STRATEGIC ANALYSIS OF CLINICAL TRIAL OUTSOURCING TO CHINA

by

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ABSTRACT

With the increasing amounts of clinical data required for drug regulatory approval and the fierce competition for patients in the Western countries, the cost of clinical trials continues to rise considerably. This study suggests that outsourcing clinical trials to China is an effective strategy to reduce cost and cycle time of drug development. China offers a high market potential and strong research capacity that can provide long term benefits to pharmaceutical and biotech companies.

An internal analysis of the British Columbia biotech companies indicates that lack of capital limits the growth potential of these biotech companies. Outsourcing of clinical trials to China provides small biotech companies with an opportunity to effectively utilize the limited capital and maximize their growth potential. This study discusses the challenges and strategic options for small biotech companies to capitalize on the opportunity and minimize risks.

Keywords: Outsourcing, clinical trial, biotechnology, pharmaceutical industry

DEDICATION

This project is dedicated to my husband, Peter Anderson.

Without his support, encouragement, and inspiration, I would not have made it this far.

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GLOSSARY

Clinical trial	A controlled study involving human subjects that is designed to prospectively evaluate the safety and effectiveness of new drugs or devices or of behavioral interventions
Core Competency	Activities or processes that define an organization's competitive advantage
CRO	Contract Research Organization
FDA	an agency of the United States Department of Health and Human Services and is responsible for the safety regulation of most types of foods, dietary supplements, drugs, vaccines, biological medical products, blood products, medical devices, radiation-emitting devices, veterinary products, and cosmetics.
GCP	Good Clinical Practice. The GCP is an international ethical and scientific quality standard that ensures the credibility of the clinical trial and protects rights and safety of human subjects in the clinical trials.
ICH	International Conference on Harmonisation is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration. The purpose of ICH is to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines by recommending ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration
IND	Investigational New Drug. The US IND program is the means by which a pharmaceutical company obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved. The FDA reviews the IND application for safety to assure that research subjects will not be subjected to unreasonable risk. If the application is approved, the candidate drug usually enters a Phase 1 clinical trial.

NDA	New Drug Application. It is the base of the regulation and control of new drugs in the United States. The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational New Drug become part of the NDA.
New molecular entity	A drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.
Pharmacodynamics	The study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of actions and effects of drugs with their chemical structure, also, such effects on the actions of a particular drug or drugs.
Pharmacokinetics	The action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation and excretion.
Risk capital	Funds made available for start-up firms and small businesses with exceptional growth potential.

1: INTRODUCTION

1.1 The benefits of clinical trial outsourcing

Clinical development is one of the most important stages in the drug development cycle, and also has very high costs. It is estimated that clinical trials cost approximately $800 million for every approved drug (Gilbert et al., 2003). Pharmaceutical and biotech companies are under great pressure to reduce the clinical development costs.

One of the strategies for controlling the cost is outsourcing clinical trials. Clinical trial outsourcing involves subcontracting activities in clinical development to third parties such as contract research organizations (CROs). By outsourcing, pharmaceutical and biotech companies convert the fixed costs of resources and infrastructure for executing clinical development activities to variable costs. Outsourcing clinical trials to CROs has many benefits. It allows the pharmaceutical or biotech firms to focus on their core competency, gain access to external expertise, ideas and economies of scale of the CROs, reduce human resource and infrastructure costs, and to be more flexible in their capital investment. The main disadvantages of outsourcing are the significant loss of management of the activities and exposure to risk for intellectual property (IP). Therefore outsourcing requires high transparency in clinical trials management and sufficient infrastructure (such as legal system) for IP protection.

A second strategy for controlling clinical development cost is shifting clinical trials to low cost emerging regions such as China, India, and Eastern European countries. Emerging regions offers reduced clinical trial cost, large patient pool, easy access to

treatment naïve patients[1], shortened time to market, and high market potential. Although the IP protection and regulatory compliance in these regions are less than ideal, the continuous improvements in these perspectives indicate that emerging regions will be powerful players in conducting clinical trials in the future.

China has been ranked as the best clinical trial outsourcing location (AT Kearney, 2007; PricewaterhouseCoopers, 2008). China outperforms other emerging regions in terms of patient pool, study cost, market potential, and research capacity. The short term benefits of outsourcing to China are cost savings and shortened time to market. Long term benefits are helping companies to achieve high R&D efficiency and profitability as well as access to the Chinese pharmaceutical market and R&D expertise. This unique combination makes China stand out among many emerging regions as the most favorable clinical trial outsourcing location.

1.2 The application of clinical outsourcing to biotech companies in British Columbia

The British Columbia (BC) biotech cluster is the 7th largest biotech cluster in North America and is the fastest growing biotech cluster in Canada (LifeSciences British Columbia, 2008). It is the home of three profitable biotech companies: QLT Inc., Angiotech Pharmaceuticals and Aspreva Pharmaceuticals.

With the exception of the above mentioned companies, most BC companies do not yet have products on the market. Majority of BC biotech companies are research-focused and have limited capacity to undertake value chain activities such as clinical development, manufacture, marketing and sales. Traditionally, BC biotech companies

[1] Treatment naïve patients refer to the patients who have not been treated for the medical conditions.

outsource the majority of their contract clinical development to the US. However, due to the high cost of clinical trials in the US and the insufficient risk capital held by BC companies, the companies often can not conduct the critical proof-of-concept phase II clinical trials and other late stage clinical trials by themselves. Therefore, they form strategic alliance with large pharmaceutical companies to gain capital investment in order to carry the product to phase II trials. The valuation of drug products and BC biotech companies are often less than optimal as a result of the premature partnership.

Outsourcing of clinical trials to China is identified as a potential avenue for BC biotech companies to advance drug product development to phase II or other late stage clinical trials at a low cost. This avenue has the potential to increase the valuation of the drug products in strategic alliance deals. In the long term, the outsourcing model increases the companies' R&D efficiency and profitability, provides access to Chinese pharmaceutical market, risk capitals, and research capacities. As this practice has been used by very few biotech companies, BC biotech firms can gain a competitive edge after successfully implementing outsourcing.

1.3 Report Scope

The structure of this report is as follows: Chapter 2 provides an introduction to the clinical development process in the pharmaceutical industry, describes the challenges and trends in clinical development, and outlines several strategies to control clinical development cost. Chapter 3 focuses on the analysis of China as a clinical outsourcing destination, describing the advantages and disadvantages of outsourcing to China. It also presents a competitive analysis of China, India, and Eastern Europe countries as outsourcing destinations. Chapter 4 provides an overview of the BC biotech cluster

emphasizing the weakness of BC biotech firms in the framework of key success factors (KSFs) in the biotech industry. This chapter argues that outsourcing clinical trials to China can provide BC biotech companies competitive advantages. In Chapter 5, five strategic options regarding outsourcing to China are presented and evaluated against a set of weighted criteria. The recommendation based on the strategic analysis is summarized in Chapter 6.

2: CLINICAL DEVELOPMENT OVERVIEW

2.1 Introduction

In the pharmaceutical industry, drug development cycle includes Discovery Research, Preclinical Research, Clinical Development, Marketing and Sales. Clinical development, involving testing new drugs in well designed clinical trials, is one of the most time-consuming and costly stages. The cost of clinical development has increased considerably as a result of: 1) the increasing amount of clinical data required for drug regulatory approval, and 2) difficulties in recruiting sufficient patients for clinical trials. In addition to the increase in clinical cost, the new drugs approved to market annually are in decline. Pharmaceutical and biotech companies are under pressure to cut the development cost and increase productivity. The strategies to control clinical development costs are the focus of this chapter.

In this chapter, the background and the value chain of the pharmaceutical industry and the role of clinical development in the value chain are described. The regulatory approval process for clinical trials and drug registration is briefly introduced. Lastly, three strategies to control the clinical development cost are discussed: 1) co-developing; 2) shifting clinical trials to low cost emerging regions; and 3) outsourcing clinical trials to CROs.

2.2 Drug clinical development background

2.2.1 Pharmaceutical industry value chain

In the pharmaceutical industry, the drug development cycle includes Discovery Research, Preclinical Research, Clinical Research and Development (R&D) (Phase I-IV human trials), and marketing (including manufacturing and distribution) (Industry Canada, 2006) (Figure 2.1). Based on their activities in the value chain, drug developing companies can be classified as fully integrated pharmaceutical companies (normally called "Big Pharma"), fully integrated biotech companies (FIBCO), "R&d" biotech (focusing on discovery research), "r&D" biotech (focusing on pre-clinical and clinical development), and other specialty pharmaceutical companies focusing on certain value chain activities. Traditionally, the pharmaceutical industry has been dominated by the fully integrated business model. Fully integrated companies such as Big Pharma and FIBCO have the capacity to conduct and control the activities across the whole value chain. "R&d" and "r&D" biotech companies, with their activities focus on Discovery research or pre-clinical and clinical R&D, respectively, rely on outsourcing to contract organizations (CROs, contract manufacture organizations (CMOs), or contract sales organizations (CSOs)) or forming strategic alliances with fully integrated companies to carry out the activities in which they lack in-house expertise and resources to perform. The establishment and rapid growth of various contract organizations such as CRO, CMO, and CSO continue to drive the restructuring of the fully integrated business model. Consequently, the pharmaceutical industry is adapting a specialty business model in favor of smaller, more specialized, faster moving companies in the value chain (as compared to the fully integrated model).

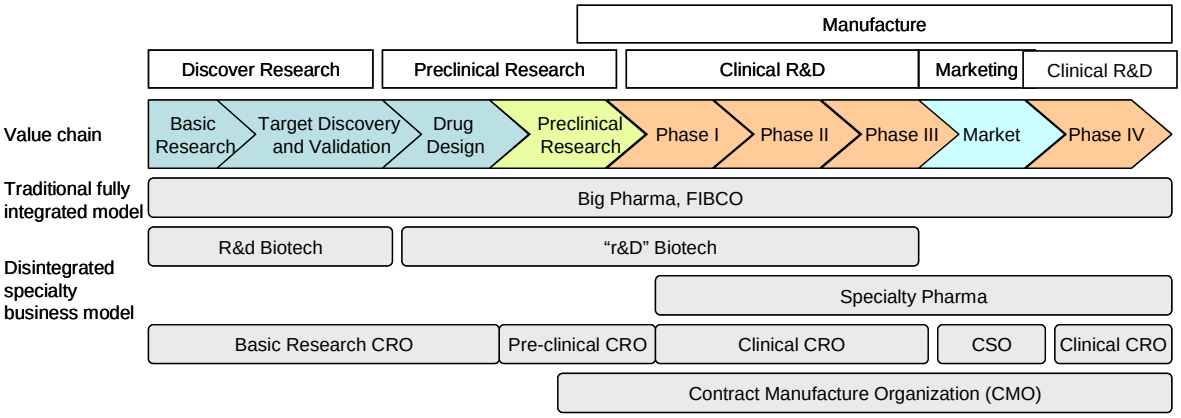

Figure 2.1. The pharmaceutical industry value chain and the pharmaceutical or biotechnological companies that carry out the value chain activities.

2.2.2 Clinical development path

Clinical development is one of the most important stages in the drug development value chain. It involves testing new drugs in well designed clinical trials. As defined by the Department of Health and Human Services of US, a clinical trial is "a controlled study involving human subjects that is designed to prospectively evaluate the safety and effectiveness of new drugs or devices or of behavioral interventions (Penslar and Porter, 1993)." As clinical trials pose potential risk to human subjects, they are strictly regulated by government agencies, for example, the Food and Drug Administration (FDA) in the US, the State Food and Drug Administration (SFDA) in China, and the European Medicines Agency (EMEA) in Europe. In the US, clinical trials must be performed according to the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). The ICH GCP is an international ethical and scientific quality standard that ensures the credibility of the clinical trial and protects rights and safety of human subjects in the clinical trials.

The FDA clearly defined a clinical development path for new drugs, in which the drug candidates are to be tested in four sequential, sometimes overlapping, clinical trial

phases. Phase I introduces the investigational drug into human test subjects and is used to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic of the new drug. Phase I trials typically involves about 20-80 healthy volunteers. Phase II trials are proof-of-concept trials obtaining preliminary evidence on the effectiveness of the drug on treatment of patients with the target disease or condition. Phase II trials typically involve several hundred patients. Phase III clinical trials use double-blinded studies to obtain data on the effectiveness and safety of the drug and compare an overall benefit-risk relationship of the drug with the current standard treatment. Phase III trials typically include several hundred to several thousand people. Phase IV is also known as Post Marketing Surveillance Trial which involves ongoing safety surveillance and support as required by regulatory agencies (FDA, 1998). This clinical development path has been adopted by many other countries, including China.

2.2.3 Drug registration regulatory application process

In most countries, government authorities regulate clinical trials, marketing and sales of pharmaceutical products. The regulatory approval process varies. In the US, the first regulatory filing for a potential new drug candidate is the investigational new drug (IND) application (FDA, 1998). The FDA can grant the IND status within 30 days of filing. This requires sufficient data on animal pharmacology, toxicology, the manufacturing process, and pharmacokinetics. It also requires a clinical trial design proposal that demonstrates the safety and efficacy of the drug for testing human subjects. After obtaining IND status, the company can perform phase I-III clinical trials. With adequate non-clinical and clinical data, the company files a new drug application (NDA), upon which the drug safety, efficacy, and benefit-risk ratio are evaluated by FDA. If data

provided is deemed to be sufficient the drug can be approved for market. If the FDA does not think that the data or the benefit-risk ratio of the drug product are sufficient, it may require the sponsor to conduct additional phase III or even phase II trials with more study subjects or of different designs (as compared to the previous phase II or III trials) to address concerns over drug safety or efficacy. As a result, the size and number of clinical trials per approved drugs significantly increased. Figure 2.2 demonstrates the timing for regulatory filing as well as the time period for each stage in the drug development process.

The regulatory process has tremendous effects on the commercialization of pharmaceutical products. A lengthy approval process is considered to be a significant barrier for drugs to reach market. Delay in approval reduces the revenue potential of the product and keeps the patients from benefiting from the product. The 30-day IND approval time by FDA is the fastest in the world. Many other countries are trying to streamline their regulatory approval process to shorten the regulatory approval time.

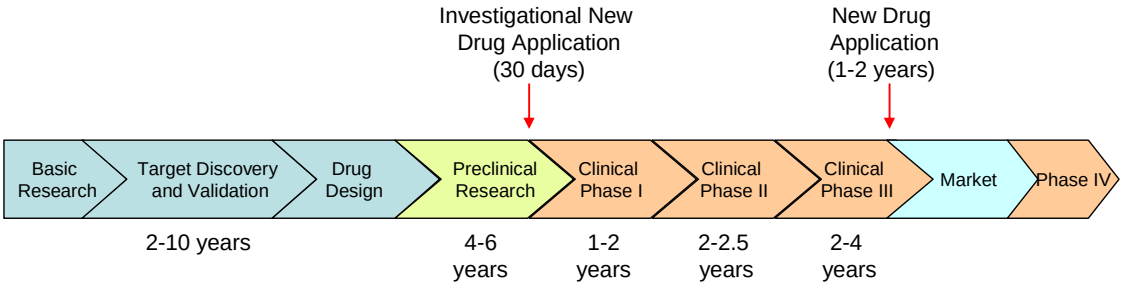

Figure 2.2. Stages of drug development and estimated time for each stage (adapted from Industry Canada, 2006).

2.3 Clinical development cost

The cost of clinical development accounts for more than 50% of the total R&D cost in the drug development process (DiMasia and Grabowski, 2007). The cost of clinical development is increasing rapidly. Between 1995 and 2000, the average clinical development cost per approved drug was about $400 million, which almost doubled by 2002. Meanwhile, the productivity of drug development decreased. Only one compound now reached the market for every 13 drugs entered into Phase I trials, compared to one for every eight between 1995 and 2000 (Gilbert et al., 2003). Two factors have been associated with the increasing clinical development costs:

- Increasing amounts of clinical trial data required by FDA. Owing to safety concerns, FDA increased the amount of the clinical data needed for NDA application and post marketing surveillance. As mentioned in 2.2.3, the FDA frequently requires additional clinical trials to be done after reviewing the NDA application, therefore the number and size of clinical trials for each approved drug (NDA approved) has significantly increased. In the last ten years, the number of patients needed for every FDA approved drug has almost doubled (Rowe et al., 2002).
- Difficulties in patient recruitment. Difficulties in patient recruitment and retention are the most frequently cited cause for delay in clinical trials (Rowe et al., 2002). In the US, patient recruitment is becoming more and more difficult. Only one in 350 American is willing to participate in clinical trials. According to CenterWatch, “86 % of all US clinical studies fail to recruit the required number of patients on time and as a result are delayed an average 366

days." Consequently, the time, study sites and cost required to recruitment sufficient patients significantly increased. Delay in recruitment incurred an average direct cost of $37,000/day. The indirect cost due to subsequent delay in drug launch can be as much as $3.8 million per day for blockbuster drugs (Xu, 2005).

2.4 Strategies to control clinical development cost

Various strategies have been used by pharmaceutical and biotech companies to reduce the cost of clinical development. These strategies include forming strategic alliances with external partners to co-develop drug products, shifting of clinical trials to low-cost emerging regions, and strategic outsourcing clinical development to cost-effective CROs. The three strategies are used in various combinations to maximize cost savings. For small pharmaceutical or biotech companies, the most frequently used strategies are co-development and outsourcing to CROs. For large pharmaceutical companies, all three are adopted.

2.4.1 Co-developing

Co-development is one of the most common strategies used in the pharmaceutical industry, and normally involves a small biotech firm (usually the originator--inventor/patent holder of the product) and a large pharmaceutical company (usually the commercialization partner). This strategy has shown to be quite successful. A large percentage of approved new molecular entity and Biologics came from the co-development between such partners.

In a co-development alliance, the partners have complementary core competencies, infrastructure, or synergy; therefore, the partnership allows the companies to access each other's expertise and resources. The access to expertise in the value chain can increase R&D efficiency and decrease development cost.

In addition, the partners share the activities and cost in drug development process as defined in an agreement. Prior to the commercialization of the product, the originator normally receives an up-front payment that reflects all or portion of the originator's expense and risk in bringing the compound or technology to its stage at signing. After signing the agreement, the originator may receive partial or full reimbursement of R&D cost (carried out by the originator after signing), milestone payment (payment to originator when milestones in development are achieved), or equity investment from the commercialization partner. After the commercialization of the drug products, the partners share the revenue in forms of sales royalty, transfer prices (payment for manufactured goods by the commercialization partner to the originator as supplier of bulk or final product), or sales-threshold payment (Edwards, 2007). In this way, the originator receives payments to cover the full or partial development cost of the product, and the commercialization partner retain the option to purchase the product. Depending on how the deal is structured, the originator may bear 0-50% of the development cost. In turn, the revenue share each partner receives is associated with its share of development cost as well as the development stage of the product at signing. Overall, in co-development, the partners share development cost and risk.

2.4.2 Shifting clinical trials to low-cost emerging regions

At present, the majority of trials (66%) are still conducted in traditional regions, i.e. North America, Western Europe and Oceania, with the U.S. (48.7%) dominating by a large margin. Only 17% are in emerging regions such as East Europe, Asia, and Latin America (Thiers et al., 2008). However clinical trials in emerging regions are undergoing rapid growth, most notably in China, Russia and India, which have average relative annual growth rate (ARAGR) of 47%, 33%, and 19.6%, respectively. These countries have great potential to grow into major players in the future as they have very low density of trials and are investing heavily to expand their vast clinical research infrastructure (Their et al., 2008). A study by TUFT predicted that "within next three years, up to 65% of FDA regulated clinical trials for the top pharmaceutical companies will be conducted outside the U.S., up from 43% today (Tufts Outlook, 2008)."

Shifting clinical trials to low-cost regions significantly reduced development cost. The cost savings range from 50-90%, depending on the location (Kermani and Langer, 2007; Varawalla, 2006). In addition to cost deduction, many other factors drive the shifting of clinical trial to emerging regions. These factors include:

- the fast recruitment of a large number of patients;
- the growing importance of new pharmaceutical markets and research capacity in emerging regions;
- the alignment of GCP to international standards.

These factors will continue to be the prominent drivers of the clinical trial globalization (Leslie et al., 2007).

2.4.3 Outsourcing clinical trials to CROs

Clinical CROs are service providers specialized in conducting and managing clinical development. Their services cover a wide range of activities from protocol development, regulatory registration, identification of study sites and principal investigators (PIs, the physicians lead the study), to clinical sample analysis, and statistic analysis.

Clinical trial outsourcing to CROs serves at least three purposes (Winter and Baguley, 2006) :

- Providing instant access to clinical development capacity;
- Being financially flexible by improving leverage on infrastructure and resources;
- Allowing companies to focus on their core competencies.

The core competency of the clinical CRO is clinical trial management. Multiple clinical trials managed by the CRO share the overhead, human resources and expertise, as well as infrastructure and network. Clinical trials done by CROs have economies of scale. Indeed, while maintaining comparable quality, CROs completed clinical trials up to 25-30% faster than those conducted in-house by pharmaceutical companies. It was estimated that an 18.9% reduction in drug development time can save $100 million development cost and a 41.3% reduction in time results in cost savings of $200 million (Chu, 2006). So outsourcing to CROs can significantly decrease drug development cost.

High efficiency is a key factor for fast growth of CROs. The benefits of outsourcing clinical trials to CROs are summarized below (Winter and Baguley, 2006):

- Access to the expertise, ideas and economies of scale of the CROs

- Access to global or regional capacity
- Cost efficient
- Reducing human resource and infrastructure costs

It is worthwhile noting that an increasing number of CROs are conducting clinical trials globally, at traditional sites and emerging regions. CROs are frequently used by large pharmaceutical companies to carry out clinical trials in emerging regions where these companies do not have geographic coverage (Nyachoto, 2007).

While maintaining the overall control of their products, companies do significantly lose control over the management of the activities and their intellectual property (IP) which may be exposed to risk. Therefore outsourcing requires high transparency and good communications in clinical trials management. Sufficient infrastructure needs to be in place to enforce IP protection. The involved parties will sign confidential agreements, and once the mutual trust is established, a long term partnership becomes possible.

2.5 Summary

The ever increasing costs in drug clinical development force pharmaceutical and biotech companies to develop strategies to cut costs and increase productivity. The three strategies presented in this chapter demonstrate the trends in the pharmaceutical industry: 1) the globalization of drug development; 2) the restructuring of the traditional integrated business model to the specialty business model (discussed in 2.2.1; Industry Canada , 2006); 3) the prevalence of strategic partnership in drug development. These trends demonstrate that the business model in the drug development will become more complex. The drug developers are trying to leverage the complementary capacities that different

industrial sectors, geographic locations, and different companies can offer to achieve high R&D efficiency and to reduce the financial risks and burden to individual firms. Small biotech companies must understand the impacts of these trends and adjust their strategies accordingly to gain competitive advantages.

3: CHINA AS A CLINICAL TRIAL OUTSOURCING DESTINATION

3.1 Introduction

China has received considerable media attention as a destination for clinical trials, especially after the US consulting firm AT Kearney (2007) ranked it above India as the most favorable low-cost clinical trial outsourcing site. China offers faster time to market, reduced development cost, and comparable high clinical trial quality. China has significant advantages as a destination for clinical trial outsourcing, including:

- World's largest urban population and a large infrastructure of hospitals, which are translated to fast recruitment of patients thus significantly speeding up the launch of the drug products to market.
- Low study cost. The low salaries of researchers and physicians, and the low cost of health care mean that conducting clinical trials in China costs a fraction of what they would cost in the US.
- Huge future market potential. Chinese pharmaceutical market is expected to reach $24 billion by 2010 (Wong and Yin, 2002) and $48 billion by 2015 (Ernst & Young, 2007a). Some estimates suggest that China will overtake the US to be the largest pharmaceutical market in the world by 2025 (AT Kearney, 2007).

In addition, the increasing Chinese expertise across the pharmaceutical industry value chain, the government's initiatives and measures to improve the drug development

landscape, and the burgeoning biotech industry in China also provide the Western pharmaceutical/biotech firms incentives to become players in the Chinese pharmaceutical industry. Outsourcing clinical trials is considered an initial step to test the water.

China still has its drawbacks. The lengthy and uncertain regulatory approval process for clinical trials has been considered to be the biggest challenge. China also needs to strengthen its legal system, enforce IP protection, and ensure research quality. Language and culture differences may also pose some barriers and incur additional cost for clinical trials to be conducted in China.

In the following sections, I will briefly review the current clinical activities and the clinical trial framework in China. A detailed analysis of business environment related to clinical trials in China will be performed. The drivers and challenges for outsourcing activities will be presented. Based on the analysis, Key Success Factors (KSFs) are discussed with the emphasis on the fundamental issue: identification and collaboration with appropriate CROs.

3.2 Current clinical trial activities in China

The clinical trial activity is increasing rapidly in China. The ARAGR of clinical trial in China is 47%, which is the fastest in the world, outpacing the growth of India and Russia by large margins (Thiers et al., 2008). The total share of China in global clinical trial activities is still low; only less than 1% of global clinical trials are done in China. The high growth rate, coupled with the very low density of trials and the vast clinical research infrastructure available, indicates that China has great growth potential.

As of September 2008, there were 856 registered trials in China with 423 trials that were actively recruiting, more than the 754 registered and 368 recruiting trials in

India[2]. The trials consist of 4% phase I, 14% phase II, 37% phase III and 17% post marketing phase IV[3]. Since China does not allow foreign companies to conduct phase I clinical trials of their new drugs in China, the percentage of phase I trial is low. The clinical trials are sponsored mostly by Chinese research institutes and hospitals (46%), or foreign/international pharmaceutical companies (44%), especially the top 10 pharmaceutical companies in the world (aka Big Pharma). Big Pharmas such as GSK, Hoffmann-La Roche, Novartis, Pfizer, have 20-40 trials each in China. Trials sponsored by biotech have a very small presence (< 4%). The leading indications are cancer (18%), viral and bacterial infection (6%), diabetes (6%), and cardiovascular diseases (5%). Chronic diseases, such as dementia, autoimmune diseases, bipolar disorder also constitute a large portion of the ongoing trials.

The status of ongoing clinical trials in China reflects the current trend of clinical trial outsourcing to China led by Big Pharma, involving late stage trials which requires large patient size, and covering the diseases with high incidence in China. The lack of presence of biotech-sponsored trials in China is not surprising. Unlike Big Pharma, small-to-medium biotech firms do not have the financial resources to develop their own infrastructure in China to better control the quality of clinical trials. These firms need to carefully weigh the risks and benefits of outsourcing; their outsourcing activities will only gear up when they have a deep understanding of and grow more confidence in the Chinese business environment. The rapid increase of international clinical trials signals the growing confidence in undertaking clinical trials in China.

[2] Data retrieved by the author from www.ClinicalTrials.gov

[3] 28% of the clinical trials did not provide information on the phase of the trial.

3.3 Clinical trial process in China

3.3.1 Stakeholders and regulatory policy

A clinical trial normally involves the drug developer (sponsor), PIs and staff, patients (human subjects), hospitals (study sites), and CROs (if the sponsor chooses to contract out the clinical trial). Any clinical trials performed in China are under the regulation of the SFDA. SFDA, the equivalent of the FDA in the US, is the Chinese government authority that supervises and regulates the safety management of food and drug products. To protect the rights, safety and well-being of trial subjects, and to ensure the credibility of the clinical trial data, SFDA issued a Chinese Good Clinical Practice (GCP) based on the GCP guidelines of the World Health Organization (WHO), ICH and European Union (EU). GCP is an ethical and scientific standard for design, conduct, recording and reporting clinical trials that involve human subjects to ensure the study is carried out in an ethical manner (Health Canada, 1997). Clinical trials in China need to be GCP compliant. As required by GCP, each clinical trial is to be approved by an Ethic Committee to ensure the study is performed in an ethical manner.

3.3.2 Clinical trial process

The clinical trial process can be divided into three stages, e.g. planning, conducting, and evaluation. A clinical trial in the West or in the emerging regions follow the same planning, conducting and evaluation stages, while the stakeholders and the timeline in the stages are country-specific. The clinical trial process, the stakeholders and the activities in each stage of the process in China are depicted in Figure 3.1. At the planning stage, the sponsors determine what activities to outsource and which CROs to

use. The study protocol is developed during this stage by the firms, CROs, and clinical trial experts including statisticians and physicians.

The conducting stage is the most complex stage, involving multiple stakeholders. To conduct clinical trials in China, the sponsors need to obtain regulatory approval from the SFDA first, which normally takes 9-12 months (discussed in detail in 3.5.1). Once the application for a clinical trial is approved, the sponsors or the CROs need to inform the local government and obtain the approval from the Ethic Committee. Upon regulatory approval, the sponsors or clinical CROs are to select study sites and PIs, and recruit patients according to the approved study protocol. During this stage, it is of utmost importance to ensure successful and timely patient recruitment.

In the evaluation stage, statistic analyses of clinical data are performed and study reports are written. SFDA requires that the data and reports to be submitted to the agency.

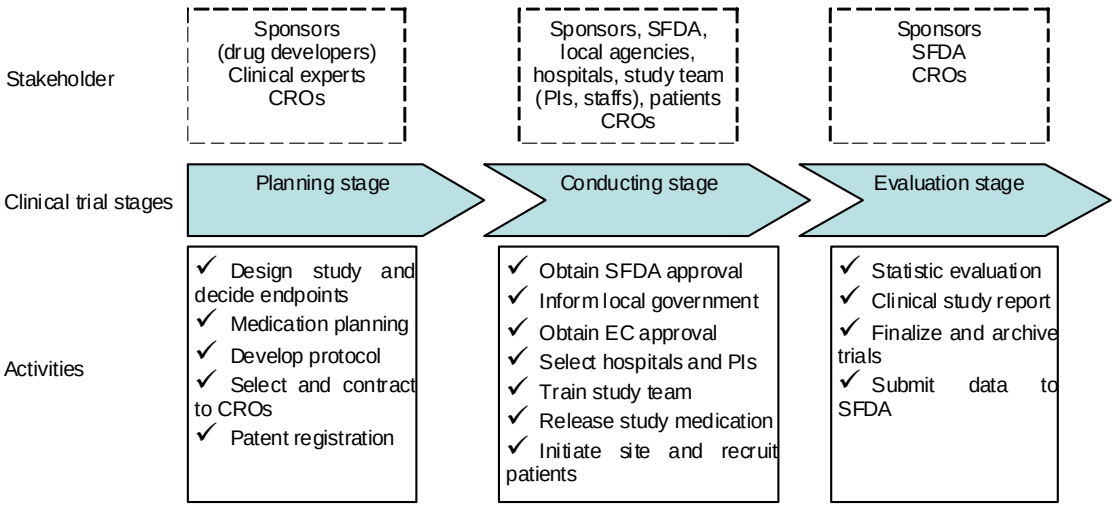

Figure 3.1. Clinical trial process in China (adapted from Henke, 2008)

3.4 Main drivers for outsourcing clinical trials to China

3.4.1 Cost efficiency

Cost saving is a major driver for outsourcing to China. For example, major phase IV trials for two cardiovascular drugs by AstraZeneca involving 46,000 patients cost a mere $3 million in China (Kermani, 2008). A trial like this may cost $240 million in the US (calculated based on the average cost per patient in the phase IV trial in the US ($5239)) (Gallen, 2007).

The cost effectiveness of conducting clinical trials is achieved by several means:

- fast patient enrolment, high retention rate and the high site efficiency -- reducing time, infrastructure and personnel cost
- low salaries, low health care and logistic costs in China -- reducing direct study cost.

3.4.1.1 High rate of patient recruitment and retention

Key determinants of the success of a clinical trial are the recruitment and retention of an adequate sample size of target population. The clinical trial cost is associated with the cost of the infrastructure and human resources supporting and managing the trials over time. Low rates of recruitment and retention result in long recruitment period and highly expensive clinical trials. Failure to recruit required sample size means less statistical power for both the study and the validity of the results, and could result in termination of the trial.

In China, patient recruitment is fast and retention rate is high. Patient enrolment time can be reduced by ~ 30% as compared to the West (PricewaterhouseCoopers, 2008). The fast recruitment is attributed to the large population base and high patient density in

China (examples see Table 3.1). Approximately 80% of medical resources are allocated to big cities, especially in Beijing, Shanghai and Guozhong (Kong, 2007). The patient densities in these cities are very high. For culture and financial reasons, patients tend to be more compliant to the study protocol which also results in low attrition rate.

China also provides easy access to a large number of treatment naïve patients. Treatment naïve patients are highly desirable for many clinical studies, as it minimizes the interference of other medicines. As more than 70% of Chinese population has no or limited access to health care, large pool of treatment naïve patients exists in China. Access to treatment naïve patients is significantly easier in China than in the US or the EU. Clinical trials are also beneficial for patients who have no access to formal health care due to poverty.

Table 3.1. Cancer patient population in China (Xu, 2005).

DISEASE	INCIDENCE (PER 100,000)		PATIENT POPULATION
	Male	Female	
Lung Cancer	67.5		877,500
Stomach cancer	39.2	19.1	378,000
Liver Cancer	35	9.7	290,550
Colorectal Cancer	22	12	221000
Breast Cancer	N/A	13.3	172,000
Cervix Cancer	N/A	12.3	159,900

3.4.1.2 High efficient study site

China has about 17,000 hospitals (Chow, 2005), among which only medical institutes officially certified as "National Institutes of Pharmaceutical Clinical Trials" by SFDA may carry out pharmaceutical clinical trials (SFDA, 2005). Over 200 hospitals have been certified by SFDA to perform clinical trials. These state-funded hospitals are well suited to serve as investigative sites. The hospitals have state-of-art facilities and

technologies, experienced and enthusiastic physicians, and thousands of impatient beds. For example, Shanghai Cancer Hospital has 600 beds which are running at 100% occupancy, and out-patient number reaches ~20,000 per month (Xu, 2005). The recruitment per site can be 5-fold higher than that in the West (Koppal, 2008). With the highly efficient study sites available, patient recruitment can be done in a handful of study sites in a timely manner, which significantly reduces the infrastructure and logistic cost.

3.4.1.3 Low study cost

In a clinical trial study, the sponsor gives PIs grants for conducting the trial, pays site fee to the hospital, covers the cost of lab tests, hospitalization and other logistics, provides financial compensation for the patients participating the clinical trial, and pays service fee to CROs . Cost savings in a clinical trial in China result from a combination of the following factors. Investigator and site fees are approximately 20-30% of those in the US; cost of trial-related medication, diagnostic procedure, lab test and hospitalization could be as low as 10% of those in a Western country (Kermani and Langer, 2007). Support services such as printing, translation, and local courier fees are also less expensive. On average, for Phase I trials, the cost is about 10-15% of the cost of the US, while Phase II and III cost about 20-30% of the cost in the US (Kermani and Langer, 2007; YYSJ, 2007). It is worthwhile noting that, although the cost of labor is lower, sponsors need to invest in training and support systems throughout the clinical trial period (e.g. providing GCP training to hospitals and physicians, translating protocols) to ensure data quality.

3.4.2 Huge market potential in China

3.4.2.1 High growth Chinese pharmaceutical market

Conducting clinical trials in China is not only driven by cost factor, but also by the growing importance of the Chinese pharmaceutical market. The Chinese market is one of the fastest growing pharmaceutical markets in the world, with a growth rate of 18-20% in the last three decades (DataMonitor, 2007b). The aging population, growing gross domestic product (GDP), and increasing expenditure on health care are fueling the market growth.

The importance of Chinese pharmaceutical market was recognized only more recently. Historically, a low price cap and limited reimbursement for imported drugs issued by Chinese government make it unattractive for foreign companies to market their products in China. This is going to change as China raises the price cap and relaxes reimbursement policy for innovative drug products. Chinese market will become very lucrative. It is expected that in the next decades, foreign companies are going to enter Chinese market and take over majority of the market share.

Conducting clinical trials in China provides a great opportunity for foreign companies to enter the Chinese market. Imported drugs, including those already launched in the Western countries and those in Phase II/III clinical trials, need to be tested in clinical trials in China, normally Phase II or III trials before they can be marketed in the country (Kong, 2007). To take the advantage of the cost saving offered by China and to accelerate the entry to Chinese market, the best approach is to design and conduct a multi-national phase II or III clinical trial with study sites in China as well as in other major pharmaceutical markets.

3.4.2.2 Development of niche market

The unique gene pools and the high incidence of certain diseases in China provide an opportunity for companies to develop personalized medicines targeting specific patient pools and are valuable for pharmacogenomic studies. Examples include gastrointestinal cancers, hepatatitis, nasopharyngeal cancers, and neural tube defects (Douglas and Hirsch, 2008). The success rate of personalized medicines is expected to be higher than the "one-for-all" approach. Small biotech companies can benefit from this low-risk approach.

3.4.2.3 Clinical trial as effective marketing tool

Clinical trials conducted in China are also an effective marketing tool for companies to break into Chinese market. The hospitals and PIs running the clinical trials are very influential in drug registration, distribution, pricing and reimbursement. In China, hospitals serve as the main drug distributor; approximately 70-80% of drugs are sold in hospitals (Paessler and Wolff, 2005). PIs in clinical trials are normally renowned physicians and opinion leaders in various therapeutic areas. SFDA often consults the opinion leaders on new drug registration, pricing and reimbursement policies. Clinical trials allow physicians and hospitals to gain first-hand experience and knowledge about the drug products, therefore open regulatory and marketing channels for drug products.

3.4.3 Achieving long term R&D efficiency

In addition to offering cost effective clinical development and huge market potential, China also has R&D expertise and a burgeoning biotech industry, which will have long term effects on the value chain of the global pharmaceutical industry. China

had more than 1.6 million science and engineering graduates by 2007 (PricewaterhouseCoopers, 2008). More recently, the biotech R&D expertise in China has been boosted enormously by the overseas Chinese life science professionals returning to China (Engardio, 2008). The high quality biotech and pharmaceutical companies founded by the Chinese returnees, in combination with the low cost labor and large talent pool are building the momentum for the Chinese biotech industry. It is anticipated that China will be able to perform most R&D activities in the value chain more cost-efficiently than in the West. Outsourcing clinical trials to China provides pharmaceutical and biotech companies access to the R&D expertise in China, and allows them to establish connections with scientific and business communities. This knowledge and connections will be very important for the western companies to utilize the complementary R&D expertise that China and the western countries can offer, thus increasing value chain productivity and gaining competitive edge.

3.5 Challenges for outsourcing clinical trials to China and signs of improvement

3.5.1 Clinical trial regulatory approval process

The lengthy and uncertain clinical trial approval process (the equivalent of the IND approval process in the US) has been considered the biggest barrier for foreign companies to conduct clinical trials in China. To conduct a clinical trial, a foreign sponsor needs to get approval from six regulatory bodies and the whole process takes 160-200 days (Figure 3.2). The regulatory approval time in China is much longer than that in many other countries, including the US, South Korea, India, Russia, and Poland, which typically have regulatory approval times between 30-90 days (Varawalla, 2006).

Owing to the complexity and evolving regulatory environment, a thorough understanding and updated knowledge of the central agency's and local regulatory requirements and extensive network are necessary to ensure timely approval of clinical trial registration. Foreign companies should take the regulatory approval lead time into account when planning clinical trials in China.

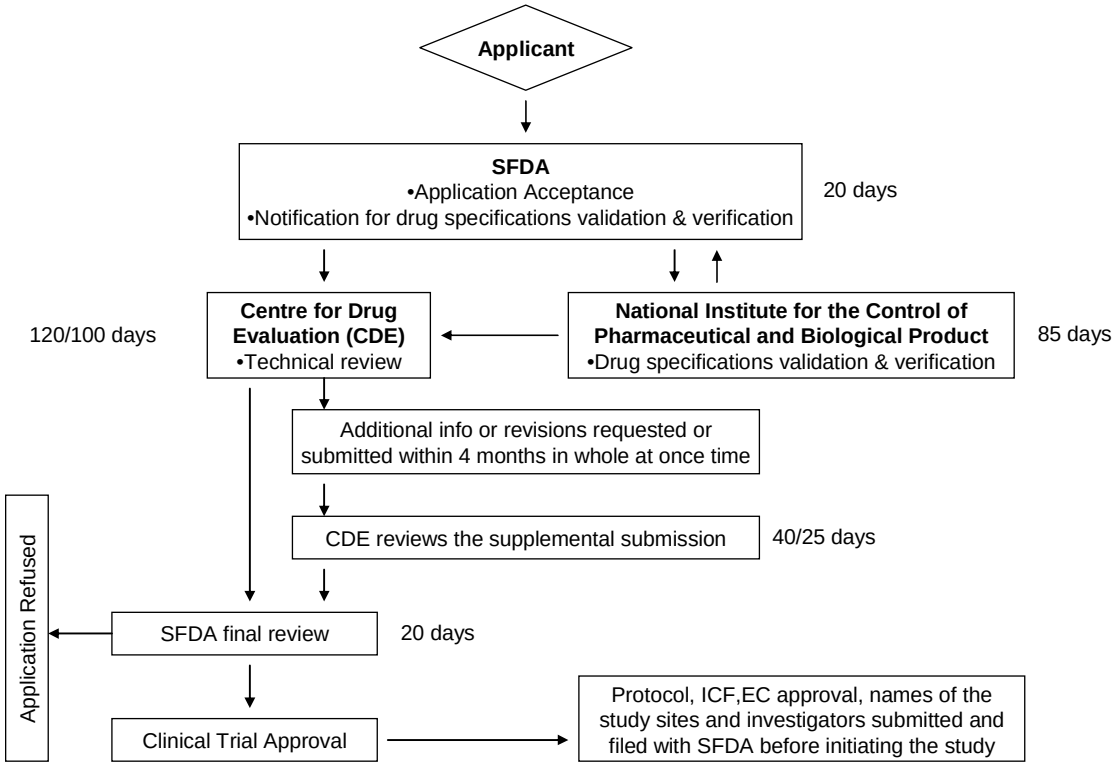

Figure 3.2. Clinical trial approval process and time line (regular/fast track) in China (Xu, 2005).

3.5.2 GCP Status and clinical trial quality in China

SFDA enforces GCP compliance by allowing clinical trials to be carried out only in "certified" GCP compliant clinical trial centers and hospitals and the certified hospitals are audited by SFDA on ongoing basis to ensure GCP compliance. SFDA also provides the GCP training in the hospitals. However, GCP performance in China needs further

improvement to align with international standards. The challenges in GCP compliance include lack of experience on GCP implementation and enforcement; gap between Chinese GCP and ICH GCP; poor understanding of GCP by local sponsors and investigators; insufficient protection of human subjects; inadequate GCP training for investigators and sponsors; poor understanding of Informed Consented Form by patients and physicians. Take the Ethics Committee as an example, unlike the Ethics Committee or Institutional Review Boards in EU and the US, Ethics Committee members in China are not independent third-party members, but are mainly directors from trials sites who emphasize the administrative and scientific aspects of trials (Kong, 2007). Ethical, legal and social aspects are often overlooked, which results in insufficient protection of patients.

With the understanding of the GCP status in China, foreign companies will need to ensure that their Chinese-based clinical trials can meet international standards, otherwise the data will not be acceptable to regulatory agencies such as the FDA and EMEA.

3.5.3 Intellectual property protection

Insufficient IP protection is one of the key risks for outsourcing clinical trials to emerging regions including China. A survey by Ernst & Young (2007b) showed that over 70% of the international pharmaceutical and biotech senior executives cited that IP protection is the main concern when outsourcing to emerging regions. Pharmaceutical companies are particularly active in protecting their IP in China.

China has passed three national patent laws to strengthen its legal framework and to align IP protection with the World Trade Organization (WTO) Agreement on Trade-

Related Aspects of Intellectual Property Rights (TRIPS). Consistent with WTO standards, the period of patent protection for novel pharmaceutical products has been extended to 20 years. Improvements were also made in the areas of data protection and patent linkages in 2000 (EIU, 2005). However, enforcement at the local level often remains less than ideal. Damages can be difficult to collect and damage caps set by the Chinese government are normally inadequate as a remedy or deterrent.

China is doing more to improve its legal framework and to enforce patent protection. Increased legal activity and some high-profile cases are also signs of Chinese government's commitment to creating an effective patent-protection environment and boosting confidence of the business community in China (Chervenak, 2005). For example, in 2006, Pfizer overturned a previous ruling and regained its patent on Viagra in China, against the challenge of leading generic-drug makers in China (China Daily News, 2006). With the increasing confidence in the Chinese IP protection, Pfizer started to market its full spectrum of novel products in China. The positive changes in IP protection are the main reasons the China leads India as the best location for clinical trial outsourcing.

3.5.4 Logistic, culture and language barriers

The infrastructure, logistic, culture, and language also pose potential barriers for foreign companies. For example, export of whole blood/DNA is restricted or prohibited in China. Foreign companies will need to identify trustworthy central labs in China. The registration application and other documents for the SFDA should be in Chinese, including the protocol, investigator's Brochure, and Informed Consent Form. Errors in translating administrative and research documents have been cited as one of the frequent

issues that delay the clinical trial registration approval. The relationships among the stakeholders such as investigators, SFDA officers, and hospital management are very complicated. Foreign companies may have difficulties to understand and manage these relationships to ensure efficient trial progress. Partners or collaborators such as CROs with significant presence in China or Chinese pharmaceutical companies are essential to mitigate risks associated with these barriers.

3.6 Competitiveness analysis: Attractiveness Indicators

China is ranked as the most favorable clinical trial outsourcing destination although the cost saving in China is not the highest (AT Kearney, 2007; PricewaterhouseCoopers, 2008). Factors such as the large patient pool, market potential, the research capacity, improvements in IP protection and the overall business environment strengthen the leading role of China in clinical outsourcing. As a result, China offers a combination of short term benefits (including cost reduction and reduced time to market) and long term benefits (high R&D efficiency and access to Chinese pharmaceutical market and R&D expertise). This unique combination makes China stand out among many emerging regions as the most favorable clinical trial outsourcing location. A comparison of the overall business environment of China, India, and Eastern European countries with respect to clinical trial outsourcing is presented to demonstrate the competitive advantages of China. Five weighted criteria: patient pool, cost efficiency, regulatory conditions, market opportunity, and relevant expertise, are used to evaluate the attractiveness of the three emerging regions. The score in each criterion is described as high, medium/high, medium, low/medium or low as compared to the US. The result is summarized in Table 3.2.

Table 3.2. Evaluation of the attractiveness of China, India and Eastern European countries as clinical trial outsourcing destinations.

Criteria	Weighting	China	India	Eastern European countries
Patient pool	3.0	High	Medium/High	Medium
Cost efficiency	2.0	High	High	Medium/High
Regulatory conditions	2.0	Low	Low/Medium	Medium/High
Market opportunity	1.5	High	Medium/High	Low
Relevant expertise	1.5	Medium	Medium	Low/Medium
Total	10	39	36.5	26.5

Evaluation score:
Low = 1; Low/Medium = 2; Medium = 3; Medium/High = 4; High = 5.

3.6.1 Patient pool

This criterion measures the size and availability of suitable patient pool. China and India, as the most and 2nd most populated countries in the world, respectively, clearly have the advantages of large patient pools and large number of treatment naïve patients. While the patient pools in Eastern European countries are smaller, they provide easy access to treatment naïve patients.

3.6.2 Cost efficiency

This criterion is based on the cost of labor, facilities, travel and other logistic cost. Conducting clinical trials in China, India, and Eastern European countries is much more cost-efficient than in the US. The cost saving in China and India are similar, ranging from 50-70%, while in Eastern European countries, the cost saving is about 30-60% (Varawalla, 2006).

3.6.3 Regulatory conditions

This criterion is based on the country's regulatory laws, strength of IP protection, and perspective of FDA. In this aspect, China has significant disadvantages as discussed in 3.5.1. Its regulatory approval process can take 9-12 months and lack of transparency. The legal system is less than ideal, and IP protection enforcement is sporadic. The regulatory approval process in India is better than that in China while IP protection is similar or less favorable. India has streamlined the clinical trial regulatory approval process and shortened the median approval time from 16 weeks to 10 weeks. Approval from local Ethics Committees is processed in parallel. IP protection of pharmaceutical products was still weak in India. Until 2005 only pharmaceutical manufacture processes but not the products themselves were under IP protection. Pharmaceutical product patents are recognized and are under protection since India became a member of TRIPS. The regulatory process in Eastern European countries is much more streamlined and faster than that in China and India. Most Eastern European countries including Russia, Czech Republic, and Poland, have a regulatory approval time of less than 90 days (Varawalla, 2006). Similar to India and China, IP protection in Eastern European countries still needs major improvements.

3.6.4 Relevant expertise

The criterion is based on the number of hospitals and clinical research centers, the number of clinical trials, and size and availability of labor force with relevant skills. China has a large number of hospitals and approximately 1.4 million doctors and more than one million nurses and technicians (AT Kearney, 2007). India also has a vast health care system. Although the number of health care professionals in India is less than that in

China, the training of physicians is in better alignment with the West. As an English-speaking country, India has advantages over China in performing multinational clinical trials. Physicians in Eastern European countries has more experience in clinical trials, however, the total number of relevant talents and the size of the infrastructure is much smaller than that in China and India. Overall, India and China are similar in this criterion and score higher than Eastern European countries.

3.6.5 Market opportunity

Market opportunity is estimated based on the current pharmaceutical market size of the country, the market growth rate, and the health care needs of the ageing population. As shown in Table 3.3, the pharmaceutical market in China reached $15.9 billion in 2007, and by 2012 the market size is expected to reach $44.6 billion, with an impressive CAGR of 22.9% (DataMonitor, 2007a-f). The population over the age of 60 in China will grow to 210 million by 2015 (POPIN, 2008), indicating strong health care needs of the ageing population. Indian pharmaceutical market is about $7.8 billion in 2007 and is expected to grow to $14.5 billion in 2012, with a CAGR of 13.2%. Indian market size is only 30-50% of the Chinese pharmaceutical market, and grows at a much slower rate. The ageing population in India is quite large, and is expected to reach 118 million by 2015. The pharmaceutical markets, the market growth rate, and the ageing population in Eastern European countries are significantly less than those in China and India.

Table 3.3. Pharmaceutical market size, CAGR of the pharmaceutical market, and aging population in China, India, and Eastern European countries.

Country/region	**China**	**India**	**Eastern European countries**			**World**
			Russia	Poland	Czech	
Market size in 2007 ($ billion)	15.9	7.8	5.6	5.6	2.1	577.1
CAGR 2003-2007 (%)	18.3	8.8	23.5	6.6	10.4	5.6
Market size in 2012 ($ billion, expected)	44.6	14.5	10.7	7.4	3.4	737.9
CAGR 2007-2012 (%, expected)	22.9	13.2	14	5.7	9.5	5
Population over the age of 60						
2005 (in million)	144	85	24.6	6.6	2	673
2015(expected, in million)	210	118	26.6	8.5	2.6	897

3.7 Summary

China leads the race in attracting clinical trial outsourcing as it provides tremendous opportunities relative to the patient pool, cost savings, and market potential. Although the regulatory status, IP protection, GCP compliance, and infrastructure are less than ideal, continuous improvements have been shown in these aspects. The increasing number of FDA IND clinical trials in China signals the growing confidence in China. Small biotech companies should realize that they can benefit from outsourcing to China as well, despite their limited resources. The key is to identify and execute the appropriate strategy in a high quality manner.

4: OUTSOURCING CLINICAL TRIALS TO CHINA BY BC BIOTECH COMPANIES

4.1 Introduction

Outsourcing of clinical trials to China is cost effective, and provides access to the high growth Chinese market, and other business opportunities such as risk capital. BC biotech firms can gain a competitive edge and establish a leadership role in the industry by choosing and implementing appropriate outsourcing strategies to leverage the value chain specialty in BC and China. In the short term, outsourcing allows the company to take the drug candidate to a later development stage at a reduced cost, or to carry out clinical trials for multiple products in its portfolio. By doing so, the company reduces the financial risk associated with drug failure and increases the chance of success by developing multiple drugs at the same time. The valuation for the drug products and the company will increase significantly with completion of the late-stage clinical development (Figure 4.1). In the long term, the outsourcing model increases the company's R&D efficiency and profitability, and provides access to Chinese pharmaceutical market, risk capitals, and research capacities.

This chapter focuses on whether BC biotech firms should take this opportunity to advance product clinical development and increase shareholder value. An overview of the biotech cluster in BC is presented, with emphasis on the weakness of BC biotech firms in the framework of KSFs in the biotech industry. A SWOT analysis of the BC biotech industry is performed with respect to the opportunity of outsourcing clinical trials

to China. As outsourcing clinical trials to China provides solutions to multiple problems that BC biotech firms are facing, BC biotech firm should explore this opportunity. Five strategic alternatives are proposed and evaluated. Based on the analysis, BC biotech should outsource clinical trials to CROs in China under the current conditions.

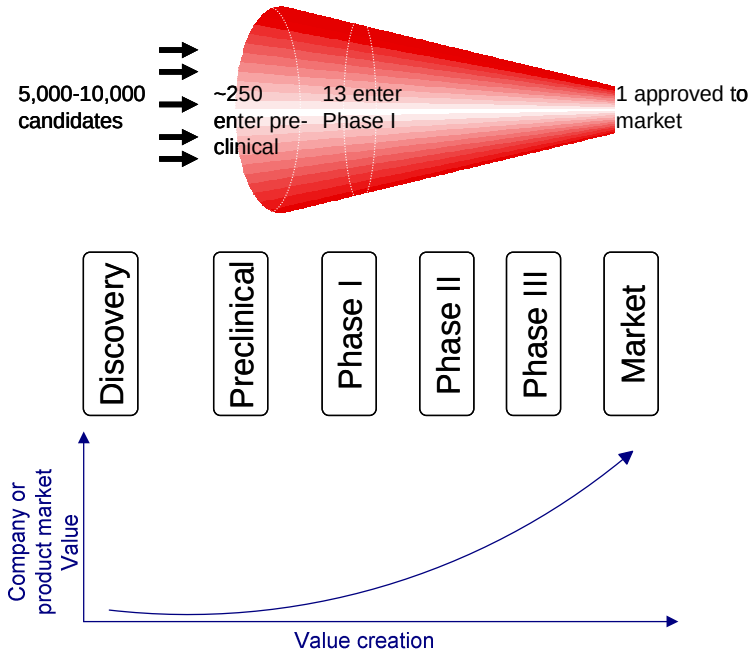

Figure 4.1. Risk, valuation, and product success along the pharmaceutical industry value chain (adapted from Industry Canada (2006)).

4.2 Overview of BC biotech

The BC biotech cluster emerged in the 1980s, experienced rapid growth in the 1990s, and is now the 7th largest cluster in North America (LifeSciences British Columbia, 2008). The BC biotech cluster, which centers on human health, has about 80 companies that are developing biopharmaceutical products. The BC biotech cluster has four of the most valuable biotech companies in Canada (measured by market capitalization): QLT Inc., Angiotech Pharmaceuticals, Aspreva Pharmaceuticals, and

Cardiome Pharma Corp. BC's 16 public companies are collectively profitable, and have a total market capital of approximately $3 billion (LifeSciences British Columbia, 2008).

The majority of the biopharmaceutical companies in BC are small companies at various stages of R&D (Ernst & Young, 2008). The companies have limited capacity to undertake other activities (such as manufacturing, marketing and sales) in the industry value chain. They rely on outsourcing or forming strategic alliance with large pharmaceutical companies to carry out those activities. The US is the most favorable location where the contract research and manufacture activities are outsourced to (ResTech Consulting, 2004).

Strategic alliances with large pharmaceutical companies is an important means by which BC biotech firms gain capital investment and access to external expertise. Such alliances normally involve BC biotech firms (originator) transferring the innovations (drug products) to or sharing the products with large pharmaceutical companies (commercialization partners) in exchange for capital investment, and access to the clinical, regulatory, marketing and sales network of the large companies. The alliances may be structured as out-licensing or co-development deals. In an out-licensing deal, the commercialization partner covers the expense and expertise of development, while in co-development the partners share the expense and expertise of development. In either case, prior to the commercialization of the product, the originator normally receives an up-front payment, reimbursements of R&D cost after signing, milestone payments, equity investment from the commercialization partner. The partners share the revenue as defined in the agreement after the product is commercialized (Edwards, 2007). The development stage of the products significantly affects the value of the strategic alliance.

Take the strategic alliance deals in the central nervous system area as an example: the average deal size (the pre-commercialization payment from a commercialization partner to an originator) was $156.3 million for phase I products, $233 million for phase II, and $388 million for phase III products (Otieno, 2006). Products in later development stage also increase the valuation of the company and attract investors. It is of BC biotech firms' best interest to carry clinical trials to a later development stage for a higher valuation.

4.3 Analysis of BC biotech cluster

For biotech companies developing biopharmaceuticals, the KSFs include access to technology, access to risk capital, supply of highly qualified scientific and business personnel, and access to global market. A critical analysis of the performance of the biotech companies/biotech cluster regarding the KSFs is an important step for developing suitable strategies. The BC biotech companies have access to high quality research, however, the research capacity (the quantity) in BC biotech cluster is low. The growth potential and sustainability of the BC biotech companies are also threatened by the lack of capital and experienced senior management personnel in the cluster. A detailed analysis of the BC biotech cluster is presented in the following sections.

4.3.1 Access to technology

Access to new technologies and scientific discoveries is the foundation for the biotech industry. Biotech companies develop drug products around new technologies and scientific discoveries. New technologies are applied to test, optimize and manufacture the drug candidates during the development process.

In BC biotech cluster, the University of British Columbia (UBC) and affiliated teaching hospitals are the powerhouses for innovations and new technologies. BC biotech strongly relies on technologies spun-off from UBC-- about 70 biotech companies have spun out of UBC's research activities. Two of the largest biotech companies in BC, QLT and Angiotech, are just a couple of examples.

However, the research capacity (an estimation of the quantity of potential innovations) of BC universities, institutes, and biotech companies is relatively weak when compared with other major biotech clusters in the North America. The research capacity is calculated based on biomedical research funding and university/firm patents. The research capacity of the BC cluster scored at 0.25. By comparison, the average research capacity of the 55 biotech cluster across North America is 1 and the research capacity of top nine clusters in the US is 3.9 (Graytek Management Inc., 2004). The research capacity of the BC cluster is not sufficient to support the survival and growth of its biotech companies, so BC biotech companies must access technologies and innovations from other resources.

4.3.2 Access to capital

The biotech industry is R&D intensive requiring a copious flow of capital investment over a long period of time (average 8-12 years) before the drug product reaches the market. The capital requirement for a start up is about $1-2 million for the first two years, rising to $5-10 million in the second two years. The capital requirements increase considerably in the later stages and vary for different therapeutic areas, especially when the products enter into critical proof-of-concept phase II clinical trials. For the first 10 years, the capital of biotech companies comes from venture capital (10%),

public equity (40%) and big pharma (50%) (Industry Canada, 2006). Venture capital investment normally carries the company up to the first proof-of-concept study (phase II clinical trials), after which equity funding and/or strategic alliance are more common.

BC biotech companies suffer from lack of capital. Compared with companies in the top nine North America biotech clusters, companies in BC attract on average 70% less venture capital funding and 80% less strategic alliance investment (Industry Canada, 2006). The BC biotech cluster is far away from the Canadian financial capital (Toronto). The US venture firms provides majority of the risk capital in the cluster. For example, in 2007, BC companies received about $370 million venture fund, among which $250 million were from the US (Ernst & Young, 2008). Compared with its US competitors, such as the San Diego biotech cluster and San Francisco biotech cluster, the BC biotech cluster does not have competitive advantages in terms of technologies, R&D expertise, infrastructure, and investment environment (e.g. investment taxation policy) (Industry Canada, 2006). Owing to the above mentioned reasons, it is difficult for the BC biotech cluster to attract large amount of risk capital from the US.

The lack of risk capital forces BC companies to partner their drugs at early development stages (preclinical or Phase I) and for less than optimum values. The pre-mature partnerships in turn result in the low value of strategic alliance deals. Lack of capital has hampered the growth of BC biotech companies--the market cap of Canadian biotech companies on average is only 10% of the market cap of US biotech companies (Industry Canada, 2006). To increase the valuation of the products, BC biotech needs to attract more venture capital funding or developing mechanisms to advance the drug products to phase II clinical trial with their limited financial resources.

4.3.3 Supply of highly qualified research, business, and management personnel

Successful commercialization of biotechnology needs experienced management teams with a combinational of technical, financial, clinical, regulatory, marketing knowledge and skills. The management teams provide vision, leadership, and financing capability. The ability to attract and retain scientific team is crucial to a biotech cluster.

BC biotech cluster has scientific founders with strong entrepreneurial spirit, and a good supply of research personnel. The industry has more than 1,500 employees; students and researchers from UBC, BCIT, and University of Victoria are the main suppliers of research teams. However, BC biotech has difficulties attracting and retaining experienced senior management with track records of success. As a result, despite the large number of spin-offs, few companies have successfully commercialized their products. The BC biotech cluster is still viewed as an early stage research center, and exports innovations at a low valuation.

4.3.4 Access to global market

Before any drug product enters into development stage, the market demand is estimated. The potential market should allow the companies to recover the substantial development cost shortly after the drug launch. To maximize sales and profit, pharmaceutical companies need to penetrate the global market in the shortest time possible. This marketing and sales strategy is becoming more and more important as the market share of emerging regions increases.

BC biotech companies focus on therapeutic areas with high growth rate and high demand, namely, cancer, neurological disorders, cardiovascular diseases, autoimmune diseases, and infectious diseases. Therefore, their products have good market potential.

With no marketing and sales capacity of their own, BC biotech companies rely on external partners for marketing and sales. Again, the revenue shares for BC biotech firms depend on the valuation of the product when the partnership is structured.

4.4 SWOT analysis

An important mechanism for BC biotech to gain high valuation for their products is to complete proof-of-concept phase II clinical trials. As reviewed in Chapter 3, China outperforms other emerging regions as a low-cost clinical site. Therefore China is a rational choice for BC biotech companies when considering outsourcing clinical trials. A SWOT analysis (Table 4.1) is performed to summarize the internal and external environment of BC biotech industry with respect to this outsourcing option. The purpose of the SWOT analysis is to provide a rationale supporting the growth opportunities in China, and to identify the risk and threats that the companies need to mitigate as they conduct clinical trials in China.

4.4.1 Strengths

The strengths of BC biotech include its access to the world-class research in UBC and affiliated hospitals. The cluster has a sufficient supply of research personnel and world renowned scientists with entrepreneurial spirit. The companies in the cluster have undergone a 20-year learning curve and have a keen understanding of the industry. Many initiatives and government funding are invested to build a strong research infrastructure. In addition, Vancouver, as the gateway to Asia, has many Chinese biotech professionals who were trained in North America that can serve as the business liaison, which can help building strong and trustworthy partnerships between Chinese and BC companies.

Table 4.1. SWOT analysis of BC biotech industry.

Strengths	**Weaknesses**
• Access to world class research (high quality) • 7th largest biotech cluster in North America • Renowned scientist with entrepreneurial spirit • Approximately 70 drug candidates targeting therapeutic areas with high market demand in clinical development stages • High R&D input • Gateway to Asia (geographic proximity) • Availability of Chinese biotech professionals trained in North America that can serve as business liaison to China • Experience in managing outsourcing to CROs	• Low research capacity (low quantity) • Lack of risk capital and low strategic alliance value • Lack of presence of large multinational pharmaceutical companies • Lack of experienced senior management • Lack of knowledge and experience in the business environment in China
Opportunities	**Threats**
• Advance clinical development at a low cost • Access to high growth Chinese market • Access to technologies, risk capitals, and R&D expertise in China	• In sufficient IP protection or enforcement • Regulatory barriers such as lengthy regulatory approval process • Difficulties to ensure clinical trial quality • Language and culture barriers • Technology transfer to China which will may help to build future competitors

4.4.2 Weaknesses

As discussed in 4.3, BC biotech cluster has a much lower research capacity and much less risk capital and financial resources when compared with the top nine US biotech clusters. The BC biotech cluster has no anchor tenants—no large multi-national pharmaceutical companies. The majority of the biotech firms in BC have less than 10

employees and have no products in the market (based on websites of biotech companies in BC). The cluster has not reached critical mass yet. Consequently, it is difficult for companies in the cluster to attract experienced senior management personnel due to the lack of job opportunities. The lack of experienced senior management and the low research capacity contributed to the recent downturn (from profitable to not profitable; massive layoff, factory closing down) of QLT (FierceBiotech News, 2008) and Angiotech (BioSpace News, 2008) , the largest and profitable biotech companies in BC. With the downturn of QLT and Angiotech, the sustainability of BC biotech cluster is in doubt.

4.4.3 Opportunities

Outsourcing clinical trials to China is especially attractive to BC biotech since this option can leverage the strengths and address the weakness of the cluster. BC is the Canadian gateway to Asia. The geographic proximity (as compared to the competitive biotech companies located in the eastern provinces), and the availability of Chinese students or graduates from Simon Fraser University (SFU) and UBC, especially those working in the BC biotech industry can facilitate building business connections between BC biotech companies and Chinese partners.

Outsourcing clinical trials to China addresses the financial barriers that limit the potential and growth of the BC biotech companies. The low cost of the clinical trials would allow BC biotech firms to carry the clinical trials to late development stages with limited capital, and reduce the financial risk associated with drug failure. The valuation for the drug products and the company will increase significantly with the completion of late stage clinical trials, thus increasing the potential capital injection from strategic

alliances, and attracting additional investments by boosting investors' confidence in the company.

4.4.4 Threats

Owing to the significantly different business environment, conducting clinical trials in China is risky for BC biotech as they enter the unfamiliar territory. As discussed earlier in 3.5, the risks are associated with uncertainty of clinical trial quality, lengthy regulatory approval process and weak IP protection and enforcement. In addition, outsourcing clinical trials to China, in the long run, fosters the growth of Chinese biotech industry by transferring industry knowledge, skills and technologies to China. The Chinese biotech industry will be future competitors of BC biotech companies.

4.5 Key success factors in clinical trials outsourcing to China

The KSFs of outsourcing include:

- Chinese partners with strategic fit, such as CROs in China or Chinese Pharmaceutical companies. Strategic fit means that the partners have complementary core competencies or/and synergy. BC biotech companies have experience in managing clinical trial outsourcing, however lack China-specific experience and knowledge. So an external partner with clinical development experience and knowledge in China will be beneficial to the BC companies. Collaborating with partners that are strategic fit allows BC companies to focus on their strengths, and gain access to the partners' expertise. At present, China has about 300 CROs and over 2000 biotech companies (Langer, 2006) whose service quality or technology expertise vary

greatly. It is feasible for BC companies to identify Chinese partners with strategic fit. Strategic alliances with Chinese companies to co-develop drug products have been adopted by a few foreign biotech companies. For example, US-based Genzyme and Shanghai-based Sunway Biotech are collaborating on developing Genzyme's gene therapy product. In this alliance Genzyme transfers its technology to Sunway; Sunway manufactures and carries out the phase I and II clinical trials in China (Ernst & Young, 2008). Sunway is one of the only two companies in the world which has successfully commercialized gene therapy products. By forming strategic alliance with Sunway, Genzyme not only finds a partner to conduct the clinical trials in China, but also gains access to Sunway's expertise in commercialization gene therapy products. BC biotech companies may adopt similar strategies to gain access to the expertise of its Chinese partners in clinical development in China and other R&D expertise. The chances of successful clinical outsourcing or even drug commercialization are significantly increased in these strategies.

- Advance planning to gain regulatory approval and IP protection in China. As the biggest barrier (time-consuming step) is to get regulatory approval for clinical trials, early planning is necessary. For example, application for clinical trial approval should be submitted to SFDA one year prior to the expected clinical trial starting date; patent registration in China is done before any confidential information is exposed to a third party in China.
- Providing training and support system by the sponsors (i.e. BC companies). To address the concerns over clinical trial quality and ensure the trial is

conducted according to ICH GCP, BC companies need to provide GCP trainings to hospitals, physicians and perform frequent site audits of the clinical trials sites. BC companies may also need to have translational system in place to avoid any misunderstanding of the study protocols and miscommunication.

- Management personnel with excellent project management skills and knowledge of Chinese culture and business environment. As language and culture pose potential barriers for successful outsourcing, management personnel with good understanding of Chinese language and Chinese culture will help to avoid the problems caused by miscommunications.

4.6 Selecting CROs in China

An appropriate and experienced CRO is one of the most important KSFs in clinical outsourcing to China. What kind of CRO should a BC biotech company choose to collaborate with? What are the advantages and the disadvantages of the different types of CROs? This section will analyze the different tiers of CROs in China and make recommendations on criteria for selecting CROs for BC biotech firms.

4.6.1 CROs in China

Approximately 300 clinical CROs are currently operating in China. These clinical CROs can be classified into four tiers based on their price, customer base, service quality, global and local capacity. The four tiers are Chinese branches of large global CROs (Tier 1), small-to-medium foreign CROs (Tier 2), Joint Venture CROs (Tier 3), and domestic CROs (Tier 4). Their pros and cons are summarized in Table 4.2.

Tier 1. Chinese branches of large global CROs such as Quintiles, Covance and MDS. These companies have a large share in the global market (10-15% each), and provide a high quality one-stop shop service (CROChina, 2008). Their customers are mainly Big pharma. They normally conduct multinational clinical trials in support of NDA. To ensure GCP compliance and fast recruitment, they established their own central labs in China to analyze clinical samples, have long-term collaboration with top Chinese hospitals (such as Peking Union Medical College Hospital), and provide GCP training to the hospitals. However, these large CROs are expensive and are less responsive to small trials or customers. Chinese pharmaceutical companies and small to medium foreign companies rarely contract clinical trials to them.

Tier 2. Small-to-medium foreign CROs. These companies have a customer base in foreign regions and provide high quality professional services primarily to small-to-medium pharmaceutical and biotech companies. They normally have extensive experience conducting FDA IND clinical trials. They are less expensive (30-70% of cost in the US) than Tier 1 CROs. In China, they make extra effort to ensure GCP compliance and study quality to attract customers. One of the most recent examples is Danish Center for Clinical and Basic Research which planned to open its first own clinical research facility. However, as new players in China, they are not familiar with the business environment and have a limited network. These companies have great potential in the near future as they grow more familiar with local business environment. In addition, with the maturity of Chinese pharmaceutical industries, new drugs developed by Chinese companies will need high quality clinical trial data to support their FDA approval. This tier of CROs will be their best choice in terms of price, quality, and global capacity.

Tier 3. Joint Venture CROs. They are joint ventures of Chinese and foreign CROs. These CROs are similar to Tier 2 in terms of quality, customer base, and growth potential. Their price is about 30-60% of US price. They normally have more experience with SFDA drug registration, a better network in China and are less experienced with IND clinical trials than Tier 2.

Tier 4. Chinese CROs. The services provided by domestic CROs vary, although are relatively poor compared to the other 3 tiers. Their GCP compliance is questionable; they also have little knowledge about NDA; some companies may even just function as public relationship management. These CROs compete on price. Their clients are Chinese pharmaceutical companies, and majority of the trials are for generic drugs. The data are in support of SFDA registration. On the other hand, they have extensive network, have good relationships with hospitals and local government, and have great lobbyists, which facilitate clinical trial registration and drug approval process. Their price is the lowest (10-50% of cost in U.S.) among the four tiers of CROs. These companies are expected to go through extensive M&A or form strategic alliances in the next decades. Improvement in quality and management is essential for the survival and growth of this tier of CRO. At present, they are not suitable candidates to conduct clinical trials for foreign companies.

4.6.2 Competitive analysis of CROs in China

The four tiers of CROs are compared in the following aspects (Figure 4.2):

- Clinical trial quality and GCP compliance. The quality of clinical trials is the most important determinant when choosing CROs in China as the quality varies greatly. Also, since these is gap between ICH GCP and Chinese GCP,

the sponsors must communicate with and make sure the CROs will perform clinical trial according to ICH GCP.

- Experience with innovative drug clinical trials. This factor is important since many CROs only have experience with clinical trials for generic drugs.
- Familiar with NDA. The US market is the largest pharmaceutical market in the world. It is essential that the CROs are familiar and have experience with NDA to ensure the clinical trials in China will be acceptable by FDA.
- Cost savings. This is the driver for pharmaceutical and biotech companies outsourcing clinical trials to low cost regions such as China, despite significant risks associated with the decision.
- Familiar with SFDA. CROs play an important role in navigating the regulatory approval process. Familiarity with SFDA requirements is essential.
- Network. CROs should have broad and excellent networks connecting SFDA, local government, hospitals, and physicians in order to maximize the roles of these stakeholders in the clinical trials and to ensure that trials are processed and executed with efficiency.
- IP protection. IP is exposed to risk in the outsourcing. The sponsors must make sure that the CRO partner in China will not violate IP protection.

The analyses and comparison of the four tiers of CROs indicate that for small-to-medium biotech companies, Tier 2 and 3 CROs are the best options as the outsourcing contractor. They provide quality clinical data that meet the requirements of the FDA and the SFDA, and are more cost-effective and more responsive to small companies than Tier 1 CROs. Additional criteria, such as experience in the

therapeutic area, experience in the particular trial phase, resources to handle the job and history of prior relationship can applied to the final decision making.

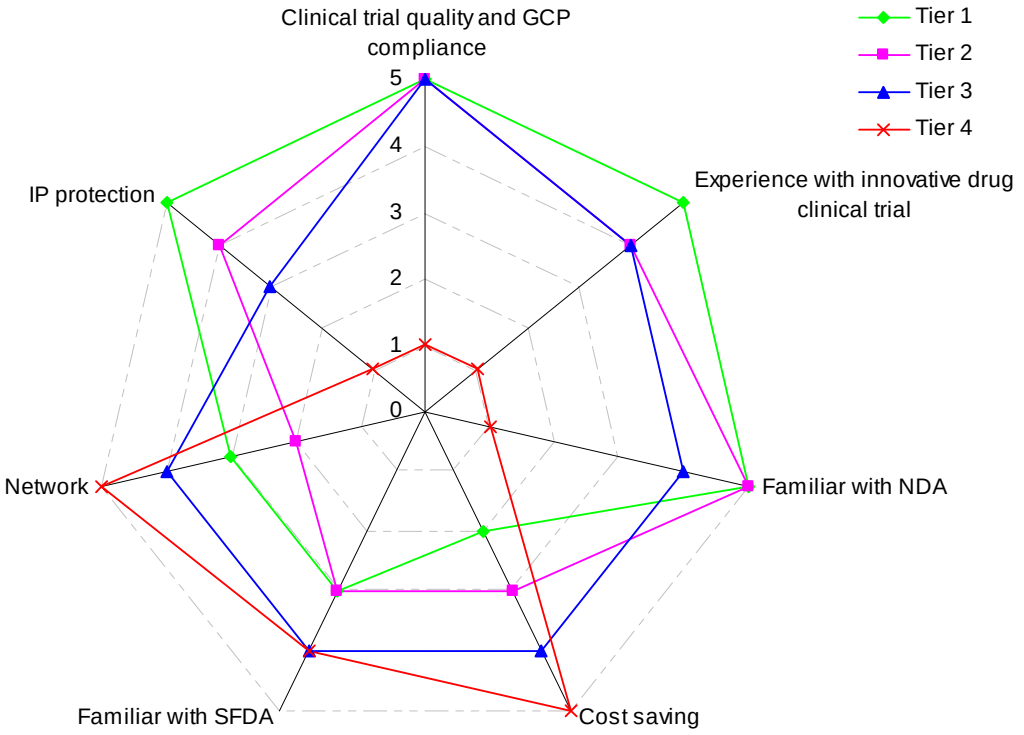

Figure 4.2. Competitive analysis of four tiers of CROs in China.

4.7 Summary

The internal analysis of BC biotech companies showed that BC biotech companies have incentives and demand to outsource clinical trials to China. Successful outsourcing will create a positive feedback loop to the drug commercialization process in BC biotech companies. Since there are significant risks associated with outsourcing clinical trials to China, BC biotech companies must develop understanding of the business environment in China, and have a comprehensive risk mitigation plan before venturing into the new avenue. Collaboration with the right external partners is one of the mechanisms to control risk.

Table 4.2. Comparison of clinical CROs operating in China[4].

Tier	1	2	3	4
	Global CROs	Small-to-medium foreign CROs	Joint Venture CROs	Chinese domestic CROs
Example	Quintiles, Covance	EPS, Accelovance , CCBR	Excel Kindlewits. VenturePharm CRO Service Excel PharmStudies	NewSummitBiopharma' VPSCRO
Number of CROs	3-4	~10	10-20	> 200
Customers	Big Pharma	Small-to-medium foreign biotech and pharmaceutical companies	Mostly small-to-medium foreign biotech and pharmaceutical companies	Chinese companies only
Pros	High quality, GCP compliant, experience in IND clinical trials own central labs; long term collaborations with top hospitals in China, experienced; familiar with FDA requirements	High quality; normally GCP compliant; experience in IND clinical trials; familiar with FDA requirements; international network	Relatively high quality; normally GCP compliant; experienced; familiar with FDA requirements; good network	Extensive networks, good relationship with hospitals, investigators SFDA, and local government; familiar with SFDA regulatory requirements; low cost
Cons	Expensive; not responsive to small-to-medium companies	Relatively expensive; not familiar with business environment and common practices in China; limited network	Relatively expensive	Little experience in new drug clinical trials; poor quality; GCP compliance is questionable
Years in operation	~10 years	~ 10 years	~10 years	8-10 years
Price competition	No	Limited	Limited	Yes, within Tier 4.

[4] Note: Descriptions of CROs in China can be found in the following websites: http://www.asiabizco.com/pharmavoice0904.pdf; http://topic.xywy.com/wenzhang/20030531/362645.html; http://www.chnmed.com/html/news/keyanqianzhan/20080721/926_2.html http://www.chinamtcm.com/html/root/OtherChannel/JiaoDianZhuanTi/075/26422.htm; http://www.crochina.com.cn/bbs/read.php?tid=29.

5: STRATEGIC ALTERNATIVES FOR BC BIOTECH COMPANIES

5.1 Identification of alternatives

BC biotech firms face a few challenges including lack of capital, low strategic alliance values, and limited research capacity. As the valuation of a company and its product increases significantly with the completion of each phase of clinical trials, especially phase II and III, the company needs to develop strategies that allow them to use the limited risk capital to carry the drug candidates to at least the critical proof-of-concept phase II clinical trials. Cost-reduction in phase II and phase III clinical trials offer solutions to these challenges.

In the BC biotech cluster, there are a number of product candidates for potential outsourcing. In the largest 20 biopharmaceutical companies in BC, approximately 70 drug candidates are in various R&D stages, among which, 39% are in preclinical research stage, 23% in Phase I and 34% in phase II. Only three products entered phase III clinical trial. The leading indication is cancer (38%), followed by neurological disorders (16%), cardiovascular disease (10%), autoimmune disease (9%), and infectious disease (6%), all of which have high incidences in China. Based on the product pipeline, about 40 products will enter phase II and III clinical trials within the next 1-3 years. These products represent the potential outsourcing demand in BC biotech cluster.

BC biotech companies traditionally contract their clinical trials to CROs or depend on their strategic alliance partners to carry out the clinical development. The

majority of the clinical studies are done in the US or Canada. With the opportunity of outsourcing clinical trials to China, what strategic options do BC biotech firms have in carrying out drug clinical development?

There are two scenarios consisting of a total of five strategic alternatives available to the companies. The alternatives are:

Scenario A: not outsourcing clinical trials to China under current conditions

1. Maintain status quo
2. Wait and see

Scenario B: outsourcing clinical trials to China

3. Strategic outsourcing to CROs in China
4. Co-development with a Chinese pharmaceutical/biotech company
5. Forward integration

5.1.1 Scenario A: not outsourcing clinical trials to China

5.1.1.1 Maintain Status quo (S1)

By choosing the option, the company continues to conduct clinical trials in the US or/and Canada by contracting to CROs or through other external partners such as its strategic alliance partner. In this option, the company weighs the risks and threats associated with outsourcing over the benefits, thereby missing the opportunity presented.

As discussed in Chapter 3, the drawbacks of this option are highly expensive clinical trials, potential delay or failure of clinical trial due to difficulties in recruiting and retaining adequate number of study subjects, lack of treatment-naïve patients, and no access to Chinese market. If the clinical development is carried out by strategic alliance partner, it usually means that BC firms export the innovation at a low valuation. In turn,

companies retain a better control of the regulatory and quality issues. As there is risk and a significant learning curve associated with outsourcing clinical trials in China, companies that are in good financial position (sufficient to completing phase II trials) may choose this option since they are not under immediate financial pressure. However, very few BC biotech firms can afford to do this as more than 30% of the BC biotech firms have insufficient capital to carry out operations for even one year. In the long term, the BC biotech firms can not increase R&D efficiency therefore will lose their competitive advantages.

5.1.1.2 Wait and see (S2)

In this option, the companies will initiate clinical trials in the US or Canada. At the same time, the companies will observe closely on the clinical research environment in China and determine an appropriate time to conduct trials in China as the risks decrease.

The business environment in China is improving rapidly. Conducting clinical trials will be much easier for foreign companies in the near future. The risks associated with regulatory uncertainty, trial quality, and infrastructure will be significantly decreased. Consequently, the cost of clinical trials, the competitions of study sites, PIs, patients and other resources from other companies will rise.

In this strategy, timing of entry is important. The company needs to closely follow up on the progress of clinical research development in China, evaluate the benefit/risk ratio in order to determine a suitable timing of entry. In addition, the company also needs to monitor whether and when other biotech companies start to outsource clinical trials in China as there are first-mover advantages in outsourcing. At

present, very few biotech companies have been conducting clinical trials in China (discussed in section 3.2).

This strategy may delay the company's access to Chinese market for several years and does not answer the company's immediate needs of carrying out proof-of-concept study at a low cost. More importantly, without including Chinese clinical trials in the initial planning, incorporation of Chinese data into the study may be problematic.

5.1.2 Scenario B: Outsourcing clinical trials to China

5.1.2.1 Outsourcing to CROs in China (S3)

In this strategy, a large proportion of a multi-national phase II or III trials are outsourced to CROs in China. This approach takes the full advantages offered by outsourcing, and saves at least two years for the drug to enter Chinese market. The KSF in this strategy is a CRO in China with the capacity to perform high quality clinical trials in alignment with FDA's requirements in a timely manner. For the long term benefit, the outsourcing should be planned according to the company's long term strategic development plan and the portfolio of pipeline products.

The strategy requires that the company plan in advance. For example, the application for regulatory approval to conduct clinical trials should be submitted one year before the planned clinical trial starting date. The company also needs to invest more in training and support systems, and plan to have regular audit of study sites and CROs. A comprehensive risk mitigation plan needs to be in place, and it may even be necessary for the company to establish a local branch in China.

The other advantage of this strategy is that the company gains knowledge and experience for conducting clinical trials in China, and expands its business network.

With this knowledge and network, BC biotech firms have access to risk capital and research capacity in China in the future, which increases the possibility to establish a company subsidiary in China.

5.1.2.2 Co-development with a Chinese pharmaceutical/biotech company (S4)

In co-development, the partners in the alliance undertake defined aspects of the activities in the value chain. In the case of outsourcing clinical development, the BC biotech firm can partner with another foreign/Chinese company which has presence and extensive experience in drug registration and clinical trial management, and with drug commercialization in China. The partners share the cost of clinical development and the potential revenue from the Chinese market.

With this strategy, BC biotech firm can reduce the risk and cost associated with outsourcing. The local presence of an experienced alliance is better for management and monitoring of the clinical trial. Compared with CRO, the alliance has more incentives for successful collaboration.

The main challenges with the co-development partnership are management and coordination problems since the priorities of the partners may not be the same. BC biotech firm may loss control over the clinical trials, and will depend on the partner to conduct clinical trials in its pipeline.

5.1.2.3 Forward integration (S5)

In the forward integration, the company conducts and manages clinical trials in China without external partners. Considering the low cost of labor in China, the financing requirement for the forward integration is not high. However, BC biotech

firms do not have the necessary expertise, network, or knowledge for the forward integration. Therefore, the risk for forward integration is high.

Each of the strategic alternatives is evaluated using the weighted criteria above. The scores of the alternatives are shown in Table 5.1. The evaluations are described in detail in the following sections.

5.2 Evaluation of strategic alternatives

The criteria for evaluating the strategic alternatives should be in alignment with the goals of the companies. For most companies, the goal is to maximize the shareholders' value. It is for the shareholders' best interest to increase the valuation of the products and the company, to efficiently use the capital, and to decrease the risk associated with product development. The long-term profitability and the capability to attract financial investment are also important. Good strategic alternatives should address the weaknesses of BC biotech companies.

To evaluate the strategic alternatives proposed above, the following weighted criteria will be used:

- R&D efficiency: R&D efficiency is essential to the survival and growth of a biotech company. R&D efficiency can be increased by reducing capital and time cost of clinical trials. The criterion is assigned a weighting of 2.5.
- Valuation of product and company: The valuation of product and company determines the capability of a company to get short term cash injection by financing or by forming strategic alliance. As lack of capital is a big challenge for BC biotech, this criterion is assigned a weighting of 2.5.

- Long term profitability: This criterion addresses the sustainability of the company, therefore is assigned a weighting of 1.5.
- Risk: There are potential risks associated with outsourcing especially that BC biotech companies have very limited previous exposure to the Chinese business environment. However, the rapid growth of clinical trials in support of NDA in China signals that risks can be mitigated. This criterion is given a weighting of 1.5.
- Organization capacity: BC biotech companies' core competency is innovative research and development of novel compounds in treated disease with high unmet needs. The companies should focus on their core competency. The criterion is given a weighting of 1.
- Expanding business network: With clinical trials outsourcing to China, BC biotech companies gain access to Chinese market, R&D expertise, and risk capital. The effect of this expansion will take a relative long term to recognize. It is given a weighting of 1.

5.2.1 R&D efficiency

BC biotech companies are under pressure to increase their R&D efficiency. BC biotech firms spend on average 50% of their revenue/capital on R&D. With difficulties to raise capital from various channels, BC biotech companies need to use the available capital efficiently. In scenario B, outsourcing clinical trials (S3, S4, and S5) to China significantly cuts the cost of study and increases R&D efficiency. As the company gets more experienced in conducting clinical trials in China, further improvement in R&D efficiency can be expected. Among the three options, cost savings from co-development

is the highest, while from forward integration is the lowest. In co-development, the clinical development cost is shared between the partners, individual company's financial burden decreases. BC biotech companies also gain access to their partners' expertise in China which may help to improve clinical development efficiency. Forward integration is least cost efficient. A forward integration lacks economies of scale and scope. In addition, developing in-house clinical trial capability needs to go through a learning curve before reaching the optimal efficiency in the model. The increase in R&D efficiency by this strategy will be less than co-development and outsourcing to CROs in China. Outsourcing to CROs is cost efficient as discussed in Chapter 2.

If a company continues to conduct clinical trials in the developed countries (S1), it remains to be R&D inefficient. As more and more biotech and pharmaceutical companies are shifting clinical trials to China or other emerging regions, it will be difficult for companies choosing this option to be competitive. Wait and see (S2) does not address the company's immediate needs. Future cost savings from outsourcing to China will be also less as the cost of labor increases in China.

5.2.2 Valuation of product and company

Very few BC biotech companies have products in the market. As mentioned earlier in Chapter 4, the capital of biotech companies comes from venture capital (10%), public equity (40%) and large pharmaceutical companies (50%). The capital injection from large pharmaceutical companies is based on the valuation of the product in the partnership deal. Completion of each phase of clinical trial increases the success rate of the drug product, in turn increases the valuation of the product and the company (Figure 4.1). The valuation for phase II product about 60% higher than phase I product (Otieno,

2006). Moreover, the development stages of a company's portfolio products can affect the size of IPO. A company with multiple late stage products in its pipeline are more likely to raise a large amount of capital through financing or IPO. Maintain status quo (S1) or wait and see (S2) may not allow the completion of phase II trials because of lack of capital, therefore can not increase the valuation of the product. In contrast, outsourcing to China (S3, S4, and S5) provides the opportunity to carry out phase II clinical trials with limited capital.

5.2.3 Long term flexibility and profitability

Clinical trials must be performed before an imported drug can be marketed in China. The potential of the Chinese pharmaceutical market is tremendous. It can not and should not be ignored by BC biotech companies. A new revenue stream is particularly important to small companies.

In Scenario A, the company will not outsource or will delay outsourcing to China. The consequence is that it will not benefit from the growing Chinese market or the access to the market will be delayed. The company does not maximize the revenue potential of the drug product. The long term profitability and financial flexibility are negatively affected.

In scenario B, outsourcing clinical trials to China allows the fast penetration of the Chinese market, and generates revenue for the sponsor company. All three options increase the company's long term profitability and financial flexibility by increasing revenue and decreasing cost. The amounts of the revenue are different for the three strategies. Assuming all three strategies create the same degree of market penetration, the revenue share for the company is: S3 = S5 > S4. In co-development (S4), the BC

biotech company may have less revenue share than the other two options because the revenue is shared between the partners.

5.2.4 Risk

The risks associated with outsourcing clinical trials to China have been discussed in detail in Chapter 3. Maintain status quo is an option with the lowest risk. In the US and Canada, the regulatory and legal system are mature enough to ensure IP protection and clinical trial quality. In the option Wait and see, clinical trials are outsourced to China when the business environment in China is improved significantly, therefore associated with lower risk.

In scenario B, companies will be exposed to risks discussed earlier. For small BC biotech companies without resources in China, working with external partners that have significant presence in China can help capitalize on the opportunity and minimize risk. Outsourcing to experienced CROs decreases the company's exposure to risks by leveraging the CROs' expertise, experience, and network. In co-development, the risk for the BC biotech company is lowered by sharing the risk with the partner. However, the company will need to cede substantial control to the partner, and is at risk of losing control. It is worthy to note that Chinese pharmaceutical/biotech industry is still immature. Most companies have no or limited experience developing novel compounds and do not have sufficient knowledge about NDA. Their quality control over clinical trial and their strategic plan may not in alignment with those of the BC company's. In this option, the BC company must partner with a Chinese pharmaceutical company which has experience in developing innovative drug products and is a strategic fit to control the risk. In forward integration, the company will bear the risk itself. The risk will be high

since the company has no expertise in clinical trial management or knowledge and foundation in China.

5.2.5 Expanding business network

The BC biotech cluster is facing some challenges to become a sustainable biotech industry. Two main challenges are lack of risk capital and low research capacity. BC companies should explore other regions for additional financial resources and research capacity. Outsourcing clinical trials to China can help BC companies to gain access to risk capitals and research capacity in China.

The Chinese biotech venture capital pool is estimated to be $300-400 million per year ($87 million in the first quarter (Q1) 2008), and is growing at a rapid speed (a 33% increase from Q1 2007 to Q1 2008). In comparison, the US venture capital is $2 billion per year (Daverman, 2007). The average investment deal size in China is $11.1 million (ChinaBio Today, 2008) , similar to the deal size in North America (Daverman, 2007). The growth of venture capital in biotech sector is slower than the overall venture capital growth (a 125% increase from 2007 to 2008) in China. Part of the reason is that investors lack confidence in the immature Chinese biotech industry and there is no exit strategy for venture firms (Bioentrepreneur Bioe News, 2003). Compared with the Chinese biotech industry, BC biotech companies have significant advantages in terms of products, technologies, management, and exit strategy, and therefore are more likely to attract venture capital from Chinese venture firms. Some US companies have adopted the strategy. For example, a start-up biotech company LEAD therapeutic Inc. in the US have successfully obtained risk capital from Chinese venture firms (LEAD therapeutics, 2007).

As mentioned in 3.4.3, China can also provide research capacity and R&D expertise in the value chain activities. China has a large pool of scientists. There are more than 1.6 million science and engineering graduates in China (PricewaterhouseCoopers, 2008). More recently, the biotech R&D expertise in China has been boosted enormously by the so-called "sea turtles"—oversea Chinese life science professionals returned to China (Engardio, 2008). Multinational pharmaceutical companies are outsourcing their R&D activities to pharmaceutical and biotech companies founded by "sea turtles". One example is that Pfizer, the world's biggest pharmaceutical company, contracted its drug screening activities to WuXi PharmaTech founded by returning Chinese nationals (FierceBiotech News, 2008).

Outsourcing clinical trials to China can be used as an effective tool to establish the company's presence in China, to extend its business network, and to increase the exposure of the company and to facilitate its access to the risk capital and research capacity in China. In addition, the external partners such as CROs or Chinese pharmaceutical companies may also be helpful in expanding the company's business network in China. So Strategic outsourcing to CROs, co-development, and forward integration can facilitate the process of network building in China. By maintaining status quo or delaying clinical trial outsourcing, the company will have much less opportunities to present itself to Chinese venture investment and research communities.

5.3 Summary

BC biotech companies are primarily research focused with the majority of the clinical development activities carried out by external partners. The current business model of BC biotech companies does not create high valuation of the drug products and

the companies, so they should explore strategies that allow the companies to gain optimal value for their innovations and drug products.

Outsourcing clinical trials to China provides an opportunity to develop such strategies. However, conducting clinical trials in China is of risk especially because BC biotech companies have very limited knowledge and experience in China. Two scenarios consisting of five strategic options are available for BC biotech companies. Scenario A avoids the risks associated with outsourcing to China. In the short term, the two strategic options in scenario A are not able to address the companies' immediate needs to advance product clinical development at a low cost. In the long term, maintaining status quo cannot improve R&D efficiency nor profitability of the company. Wait and see delays the entry to Chinese market and does not gain full benefits in cost savings. Options in Scenario B have various degrees of risk mitigation design while embracing the opportunity presented by outsourcing clinical trials to China. The two strategic alternatives with the highest weighted scores, strategic outsourcing to CROs in China and co-development, balance the potential risks and benefits.

Table 5.1. Evaluation of the strategic alternatives using weighted criteria.

Criteria	Weight	S1	S2	S3	S4	S5
R&D efficiency	2.5	Low	Low/Medium	Medium/High	High	Medium
Valuation of product and company	2	Low/Medium	Low/Medium	High	High	High
Long term profitability	2	Low	Low/Medium	High	Medium	High
Control of Risk	2	High	Medium/High	Low/Medium	Low/Medium	Low
Expanding business territory	1.5	Low	Medium	Medium/High	Medium/High	Medium/High
Total	10	20	25.5	40	38.5	35.5

S1 = Maintain status quo; S2 = Wait and see; S3 = Strategic outsourcing to CROs in China;

S4 = Co-development with a Chinese pharmaceutical/biotech company; S5 = Forward integration.

Evaluation score:

Low = 1; Low/Medium = 2; Medium = 3; Medium/High = 4; High = 5.

6: RECOMMENDATION AND CONCLUSION

6.1 Recommendation

The report recommends that BC biotech companies should choose to conduct clinical trials with CROs in China. The evaluation of this strategy has been discussed in detail in Chapter 5. Strategic outsourcing to CROs aims to establish a long term partnership with a CRO, given the service provided is satisfactory. With a long term partner available, advance planning for clinical trials in China is made easy, and the costs associated with selecting, training, auditing, and monitoring of CRO will decrease over time. This option is scored very closely with another option, co-development, but provides BC biotech companies better control of the clinical trial and larger potential revenue in the future. In co-development, although the cost of the clinical development is shared among partners, the BC biotech company may lose control of the clinical development including quality of clinical trial, GCP compliance, and development time line. Maintaining the status quo or delaying outsourcing to China does not meet the needs of the companies to advance drug clinical development at a low cost. Forward integration is risky and is not cost efficient.

Strategic outsourcing to CROs in China by BC biotech companies provides the companies opportunities to advance drug clinical development at a low cost and to gain access to the R&D expertise, risk capital and the pharmaceutical market in China. However, the companies must be fully aware of and anticipate the risks associated with

outsourcing to China. It is important for the companies to develop comprehensive risk mitigation plans in advance.

A starting point for BC biotech companies to plan strategic outsourcing is the assessment of the company's capacity, needs, and long term strategic plans. The areas for the company to consider are (Winter and Baguley, 2006):

- Therapeutic area expertise and product pipeline and timeline in these areas. BC companies have drug candidates targeting primarily cancer (38%), neurological disorders (16%), cardiovascular disease (10%), autoimmune diseases (9%), and infectious diseases (6%). Most of the companies have multiple products in the pipeline targeting the same therapeutic areas.
- Type and number of studies needed for each therapeutic area
- Commercial market of the products
- Number of patients and countries/site locations of each therapeutic area
- Financial framework
- In-house resources and expertise

With a good understanding of its own capacity and needs, the company can determine what activities to outsource and which CRO to use.

The companies should use various resources and information available to gain a good understanding of the CROs and the pharmaceutical industry in China when planning for outsourcing. For example, the companies may use databases (e.g. China Therapeutics Database: 2006) that detail biopharmaceutical research institutes, CROs and manufactures in China to help them identify and locate potential outsourcing partners in

China. A good overall understanding of the Chinese pharmaceutical industry will be very helpful for the BC companies to design the best route to conduct clinical trials and eventually commercialize a new product in China. For examples, the BC companies may consider outsourcing to manufacturers in China to produce the drugs for the clinical trials. By doing so, the companies will/can reduce the manufacturing cost, cut the transportation expense and avoid duty and value-added-tax which are applied to imported drugs.

With a good understanding of Chinese pharmaceutical industry and various CROs, the BC companies are in a better position to identify a CRO partner in China with strategic fit. As discussed in Chapter 4, CROs in China are quite fragmented. The quality and cost of CRO services vary greatly. Based on the analysis of CRO industry in China, the project recommends that BC biotech companies should choose a CRO in Tier 2 small-to-medium foreign CROs or Tier 3 JV CROs. Well-defined requirements on CRO capacity will be applied to screen for suitable CROs. Some CRO capacities that can be used for screening are listed below (Winter and Baguley, 2006):

- Organizational size and structure
- IP protection
- Operational expertise and experience
- Therapeutic expertise
- Costs and financial stabilities
- Risk-sharing opportunities
- Communication
- Relationships with hospitals, physician and SFDA

Among these capacities, the BC companies should pay extra attention to IP protection, communication, and relationships with hospitals, physicians, and SFDA, as they are highly important in the context of China.

The BC companies need to develop effective means to decrease the risks associated with outsourcing clinical trials to China. As reviewed in 3.5, the risks are uncertainty in clinical trials quality and ICH GCP compliance, lengthy regulatory approval process, and weak IP protection. To ensure the quality of the clinical trials, the sponsors should communicate with its CRO partner frequently and provide GCP training and support to the CRO, hospitals, and physicians where necessary. The company must address quality concerns to its CRO to ensure that the studies are ICH GCP compliant. Advance planning to gain regulatory approval will be necessary to avoid delay of clinical trials. Dossier for Clinical Trial Application should be submitted in advance, approximately one year before the proposed phase II or III clinical trial starting date. The protocol is not necessary to be final before submission of the Clinical Trial Application. The CRO partner in China should be involved or accounted for the application process since they have much more experience than BC companies in this aspect.

When outsourcing clinical trials to China, the BC biotech company must address the cultural, language and logistical challenges. Understanding the Chinese culture is critical for establishing strong business relationships with the CROs. The company needs to have a comprehensive understanding of Chinese cultures from various perspectives to best coordinate and benefit from the stakeholders in the clinical trials. Language presents another barrier. The company should have proper translation and interpretation to define

goals and clarify expectations of all parties. The supporting cost and other general travel costs must also be factored into the business decision.

To better coordinate and oversee the clinical trials, and to expand its business network in China, the BC biotech company should set up an office in China. The local presence can solve many logistic problems such as the requirement of frequent travel and working in different time zones. The local presence also facilitates interactions with local scientific and business communities, providing opportunities for BC biotech companies to acquire research capacities and venture investment.

Outsourcing clinical trials to China potentially can bring a new revenue stream to the company which is very important to small biotech companies. BC biotech companies should take the opportunities provided by clinical outsourcing to select potential partners in China to commercialize the drug products. Getting connected through the CROs is an effective way to get introduced to the Chinese pharmaceutical companies.

6.2 Conclusions

The strategy of outsourcing clinical trial to CROs in China allows the BC biotech companies to significantly reduce the cost of clinical development thus reducing short-term capital requirement. With successful completion of the phase II trials or phase III trials, the company will be in better position to negotiate a strategic alliance deal around the product and generate significantly more capital for pipeline products development. Conducting clinical trials in China also accelerates the drug registration in China and brings BC companies a new revenue stream. In addition, the experiences and knowledge the company gained during the outsourcing have a long term contribution to the company's R&D efficiency. The outsourcing strategy reduces risks by undertaking

clinical trials at a low cost, and by collaborating with CROs with expertise in conducting clinical trials in China. BC biotech companies should plan for and anticipate any logistic, cultural, or language challenges that may arise. The outsourcing to CROs strategy represents the best option for BC biotech companies to increase shareholders' value while retaining significant control over the clinical development activities.

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