production equipment, *ÄKTAexplorer*, used for R&D, resulted in *ÄKTA systems* in production to facilitate the scale-up. In order to produce on a larger scale, new investments in production equipment are necessary.

There are also strong interfaces between the HAV vaccine and other *d) products* belonging to the Wison Group. *Through the sales of other products* it has been possible for Wison Group to act as the main financing unit of the HAV vaccine in the production setting. Also, *through other vaccine products*, the main

user, the CDC, has established a distribution network that Wison can tap into when producing and distributing the new vaccine.

HAV Vaccine and Interfaces in the Using Setting

There are strong interfaces between the HAV vaccine and *a) organizational units* in the using setting. More specifically, there are strong interfaces between the new vaccine and the main using unit, the government health bureau, *the CDC*. As mentioned earlier, the CDC has been active in both developing and producing the vaccine; especially CDC clinical hospitals units have been active in performing clinical trials. Since the CDC has had a monopoly position supplying the Chinese population with vaccines, for a long time, the unit can be characterized as an established organization including an established resource structure including experienced personnel and established contacts to *end-users, i.e. patients*. Thus the CDC can be seen as an active unit stretching all three settings both related to *the knowledge units and the producing unit*. There are strong interfaces between the HAV vaccine and the Chinese government through the main financing unit, *MOH*. Thus, the strong embedding of the vaccine in the using setting is due to the fact that the government pays for the new vaccine, not the end-users themselves. *Sinovac and KIMB* also supply HAV vaccines to the CDC and the CNIP.

Due to the fact that CDC is the main using unit of the HAV vaccine, the unit is also present in important *b) organizational relationships* embedding the new vaccine in use. For instance, *the strong relationship between the knowledge unit and CDC* was crucial in developing the vaccine, but the relationship was also an important point of departure when establishing *the relationship between the producing unit and CDC*. Thus it is evident here that established relationships are important in establishing new relationships and thereby further embedding the new vaccine into the using setting.

There are no visible interfaces between the HAV vaccine and *c) facilities* in the using setting.

When embedding the HAV vaccine into the using setting, there are interfaces with other *d) products* that will affect the final use of the new vaccine. More specifically there are *two other HAV vaccines* within the CNIP used in the same way as the Wison HAV vaccine. I do not have any information about how the CDC divides the quantities between the vaccine producers, but it is important to bear in mind that there is a general lack of supply related to the vaccines included in the CNIP. Due to the supply shortage for HAV vaccines, future sales and use of the new vaccine are promising, as is the fact that the price for the HAV vaccine is relatively high compared to other drugs within the CNIP. Moreover, foreign sales of the new HAV vaccine have opened up for further spread the use of the new vaccine outside of China.

Summing Up

The HAV vaccine was developed through strong interfaces to scientists belonging to two knowledge units partly supported by the Chinese government. The scientists have long experience in vaccine development and could therefore stabilize the discovery into a functioning vaccine. While the knowledge units were experienced, the main producing unit, Wison, was not. Instead the producing unit was actually established by a company group with no earlier experience with vaccines or pharmaceuticals. The producing unit was established first; then the HAV vaccine was found through the new deputy general manager with extensive experience and contacts within the Chinese vaccine industry. Thus the producing unit bought a finished vaccine from the main knowledge unit, the research institute. As a consequence the producing unit did not have to get involved in the development of the vaccine; instead, a partnership with the knowledge unit was formed to be able to focus on establishing a manufacturing platform for the new HAV vaccine. The producing unit is highly focused on manufacturing, and the unit is open to provide a manufacturing platform for other organizations. In the production of the HAV vaccine the private-owned Wison Group is important as main financing unit. The case display strong interfaces to supplying units and regulation units in the producing setting. Also, the support of the Chinese customs to allow "tax free" import of equipment facilitated the embedding of the vaccine into production. The fact that the vaccines industry in China is well established has been helpful in the development, production, and use of the HAV vaccine. There is only one main using unit, the CDC, and it is an established organization with an established distribution network including clinical hospitals units and experienced medical expertise connected to end-users, patients. Moreover the embedding of the vaccine is related to the fact that the Chinese government pay for the new vaccine. One distinct feature of the HAV vaccine is the relatively low margin that the product is allowed within the CNIP; however, the quantities of the vaccine sold can make up for the low margin. The case also reveals future sales to foreign companies as a way to enhance the spread of the vaccine.

As the following table reveals the new HAV vaccine is embedded in all three settings, the developing, producing and using settings. Especially the new vaccine has strong interfaces to the main using unit, the CDC, spanning all the settings. Since the vaccine is strongly embedded into the three settings, the new HAV vaccine can be regarded as a new innovation.

The HAV vaccine	**Developing**	**Producing**	**Using**
Org. Units	Strong interfaces	Strong interfaces	Strong interfaces
Org. Relationships	Strong interfaces	Strong interfaces	Strong interfaces
Facilities	No interfaces	Strong interfaces	No interfaces
Products	Strong interfaces	Strong interfaces	Strong interfaces

Table 9. Summary of resource interfaces related to the HAV vaccine.

CHAPTER 11: MAKING MONEY OUT OF MONOCLONAL ANTIBODIES — THE CASE OF MAB1

Shanghai MAB Pharmaceutical[96] is one of few Chinese companies involved in producing biopharmaceutical drugs based on monoclonal antibodies. In 2005 the company was approved NDA of the first product, MAB1, targeting rheumatoid arthritis. The following case is focusing on revealing the innovation process of MAB1.

Introducing the Commercialization of Monoclonal Antibodies

When bacteria or viruses attack the human body, there are naturally specified proteins or so-called antibodies designed to fight off these attacks or antigens. Antibodies that bind to a specific and single type of antigen are called monoclonal antibodies. By using monoclonal antibody technology naturally produced antibodies can be strengthened; in practice this means that scientists extract antibodies and grow them in large numbers and then inject it to the human body in order to fight off the most intense invaders. Monoclonal antibodies are also referred to as "biological missiles" and can be used for various diseases, such as cancer and autoimmune diseases, and there is increased interest and expectations regarding the industrialization of monoclonal antibodies.

However, the innovation process of drugs based on antibodies is difficult for many reasons. Firstly, the drugs are based on larger and more complicated molecules; thus the process requires a highly technical and difficult production process. Secondly, treatment with antibody drugs requires large doses; thus the production of large quantities of active substance is a necessity. As a consequence high-end large-scale production equipment along with large quantities of consumables are required. These difficulties result in high costs and major financial investments related both to equipment and expertise. Still the expectations on the commercialization of monoclonal antibodies outweigh the

[96] Company name re-named for anonymity reasons, from now on only referred to as MAB.

difficulties associated with the commercialization, and many companies have entered the field of monoclonal antibodies since the mid 1990s. This interest is not only limited to the Western world but also a fact in contemporary China.

The Commercialization of Monoclonal Antibodies in a Chinese Setting

In the late 1990s Chinese companies became interested in the economic potential in developing and producing drugs based on antibodies. At the time there were few Chinese firms focusing on antibodies. Moreover, none of these firms yet had a final product to sell. The main part of antibody drug products on the Chinese market was supplied by large MNCs such as Genentech, Johnson & Johnson, and Amgen. Along with the increased interest in antibody drugs, a Chinese company, MAB, was established in 1998 with the aim to commercialize these types of drugs. The company's ambition was to become the largest producer of monoclonal antibodies in China. The company is a joint venture between a Hong Kong based investment firm and a Chinese Import/export (I/E) firm. Hong-Kong Invest, owning 51% of MAB, is listed on the Hong Kong stock exchange and focusing on four traditional business areas; infrastructure, steel manufacturing, real estate, and marketing & distribution. The Chinese I/E firm, owning 49% of MAB, is listed on the Shanghai stock exchange and belongs to a state-owned group involved in various traditional business areas, such as transportation, manufacturing, real estate, and the service industry. To sum up neither of the two companies had earlier experience with biopharmaceuticals and monoclonal antibodies in particular.

Point of Departure — Buying Military Science

One crucial aspect in establishing MAB as a producer of monoclonal antibodies is the actual decision to focus on antibodies within biotechnology. To enter the biotechnology arena is not an easy task; with no earlier experience from biotechnology and biopharmaceutical drugs, MAB decided to focus on a part of biotechnology where few Chinese companies were present. Also, the fact that there was an increased focus on the possibilities of using antibodies technology in other parts of the world might have played some role in prompting the company to proceed with antibodies. Since neither of the two joining companies had earlier experience from biopharmaceutical drugs, the new company had to find suitable development projects externally. By finding the right research partner the company could focus on establishing the production of monoclonal antibodies.

To develop drugs based on monoclonal antibodies, MAB approached the Shanghai 2nd Military Medical University (SMMU),[97] the most prominent university and research center for monoclonal antibodies technology in China. As it turned out the military university had many research projects under development that they wanted to commercialize. One project was more interesting than others, a drug for treatment of rheumatoid arthritis. Actually the drug was developed as a "bio-similar" drug of an American drug belonging to an MNC. But the military university wanted to develop a similar product at a lower price. In the mid 1990s the military university decided to develop the drug and in the late 1990s the first clinical trials started. The first research agreement between MAB and the military university was signed in early 2000, and in 2003 the company was approved by the SFDA to perform late clinical trials on the new drug, MAB1. In mid 2005 the drug was granted an NDA by the SFDA.

The division of labor between MAB and the military university was that the company would focus on the production and process development, while the military university would supply the research input. After finishing basic research and drug discovery of new antibodies drug projects, these are transferred to the company for further development and industrialization in close collaboration with the university. For every new research project there are separate research agreements between the two parties. Since the cooperation with the university began, the company has employed scientists from the military university part-time in order to get detailed information about the original development to facilitate the downstream drug development process. As the cooperation between the parties evolved over time a new research center was established in 2006 by MAB in cooperation with the military university, but also supported by the Shanghai government.

Production of Monoclonal Antibodies and the Need for Equipment

When MAB got the military university as their research partner, the company needed to develop a manufacturing platform for the production of monoclonal antibodies. Since the basic research along with pre-clinical studies would take place at the military university, MAB started off by developing an R&D department, where the production of samples for clinical trials would take place, with the main focus on MAB1, but also for a second drug, MAB2, also originating from the military university. In order to produce clinical substances the company needed equipment to be based in the R&D department. At this stage

[97] The university was founded in the beginning of the 1950s and from now on referred to as the military university.

MAB was approached by GE Healthcare[98] and introduced to several of GE's separation equipment, GE suggested that MAB should use GE separation equipment for the clinical production along with the coming production process.

Why did GE approach MAB? The military university was and still is one of GE's oldest customers in China. The university has used separation equipment from the supplier since the early 1970s. For instance, ÄKTAexplorer has been used as standard equipment at the military university for a long period of time. GE was therefore informed about the new research agreement between the military university and MAB through the military university. At the starting point MAB decided to invest in equipment for R&D and bought two lab systems, ÄKTAexplorer, to produce samples for clinical trials and ÄKTAprime, for the simplest lab purification at the company.

As MAB developed the drug, the need for more equipment to perform later stages of development became obvious; the company needed more equipment to perform small-scale production of the first product MAB1 but also for projects further upstream. At this stage ÄKTAexplorer was used in the R&D department in order to produce samples for clinical trials, both for MAB1 and MAB2, which meant relatively large quantities of clinical substances. Since the planning and set-up of clinical production will direct downstream production, the company developed R&D and the production at the same time and at the same place. Due to the need for close connection between clinical production and actual production, MAB established the production department in the same facilities as the R&D department. This was possible due to the small scale of the drugs at this stage.

In order to develop both the clinical production and the actual production process, MAB approached GE in mid 2004 for further investment in equipment. First of all the company invested in two bio-process systems for the production of MAB1 and MAB2. A few months later the company received information from the sales representative about a relatively new system, ÄKTApilot, that would be suitable for the production of samples for the clinical trials but that could also be used for final production on a smaller scale. MAB decided to buy the ÄKTApilot system as a complement to ÄKTAexplorer for producing samples for clinical trial.[99] ÄKTApilot would therefore be based in the R&D department indirectly linked to the production further downstream. Since the company already used ÄKTAexplorer and ÄKTAprime, it was an easy choice to use another ÄKTA system for the clinical production on a larger scale. Also, the fact that the military university had used ÄKTAexplorer in earlier research facilitated the choice to use further GE equipment. Together with

[98] From now on only referred to as GE.

[99] MAB decided to buy ÄKTApilot because of the suitable scale, as an intermediate system between lab and process scale and also due to the good quality and high purity of the proteins separated.

the military university, the company had designed the whole clinical process along with the coming production, and GE advised which system would be the most suitable in various steps. When the bio-process systems arrived in spring 2005 and ÄKTApilot arrived in late 2005, GE helped to install the systems and provided training to the employees. ÄKTApilot was bought with the intent to use it for producing clinical samples; however when the system arrived MAB decided to use it for production instead.

Around 30 people were working with the clinical production and the production development process. These employees had earlier experience from using various systems from GE. The main part of the employees working with R&D and production have university degrees from prominent Chinese universities in biochemistry or similar fields. Also, the production manager had several years of experience from product development in the biotechnology industry. An important part in developing R&D and the production has been the training of the personnel, and the main part of this has been performed by the production manager, though with support from the military university. The R&D and production personnel have worked in close collaboration in establishing the production process. There have been extensive contacts between the R&D and the production team, which have been facilitated by the fact that R&D and production were set up at the same place.

Setting up the Production Process

In April 2005 MAB was granted an NDA for MAB1. A short time thereafter MAB2 was also granted an NDA. At this point the production process needed to be cGMP approved. Looking deeper into the production process, it starts with the fermentation step, where the company using bioreactors of 750 l from a German supplier followed by a two-step process with a centrifuge to gather the proteins followed by filtration where the substance is filtered and a higher concentration of the proteins is obtained. This two-step process is performed by using centrifuge and filtration equipment from domestic Chinese suppliers. Secondly, in the purification step, bio-process systems from GE handle the first part of purification, but due to the fact that the scale and amount of substance diminishes with each purification step, ÄKTApilot is used in later stages of the purification step when the scale is smaller. In the last formulation step the sample is transformed into a product and mixed with other solutions to become an injection substance.

Investing in Equipment

When investing in equipment for both for R&D and production of the MAB1, the production manager had been evaluating the need for certain equipment for MAB, which was an easy and relatively quick process. The choice to invest in main separation equipment from GE was due to the fact that the military university uses ÄKTA systems for basic research and drug discovery; in particular ÄKTAexplorer is used by the military university. Using bio-process systems for production was an easy choice as large-scale production equipment was needed. Similar bio-process systems could be supplied by American Millipore, but it is easier to scale up based on the same equipment as for upstream activities in the drug development process, such as clinical production and research. The choice to buy ÄKTApilot was different, because there were no other systems available that could be used both for lab and production purification. However, initially MAB bought ÄKTApilot for clinical production but in the end the company used it for actual production.

Even though the actual decision as to what equipment to use was easy, the internal approval of the purchasing process at MAB was complicated; the vice president needed to approve the purchase, followed by transferring the purchasing process to the purchasing department for evaluation and final decision. This was followed by a price negotiation between the purchasing department and GE. Several departments need to agree in order to purchase new equipment at MAB, but since the company established a manufacturing platform there have been no major problem in getting a request for investment in equipment approved, though it will take long time for the purchase to be agreed upon within the organization. Every purchase above RMB 5000 (US$ 625) needs to be decided on a higher level, i.e., the production manager must turn to the vice president of the company in cases of investment in equipment. The whole process from planning to signing the purchase agreement for both the two bio-process systems and ÄKTApilot took more than a year. Along with it came the delivery of the systems, which took another four months for both the bio-process systems and for ÄKTApilot.

Developing the R&D Department into a Research Center with Government Support

When MAB was granted an NDA for MAB1, the company needed to separate R&D and production. First of all it would be impossible to receive cGMP approval when R&D and production was at the same place. In addition, MAB had transferred more and more projects from the military university, resulting in an increase in production of clinical samples and thus a need for more space and more equipment for clinical production within R&D. The work of separat-

ing R&D and production into separate departments started in early 2005 and was a completed in mid 2006. The company developed the existing R&D into a separate research center called MAB Biotechnology Institute. In establishing the research institute, the company also received financial support from the local Science and Technology Commission of Shanghai Municipality (STCSM). Since the local government financially supported the establishment of the institute, it also implied that the center would strengthen research in monoclonal antibodies within the Shanghai area. As a result, other companies and research teams were invited to run tests at the institute, and MAB could also run certain tests for external companies or organizations. The military university became an important partner in establishing the research institute, and employees from the military university became main users of the institute, not to mention that the president of the new research institute is a professor at the military university. In late 2007 the research center consisted of high-end international equipment, where more than 15 types of antibody products could be screened at the same time.

Government Regulating the Development Process

During the drug development process of MAB1 there have been extensive contacts between MAB and the regulating authorities represented by the SFDA. First of all MAB's R&D department and the SFDA have been in frequent contact, since the R&D department has been in charge of producing samples for clinical trials, which includes strict documentation requirements set up by the SFDA. Also, the R&D department has been in contact with clinical hospitals performing the actual trials; these trials are also regulated and determined by the SFDA. MAB is in obliged to send in all the documents of the clinical production and the clinical trials of the two developed products to the SFDA. It is the SFDA that approved the clinical trials 1-3 for MAB1, along with the final NDA-approval. However, the military university has also been involved in the contact with SFDA. First the pre-clinical trial needed to be performed in accordance with SFDA regulations, and secondly the university has been important in giving detailed information about the research for the following clinical trials. Since the company has many products under development, the R&D department needs to produce all the clinical samples for all the clinical trials in a short period of time. Thus there is high pressure to provide documentation for ongoing applications to the SFDA.

Developing Monoclonal Antibodies, an Expensive Journey

Being involved in the commercialization of drugs based on monoclonal antibodies is an expensive task. It is estimated that an investment of more than US$ 500 million is needed when setting up production based on human cells in the US. The investment in production equipment is the same in China, although labor costs are somewhat lower; thus MAB1 was dependent on financial support to realize the innovation journey. The basic research on MAB1 was financed by the government since the drug was originally developed at the military university. Hong-Kong Invest has invested more than US$ 40 million to develop MAB into a producer of monoclonal antibodies, while the second owner, the I/E firm, has also invested a large sum of money in MAB.[100] MOST have granted MAB around RMB 10 million (US$ 1.2 million) from the national high-tech program, 863 program, in 2005. Local government also paid attention to MAB the same year by granting the company a government loan of RMB 4.5 million (US$ 540 000) with special interest conditions from the Shanghai Pudong New Area Science and Technology Bureau. Moreover, MAB has been the object of other regional government attention such as a "Shanghai Hi-tech company," "Shanghai Key Cell Engineering Laboratory," "Shanghai Pilot Technology Platform for Humanized Monoclonal Antibody," "Shanghai Experimental Unit for Protection of Intellectual Property," "Shanghai Scientific Research Station for Post PhDs," and "National Award for Technical Innovation." Also, MAB has received national attention though the product, MAB1, when the product was named a "national new crucial product" in late 2006. A total of more than RMB 1.2 billion (US$ 144 million) has been invested in MAB to establish the production of monoclonal antibodies, and more investments are on the way.

Scale-up and Future Developments

The scale of the production of MAB1 is small, using bioreactors holding 750 l, compared to Western pilot scales of around 1,500 l. However, due to good sales, the production process of MAB1 has been scaled up, from bioreactors at 750 l to bioreactors at 3,000 l. The scale-up was realized in 2008, and the same year the annual sales of MAB1 reached around RMB 140 million (US$ 17.5 million), thus the drug reached Chinese "blockbuster status." A Chinese blockbuster drug is referring to a drug with annual sales of more than RMB 100 million (US$ 12.5 million). Although the scale is large compared to other Chinese

[100] It is estimated that the I/E firm has an average annual turnover at around RMB 200 million (US$ 25 million).

producers, it is still small compared to Western production scale, holding around 15,000 l. If we compare MAB1 to the original drug sold by a large American MNC it is obvious that MAB1 has a price advantage compared to the original product. Comparing MAB1 with the original drug, the annual cost of the drug is estimated at around US$ 6,000, a cost of around 120 US$ per week (for two injections), while the annual cost for treatment with the original drug is estimated at somewhere between US$ 12-20,000.[101] The injection of MAB1 is rather simple but needs to be supervised by a doctor, due to some risks of infection.

When MAB1 was first developed there were no drugs based on monoclonal antibodies produced by a Chinese company; in 2008 there were still antibody drugs supplied by MNCs on the Chinese market but there were also between 12-15 monoclonal antibody drugs under development by Chinese biotechnology companies; ten of these are developed in Shanghai, the majority of which are being developed by MAB. Thus the company, together with the military university, has developed several new antibody drugs in parallel to the development of MAB1. So far MAB has been granted NDAs for two drugs, MAB1 and MAB2. Another handful drugs are in late stages of clinical trials, and some other drug projects are waiting for clinical trial approval by the SFDA. The establishment and development of the research institute has been an important factor in being able to develop several drugs in parallel. MAB's determination to continue developing antibody drugs is reflected in the annual R&D expenses of around RMB 30 million (US$ 3.75 million), which is more comparable to Western R&D expenses estimated at around 15-20% of annual sales than Chinese expenses estimated to around 2.5 % of annual sales (Kermani and Zhou, 2007).

Epilogue

Today around 200 people are working at MAB with the whole development process from R&D, production, sales, and marketing, and in 2011 a third drug was NDA approved by the SFDA.

[101] In 2005 an average monthly salary in China was around RMB 1500 (US$ 187). (China statistical yearbook, 2006)

A Timeline of the Innovation Journey of MAB1

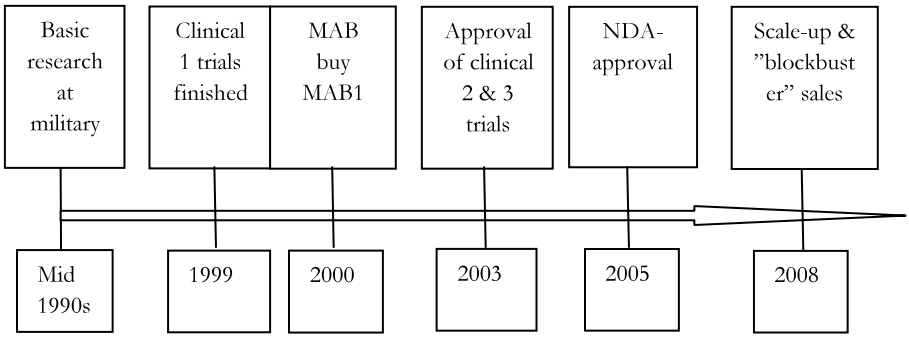

Figure 12. Timeline of MAB1's innovation journey.

Analyzing the Embedding of MAB1

When analyzing the MAB1 case, we will once again focus on what resources the new solution has interfaces with, in a developing, producing, and using setting. The four resources elements of the 4R model are used as a point of departure, and the focus is on two main types of interfaces: MAB1 and interfaces involving social resources and MAB1 and interfaces involving technical resources. The following figure summarizes the resource interfaces related to MAB1 in the developing, producing, and using setting and in this case resource interfaces are present in all three settings.[102] The following sections will further analyze the resource interfaces that MAB1 has encountered while being developed, produced, and used.

[102] Organizational relationships are not included in the figure.

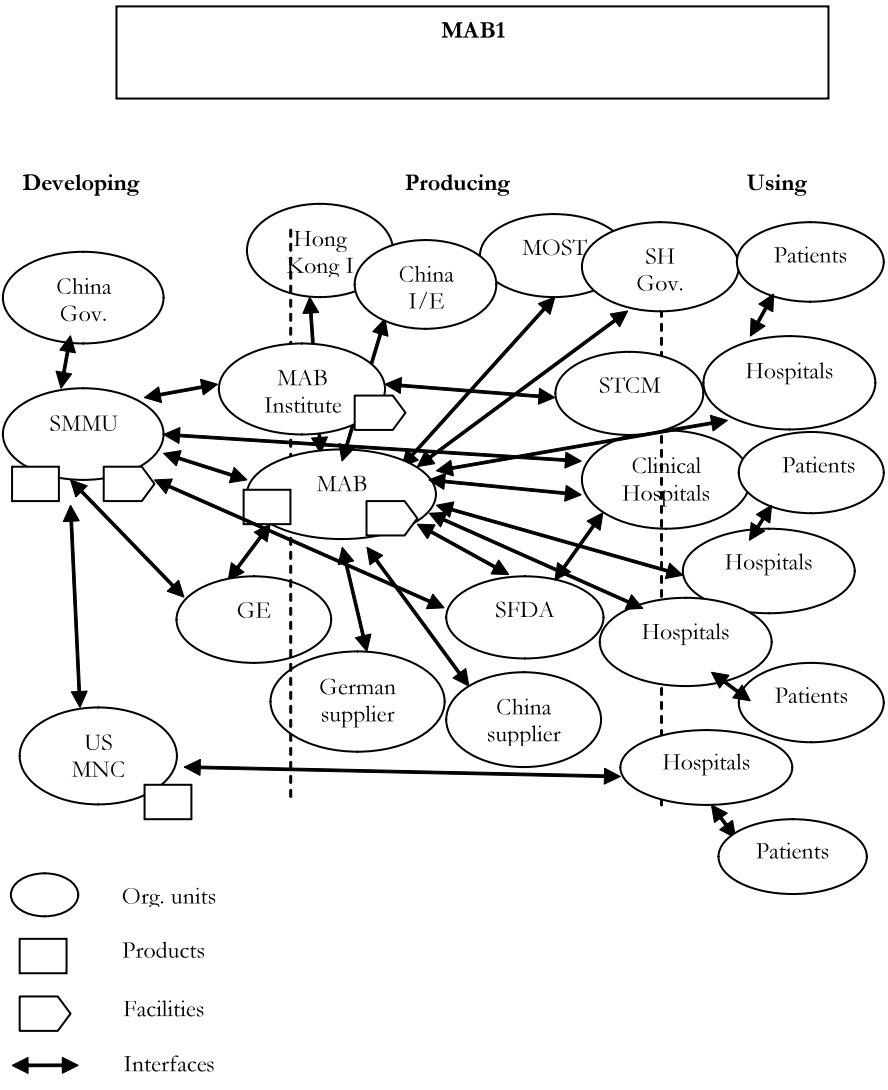

Figure 13. The embedding of MAB1.

MAB1 and Interfaces in the Developing Setting

There are strong interfaces between MAB1 and *a) organizational units* in the developing setting. To start with *the military university, SMMU,* can be considered as main knowledge unit in developing MAB1. Here the features of the military knowledge unit have been important for the development of the new drug. Since the unit is a military unit, it consists of experienced scientists and a well-

developed organization, and thus the established military knowledge unit has been crucial in developing the new drug. Another important unit for the development of MAB1 is *the American MNC* producing the "original drug". Moreover, the new drug has strong interfaces with *the Chinese government* since the government promotes the commercialization of new antibody drugs. The Chinese government has been main financing unit in developing MAB1 within the military knowledge unit and military research can be further financed through the commercialization of science. The main supplier unit, *GE Healthcare,* has been important in realizing the development of MAB1. Also, the new drug is connected to both *clinical hospital units* and the regulatory unit, *the SFDA,* while being developed. Clinical hospital units have performed clinical trials, and the SFDA has approved both the pre-clinical and clinical trials of the new drug.

There are also strong interfaces between MAB1 and *b) organizational relationships* in the developing setting. First of all, it was the changed *relationship between the Chinese government and the military knowledge unit* that spurred the development of MAB1. Moreover, another important relationship is between *the military knowledge unit and the main supplier unit,* a relationship dating back 40 years and characterized with frequent interaction. This relationship became important in connecting the developing and producing setting together while developing the new drug. Finally *the relationship between the military knowledge unit and the producing unit, MAB,* has been important in the further development of the new drug. For instance, in realizing late clinical trials the relationship was necessary in producing clinical substances.

In being able to develop MAB1 into functional new drug *c) facilities* have been necessary. For instance in producing pre-clinical and clinical substances, *ÄKTAexplorer* from the main supplier unit, GE, have been used.

There are strong interfaces between MAB1 and *d) products* in the developing setting. More specifically the new drug was developed in response to an *"original drug"* supplied by an American MNC. It was this "blockbuster drug" with several billion US$ in annual sales that prompted the military knowledge unit to start the development of a Chinese version of the drug, as a "biosimilar" drug. As a consequence the "original" American drug became the reference drug during the whole innovation journey of MAB1. Moreover, the military knowledge unit has *experience from several drug development projects*, from which knowledge is generated to be used in new drug developments. Thus other drug development projects have indirectly affected the development of the new drug.

MAB1 and Interfaces in the Producing Setting

There are important and strong interfaces with *a) organizational units* when embedding MAB1 in production. First of all the main producing unit, *MAB*, has been active in embedding the new drug into production. Since the unit did not have earlier experience within biotechnology, *the military knowledge unit* became

crucial, not only in supplying the new drug but also in supplying the expertise necessary for further commercialization. The military knowledge unit is part of an already established resource structure where the knowledge and experience from producing science have been developed since the mid 1950s, although since the late 1970s the unit has been more and more focused on commercializing this military science into actual products. Both units, the military knowledge unit and the producing unit, are active in embedding MAB1 in production and want to gain revenues from a final drug. There are two *internal units within MAB* that have been in charge of driving the embedding of MAB1 in production, namely *MAB R&D and MAB production*. MAB R&D has been mainly responsible for clinical production of the MAB1, while MAB production has been involved in setting up the production process in small scale, but the units are interconnected and during the production set-up the units have been co-located. However after the NDA-approval of the new drug, the two units are separated and MAB R&D is transformed to the *MAB Research Institute* as the new main R&D center for MAB. Production of monoclonal antibodies is an expensive task requiring large financial investments in both equipment and personnel. The main financing units related to the new drug are the main owners of MAB, *Hong-Kong Invest and the Chinese I/E firm*, which invested around RMB 700 million (US$ 87 million) so far. Also, *MOST* can be regarded as a financing unit along with the *STCSM*; thus both the central government and the regional Shanghai government have been involved in supporting the production of the new drug. In being able to produce the new drug, production equipment has been a necessity; therefore supplier units such as the international suppliers *GE Healthcare* and *the German supplier* have been important in supplying high-end equipment supporting FDA sanitary requirements. Moreover domestic *Chinese suppliers* have also played a role in embedding the new drug in production by supplying more "simple" equipment. The new drug display strong interfaces to the regulating unit, *the SFDA*. In being able to get NDA approval, the drug needed to correspond to the regulations set up by the SFDA; also, the production process needed to be cGMP approved by the SFDA. Moreover, the production of MAB1 is directly related to the clinical trials of the drug; thus the clinical trials direct the production process of the new drug. As a consequence *government clinical hospital units* are important in performing clinical trials of the new drug.

In embedding MAB1 in the production setting there are important *b) organizational relationships* present. First of all there is a strong relationship between *the producing unit and the military knowledge unit*. During the production set-up a highly interactive relationship was established between the parties where both actively promoted the production of the new drug. The relationship was important in establishing interfaces between the developing and the producing setting. Scientists from the military university are employed part-time at MAB to help with clinical production and indirectly with the production set-up. Due to its interactive nature, and along with several drug development projects in parallel the relationship result in the establishment of a new knowledge unit, *the*

MAB research institute. Moreover, another important relationship involves *the military knowledge unit, the producing unit*, *and the supplier unit, GE*. Here the supplier units combining capabilities become visible; the established relationship with the military knowledge unit is used in order to establish new relationships with the producing unit. Thus GE Healthcare creates interfaces between the developing and producing setting. Also, the supplier unit has extensive expertise and experience in setting up production processes according to FDA standards, and this experience and knowledge is used in embedding the new drug in the producing setting. In order to produce MAB1 the production process needs to be interlinked by using production equipment. Since the military knowledge unit already used the main supplier, GE, for the development of MAB1, while taking the drug into production, the main supplier unit once again became important. *The relationship between the producing unit and clinical hospital units was a result of an already established relationship between the military knowledge unit and the clinical hospital units*. The production of MAB1 is dependent on *a strong interactive relationship within MAB, between MAB R&D and MAB Production*. Thus there has been a strong interface between these two internal units in linking and connecting the developing of MAB1 to the production of MAB1. The co-location of the units facilitated the interaction and communication between the units, thus also embedding the new drug in the producing setting. Importantly, the internal units have developed R&D and production in close cooperation with the military knowledge unit, supplying the units with detailed information of earlier development aspects, etc. The embedding of MAB1 in production display strong interfaces to the government, especially in terms of financial support. One advantage of being partly state-owned is that MAB can use the *government relationships* to get both financial support and public attention.

There are strong interfaces with *c) facilities* in the production of MAB1. In being able to produce the new drug, equipment for production of clinical trials has been important, for instance *ÄKTAexplorer* has been the main separation equipment for the production of samples. In the actual production process there are interlinked equipment to each step, starting with *bioreactors* along with a *centrifuge and filtration system*, followed by purification through the use of *bioprocess system and ÄKTApilot*, ending with formulation by using *formulation equipment*. In seeking an effective production process, a *resource fit between bio-process and ÄKTApilot* was achieved, resulting in less waste. Also, the main producing unit starts off with small-scale production and when sales take off the unit decided to scale up the production using by for instance investing in larger bioreactors. Moreover the production facilities need to comply with the regulations set up by SFDA and especially the cGMP approval of the production process.

The possibility of embedding MAB1 in production is a result of other *d) products*. The main financing units (the owners of MAB) have been able to *finance MAB1 through the production and sales of other products*. In parallel to the production of MAB1, there is also the production of *MAB2*, where the same R&D and production employees have been involved. Moreover, one direct effect of *interfaces to other products in MAB's product pipeline* is the transformation of the

R&D unit to the MAB Biotechnology Institute. It was not possible to keep the R&D together with the production unit because there were too many products being developed in parallel; also to receive cGMP approval of the production process, R&D and production needed to be separated.

MAB1 and Interfaces in the Using Setting

There are strong interfaces between MAB1 and *a) organizational units* in embedding the drug in the using setting. Main using units are *government hospital units*. It is through these using units that end-users, *the patients*, are reached. Also government *clinical hospital units* have been important and involved during all clinical trials; thus these using units are aware of the benefits of the new drug along with the fact that the medical expertise knows how to use the new drug. The MAB1 drug needs to be supervised by clinical doctors, although the actual injection of the drug seems to be rather simple. The combination of the fact that the clinical units have been involved in both the developing and producing the new drug and that the injection is rather simple facilitates the spread and use of MAB1. The main financing units of the new drug in the using setting are actually *the patients*, since individual Chinese are paying for the new drug out of own pocket. The *American MNC* is also present in the using setting since the company produces and supplies the original drug to Chinese users and end-user.

In embedding MAB1 in use there is a strong *b) organizational relationship* visible: the established *relationships involving the military knowledge unit, the producing unit, and clinical hospital units* have been crucial in linking the development, producing, and using of the new drug.

There are no interfaces between MAB1 and *c) facilities* in the using setting.

There are strong interfaces between MAB1 and another *d) product* already in use. Within three years after NDA approval of the new drug, MAB1 reached "blockbuster" status in China. One reason for the good sales is probably the price advantage that the new drug has in relation to *the original MNC drug,* due to a better price Chinese patients are willing to pay for the new drug. During the whole innovation journey of MAB1, the new drug could be compared and related to the original MNC drug. Hence the innovation journey of the new drug was facilitated by the fact that it was a "biosimilar" drug.

Summing Up

One important aspect of the case is that the focal drug, MAB1, is a "biosimilar" of an American blockbuster drug. However, MAB1 originates from a military knowledge unit; thus the new drug was developed by experienced scientists and within an established organization dating back to the 1950s. The producing unit, MAB, did not have earlier experience from biotechnology; the unit was

first established as a company then the new drug was found. As a result the producing company needed to connect to an established knowledge unit with the knowledge to develop and commercialize new drugs. Thus there are strong interfaces between the military knowledge unit and the producing unit in realizing the development, production, and use of MAB1. As the case points out, the interactive relationship between the military knowledge unit and the producing unit resulted in an intensive partnership, where the producing company gradually increases its commitment not only in producing the new drug but also in developing new drugs. For instance, the establishment of the research institute together with the Shanghai government and the military knowledge unit reflects an engagement of the producing unit also in development issues related to monoclonal antibody drugs. A strong interface between the main supplier unit, GE, and the military knowledge unit realized the development of the new drug including the establishment of further production of the drug. An interesting fact about the creation of the new drug is the simultaneous development of MAB R&D and MAB production, which facilitated both the development and the production of the new drug. The case also reveals that the producing unit is developing several drugs in parallel to MAB1. In being able to get a cGMP approval of the production facility, along with the fact that there were many drug projects developed in parallel, MAB R&D and MAB production were separated. As a result the new research institute was created in cooperation with the military university, partly through government funding. The case reveals the importance of having financing units providing long-time financing; the Chinese government and the Hong Kong investment firms are solid owners with big pockets. Also, clinical hospital units have been involved in developing and producing the new drug, and sales of MAB1 started out at the clinical hospitals. The sales of the new drug have been very good, resulting in a scale-up of the production process. One reason for good sales is the price advantage in relation to the original drug; also, the use of the new drug is rather simple, though the treatment still needs to be supervised by doctors at hospitals. To conclude, the fact that the use of the drug is rather simple along with the fact that the MAB1 has been compared to the "original" drug all along the innovation journey has facilitated the development, production, and use of the new drug.

As the table below shows, MAB1 is embedded within all three settings, the developing, producing and using settings. Sales have reached above the limit for a Chinese "blockbuster drug" and the new drug should therefore be regarded as a new innovation with widespread use.

MAB1	**Developing**	**Producing**	**Using**
Org. Units	Strong interfaces	Strong interfaces	Strong interfaces
Org. Relationships	Strong interfaces	Strong interfaces	Strong interfaces
Facilities	Strong interfaces	Strong interfaces	No interfaces
Products	Strong interfaces	Strong interfaces	Strong interfaces

Table 10. Summary of resource interfaces related to MAB1.

CHAPTER 12: CONCLUDING DISCUSSION

The following chapter is devoted to a concluding discussion with the purpose of answering the research question and discussing the main findings of the thesis. The aim of the thesis is to gain a deeper understanding of the creation of biopharmaceutical drugs in China, and the research question was formulated as: *How are new biopharmaceutical drugs created in a country that lacks an established modern biotechnology science base, a pharmaceutical industry related to advanced biotechnology, as well as experienced users of biopharmaceutical drugs in the healthcare setting?* In order to shed light on this research question, three empirical aspects have been considered, concerning how government-initiated innovation processes materialized in terms of a) development of new biopharmaceutical drug solutions and b) in terms of embedding these into large-scale production and c) into large-scale use.

The investigation of government-initiated innovation processes focused on five new drug innovation processes in China, including the development, production, and use of these drugs. These five innovation processes were found through a focal resource, the chromatography system ÄKTApilot, and represents a significant part of all Chinese attempts that have reached a stage of being close to large-scale production and use. By using a focal resource as a point of departure I could delimit my study to a manageable number of innovation processes. Although the five innovation processes display some differences—for instance, the degree of embeddedness of the new drugs in the developing, producing, and using setting varies—there are some distinct commonalities between the cases. Through the five innovation processes three main components are crystallized as important in order to create biopharmaceutical drugs in China: 1) the active support, especially in terms of mobilizing and financing, from the Chinese government, 2) the utilization of Chinese military research along with 3) a pragmatic transnational networking, both related to biotechnology science and business. The first component, the Chinese governments' active role very much affects the two other components, Chinese military research and transnational networking. The three components are further discussed and elaborated on in the following sections, followed by a wider discussion on China's breeding of a biopharmaceutical business through something that could be characterized as a "command network economy." The chapter ends with a discussion concerning contributions of the study along with some suggestions for future research.

The Chinese Government as Actively Involved in the Creation of Chinese Biopharmaceutical Drugs

The empirical investigation reveals one important component in creating biopharmaceutical drugs in China, namely *the active involvement and participation of the Chinese government*. The fact that the Chinese government is important in creating new drugs is not surprising since it was the government that initiated the promotion of biotechnology and biopharmaceutical drugs in particular. Instead the main finding is related to *how* the government actually is both *actively and interactively* "steering" the creation of biopharmaceutical drugs, not only by issuing policies and programs but more importantly by participating on a company level, directly or indirectly involved in embedding new biopharmaceutical drugs. The Chinese government is present in all five embedded cases, reflecting government units on both a national and a regional level. Moreover the government is also present in all three settings, the developing, producing, and using settings. For instance, the Chinese government has acted as the main knowledge unit, financing unit, and regulating unit within the developing setting. In the producing setting the Chinese government has been present as the main producing unit, regulating unit, financing unit but also as an active knowledge unit in setting up production. In the using setting the government has been the main using units in the form of clinical hospital units, which play an important role not only in developing and producing new drugs but in reaching end-users, the patients. For instance, the new drugs have first been distributed to the clinical hospital units in facilitating the sales of new drugs.

But the Chinese government realizes that new biopharmaceutical drugs cannot be created in isolation, so the government allows an "openness" in how new drugs are created; hence the resource combinations range across both organizational and national borders and are both technical and social in character. As a result the government invites a variety of actors to participate in the creation of biopharmaceutical drugs. With an increased focus on biotechnology and especially the commercialization of biotechnology science, the Chinese government has encouraged companies, scientist, universities, and the military to get involved in creating new biopharmaceutical drugs. Under these "open" conditions it does not matter where the resources originates from as long as they can be combined to create new drugs. Thus the Chinese government has "encouraged" the interaction between science and industry, between public and private, between military and civil society, and between domestic and international resources to support the creation of biopharmaceutical drugs. Another aspect that characterizes the active participation of the Chinese government in creating new drugs is "endurance." The Chinese government has played an important role by providing long-term financing through direct and indirect government funds, venture capital, ownership, etc. As a result new drug solutions have the time to evolve without the pressure to keep "time-to-market" as short as possible. This has been especially important in China since the country

has started more or less from scratch with the "open-door policy" issued in the late 1970s.

This active role of the Chinese government has resulted in the increased growth of Chinese biopharmaceutical companies. Especially interesting is the finding that the main producing units present in the five innovation processes were established with no earlier experience with biopharmaceutical drugs. Moreover these producing units were first established without having a basic research result to develop. Clearly the Chinese governments' promotion of biopharmaceutical drugs has encouraged companies and organizations in other industries to get engaged in biopharmaceutical drug development. This is very different compared to how biopharmaceutical companies are established in the Western world: here it is common that new companies are established around new drug discoveries, as spin-offs of new scientific discoveries; thus companies are established with the aim to further develop specific drug projects (Owen-Smith et al., 2002; Powell et al., 2002; Pisano, 2006). Although the number of biopharmaceutical companies is increasing in China the case study reveals that Chinese biopharmaceutical companies usually develop few projects in parallel; instead companies focus on one or two developing drug projects at a time. This reflects the lack of biopharmaceutical knowledge within Chinese companies and the need for companies to focus on a limited number of drug projects in order to gain biopharmaceutical knowledge step by step. Moreover, the fact that a majority of late developments receive NDA approvals by the SFDA entails that Chinese biopharmaceutical companies can concentrate on a lower number of drug development projects than their Western counterparts.

Due to lack of earlier drug development experience Chinese biopharmaceutical companies establish strong relationships to knowledge units to "bridge" the lack of biopharmaceutical knowledge and biopharmaceutical drug projects. Thus in order to overcome the lack of biopharmaceutical drug experience and knowledge the Chinese government has "opened up" for resource combinations stretching across organizational borders. Also this "openness" manifests itself through the possibility by companies to "negotiate" with the government, for instance the Chinese customs has through negotiations allowed import of "tax-free" equipment. Moreover the Chinese government is important in regulating the drug development process, although, compared to FDA regulations, SFDA regulations are "slack." For instance, regulations allow reversing the drug development process and interaction between producing units and clinical hospital units, along with the use of lab equipment in production, etc. As a consequence China can shorten the drug development process in comparison to the Western world. In the light of having the possibility of exporting the new drugs to the Western world, the Chinese government needs to emphasize stricter regulations. Thus "slack regulations" in China are utilized in order to create new biopharmaceutical drugs within China; however, on the other hand, "slack regulations" are a disadvantage when creating a widespread use of Chinese biopharmaceutical drugs in the Western world.

Nevertheless, one dark side of the Chinese governments' promotion and focus on creating biopharmaceutical drugs is related to the use of the same. As the thesis points out the Chinese healthcare system is underdeveloped, and due to the transition of the Chinese economy a majority of the Chinese population stands outside any healthcare insurance programs and thereby need to pay for healthcare services and drugs by themselves. At the same time the Chinese people are important in speeding up the creation of new biopharmaceutical drugs by participating in clinical trials. Having a large Chinese population where a majority of the population is outside of the healthcare insurance system forces many Chinese to engage in clinical trials and thereby contribute to the creation of biopharmaceutical drugs. Having a healthcare insurance system that only covers a minority of the Chinese population along with the fact that the healthcare insurance only includes basic healthcare services and drugs, not biopharmaceutical drugs per se, is a disadvantage in creating widespread use of biopharmaceutical drugs, since these types of drugs need to be paid by Chinese individuals. Therefore the creation of biopharmaceutical drugs in China is very much related to the "ethics" of fast clinical trials and its relation to an underdeveloped healthcare system. Hence the Chinese government needs to address the issue of including a larger part of the Chinese population in the healthcare system along with broadening the insurance system to also include biopharmaceutical drugs in order to further promote and support the creation of these drugs.

The Utilization of Military Research in the Creation of Chinese Biopharmaceutical Drugs

A second component in creating biopharmaceutical drugs in China is *the utilization of Chinese military research*. However, this component is also dependent on the first component, namely the Chinese government. It was the Chinese government that initiated the new role of the military to open up not only to business but also to civil society, enhancing military involvement especially in high-tech industries. In several of the investigated innovation processes Chinese military science is present, mainly as a knowledge unit within the developing setting. The reason behind the importance of Chinese military sciences in the creation of biopharmaceutical drugs is to be found in Chinese history. Chinese military science has been affected by the Chinese government's investment in the defense industry and the establishment of the military organization from the mid 1950s and onwards. As other science producers Chinese military science was also crippled due to the Cultural Revolution, but the military organization stayed relatively intact in comparison to other universities and research institutes. After the "decade of destruction" the military organization was the best developed organization in China, and as a consequence the military was consid-

ered as a productive force in modernizing China and in leading the transition from a plan economy to a "socialistic market economy." Hence, the military became more engaged in civilian and industrial use of military science. More specifically the established resource structure belonging to the Chinese military organization connected to both organizational and technical resource became important not only for the defense industry but for the industrial development and modernization of China. As a consequence the Chinese military developed science to be commercialized and used by civilian society. In overcoming a weak science base China has used established resources belonging to the Chinese military in creating new biopharmaceutical drugs. Thus the creation of Chinese biopharmaceutical drugs is intimately related to established Chinese military research. Hence, military research has played a central role in providing knowledge and experience crucial for the development of new drugs, and the Chinese military is a main knowledge unit providing drug discovery or applied sciences of already established drugs. But military knowledge units are not only present in the developing of new drugs but also in the production of new drugs. Due to lack of biopharmaceutical knowledge, producing units and military knowledge units establish strong interactive relationships in order to take new drug solutions not only through developing of them but also in establishing and proceeding with the production of the same. The producing units are dependent on military knowledge units to establish production of clinical substances along with setting up the production process. The military knowledge units are dependent on the producing units to be able to produce the new drugs to generate money for new drugs development projects and thereby contribute to the modernization of China.

A strong interface between military and industrial development is not unique to China and the biopharmaceutical context. Instead, history has shown that it is rather common for new solutions and innovations to have their origins in military science and the defense industry (Agrell, 1989; Ikegami-Andersson, 1992; Edgerton, 2006; Lundin and Stenlås, 2010). Saxenian (1994) and Leslie (2000) specifically discuss the industrial development of Silicon Valley, where biotechnology business is pointed out as one key business, and emphasize the importance of the defense industry and military sciences in establishing the industrial area and its innovative products and companies.

The Utilization of Transnational Networking in the Creation of Chinese Biopharmaceutical Drugs

In creating new biopharmaceutical drugs in China the thesis reveals a third important component that is also is dependent on governmental support, namely *the utilization of transnational networking*. As mentioned, the Chinese government allows an "openness" that encompasses the creation of biopharmaceu-

tical drugs in China, resulting in the combining of resources wherever these originates from. Foreign resources are present and involved in all five cases, mainly concentrated in the developing and producing setting, although there are some interfaces with foreign users of the new drugs. The importance of foreign resources in creating new biopharmaceutical drugs in China is both social and technical in character; more specifically, the resources are constituted mainly as foreign knowledge units, foreign supplying units, and foreign equipment and facilities, along with foreign products. China opens up to foreign resources by inviting foreign companies and organizations to share knowledge and thereby gain business opportunities. Foreign companies are attracted to China due to its market potential but the attraction is also supported through the Chinese government's encouragement of the creation of new biopharmaceutical drugs, thereby allowing the import of foreign equipment, along with tax reductions in Chinese science parks, etc. Through this "openness" it is possible to connect to foreign resources, and the study indicates that there is a systematic use of foreign resources to bridge the lack of biopharmaceutical knowledge within the Chinese biopharmaceutical context. As a result the creation of biopharmaceutical drugs is constituted by a resource network crossing organizational and national borders. The thesis especially points out the importance of the foreign supplier unit, GE Healthcare, as important in both developing and producing Chinese biopharmaceutical drugs. The unit not only provides technical resources but also social resources such as training, practical experience, and producing according to regulations. Being a world-leading equipment supplier unit it is connected to an established organization including experienced personnel that can be used in creating new drugs in a country like China. However, foreign knowledge units have also played a significant role in the development of Chinese biotechnology drugs. By connecting (directly or indirectly) to foreign knowledge units, it is possible to connect to new drug discoveries made by foreign scientists with experience from drug development. Nevertheless, the "openness" that the creation of biopharmaceutical drugs in China reveals also has a dark side. By allowing this "openness," foreign regulations such as IP rights can be neglected (for instance in the VB2 case), along with the fact that new drugs can be approved in spite of a low number of patients enrolled in clinical trials due to "slack regulations."

The empirical data of the thesis shows that China is focusing on scaling up and establishing a producing structure related to biopharmaceutical drugs – whatever the origin of the drug. The most common view of China is that it is the "the world's manufacturer" of "low-tech" goods such as toys and clothes. This study indicates, however, that Chinas' role as "the world's factory" (Shenkar, 2005: 17) is changing to also include the production of "high-tech" and "science-based" products. The fact that more biotechnology MNCs are establishing business relationships with Chinese counterparts in order to jointly develop, scale up, and produce new drugs gives an indication that China's future may be focusing on also becoming an important player in both the development and the production of biopharmaceutical drugs. This movement is

slightly different from China's original governmental ambitions, where the biopharmaceutical industry was supposed to emerge from domestic inventions. The change is probably a result of the empirical experience of the complexity behind the establishment of new biopharmaceutical drugs, i.e. a pragmatic adaptation to reality. As a consequence the Chinese government allowed "openness," "encouragement," "endurance," and "slack regulations" in order to support the creation of biopharmaceutical drugs.

The Chinese "Socialistic Market Economy" in Practice; a "Command Network Economy"

To summarize, the study emphasizes that China has made major progress in creating new biopharmaceutical drugs by an active Chinese government allowing interaction between social and technical resources spanning the developing, producing, and using setting. Also China has realized the importance of connecting to and using "others" in the creation of new drug solutions and innovations (Håkansson and Waluszewski, 2007b). Moreover, China uses the established resource structure related to the Chinese military, more specifically military research, in developing these new drugs. By systematically combining resources across organizational and national borders, new drugs come alive; thus Chinese biopharmaceutical drugs are not only spread within China but also out into the world. The endurance and determination of the Chinese government in achieving new drugs is paying off, even though China has a long way to go in becoming a biotechnology and biopharmaceutical superpower. To succeed in creating new drugs, a future reformation of the healthcare system is required.

As the thesis shows, innovation is not an isolated phenomenon; instead it is a process reaching across a multitude of organizations, companies, and places. Moreover, any innovation process takes place within a specific business landscape that sets the conditions and the directions for any innovation process (Whitley, 1994; Whitley, 2000; Lundvall et al., 2002; Malmberg and Maskell, 2002; Casper and Whitley, 2004). Thus besides being an illustration of new drug innovation processes in a country with weak developing, producing, and using conditions, the study also gives an indication of the larger Chinese business landscape, which of most is characterized as a "socialistic market economy." The thesis gives a picture of a country that has left the command economy characterized by centralized production plans, hierarchical organization of business, and limited interaction processes between companies and between foreign counterparts (Nee, 1992; Johanson, 2001; Lu and Lazonick, 2001). Instead the Chinese government promotes another way of organizing business, characterized by an "openness" to facilitate the combining of resources on a decentralized level. Hence, the Chinese government is allowing an "openness" towards almost any way of utilizing domestic and foreign resources in order to

create biopharmaceutical drugs. In contrast with the command era, companies and organizations are allowed to interact with each other, with support from the Chinese government. A multitude of organizational units interact with each other, developing relationships and exchanging resources. Thus, it seems like "thick interaction processes" (Håkansson et al., 2009) have become an important characteristic of the contemporary Chinese business landscape. Thus the empirical study evokes a picture of the "socialistic market economy" as an economy where organizations and companies are encouraged to interact and exchange resources, and networks of interacting resources are established over time. It was the Chinese government that initiated the promotion of biotechnology, and biopharmaceutical drugs in particular, and as the empirical data reveal the Chinese government also plays an active and interactive role in the interaction processes at the company level. Behind the innovation processes investigated there is the Chinese government "assisting" and "directing" the creation. To summarize, the Chinese government provides: a) an "openness" where relevant actors are invited to participate in biotechnology and biopharmaceutical drug development, b) "encouragement" of interactions between companies and organizations in biotechnology and biopharmaceutical drugs, c) "endurance" by providing long-term financing of new biopharmaceutical ventures, and d) "slack regulations" in order to speed up the drug development process. The case study reveals that the Chinese government is behind the scenes in these innovation processes, sometimes very outspokenly, sometimes very much in the shadows. In many of the innovation processes that on a surface seem like a smooth development, almost too smooth, the government has had a hidden role in being able to "open up" for interaction processes between companies, the military, etc. The "openness" that exists within the Chinese business landscape is very far from the plan economy but still the Chinese government is lurking behind these innovation processes – in a way which can be characterized as a "command network economy." This is similar to what Boisot and Child (1996; 1999) and Redding (2002) refer to as "network capitalism," which also highlights the fact that networks of relationships are important in the contemporary Chinese business landscape and the business landscape as imbued by: "...interdependence of economy and polity down to the bedrock of communities" (Boisot and Child, 1996: 621). The "command network economy" even more explicitly emphasizes the role of the government, whether it is central or regional government, as "steering" the companies and organizations in a specific direction through "openness," "encouragement," "endurance," and "slack regulations," where the Chinese government plays a significant role as an active and interactive participant.

The study also reveals how the Chinese government portrays innovation and industrial development from a policy perspective. The "image level" (Håkansson and Waluszewski, 2002) that the Chinese government portrays in national and regional policies is different from what is displayed through the empirical study. On a Chinese policy level, investments in science would result in new science discoveries that would be commercialized by biopharmaceutical

companies into new innovations through the input of government capital (Balconi et al., 2010). However, this study, with the investigation of five innovation processes, reveals another picture: innovation processes are more delicate and sophisticated than investments in science and transfer from science to an industrial setting, and instead new drugs are created through a systematic combining of resources across organizational and national borders. The fact that the new drugs investigated are heavily embedded into both the developing and producing setting may reflect the investments of Chinese government policy mainly being concentrated in the development of a science base, along with efforts to boost the creation of biotechnology companies and businesses. Chinese government policies point out the importance of producing and developing new drugs, while the using of new drugs is not emphasized on a policy level; instead it seems like the users are taken for granted (cf. Waluszewski et al., 2009: 114f). If we consider the investigated innovation processes, in two of five cases the new drug solutions can be considered as innovations with a widespread use. In these cases there has been an active involvement of the users during the whole process, along with the fact that there was a clear picture of what the users and the final drug would be like throughout the innovation journey. As other researchers have concluded (Rosenberg, 1982; von Hippel, 1988; Rosenberg, 1994; Van de Ven et al., 1999; Oudshoorn and Pinch, 2003; Waluszewski et al., 2009), the importance of users needs to be considered throughout the innovation journey in order to facilitate the innovation process. However, users also need to be considered by policy makers in order to create better conditions for new solutions to be widely spread and used. Thus in further developing policies to create new biopharmaceutical drugs in China, the using setting of the drugs also need to be considered, as has also been concluded by von Hippel and Jin (2008).

Main Contributions of the Study and Future Research

The investigation of the creation of biopharmaceutical drugs in China has several contributions. First it has *an empirical contribution*, where drug innovation processes are brought to the surface, and the study unfolds the "black box" of innovation processes, encompassing three empirical settings: the developing, producing, and using settings. Moreover, in general there are few studies that investigate "the socialistic market economy" in practice, more specifically by revealing what is under the surface of the Chinese socialistic market economy. Thus one main empirical contribution is to investigate and display complex interaction processes between companies, organizations, products, technologies etc. in a Chinese context. It would be interesting to investigate other innovation processes in China in industries other than the biopharmaceutical industry, to see if these industries evince similar "thick interaction patterns" including an active/interactive Chinese government, strong dependence on Chinese military

research, and dependence on transnational networks. Secondly, the study also has a *theoretical and methodological contribution*: by investigating the detailed texture of interaction processes, more specifically by using the 4R model developed by Håkansson and Waluszewski (2002), it has been possible to actually reveal the shift in the Chinese business landscape towards a "command network economy." As point of departure I have used a focal product, between lab and process scale; through the focal product it has been possible for me to delimit the study and capture new drugs in late developments. Especially interesting was the fact that the focal product enabled me to capture a significant part of Chinese biopharmaceutical drug processes in late developments. Also, through the study, it is obvious that there are many established Chinese biopharmaceutical companies but not many companies have succeeded in taking a new drug to production and, even more difficult, to create a use for the new drug. As a result my study is an example of how the focus on investigating interaction processes on the company level can capture a changing business landscape (cf. Waluszewski et al., 2009). The study yields an enhanced understanding about how resource interaction between organizations and companies influences and is influenced by a larger business landscape. Moreover, since the study points out the importance of transnational networking as a key to create new drugs, it also highlights the importance of transnational effects due the interdependence of business landscapes in a global world. In line with Redding (1996) I would encourage more researchers, to especially pursue the investigations of resource interaction processes on the company level to reveal larger business landscapes and thereafter further investigate the interdependence of business landscapes across national borders.

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APPENDIX

#	Respondent	Organization & Position	Place	Date
1	Jan-Christer Jansson	Uppsala University & GE Healthcare: Professor Emeritus	Uppsala	20031119
2	Ingemar Daniels	GE Healthcare: Product Manager ÄKTApilot	Uppsala	20040130
3	Lorentz Larsson	GE Healthcare: Sales Representative	Uppsala	20040908
4	Anneli Öberg	GE Healthcare: Sales Representative	Uppsala	20040908
5	Sophie Guo	GE Healthcare: Product Manager Bulk Media	Uppsala	20040415
6	Ingemar Daniels	GE Healthcare: Product Manager ÄKTApilot	Uppsala	20040507
7	Lars Kanon	GE Healthcare: Product Leader ÄKTApilot	Uppsala	20040511
8	Anette Öberg	GE Healthcare: Buyer	Uppsala	20040511
9	Bengt Asberg	GE Healthcare: Electronics Specialist	Uppsala	20040511
10	Jan Kranse	GE Healthcare: Mechanics Specialist	Uppsala	20040511
11	Mikael Petters-son	GE Healthcare: Software Specialist	Uppsala	20040511
12	Lorentz Larsson	GE Healthcare: Sales Representative	Uppsala	20040907
13	Magnus Löfgren	Biovitrum: Pilot Plants Biopharmaceutical Development Manager	Stockholm	20040912
14	Respondent A	Xin Pharmaceutical: Chief Scientist Biotechnology Department	Shanghai	20041012
15	Hong Yangxie	GE Healthcare: Production Plant Manager Protein Separa-tions	Shanghai	20041022
16	Respondent A	Xin Pharmaceutical: Chief Scientist Biotechnology Department	Shanghai	20041026
17	So Kam Ming	GE Healthcare: Business Manager Asia Pacific	Hong Kong	20041029
18	Sze Shun Fai	GE Healthcare: Product Manager Asia Pacific	Hong Kong	20041029
19	Cecilia Pang	Hong Kong Innovation and Technology Commission: Biotechnology Director	Hong Kong	20041030
20	Xu Yong Jun	GE Healthcare: Technical Supervisor	Shanghai	20041101
21	Zhao Ying	GE Healthcare: Sales Manager GE Healthcare	Shanghai	20041103

22	Zhu Xican	GE Healthcare: Technical Supervisor North China	Beijing	20041109
23	Respondent B	Vitamin Biotech: Pilot Plant Manager	Shanghai	20041115
24	Respondent C	Vitamin Biotech: Purification Specialist	Shanghai	20041115
25	Xu Yong Jun	GE Healthcare: Technical Supervisor	Shanghai	20041115
26	Respondent A	Xin Pharmaceutical: Chief Scientist Biotechnology Department	Shanghai	20041116
27	Magnus Breidne	Swedish Office of Science and Technology: Head of Office	Shanghai	20050510
28	Yani Liu-Wu	Chindoc: Managing Director	Shanghai	20050511
29	Ma	Shanghai Biotech Association: Director	Shanghai	20050513
30	Respondent D	Shanghai 2nd Medical University: Professor	Shanghai	20050516
31	Respondent E	Cardio Pharmaceutical: Managing Director	Shanghai	20050518
32	Respondent B	Vitamin Biotech: Pilot Plant Manager	Shanghai	20050518
33	Respondent F	Cardio Pharmaceutical: Purification Manager	Shanghai	20050518
34	Respondent G	Cardio Pharmaceutical: Production Manager	Shanghai	20050518
35	Respondent H	Cardio Pharmaceutical: Fermentation Manager	Shanghai	20050518
36	Respondent I	MAB Pharmaceutical: Production Manager	Shanghai	20050519
37	Respondent A	Xin Pharmaceutical: Chief Scientist Biotechnology Department	Shanghai	20050524
38	Xu Yong Jun	GE Healthcare: Technical Supervisor	Shanghai	20050525
39	Respondent E	Cardio Pharmaceutical: Managing Director	Shanghai	20050525
40	Mathew Cherve-nak	General Biologic: General Manager	Shanghai	20050525
41	Yani Liu-Wu	Chindoc: Managing Director	Shanghai	20050527
42	Respondent J	CAS National Key Laboratory: Professor	Beijing	2007312
43	Wu	Wison Bioengineering: Deputy General Manager	Shanghai	20070314
44	Jin	Wison Bioengineering: Production Manager	Shanghai	20070314
45	Jin	Wison Bioengineering: Purification Manager	Shanghai	20070314
46	Wu	Wison Bioengineering: Deputy General Manager	Shanghai	20070319
47	Respondent B	Vitamin Biotech: Pilot Plant Manager	Shanghai	20070320
48	Respondent C	Vitamin Biotech: Purification Specialist	Shanghai	20070320

49	Respondent G	Cardio Pharmaceutical: Production Manager	Shanghai	20070320
51	Respondent F	Cardio Pharmaceutical: Purification Manager	Shanghai	20070320
51	Respondent A	Xin Pharmaceutical: Chief Scientist Biotechnology Department (by phone)	Shanghai	20070322
52	Xu Yong Jun	GE Healthcare: Technical Supervisor (by phone)	Shanghai	20070327

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