STRATEGIC ALLIANCES IN BIOTECH/PHARMACEUTICAL INDUSTRY & OPPORTUNITY AND THREAT ANALYSIS OF WESTERN-ASIAN R&D COLLABORATION

by

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Abstract

Dramatic advances in genomics and rapid progress in the Human Genome Project have resulted in a vast number of therapeutic targets available to researchers in traditional pharmaceutical and biotech companies that aim to join or serve the pharmaceutical industry. Consequently, the total number of new drug projects and the expenditure of research and development (R&D) worldwide have increased dramatically in this decade. However, despite the rising efforts (time and money) in the industry, the actual number of new drugs that reached the markets is declining year by year. To reveal the significance of strategic alliance to the value chain of biotech and pharmaceutical (bio/pharma) industry, this report reasons the demand of external R&D resources in the present circumstances through reviewing literature of bio/pharma R&D collaboration and recent news of the restructuring in this sector. This report further identifies the advantages and disadvantages of strategic alliances to bio/pharma firms by comparing with other transactions, such as mergers and acquisitions and licensing.

In the circumstances of the globalizing drug market, Western bio/pharma firms are faced with strong challenges by confining their businesses to domestic markets. In addition, as many developing countries now have the honed skills and knowledge in drug discovery and development, intense competition now comes from all over the world. The later part of this report thus aims to discover whether Western bio/pharma companies could strengthen their competitiveness through the R&D collaboration with those in developing countries (the case of Asia). By detailing the biotech promoting policies and

incentives, the development of human capital and the overall bio/pharma environment in China, India, Singapore and Taiwan, this report provides a comprehensive analysis of opportunities and threats to Western bio/pharma companies through the Western-Asian partnerships. Finally, in light of the complex value chain of drug development, this report presents the different specialties of these Asian countries and suggests the most functional and profitable types of collaboration for the Western bio/pharma companies.

Keywords: Biotechnology; Pharmaceutical; Strategic alliance; R&D collaboration; Alliance demand; Asian biotech / pharmaceutical industry

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Glossary

bio/pharma	In this report, it refers to traditional pharmaceutical and pharmaceutical-oriented biotech companies
BLA (Biologics License Application)	With the same purpose as NDA, but for biologic products
CDER (Center for Drug Evaluation and Research)	A division of the U.S. Food and Drug Administration (FDA) that ensures drugs are safe and effective
cGMP (current Good Manufacturing Practice)	Regulations promulgated by FDA for the control and management of manufacturing and quality control testing of foods, pharmaceutical products, and medical devices.
CRO (Contract Research Organization)	A service organization that provides supports from preclinical to clinical R&D to the pharmaceutical/biotech industry
DOH (Department of Health)	In this report, it refers to the Taiwanese government department responsible for public health issues
FDA (Food and Drug Administration)	An agency of the United States Department of Health and Human Services; responsible for regulating and supervising the safety of foods, dietary supplements, drugs, vaccines, biological medical products, blood products, medical devices, radiation-emitting devices, veterinary products, and cosmetics.
GDP (Gross Domestic Product)	A basic measure of an economy's economic performance
IBD (Irritable Bowel Syndrome)	A functional bowel disorder characterized by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits in the absence of any organic cause
ICH (International Conference on Harmonization)	A unique 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 product registration

GCP (WHO Good Clinical Practice)	The WHO guidelines to set globally applicable standards for the conduct of biomedical research on human subjects, such as clinical trials
in vitro	The technique of performing a given procedure in a controlled environment outside of a living organism.
IND (Investigational New Drug) application	The means by which a drug sponsor obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved
IP (Intellectual Property)	Legal property rights over creations of the mind, both artistic and commercial, and the corresponding fields of law
LDL (Low Density Lipoprotein)	So-called “bad cholesterol”, high levels of LDL cholesterol can signal medical problems like cardiovascular disease
M&A (Merger and Acquisition)	The aspect of corporate strategy, corporate finance and management dealing with the buying, selling and combining of different companies
MS (Multiple Sclerosis)	A neurological autoimmune disease; the symptom often progresses to physical and cognitive disability and neuropsychiatric disorder.
NCE (New Chemical 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
NDA (New Drug Application)	An application proposed by drug sponsors, providing sufficient information about manufacturing process and the result of clinical trials of drug candidates to endeavour FDA approval for sale and marketing
Recombinent DNA technology	The technology used to create a form of DNA that does not exist naturally by combining DNA sequences that would not normally occur together
TB (Tuberculosis)	A common respiratory infectious disease; usually cause a chronic cough with blood-tinged sputum, fever, night sweats, weight loss or even death
VC (Venture Capital)	A type of private equity capital typically provided to early-stage, high-potential, growth companies in the interest of generating a return through an eventual realization event such as an IPO or trade sale of the company

WHO (World Health Organization)	The directing and coordinating authority for health within the United Nations system; responsible for global health matters
WTO (World Trade Organization)	The only global international organization dealing with the rules of trade between nations

Chapter 1 Overview

In the regime of rapid technological development, research breakthroughs are so broadly distributed that a single firm can hardly have all the internal capabilities required for success in innovation. Previous literature indicates that inter-firm alliance has become a common strategy in many industries in recent decades. Particularly in those sectors that heavily rely on technology, the use of alliances is an important strategy to create economic scale, facilitate resource sharing, learn new skills and technologies, reduce risks, and expand market coverage. Broadly, strategic alliances refer to inter-firm collaboration aimed at achieving a firm's strategic objectives (Yoshino & Rangan, 1995).

In the biotechnology (biotech) and pharmaceutical (pharma) industries where the knowledge base is both complex and expanding and the sources of expertise are widely dispersed, the locus of innovation can be found in networks of learning, rather than in individual firms. Additionally, it is barely possible for a research-oriented firm to complete the time-consuming and costly process of drug discovery and development all along. This process includes the elaborate preclinical and clinical R&D, manufacturing, marketing and distributing activities, which make the final products delivered to the consumers. As a result, intense collaboration within the biotech and pharma industries appears on many levels including horizontal partnership such as research partners among firms, or distributing and marketing team-ups, and vertical partnership among academic research institutes, biotech and pharma firms (Edwards, Murry, & Yu, 2003; Stuart, Ozdemir, & Ding, 2007). While there are benefits for firms to exploit strategic alliances,

studies showed that reliance on external partners involves potential hazards (Powell, 1990; Sabel, 1993). The complexity of a joint project, difficulties in relinquishing control and a lack of trust between the parties are all barriers to collaboration. As opposed to contractual relationships, the alternative would be to create an internal mode for research and development. It is evident that the traditional pharmaceutical firms mostly have bulky in-house research units, but recent news and studies all show that the vertical R&D partnership actually provides substantial benefits to pharmaceutical firms. In short, when the strategic alliances can provide more opportunities than threats, firms turn to collaboration to acquire resources and skills they cannot produce internally.

At the present time, “globalization” has had a critical impact on the economy. It first appeared in the 1960s and has been used to define a transformation process that accelerated in the 1980s. In this context, free-market economy, privatization, and liberalization are the main characteristics of globalization. Globalization, however, can also be viewed as a process aimed at increasing the growth and widespread distribution of capital. During this process, globalization has destroyed values and rules that do not serve its aims (Semin & Guldal, 2008). Globalization has also affected the pharmaceutical industry and caused serious and inevitable contradictions and conflicts. There is no easy way to measure the effect of globalization on the pharmaceutical sector in terms of production, trade, prices, profit, and consumption, as there are variations in social divisions in terms of classes and countries. As a result, several studies have discussed the motives and management of cross-border R&D alliances, such as absorptive capacity, technology learning and partner selecting (Appleyard, Lybecker, & Wang, 2008; Kim & Inkpen, 2005).

When talking about the globalization and cross-border strategic alliances, it is indispensable to study the role that Asian developing countries play under the circumstances. The emerging market economies of Asia remain a bright spot in the global picture, particularly in China and India. According to the World Factbook of the US Central Intelligence Agency, the Gross Domestic Product (GDP) - real growth rates were over 5% for both countries during the 2008 economic downturn (Central Intelligence Agency, July 2009). Besides the overall economic growth in the Asian countries, the whole pharmaceutical and biotechnology sector there is booming, including both R&D techniques and the pharmaceutical market. Considering this emerging business in Asia, as well as the well-established one in the Western developed countries (especially the United States), it seems a good opportunity to expand this industry into a global scope through the strategic alliances between Western (North American & European) and Asian pharmaceutical and biotechnology companies. In fact, several companies have already built collaboration in different stages of the drug discovery process. For example, aiming to become a global biomedical sciences hub, Singapore has attracted both the multinational pharmaceutical and small-medium biotech companies to build partnerships with domestic biotech companies.

This report presents the know-how of strategic alliances and the status quo of the Asian biotechnology and pharmaceutical industry, and provides an analysis of business opportunities and threats to the Western firms that plan for, or never think of, the Western-Asian collaboration. The structure of this report is as follows: Chapter 2 provides an introduction of pharmaceuticals and the drug discovery & development process, the differences between traditional and biotech pharmaceuticals, and the

timeline and expenditures of the conversion from biological molecules to medicines. Chapter 3 focuses on the reasons of recent restructure in the sector analyzing the urgent demand for external R&D resources, the advantages and disadvantages of strategic alliances and the trend of R&D alliances toward a global scale. IChapter 4 narrows down the geographic area to the Asian arena, analyzing the business opportunities and threats of the strategic alliances for Western-Asian pharmaceutical and biotechnology companies.

Chapter 2 Introduction of Bio/Pharma Industry

2.1 Traditional vs. biotechnology pharmaceuticals

Drugs are substances that affect the functions of living things and are administered to treat, prevent, or cure unwanted diseases and symptoms. The sacrosanct mission of medicine to cure illness, as well as the distinctive value chain of this industry, makes the business of pharmaceuticals alluring and indispensable.

With the different chemical characteristics and the unlike discovering and manufacturing process, pharmaceuticals are generally sorted into small-molecule drugs (traditional drugs) and biotech drugs. As implied by the name, biotech drugs are proteins (big molecule) that are discovered and produced through the recombinant DNA technology or other burgeoning biotechnology. The first biotech drug in the history is the bacteria-synthesized recombinant human insulin for the treatment of diabetes from Genentech, which was established in 1976 as the first biotech company in the world (Friedman, 2006). Prior to the advent of molecular biology techniques, traditional pharmaceutical development is limited to chemical synthesis. Therefore, the drugs that are produced by traditional pharmaceutical means tend to be small molecules (or chemical entities) and usually oral-taken as pills (Friedman, 2006).

Considering the nature of biotech drug development is heavily based on scientific knowledge to either design drugs from scratch or develop a rational method to identify and modify existing compounds, drug discovery is no longer exclusive to big pharmaceutical companies (Big Pharma), but contributed by many research- intensive

biotech companies as well. In the following sections, “bio/pharma” is used to embrace the drug development-oriented biotech companies and traditional comprehensive pharmaceutical companies.

2.2 Drug Discovery & Development

In the process of drug development, drug candidates are identified and subjected to increasingly stringent tests to determine if they are safe and effective. In the United States, the effective drug candidates will eventually be examined by The Food and Drug Administration (FDA), who regulates drug marketing, requiring manufacturers to prove their products to be safe, effective, and appropriately labeled, before gaining approval. The standards of evidence for new drug approval are similar across countries. For example, the three largest prescription drug markets in the world, including the United States, the European Union and Japan, have taken steps to harmonize their procedures to ensure the timely introduction of new drugs and to reduce the cost of development.

Like those in other high-tech industry, the process of producing and selling drugs consists of three basic stages: discovery, development and commercialization. However, as the products of bio/pharma industry are meant for human therapeutic use, it takes the manufacturer an average of 14 years to develop a drug. The process below, as shown in Figure 2.1, demonstrates why drug development is so labor-intensive, time-consuming and expensive.

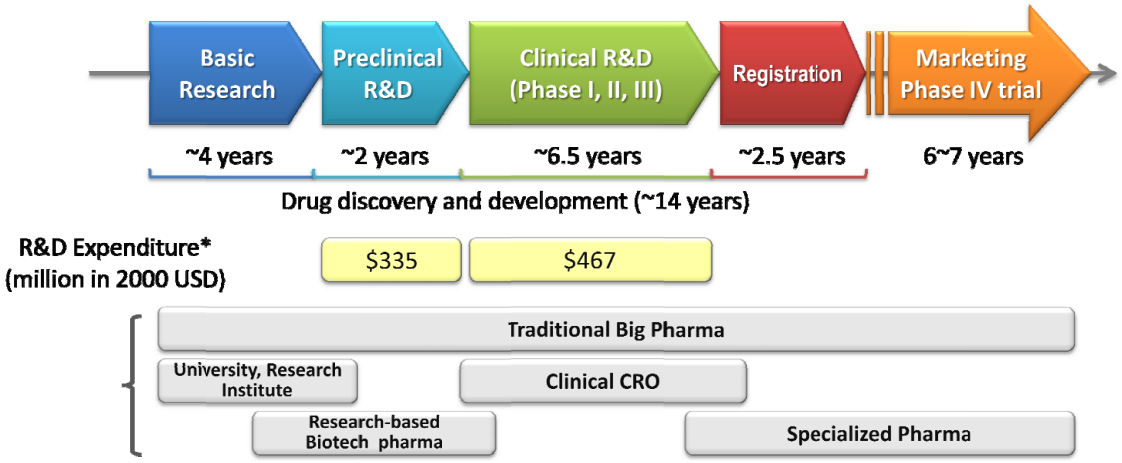


Figure 2.1 The process of drug discovery and development

Sources: Johnson & Johnson, March 2008
** Note: The R&D expenditure is estimated by DiMasi, Hansen, & Grabowski, 2003*

2.2.1 Basic research

The drug development process starts from the research of identifying useful disease targets. In many diseases, one or more proteins in human bodies do not work correctly. In the cancer drug discovery process, for example, the general approach to find out the candidate targets from the hundreds of thousands of proteins in human bodies is to compare the quantity and the quality of proteins between healthy cells and cancer cells. In illness, there might be shortage or surplus of certain proteins, as well as over-functional or dysfunctional proteins. Once the target proteins are identified, the next step is to develop the potential drugs through purifying naturally occurring compounds, synthesizing the compounds chemically, or designing them using computer simulations. To further increase the efficacy and safety and to reduce side-effects, the selected or synthesized compounds usually need to be modified. As the manufacturing costs recur over the life of a drug, it is also important to make the drug candidates easy to produce.

2.2.2 Preclinical R&D

Once the potential drug that works in a model system is identified, it is time to study the pharmakinetics and other properties of the drug candidates in the in vitro system. The potential drug that works in an in vitro model system is called a lead compound and further tested on animal models. While many studies argue that the success in animal tests does not necessarily suggest that a lead compound will work in humans, animal test so far is the only real way to determine whether the lead compound is effective and safe enough to try on humans. More importantly, through animal studies, researchers can establish the method of administration that makes the substance end up in the right place in the bodies contribute to ensure the optimal effect.

After the efficacy of the drug candidate is proved, the compound, and maybe the manufacturing procedures, is likely protected by a patent that extends 20 years from the date of the patent application. Although the innovation process in bio/pharma industry is similar with that in other high-tech sector, it is shown that at least 100 research projects could eventually lead to only one drug on the market. Because of the difficulties for preclinical research to become a drug, the gap between the traditional finishing point of research supported by an academic grant, and the sort of programs industry is interested in licensing or venture capitalists are prepared to back through a startup is usually called as “the valley of death” (Moran, 2007).

2.2.3 Clinical R&D -- Phase I, II, III Trials

Until now, all research has been conducted outside human bodies. However, no one can ensure whether the drug candidate can be delivered correctly and against the

human diseases, as the way it worked in the animal model. The answer of the question comes from years of researches in thousands of patients and healthy people. In order to pursue human studies, the first criterion is that the drug candidate must be produced under current good manufacturing practices (cGMP). Secondly, a sponsor must first submit an Investigational New Drug (IND) application to the FDA to justify testing a drug in humans. There are four phases of clinical trials. Phases I through III is to demonstrate safety and efficacy prior to approval, whereas Phase IV is to monitor safety post-approval and tests new treatment indications. The function of each stage in the clinical trial is discussed below.

PHASE I TRIALS

Beyond the purpose of finding the component that treats disease effectively, the primary consideration in drug discovery process ought to be the safety of the medicine takers. The Phase I trial is usually conducted in a small group (20-50) of normal, healthy volunteers to determine the safe dosing range and toxicity of a compound and study the clinical pharmacological mechanism, such as drug absorption, distribution and metabolite in human bodies. This phase usually takes an average of one to three years. Once Phase I trials do not reveal unacceptable toxicity, it is allowed to proceed to Phase II trial.

PHASE II TRIALS

The purpose of Phase II trial is to further evaluate a drug's safety, assess side effects, and establish dosage guidelines. The well-controlled experiment is usually conducted on a larger number of volunteers (about 100 to 300 patients), who have the medical condition that the product is intended to treat, in order to establish the range of minimal effective dosage, maximum tolerable dosage, and optimal dosage. Phase II trial

usually takes an average of two years. If Phase II trials indicate effectiveness, a drug can proceed to Phase III trials. Generally, a drug that moves on to Phase III trials has an approximately 60 percent chance of being approved by the FDA.

PHASE III TRIALS

Phase III is the largest and most expensive stage in the clinical trials. The purpose of Phase III trial is to continue the development of safety profile and the record of possible side effects and adverse reactions that result from long-term use. Phase III trial is a tightly controlled, and preferably double-blind, study that is usually conducted on at least 1,000 patients. In double-blind studies, neither patients nor the individuals treating them know whether the active drug or an alternative such as placebo is being administered. Compared to Phase I and Phase II trials, the larger and ideally more diverse populations used in Phase III trial are necessary to determine the condition where certain types of patients develop side effects or do not respond to treatment. Two successful Phase III trials are usually required to ensure the validity of the studies. The whole process usually takes an average of three to four years.

Overall, the process of clinical trials is a considerable challenge to potential drugs. Rushing each stage may require the entire repetition or lead to outright failure. It also takes vast amount of money and an average of 6.5 years to carry out three phases of clinical trials. Once a drug reaches the desirable end point in Phase III trials, the result of all stages will be filed a New Drug Application (NDA) or Biologics License Application (BLA) which are then assessed by the health organizations that decide whether to approve or reject the marketing of the drugs.

2.2.4 NDA and BLA Review & Approval

NDAs describe small molecule therapeutics, whereas BLAs cover therapeutics applications of big molecule such as antibodies, growth factors and protein-based drugs. Both applications are submitted to the Center for Drug Evaluation and Research (CDER). Following NDA/BLA submission, a drug has a better than 70 percent chance of being approved. However, approval of an application can take anywhere from two months to an extreme of several years, if the FDA requests additional information. Fortunately, the Hatch-Waxman Act permits day for day recovery of patent life for time spent waiting for FDA approval (Federal Trade Commission, 2002, pp. 3-8). Following FDA approval, a company may market and distribute a drug to the patient population determined in Phase III trials. At this point, the lifespan of the patent that was filed sometime before clinical trials began often ranges from 8 to 12 years. After that, the patent protection will expired, and the numerous entries of generic manufacturing companies decrease the profit margin of the drug.

On the other hand, the cases of disapproval usually come from the inauthentic discussion in the applications to FDA. The company with the disapproved drug can decide whether it is worth running new trials and seeking approval again. Alternatively, the company can sell it to another company, or ally with a partner to share the risk and future revenue.

2.2.5 Drug on the Market & Phase IV

Phase IV trial is also known as Post Marketing Surveillance Trial. As the drug on the market would be prescribed to larger and more diverse populations, the company

must continue to perform observational studies in an ongoing evaluation of the drug's safety during routine use. The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I to III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses: recent examples involve Baycol and Lipobay from Bayer AG (Barmen, Germany), Rezulin from Daiichi Sankyo Co.(Tokyo, Japan) and Vioxx from Merck (New Jersey, US) (Bayer Corporate Investor Relations, 2001; Johnson & Winslow, 2008).

In summary, the combination of long lead-times from discovery to NDA/BLA approval, the high probability of failure for drug candidates entering clinical testing, and the unpredictability of sales once a product is marketed creates a risky business environment. Decisions to fund clinical trials are critical to economic success, and the stakes increase substantially as drug candidates move through each successive clinical phase. Due to the frequent licensing transactions and alliances throughout the drug discovery process, it is complicated to sum up the total expenditure on drug discovery. According to the study entitled "The price of innovation: new estimates of drug development costs", the average capitalized costs of bringing a new drug, or more precisely a new chemical entity (NCE), to market was US$ 802 million in 2000 dollars, while some studies argue that the estimate was likely to be conservative (DiMasi, Hansen, & Grabowski, 2003; Frank, 2003).

Considering the distinct nature and manufacturing process of chemical entity from biologic drug, the cost of an approved biopharmaceutical would be different. Some argue that biologics are less costly to develop because bio/pharma firms need to be more nimble

and creative or that fewer safety issues arise for many biologics because they replace substances that exist naturally in the body. However, some industry insiders estimate that the cost per approved biologic drug exceed $1 billion (DiMasi & Grabowski, 2007). The study named “The cost of Biopharmaceutical R&D: Is biotech different?” shows that the estimated total capitalized cost per approved biologic was about US$1241 million in 2005 dollars. Adjusted by the past growth rates for pharmaceutical company costs, the cost was nearly the same as that of a new chemical entity -- US$1241 million versus US$1318 million in 2005 dollars (DiMasi & Grabowski, 2007). Once the drug is approved and released into market, the major revenue comes from the price and sales volume of the drug. Therefore, to ensure a certain payoff, bio/pharma firms usually need to expend another huge cost of marketing and distribution.

On the other hand, given the patent protection, the bio/pharma company usually can monopolize the market of the medicine, resulting in the emergence of blockbuster drugs (drugs that generate more than US$1 billion of revenue for its owner per year). As shown in Table 2.1, the payoffs of the leading blockbuster drugs were billions of US dollars per year (EvaluatePharma, 2008; Wikipedia, July 2009). The high up-front cost and the lion’s share of investment, turnover and sales, combined with the necessity of medicine, make the bio/pharma an interesting, risky and indispensible industry

Table 2.1 The annual sales of leading blockbuster drugs

Trade name/ Medication	Company	Sales (USD in billions)	Year
Lipitor (atorvastatin)	Pfizer	12	2007
Plavix (clopidogrel)	Bristol-Myers Squibb and sanofi-aventis	5.9	2005
Lovenox/Clexane (enoxaparin)*	sanofi-aventis	3.5	2007
Nexium (esomeprazole)	AstraZeneca	3.3	2003
Losec/Prilosec (omeprazole)	AstraZeneca	2.6	2004
Celebrex (celecoxib)	Pfizer	2.3	2007
Telfase/Allegra (Fexofenadine)	Aventis	1.87	2004
Seroquel (quetiapine)	AstraZeneca	1.5	2003
Seloken/Toprol (metoprolol)	AstraZeneca	1.3	2003
Pulmicort/Rhinocort (budesonide)	AstraZeneca	1.3	2003

Source: Wikipedia, July 2009

Chapter 3 Strategic R&D Alliances in the Globalizing Bio/Pharma Industry

As discussed in the previous chapter, it is unlikely for a Big Pharma to complete the process through drug discovery to marketing all alone, not to mention the smaller bio/pharma companies. From the constant restructuring and transaction, the need of external R&D resources in the bio/pharma industry seems very straightforward. However, due to the multifarious operational activities, literature usually focuses on a part of drug discovery chain. In the following section, the demands and reasons of bio/pharma companies' strategic R&D alliances are analyzed based on recent news and studies.

3.1 The demand of bio/pharma companies' strategic R&D alliances

3.1.1 Expending the early-stage R&D resources

As the progressive discovery in the human genomics and molecular biology, the number of identified pathological mechanisms and factors has increased dramatically in these decades. To dig out the potential therapeutic targets and develop drugs, not only Big Pharmas have expanded their R&D departments, but also more and more start-up bio/pharma companies holding their research expertise have committed themselves to new drug discovery. According to the information from consulting firm Frost & Sullivan (New York, USA), as cited in Gwynne (2002), the US bio/pharma companies held around 75,000 new drug projects in the year of 2002. It suggests that the bio/pharma industries had vital R&D activities and attempted to increase the efficiency and productivity of drug discovery at that time.

However, as the saying goes, “the lower hanging fruits would be picked sooner.” The process of new drug discovery now is not always as smooth as that was decades ago. According to the data from the Centre for Medicines Research International, a business of Thomson Reuters information company (New York, USA), while both the averages of global R&D expenditure and development time were increasing, the number of new drugs that reached the market actually declining year by year. In 2007, the amount of new molecular entity (NME) output was only 50% of that in 1997 (Figure 3.1; Harris, 2009). In the circumstances, the in-house R&D facility of the bio/pharma companies is no longer efficient or productive enough to full up their pipelines -- the lifeblood of bio/pharma companies. In other words, bio/pharma companies need the external R&D resources to enhance their competitiveness.

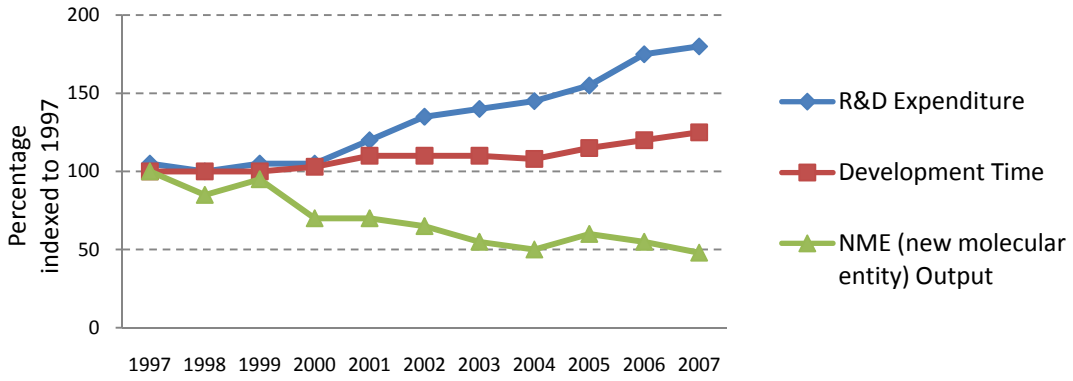


Figure 3.1 Global R&D expenditure, development times and new molecular entity output (1997-2007)

Sources: Centre for Medicines Research International, as cited in Harris, 2009

During the 2008 economic downturn, it was surprising that many Big Pharmas had goodish financial performance. Pfizer, for example, showed only 0.2% decrease in revenues and 0.4% decrease in net income (Pfizer Inc., 2008). Likewise, although Merck had a 1.4% decrease in revenues, its net income in 2008 was actually twice as much as

that in 2007 (Merck & Co., Inc., 2008). The attractive figures of their net income, however, do not mean that these Big Pharmas were not affected by the bad economy. In fact, in the latter part of 2008, many companies cut down the expenses from the sales facilities and in-house R&D teams. For example, through the broader company-wide restructuring plan that caused the major part of the doubled net income, Merck cut 6,800 employees and 400 vacant positions in all areas of the company. The large scale layoff was listed as the top 5 layoffs of 2008 (Martino, 2008). As it is said, "an evil chance seldom comes alone," during the JP Morgan event, Pfizer laid off 800 of its R&D researchers in a tacit admission that its laboratories have failed to live up to the tens of billions of dollars it has poured into them in recent years (Rockoff, 2009). As shown in Figure 3.2, the number of the bio/pharma layoffs has kept above 15,000 per year since 2003 (Simon, 2007).

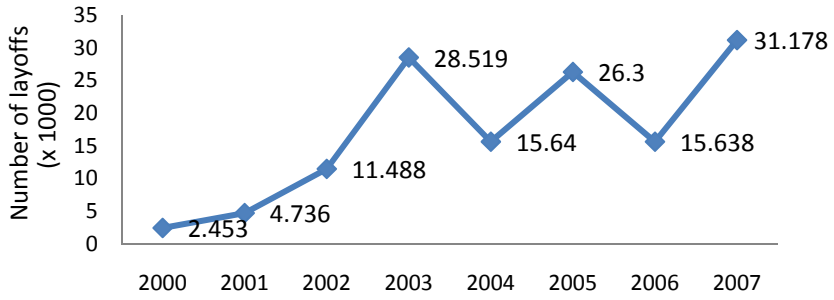


Figure 3.2 Announced job cuts in the bio/pharma industry (2000-2007)
Sources: Simon, 2007

In brief, while Big Pharmas showed strong financial performance under the economic crisis, they actually trimmed off the personnel expense of R&D and sales forces to save the profit margin. The structural changes of cutting in-house R&D also

suggested the weightiness of acquiring external R&D resources.

To small-medium bio/pharma companies, the current condition is even tougher. Due to the credit crisis, banks have run out of lending money, hedge funds as well as private equity investors have shut up shop, and the public equity markets spiraled into a free fall. The barren financing resources have made it very hard for the biotech companies to run their business. A statistics from Biotechnology Industry Organization, Washington DC USA, shows that 180 quoted US biotech companies have less than one year's cash in hand, and 120 of which have less than six months' breathing space (as cited in Mitchell, 2009).

In respect of the core competency of Big Pharmas is the unfailing supply of their pipelines, the current undervalued small-medium biotech companies provide the opportunities for Big Pharmas at bargain prices to acquire the external R&D facility. The recent sensational news of Roche's (Switzerland-based Big Pharma) aggressive acquisition of Genentech indicated that the Big Pharma is thirsty for the biotech R&D. Through this large purchase of the biotech giant, Roche successfully expended its R&D territory to the biologics and also filled its pipeline (CTV News, 2009; Jucca & Cage, 2009). Another example is that Johnson & Johnson (New Jersey, USA) acquired a New York- based bio/pharma company, Omrix, gaining access to the innovation of biosurgical and passive immunotherapy products at the year end of 2008 (Johnson & Johnson, November 2008; Carroll, 2008). Both cases show the Big Pharmas' eagerness to build up the biotech part of their business. The frequent acquisition and merger also indicated that the external R&D is critical to strengthen Big Pharmas' competitiveness.

3.1.2 Blockbusters' Patent Protection has expired

Besides the foresight of filling the pipelines, the major reason to obtain the external R&D innovation is that many splendid blockbusters have lost their patent protection recently, or will lose it soon (GlaxoSmithKline Inc., 2008). Lipitor, for example, the prescription of cardiovascular disease that brings Pfizer (New York, USA) billions of revenue every year, will lose its exclusivity in 2011. To meet this tough challenge, Pfizer has implemented a series of business restructuring, such as the purchase of Wyeth and the settlement with a generics manufacturer that produced and sold the generic vision of Lipitor (Pfizer Inc., 2008). Other Big Pharmas are also experiencing the intense pressures of the replacement of the million-dollar drugs with products of equivalent financial size. As a global leading pharma, Eli Lilly and Company (Indiana, USA) also faces the loss of market exclusivity of its best-selling drugs, such as Zyprexa and Cymbalta for neuroscience treatment and Gemzar for the treatment of non-small cell lung cancer (Eli Lilly and Company, 2008). In late 2008, Eli Lilly paid US$6.5 billion for ImClone Systems, a mid-size biotech with a colorectal cancer therapy called Erbitux. According to the Eli Lilly's announcement, the acquisition of ImClone Systems would not only boost oncology pipeline with up to three promising targeted therapies in Phase III in 2009, but also bring in ERBITUX, a blockbuster targeted cancer therapy (Eli Lilly and Company , October 2008; Kennedy, 2008).

3.1.3 The tendency toward personalized medicine

Today, most physicians, even in the United States, still rely on the trial-and- error "standards of care" where the doctor makes a "most likely" diagnosis based on a patient's symptoms and prescribes a drug or other treatment. Many drugs, particularly for mass-

market conditions, somehow are not as efficacious as that reported in the standard protocol. According to the statistics from Physicians' Desk Reference, 54th Edn., 2000 (as cited in Spear, Heath-Chiozzi, & Huff, 2001), the standard drug treatment provides a therapeutic benefit only to a limited percentage of patients who receive it, especially in the area of cancer therapy, where the major drugs show only 25% of efficacy rate (Figure 3.3). The statistic does not mean that the drugs themselves are inefficacious. Instead, it suggests the need of personalized medicine approach, by which doctors can take into account patient's unique physiology and increase the cure rate of treatment (Aspinall & Hamermesh, 2007).

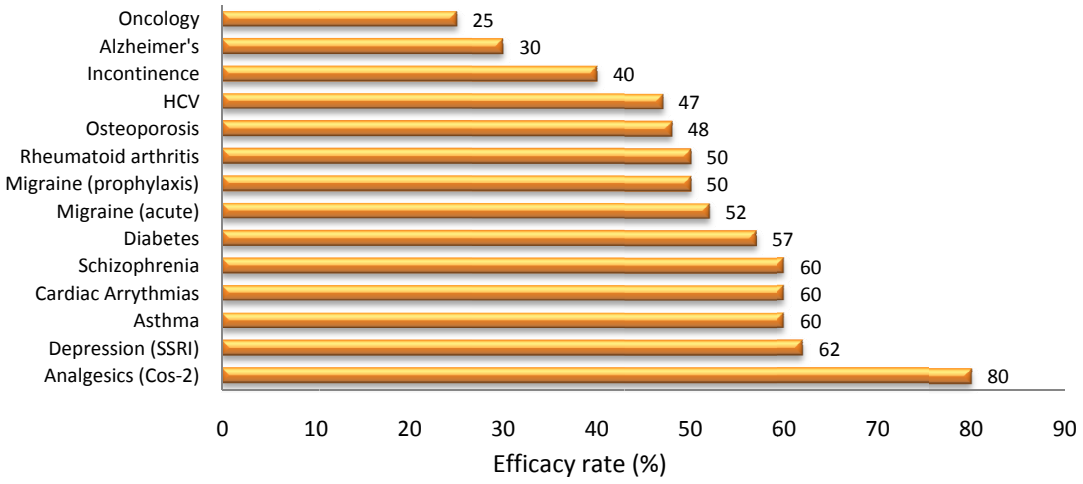


Figure 3.3 Response rates of patients to a major drug for a selected group of therapeutic areas

Source: Aspinall & Hamermesh, 2007

Instead of conducting additional clinical trials for new and improved drugs, the personalized medicine concept actually provides bio/pharma companies a more profitable way to expand their business. Through combining diagnostics with therapies, bio/pharma companies can actually improve sales by helping physicians find the most appropriate

therapeutic option. For example, AstraZeneca (London, UK) had developed Entocort EC and launched it in the United States in 2001. Entocort EC is a drug with the efficacious treatment for the Irritable bowel syndrome (IBD), a hardly diagnosed gastro-intestinal disorder. With the high efficacy, the sales of the drug, however, were only US$25 million by 2003 (Wilmington, 2001). AstraZeneca then out-licensed the drug to Prometheus Labs, a San Diego-based specialty pharma. To improve the revenue of Entocort EC, Prometheus Labs did not expand its sales force for this drug; instead, the company developed an accurate diagnostic test to help physicians distinguish IBD from other similar diseases and largely promoted the diagnostic test. With the promise diagnostic, as well as the efficacy of the drug, Prometheus did not only achieve a much bigger sales number of Entocort EC, but because of the increasing demand, the company was also able to raise the average wholesale price of this drug by 66 percent upon traditional models. Figure 3.4 shows how the alliances between diagnostics and therapeutic areas improve the sales of drugs. As discussed above, the sales of Entocort EC was improved from 9% to 59% by the launch of IBD diagnostic test. The sales of Niaspan, a treatment of hypercholesterolemia, similarly, was increased twice by combined the selling of low density lipoprotein (LDL) subfractionization test. The MRI contrast agent also reformed the traditional trial-and-error practice and improved the diagnosis of multiple sclerosis (MS); as a result, Viveo, a treatment of MS, was projected to grow at 40% compared to 7% projected increase in sales of its generics (Figure 3.4; Agarwal, 2009).

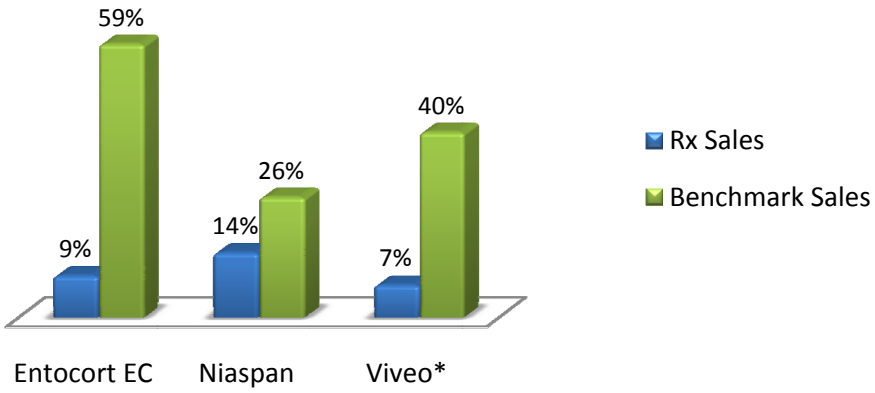


Figure 3.4 The comparison of revenue from therapeutics bundled with diagnostics and that from other drugs in the same therapeutic area.

Source: Agarwal, 2009
** See footnote*

3.1.4 More difficult to get FDA approval

Another reason for the compact R&D network in the pharmaceutical industry is the heavy financial load of clinical trials. In contrast to Big Pharmas that have integrated systems to run the clinical trials, many bio/pharma companies solely focus on the preclinical stage of the drug development. One big challenge to these small-medium companies is the complicated and costly procedures of clinical trials. As discussed in the previous chapter, the required amounts of volunteers and expenditures raise multiply through Phase I to Phase III of clinical trials. Some companies may have the financial abilities to conduct Phase I and Phase II trials, whereas Phase III trial is usually too expensive, time-consuming and difficult to run by most of small-medium bio/pharma companies. In addition, to reduce the risk of releasing unsafe drugs to the market, FDA has increased the height of the regulatory hurdles for new drug approval. As a result, it

* Viveo sales were based on equity analysis projections
Rx Sales: Sales from therapeutics bundled with diagnostics
Benchmark Sales: The average of sales from other drugs in the same therapeutic area

becomes much harder for bio/pharma companies to complete the flawless clinical trials.

In the study entitled “Drug approvals and failures: implications for alliances”, Czerepak and Ryser (2008) analyze the origins of drugs approved by the FDA and those failing in Phase III trials during the period January 2006 to December 2007. As shown in Figure 3.5, while 65% of FDA approvals were originated from biotech companies, only 45% were developed by the biotech company all alone. In addition, up to 74% of the cases that failed in Phase III trial were from biotech companies, 21% were from biotech-pharma alliances, and only 5% were from pharmaceutical companies. The study suggested that biotech-pharma alliances may not contribute to as many approved novel drugs as the biotech industry but had significantly fewer failures. In addition, the study also shows that the biotech companies’ high disapproval rate resulted from their poor-quality of NDA submissions rather than the flaws in the drugs (Czerepak & Ryser, 2008).

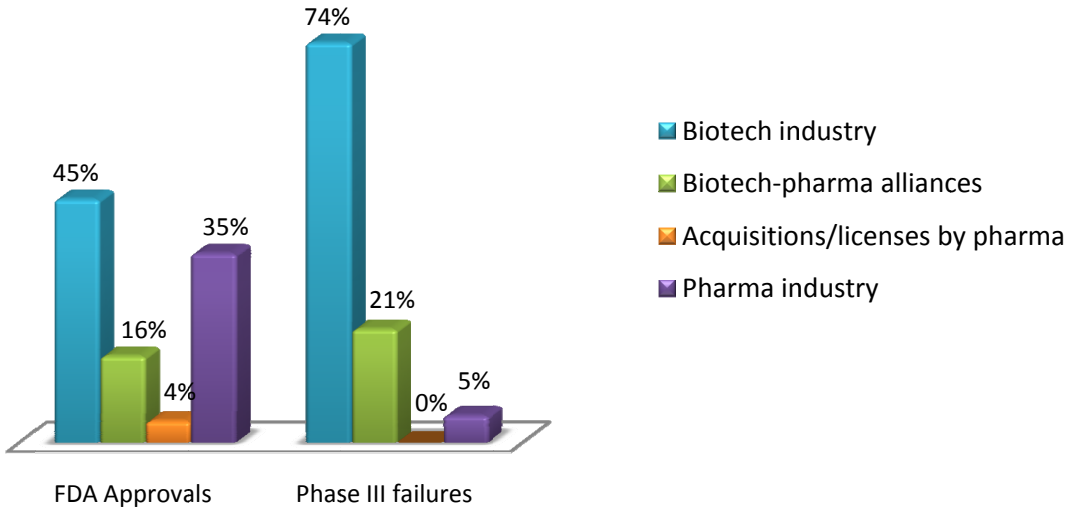


Figure 3.5 The percentage of FDA approved and Phase III failed drugs developed by different degrees of R&D alliances: Biotech only, Biotech-Pharma alliances, Acquisitions or licences by pharma, and Pharma only

Source: Czerepak & Ryser, 2008

Therefore, by partnering with Big Pharmas, the small-medium biotech companies could improve the quality of clinical research and NDA submission (caused by the lack of experience and funding); on the other hand, Big Pharmas also gain the access to the "fallen angel" products, which have high-potential to be approved by FDA with complete trial designs. Especially in the cases of biological drugs, it is usually hard to meet the primary end-points through the clinical trials in one indication, whereas trials in other indications have been successful (Sabo, 2003).

The growth of specialized contract research organizations (CROs) has also encouraged the collaboration within the pharmaceutical industry. Instead of restricting themselves to performing clinical trials of potential drugs, the current CROs have broadened their business scale to preclinical research. According to the clinical-trials information company Thomson Center Watch (MA, USA), as cited in Shuchman (2007), CROs played a substantial role in phase I, II, and III clinical studies in 2003 for about $7.6 billion in contracts, as compared with $1.6 billion in 1993 (Figure 3.6).

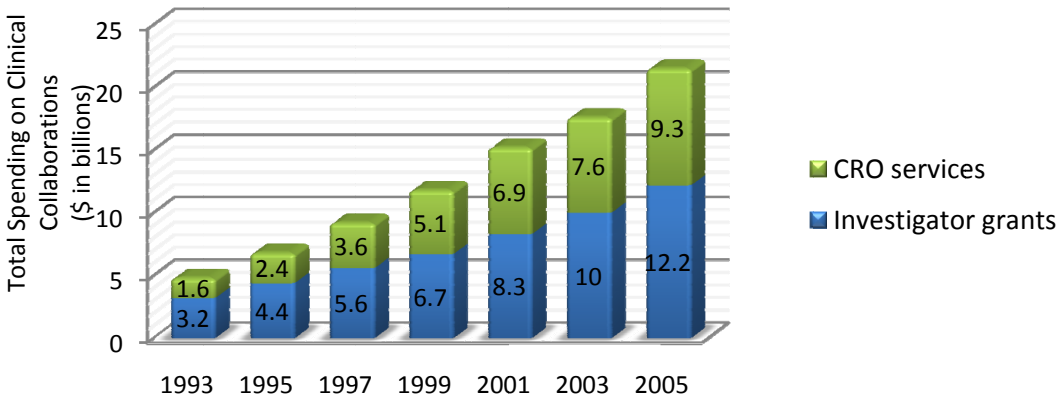


Figure 3.6 Total Spending on Clinical Collaborations by Member Companies of the Pharmaceutical Research and Manufacturers of America

Source: Thomson Center Watch, as site in Shuchman, 2007

Thus, it shows that in the bio/pharma industry, outsourcing knowledge intensive activities to knowledge process organizations, such as CROs, serves a way to reduce innovation process obstacles. In the article named "Diffusing knowledge-based core competencies for leveraging innovation strategies", Gupta et al. (2009) explore the relationship between bio/pharma companies and CROs, and then pointed out that multinational bio/pharma companies usually lose their core competencies over time and become dependent on CROs' expertise, and that CROs obtain the opportunities of knowledge sharing and learning from their pharmaceutical company partners (Gupta, Woodside, Dubelaar, & Bradmore, 2009).

3.2 The advantages & disadvantages of R&D alliances

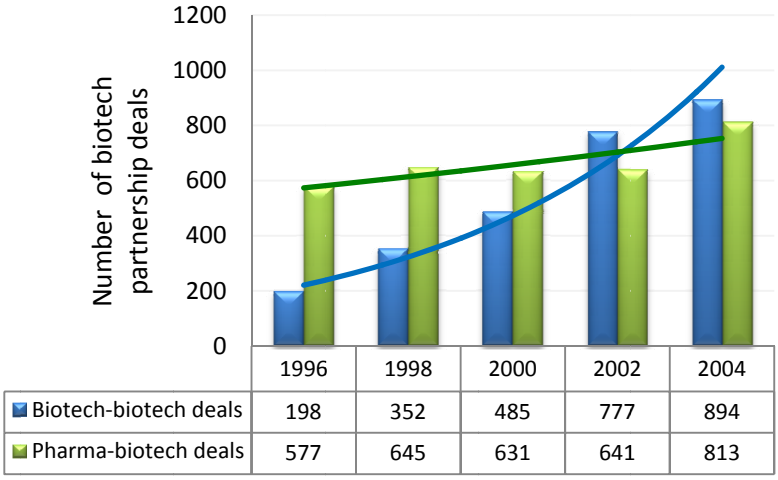
A number of factors have made it preferable for biotech companies to specialize in discrete elements of the product development pathway. As a result, bio/pharma companies need the consistent collaboration to acquire the complementary services, technologies to enhance the competitiveness. According to Deutsche BankAG estimates and company information (as cited in Mittra, 2007), an average of 30.5% of mid-late stage of R&D in the European bio/pharma sector was from external resources in 2004 (Table 3.1).

Table 3.1 Big Pharmas' mid/late-stage R&D pipelines

Company	*Phase II*	*Phase III*	*Filed*	*Internal candidates*	*External candidates*	*% External*
GSK	34	4	5	31	12	28
Sanofi-Aventis	20	11	7	30	8	21
Novartis	15	9	3	17	10	37
Roche	9	4	10	13	10	43
AstraZeneca	8	2	2	9	3	25
Average	17.2	6	5.4	20	8.6	30.8

Source: Mittra, 2007

In the same article (Mittra, 2007), moreover, the data from Recombinant Capital showed that the number of deals in both biotech-biotech and pharma-biotech partnership was increasing year by year (Figure 3.7).



	1996	1998	2000	2002	2004
Biotech-biotech deals	198	352	485	777	894
Pharma-biotech deals	577	645	631	641	813

Figure 3.7 The number of strategic alliance and collaboration deals between traditional pharmaceutical and emerging biotechnology companies

Source: Recombinant Capital as cited in Mittra, 2007
[*]See footnote

As the gradual awareness of R&D collaboration, the strategic motives for alliance formation have been a growing theme among the literature of bio/pharma companies' partnership and alliance (Audretsch & Feldman, 2003; Chang, 2008). However, other transaction means, such as merger and acquisition (M&A), in-licensing technology and outsourcing, also provide various strategic options for managing innovation and productivity deficit. Therefore, in the following two sections, I will discuss about how bio/pharma firms manipulate these transactions, and analyze the advantages and disadvantages of strategic alliance for both Big Pharmas and small-medium bio/pharma companies.

[*] The blue curve the trend of the increasing biotech-biotech partnership deals; the green curve shows the trend of the increasing pharma-biotech partnership deals

3.2.1 Advantages of R&D alliances to bio/pharma firms

While only the big M&A is most likely to jump to the front page of news, other types of transactions in the bio/pharma industry also show the various business strategies to capture and exploit new technologies and knowledge. Instead of the full-control over another company, licensing is the most common strategy for bio/pharma companies to reach the existing technologies and products from outside. As cited in Mirasol (2008), the Bio/Pharma R&D Statistics from PAREXEL, an U.S.-based pharmaceutical services group, showed that fully one third of the pipelines for the top 10 bio/pharma firms (by total numbers of products in development) comprised in-licensed products (Table 3.2).

Table 3.2 The percentage of in-licensed products in Biotech firms' and Pharmas' pipeline

Company	% of pipeline in-licensed
Leading Biotech Companies by pipeline size (as of March 2008)	
Amgen (US)	25%
Genzyme (US)	33%
Genentech (US)	50%
Leading Pharma Companies by pipeline size (as of March 2008)	
GlaxoSmithKline (UK)	34%
Pfizer (US)	24%
Novartis (Switzerland)	34%
Merck (US)	30%
Roche (Switzerland)	46%
Johnson & Johnson (US)	45%

Source: PAREXEL as cited in Mirasol, 2008

While the late-stage licensing agreements feed the short-term needs of the bio/pharma industry, such as bulking up pipelines or filling strategic gaps, to energize R&D and strengthen companies' competitiveness in the long run, the early-stage drug

discovery collaboration is more fundamental. Moreover, R&D alliances provide alternatives with a degree of flexibility, cost advantage and/or risk-sharing to approach the external R&D expertise (Jones & Clifford, 2005).

As many small bio/pharma companies and academia now have the abilities to identify and discover new drugs, Big Pharmas no longer monopolize the facilities and technologies. Therefore, through the proactive strategic alliances with bio/pharma companies, as well as academia, Big Pharmas could reinforce the upstream R&D innovation. GlaxoSmithKline Inc. (London, UK), for example, has cooperated with organizations such as Cellzome and the Harvard Stem Cell Institute to strengthen their early-stage R&D. In this 5-year, $25 million research agreement, GSK will fund research at the Harvard Stem Cell Institute (HSCI) and Harvard Medical School- affiliated hospitals, and support the annual basic research grants and staff exchange programs. The collaboration showed that both academia and pharmaceutical companies perceive the need of mutual dependence. Furthermore, GSK completed or expanded 21 new drug discovery alliances in 2007, adding significant breadth and scale to its R&D activities (GlaxoSmithKline Inc., 2008). By the same token, Pfizer, Novartis and AstraZeneca have strategically collaborated with the likes of the University of California in San Francisco, the Massachusetts Institute of Technology in Boston and Washington University in St. Louis (Huggett, 2008). As cited in Jones and Clifford, 2005, the data from Ernst & Young, one of the largest professional services firms in the world, shows the Pharma-biotech discovery alliance and acquisition highlights in 2005, where the most significant deals of bio-pharma were the AstraZeneca's monoclonal antibody alliance with Cambridge Antibody Technology and the Pfizer's US$480-million collaboration with Medarex

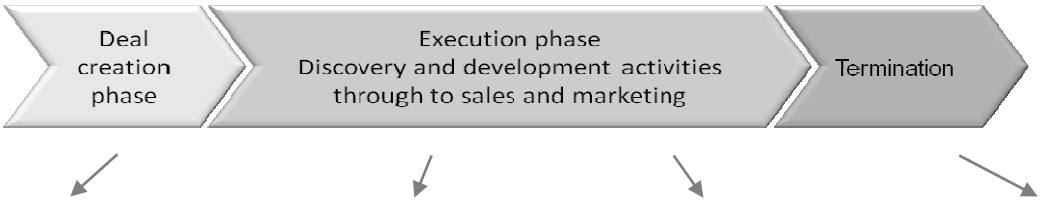
(Jones & Clifford, 2005).

On the other hand, small-medium bio/pharma companies are usually resource-constrained -- they may afford the one- or two-year operations without further financial supports (Huggett, 2008). As mentioned above, many of the small-medium bio/pharma companies have experienced the tough condition of credit crisis where these companies are short for financial resources and even disfavored by the current stock markets. Therefore, rather than develop new R&D from scratch, the small-medium bio/pharma companies should focus on the individual relative strength and core competence, and collaborate with each other to achieve their goals more quickly and inexpensively than otherwise possible. In addition, by partnering with established companies, research-intensive firms obtain the resources of marketing, distribution and sales, and thus gain the direct benefits. To stress the impact of small-medium firms' alliance network on their early performance, Baum et al. (2000) analyze the horizontal alliances with other biotech firms and vertical alliances with pharmas and research institutes of 142 Canadian biotech companies. The result suggests that it is critical for small-medium firms to enhance their initial performance by establishing alliances, configuring them into an efficient network that provides access to diverse information and capabilities with minimum costs of redundancy, conflict, and complexity, and/or allying with established rivals that provide more opportunity for learning and less risk of intra- alliance rivalry (Baum, Calabrese, & Silverman, 2000).

3.2.2 Disadvantages of R&D alliances to bio/pharma firms

Despite their strong rationale and widespread use, strategic alliances are somehow unstable and have low success rates. The study named "Instabilities of strategic alliances:

An internal tensions perspective", shows that only about half of the alliances are stable or achieve satisfactory performance (Das & Teng, 2000). As the strategic alliances are voluntary arrangements between firms to exchange and share knowledge as well as resources with the intent of developing processes, products, or services, the mutual understanding and compatibility between partners are crucial to the alliance performance. Past research has identified several factors that would affect alliance outcomes, such as goal congruence, inter-partner trust and conflict, flexibility in management, information exchange and firms' prior alliance experience (Bleeke & Ernst, 1991; Glaister & Buckley, 1998; Gulati, 1998; Hagedoom & Schakenraad, 1994; McCutchen Jr., Swamidass, & Teng, 2008; Stuart T. , 2000). In the article entitled "Minimizing leakage of value from R&D alliances", Jones summarized the risks in alliance, and categorized the risks into four groups in terms of the impacts on financial, knowledge, reputation and strategic in the alliance life cycle. In Figure 3.8, the chart illustrates the risk factors and value leakage during the alliance life cycle (Jones, 2007). At the beginning of alliances, the potential risks would result from how the deals are made, the communication with stakeholders and return on investment (ROI) assessment. During execution, the financial risks and companies' reputation would become the major concerns to the management teams, such as the payment for milestones, the management of costs and overall performance, and the contractual disputes. The risks in the termination phase would involve the timing of termination that causes the loss of value or increases costs. Furthermore, the management of the partnership and the protection of intellectual property are the core of R&D collaboration and pose serious risks throughout the life cycle of strategic alliances (Figure 3.8).



Deal creation phase	Execution phase: Discovery and development activities through to sales and marketing	Execution phase: Discovery and development activities through to sales and marketing	Termination
Failure to secure the right deals: • Deal search suboptimal/missed opportunities • Breakdown in link between deal rationale and corporate strategy • Unattractive partnering offering relative to peers	**Overpayment for milestones:** • Contract weakness, for example, poorly defined milestones • Reporting errors • Fraud	**Reputation/litigation risk arising from third-party compliance failures:** • Conduct of clinical trials • Sales and marketing practices Manufacturing and supply chain • Pharmacovigilance responsibilities	**Loss of value due to early termination by one partner (catastrophic failure, change of strategy, acquisition)**
Failure to secure deals at a competitive price and terms: • Out of step with marketplace • Poor negotiation skills • Flawed valuation methodology	**Higher than anticipated costs:** • Poor project planning • Delays in execution • Cost management	**Fraud, for example, in reporting – impact on business planning and decision-making:** • Project costs incurred • Project progress/milestones • Outcomes and sales performance	**Lock-in clauses prevent timely termination and increased costs**
Failure to communicate value to stakeholders: • Lack of investor buy-in • Impact on confidence/share price • Lack of buy-in internally	**Lack of effective operating procedures:** • Delays in project execution • Increased costs • Flawed decision making	**Contractual disputes:** • Royalty/milestone disputes • IP disputes • Failure to meet best endeavour terms	**Disputes arising from failure to cease activities on contract**
Flawed due diligence and ROI assessment: • Upfront/milestone payments set too high • Misinterpretation of IP position • Unidentified risks	**Unaligned agendas:** • Conflicts of interest • Slow progression • Disputes	**Lower than anticipated revenues:** • Poor forecasting (methods/information) • Suboptimal operational management • Failure of partner to co-promote effectively	**Higher than average attrition rates for compounds sourced externally**
Leakage of IP and know-how: • Leakage of IP • Loss of knowledge/data • Loss of talent and know-how	• Ineffective communication and knowledge sharing: Inadequate information sharing systems Inadequate security over shared systems Inaccurate reporting of data/errors in 3rd party data	• Patent disputes with parties external to alliance	
Failure to manage alliance network effectively: • Inconsistent decision making (processes, data, metrics) • Lack of effective governance structures/ processes	• Gaps in portfolio/misalignment of portfolio composition and strategy	• Resource allocation does not match resourcing needs	

Figure 3.8 Risk factors and value leakage during the alliance life cycle.

Financial risk: the direct financial loss; the lower than expected return on investment
Strategic risk: the impediment to corporate strategy
Reputation risk: the negative effect on reputation
Knowledge risk: the leakage of commercial sensitive information or intellectual property

Source: Jones, 2007

3.3 Globalization of bio/pharma industry

Because the whole value chain is built on knowledge and technology transfer, it is evident that bio-pharma is a knowledge-intensive industry. The examples discussed in the previous section present that most of the business transaction and R&D cooperation in this industry are concentrated in North American and Europe, especially the biotechnology sector -- one of the most science-intensive forms of activity in the contemporary economy. According to the statistics of the worldwide distribution of biotech firms, conducted by Organization for Economic Co-operation and Development (OECD) in 2006, European Union and the United States are the top two regions where there are the most biotech companies, followed by Japan and France. The statistics also show that over 50% of the biotech companies in the world locate in those top two regions (Figure 3.9; Beuzekom & Arundel, 2006).

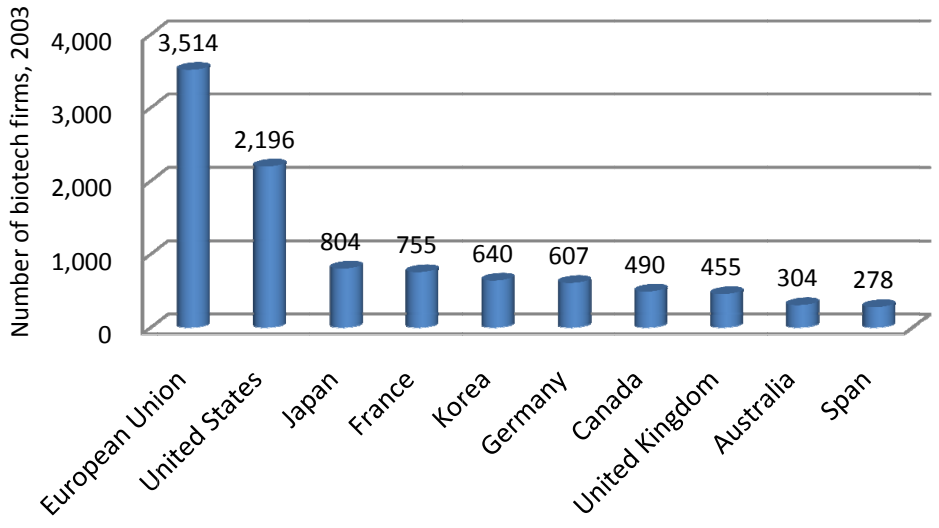


Figure 3.9 Leading Bio/Pharma industries in the world by the number of bio/tech firms
Source: Beuzekom & Arundel, 2006

Unsurprisingly, the knowledge-driven sectors are usually centralized in those developed countries. Some studies about the R&D collaboration argue that these knowledge-intensive activities are usually highly geographical concentrated because geographical concentration of the relevant actors will facilitate the process of learning-by-interacting, given the premise that innovation as an activity has become increasingly interactive and socially organized (Gertler & Levitte, 2005).

In the case of biotechnology, this pattern of spatial concentration seemed to be strong and, if anything, becoming stronger rather than weaker over time. The most notable announcement in May 2002 that Novartis was moving its research operations to Cambridge, Massachusetts may be a good example for the argument of geographic concentration. According to industry analysts, the company's decision to invest in Cambridge was motivated by the concentration of the life science expertise in the Boston area, such as the university and hospital researchers who are the key producers of potentially commercializable intellectual property, the rapidly growing biotech companies as potential partners in collaborative research, and the graduates from MIT and Harvard and other world-renowned institutions (Dyer, 2002).

Access to venture capital (VC) is another key factor emerging from prior research on innovativeness and performance in biotechnology. Only the firms with sufficient access to 'patient and knowledgeable' capital who can recognize the special characteristics of bio/pharma industry, such as the large up-front costs associated with multi-year R&D processes followed by expensive regulatory reviews and trials, have the managerial and financial resources available to realize their innovation goals. Many literatures suggest that the geographical distribution of VC available for biotech firms is

also highly concentrated. In the article entitled “Signs of Life: The Growth of Biotechnology Centres in the United States”, Cortright & Mayer (2002) report that since 1996, 75 percent of new VC investment in the USA has been located in the five largest biotech clusters, including Boston, San Francisco, San Diego, Seattle and Raleigh-Durham. In a research about biotech firm-venture capital relationships, Powell, Koput, Bowie, & Smith-Doerr (2002) also find that over 50 percent of biotech firms receive local VC support. This phenomenon may be partly explained by the risky nature and lengthy time horizon of investments in bio/pharma companies: reaping the fruits of such investments may take years. Therefore, most of the studies about R&D collaboration in bio/pharma industry usually focus on the exchange of information, the joint sponsoring of research activities and the management of performance between the United States and the European Union, whereas very little information is available for the global spread of health biotech alliances and the extent to which the linkages cross the boundaries between developed and developing countries (Aguilar, Bochereau, & Matthiessen-Guyader, 2008; Melon, et al., 2009).

In fact, however, the current trend of the gradual shift of global marketplace and business activities toward the developing world should not be ignored. In the article named “Pharma riding high?”, Stephen Burrill, CEO of Burrill & Co, a global life science industry-investing company, points out the current changes and pressures that bio/pharma companies have faced since the economic downturn in 2008. He then claims that the business models in this industry will evolve more virtually, and bio-clusters will move away from being geographic to being more globally built around diseases, pathways, markets and unique industry segments (Eisberg, 2009). In a study about spatial clustering

of economic activity and its relation to the spatiality of knowledge creation in various sorts of interactive learning processes, Bathelt et al. also question the merit of the prevailing explanatory model, where the realm of tacit knowledge transfer is confined to local milieus whereas codified knowledge may roam the globe almost frictionless. They argue that the co-existence of high levels of local knowledge transfer and many global "pipelines", which are defined as the non-random remote connections, provides firms located in outward looking and lively clusters with a string of particular advantages not available to outsiders in the knowledge-intensive sectors such as bio/pharma (Bathelt, Malmberg, & Maskell, 2004). By conducting a national survey of biotechnology firms in Canada, Gerlter et al. also emphasize the importance of the interplay or balance between global and local forces and flows in this sector (Gertler & Levitte, 2005).

As the global participation of life science discovery, the North American and European bio/pharma firms will not own the exclusive access to the drug discovery business any longer. While Big Pharmas still concentrate in the developed countries, a large number of small-medium bio/pharma companies are emerging in the rest of the world. Keeping in view of the low cost, the access to the regional resources and expertise, as well as the fast-growing markets, Melon, et al. (2009) conclude that in health biotech, substantial benefits are accrued from collaboration between firms in high-income (developed) and low- or middle- income (developing) countries. Therefore, the emerging market and the progressing R&D competence in the developing countries actually provide not only the opportunities of global business expansion but also the increasing competition to the bio/pharma firms that are rooted in the Western developed world.

In the article named “External partnering as a response to innovation barriers and global competition in biotechnology,” Greis, Dibner, & Bean (1995) build a conceptual framework to illustrate the motives of strategic alliances in the globalizing bio/pharma industry. As shown in Figure 3.10, the framework includes two levels of elements that motivate biotech companies to seek external partners -- the inner ring represents the need of primary innovation activities, including research, department, manufacturing and marketing, and the outer ring shows the environmental factors that fundamentally drive alliances, such as the existence of external barriers which impede the commercialization process and the assessments of global competitor strengths and weaknesses.

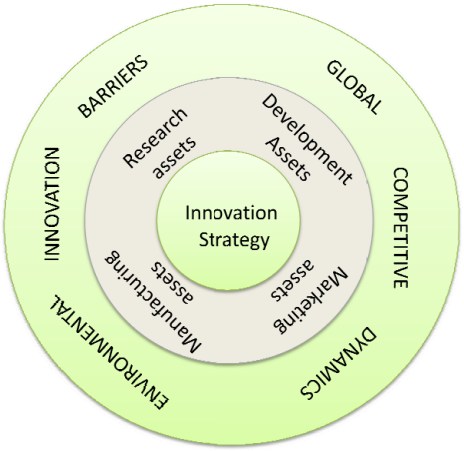


Figure 3.10 The conceptual framework of strategic alliances in bio/pharma industry
Source: Greis, Dibner, & Bean, 1995

In fact, previous literature also shows that the bio/pharma companies in North America and Europe have increasingly looked to developing countries to find new partners and develop R&D collaborations (Hardy, Seguin, Goodsaid, Jimenez-Sanchez, Singer, & Daar, 2008; Khilji, Mroczkowski, & Bernstein, 2006; Morel, Carvalheiro, Romero, Costa, & Buss, 2007).

Chapter 4 Strategic Alliances with Asian Bio/Pharma Companies

As the credit crisis broke out in the United States, the global economic circumstances have seemed to be upside down -- the developed world becomes depending on the developing world, rather than the other way round. Two-thirds of the entire global economic growth last year was from the so-called emerging economies, which are predicted to grow at an average of 6.7% in 2008 compared with 1.3% in the United States, Japan and European Union (Cohen, 2008). In Asia, even though the economic growth rates of the biggest two countries, China and India, have also been hampered by the current global recession, over the past five years their economies have grown faster than economies anywhere else in the world.

According to the recent worldwide economic forecasts that were conducted by Oxford Economics (Oxford, UK) , an economic forecasting consultancy, the future four-year GDP values of Emerging Asia, China and India are twice as many as GDPs of the United States, Canada and the worldwide average, and four times GDPs of most countries in Europe (Figure 4.1; Oxford Economics, 2009). The impressive regional GDP in Asia shows the indisputable new market for global bio/pharma sector. The strong economy also suggests that the Asian countries' have the abilities to not only become the biggest market of bio/pharma industry but also develop the advanced biotech R&D.

In fact, the recent M&A among Big Pharmas also indicate their shifting attention to these emerging markets. Farkas et al., the partners of Bain & Company consulting firm

(Boston, MA, USA) interpret the recent M&A of Pfizer and Wyeth, Merck and Schering-Plough, and Roche and Genentech as a global strategy to enlarge their economic scales for competing in the new global marketplace (Farkas & Biesen, 2009; Hoffmann-La Roche Ltd, 2008; Merck & Co., Inc., 2008; Pfizer Inc., 2008).

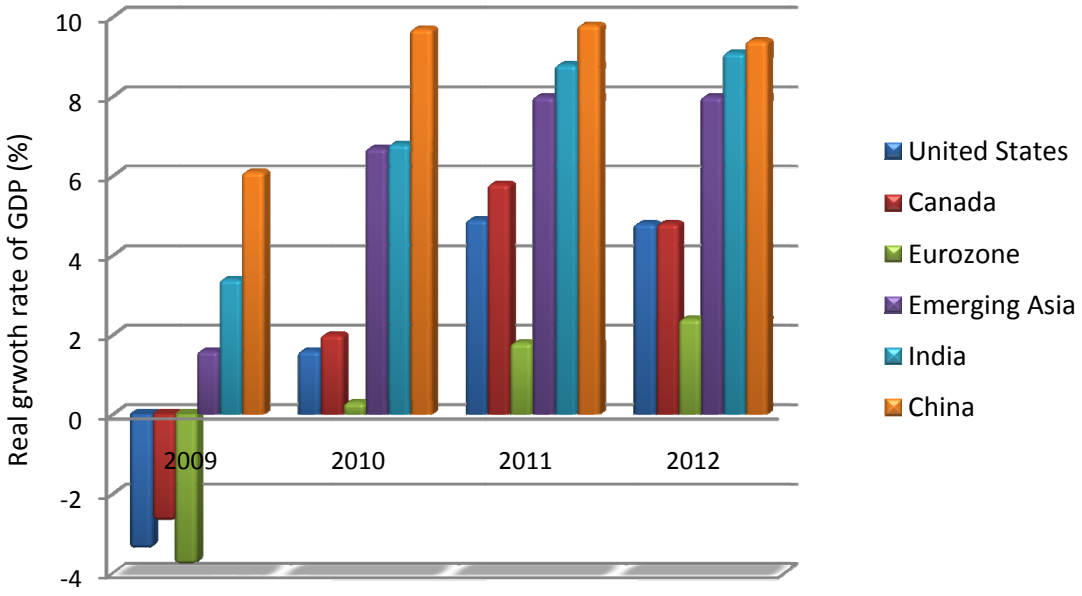


Figure 4.1 World economic forecasts

Source: Oxford Economics, 2009

Dan Bartholomew, senior managing director, PricewaterhouseCoopers (PwC) Pharmaceutical and Life Sciences Practice, said (as cited in Schooler, 2007),

"The Big Pharma business model is in transition. Right now, a lot of these companies are still focused on sales and marketing while they outsource other activities. However, there is a dearth of innovation that plagues the pharmaceutical industry, and R&D must become a greater focus. Not surprisingly, as the industry moves to this future model, strategic partnerships or long-term partnerships are a preferred route, favored by 82 percent of the multinational pharmaceutical companies we surveyed who outsource."

Through reviewing the recent news and literature on the nature and geography of market and innovation in Asian bio/pharmaceutical industry, I enumerate the business

opportunities and threats to the companies that plan to build strategic partnership with those in Asia.

4.1 Opportunities:

4.1.1 Emerging marketplace & the driven bio/pharma industry

Since decades ago, the rapid-growing economy in Asia has drawn attention of the developed countries to these emerging markets and the development of all kinds of industries in Asian countries. Among them, doubtless, China and India are the most attractive two in the developed world.

Chinese Market

In 2008, the GDP growth rate for country average of China is 9.8% and for industry sector is 49.2%. The incredible number made China listed as the number eight country with the fast economic growth in the world. However, despite the booming economy, the country did not put the equivalent effort into the national healthcare (Central Intelligence Agency, June 2009). According to the 2007/2008 Human Development Report, the Human Development Index, a measure of progress in healthcare, for China is 0.777, which gives the country a rank of 81st out of 177 countries with data (United Nations Development Programme, 2008).

The rapid economy transformation in some way presents the Chinese government with a significant challenge in delivering equitable healthcare to its citizens, particularly the 10% living in poverty. On the other hand, China's strong buying power also shows the potential of being the dazzling marketplace for the global pharmaceutical industry. Measured on a purchasing power parity (PPP) basis that adjusts for price differences,

China in 2008 stood as the second-largest economy in the world after the US, while in per capita terms the country is still lower middle-income (Central Intelligence Agency, June 2009). In addition, the dramatically growing middle-class populations in China indicate the huge demand for resources from abroad. According to a McKinsey Global Institute analysis, by 2025, the urban middle-classes of China are expected to reach 612 million, increasing their spending fivefold to more than $2.3 trillion a year (Farrell, Gersch, & Stephenson, 2006).

Indeed, several recent news and reports show that China's health biotech market starts to take off. The growing market also had China actively developed the basic and applied biotechnology to participate into the global bio/pharmaceutical industry. From 2000 to 2005, the bio/pharmaceutical sector in China grew 30% annually to $3 billion, compared with a 19% annual growth rate for its pharmaceutical industry as a whole, including the chemical medicine, the Traditional Chinese Medicine and biopharma (Jia, 2007).

India's Market

In India, another fast-developing country in Asia, the total consumer spending on healthcare products and services grew at a compounded annual rate of 14 per cent from 2000 to 2005, driven by increasing affordability, shifting disease patterns and modest healthcare reform. The forecast of Indian pharmaceutical industry by McKinsey & Co. shows that on the basis of the market size of US$6.3 billion in 2005, the Indian pharmaceuticals market could reach a size of US$20 billion by 2015. This increase of market size implies a compounded annual growth rate of 12.3 percent, which is materially higher than the annual growth rate of 9 percent witness during 2000 to 2005.

The analysis also shows that if the Indian economy continues on its current high growth path, then the Indian pharmaceuticals market will triple to US$20 billion by 2015 and move into the world's top-10 pharmaceuticals markets (Kumra, Mitra, & Pasricha, 2007).

Like China, India has growing middle-class populations and strengthening purchasing power. Even though there is still one quarter of total population whose economic conditions are below the poverty line (defined by the Central Intelligence Agency, USA), the large numbers also represent great market opportunities for affordable health products (Melon, et al., 2009).

Other Asian-Pacific Market

Although China and India might represent the most attractive emerging markets, other Asian countries also contribute parts of the large pharmaceuticals market in the world. In the PwC's report entitled "Gearing up for a Global Gravity Shift: Growth, Risk and Learning in the Asia Pharmaceutical Market," a survey result shows that 55% of the interviewed multinational companies and 62% of Asian ones agree that the centre of gravity of the global pharmaceutical market is shifting from Europe and North America to Asia as a whole (PricewaterhouseCoopers, 2007).

4.1.2 Financial Support

The huge costs of sophisticated machines, well-trained workforces and advanced R&D programs, as well as distribution and marketing expenses, build the high barrier for new entries into the biopharmaceutical industry. On the other hand, the great demand for financial supports also makes companies out of this industry very quick, if the companies cannot get return very quick or find further funding. As a result, access to venture capital that provides investment capital and the entrepreneurial and managerial know-how

necessary for commercial success is another key successful factor to bio/pharma industry (Cooke, 2002; Powell, Koput, Bowie, & Smith-Doerr, 2002).

In developed countries, where there are healthy systems of venture capital, industry estimates of the sources of capital for the first decade of a biotechnology company's existence care that 10 per cent comes from venture capital and other private equity sources, 40 per cent from public markets, and 50 per cent from senior partners (Hess & Evangelista, 2003). As it has been discussed in previous sections, however, the current economic situations make many venture capitals and public markets reduce their interests in this risky and time-consuming industry.

While the most of the public markets are relatively risk-averse in Asian developing countries, those governments actually provide many financial supports to establish the industry and to encourage private investments. Therefore, the political stimulants would be an essential element of bio/pharmaceutical industry in Asia.

In the United States, as the global economic slump influences university endowments, industry R&D budgets, and philanthropic support worldwide, the focus is shifting to the role of government in sustaining the scientific enterprise. The entire Americans are currently eyeing President Obama's $787 billion stimulus package to boost the U.S. economy. This package contains a $21.5 billion provision for funding scientific research and infrastructure: $10.4 billion for the US National Institutes of Health and $3 billion for the US National Science Foundation (Figure 4.2; Singh, 2009; Fox, 2009).

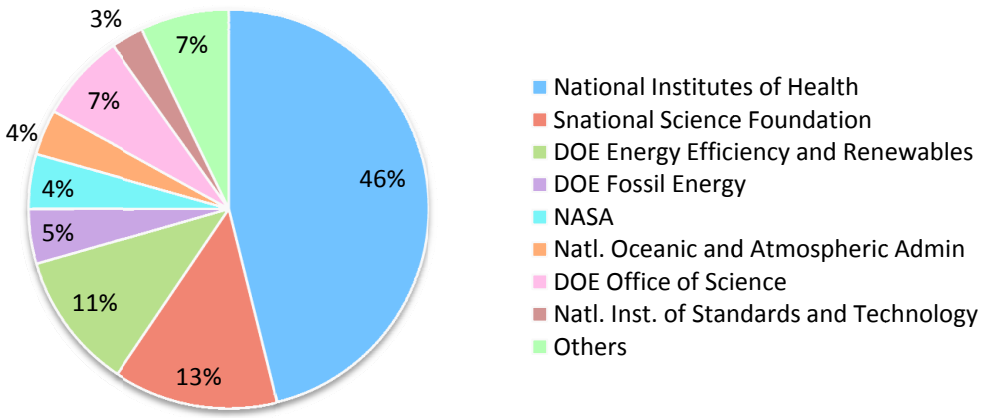


Figure 4.2 Funding for research and development in 2009 Economic Recovery Act Appropriations

Source: Source: American Association for the Advancement of Science Programs in Science and Policy, Washington, DC, USA (accessed Feb 13, 2008), as cited in Fox, 2009.

While the funding represents President Obama's campaign promises of keen interest to the biotech industry, due to the economic crisis, the anticipated changes in the health-care system are widely expected to lower the pricing of biological therapeutics by ushering in biogenerics (Fox, 2009). The changes in healthcare policy might indicate the decrease of income, if pharmaceutical companies cannot raise the sales volume at the same time.

Chinese Government Funds & Policy

The Chinese government is the primary life science investor in China. To attract Western pharmaceutical companies to the R&D collaboration, it is of first importance for Chinese government to strengthen the R&D skills and technologies in universities, research institutes and research-based biotech companies. As a result, both central and

local governments dedicate funds to support the R&D in these organizations. The two major state funding programs that support biotech in particular are the National High Technology Research and Development Program of China, or the 863 Program, and the National Basic Research Program of China, or the 973 Program. The 863 Program focused largely on the commercialization of research results. The 863 Program allotted in 2007, RMB 400 million (~ $52 million) to projects representing 11 priority biotech research areas, including product commercialization, gene therapy, and cell and immunotherapy for major epidemiological diseases. The 973 Program funds projects more focused on early-stage research, and grantees are expected to publish academic research papers on the supported work. Often, provincial and local governments will provide additional financial or other support, such as tax incentives or real estate space, to projects already funded by state grants, or vice versa (Ding, 2007; Partnering News, 2009). For several decades, China's central government has been encouraging basic research and patenting efforts, organizing the intellectual property into tangible assets for technology transfer (Frew, et al., 2008).

In addition, the Chinese government also invests in quasi-venture capital[i] companies, such as Shanghai Venture Capital, to support start-up and growth companies, and attracted capital from the private sector into life sciences. In 2006, total VC investment in China grew by 22 % over 2005 to a total of approximately RMB 15 billion. Multinational investment accounted for nearly 76 % of this total. This is accomplished through tax incentives, preferential treatment, right of first refusal agreements on technologies from institutes and universities, and a number of other means. While the total value of all VC investments in China is actually considered small, the absolute

[i] quasi-public-private venture capital

number of VC investments into China's biotech and pharmaceutical businesses is still increasing (Partnering News, 2009).

Indian Government Funds & Policy

While a large number of recent studies stressed the growing Indian market, few literatures report the government policy to develop the bio/pharmaceutical industry. As one of the biggest market in Asia, India government so far only has the first version of "millennium biotech policy" that was drafted in 2001. Recent news shows that the state government of Karnataka, whose capital - Bangalore is home for Indian biotech activity, is planning to release the revised 'millennium biotech policy' within a month. The revised policy aims "to give a number of incentives to the biotechnology industry," said Katta Subramanya Naidu, minister for Information Technology and BioTechnology, and to attract more global investments into R&D in Indian biotech industry (Chennai & Bangalore, 2009).

Taiwanese Government Funds & Policy

In Taiwan, while there is no huge domestic market, biotech is one of the six emerging industries, such as biotechnology, green energy, medical care, quality agriculture, culture creative and tourism, specially selected by Taiwanese government for intensive development. To promote this industry, the government has announced the immediate launch of an US$1.76-billion "biotechnology takeoff package", and encouraged venture capital funds as part of this comprehensive program. The program focuses on four major area, namely strengthening the industrial value chain and pre-clinical development in the commercial process, establishing a biotechnology venture capital fund, promoting an integrated incubation mechanism, and creating the Taiwan

Food and Drug Administration (TFDA) so as to bring Taiwan's medical device and pharmaceutical related regulatory environment to international standards. Taiwan is determined to lead Asia in genomic research, new drug development and human clinical trials supported by a vibrant and biotech- focused capital economy (Aldridge, 2009; Taiwanese Executive Yuan, 2009).

Singaporean Government Funds & Policy

Since the late 1990s when Singapore government decided to emphasize knowledge industries, including biomedical science, it has launched several biotech-associated plans to build up world-class capabilities across the entire bio-pharmaceutical value chain. In 2000, the government launched a nearly US$2 billion, five-year the Biomedical Sciences (BMS) Initiative to the development of public and private sector biomedical research (Normile, 2007). On the heels of the initial BMS Initiative comes the Science and Technology 2010 Plan, announced in February 2006, which will commit another US$5 billion over five years toward bolstering public and private sector R&D. The plan focused on translational research with the hope of turning basic research discoveries into clinically useful and commercially viable products (Epps, 2006).

In addition, aspiring to make biotechnology investment reach 3 percent of the country's GDP, the Singapore government has launched numerous policies, such as tax incentives, research and training grants, preferential funding from venture capitals, to attract the investment from the US and European bio/pharmaceutical companies.

As a result, Singapore has enjoyed phenomenal growth over the last four decades despite its small size and population of 4.4 million (UN Population Division). It has become recognized as a premier global hub in Asia for the manufacturing of

pharmaceuticals. It is now well-known the Singapore's ambition to be the Biopolis of Asia -- a leading international biomedical sciences cluster advancing human health, through the pursuit of excellence in R&D activities, manufacturing and healthcare delivery. Indeed, considering the entire environmental circumstances, several Western bio/pharma companies have established centres of research teams or collaborated with Singaporean companies to work in markets in India and China. Leading companies like Aventis, GSK, MSD, Schering-Plough and American Home Product (AHP), have invested over US$1.3bn in plants to produce active pharmaceutical ingredients and finished products for worldwide markets (PricewaterhouseCoopers, 2007).

4.1.3 Human Capital

In a knowledge-intensive industry such as biotechnology, the most important input to the generation of successful new products is undoubtedly highly educated people (embodied knowledge). Therefore, it stands to reason that any analysis of innovation in biotechnology requires a strong focus on human resources and labour market practices.

A key challenge faced by developing countries in trying to conduct basic research has resided in building basic scientific capacity. That has meant providing adequate funding for education and training and for constructing laboratories that could fulfil the needs of faculty and students alike. Today, these challenges remain stubbornly in place in many developing nations. Nevertheless, more and more developing countries have passed a threshold of basic competency and are now seeking to strengthen and broaden what has become a firm foundation in research.

Human Capital in China

The expansion of biotech and pharma R&D in China has considerable implications for Chinese scientists. Historically, many Chinese students have gone to the West for advanced studies and in many cases stayed because of better opportunities for trained scientists. This phenomenon has changed recently. Because of the increasing visa restrictions in the West, especially the United States, agitation of mass layoffs, and on the other hand, the better career opportunities in China, not only more Chinese students choose to take the higher education, particularly in the life science field, domestically, but also more Western-trained Chinese scientists has been encouraged to go back to China. A scientist at Roche Australia, Edmund Tsuei said, quoted from the article of Can China's supply of scientific talent keep up with demand, "There are many highly skilled, highly experienced and very successful scientists of Chinese origin working in North America and Western Europe wanting to return to their motherland to share their knowledge and experience and develop the next generation of scientists in their disciplines. With opportunities and incentives provided by both the government and private sectors, this is now possible (Wong G. , 2008)."

Human Capital in India

The Boston Consulting Group (BCG) describes how India is home to a large pool of well-trained, English-speaking scientists and managers (Wong, Bhalla, Goodall, Vaish, Wagner, & Janssens, 2006). In basic research part, India has world-class skills in chemistry and information technology. To replenish the domestic scientific human resources to jump-start the science-driven economic growth, several new initiatives have been launched, including the joint Department of Biotechnology (DBT)- Wellcome Trust

Biomedical Research Career Program, announced in September 2008. With a 5 year (2007 to 2012) budget of $1.5 billion, the DBT in New Delhi is India's largest federal funding agency for the life sciences. One of their biotech-related programs that launched in 2008 is a 2 year, $6.5 million pilot program called the Biotechnology Industry Research & Development Assistance Program (BIRAP). Another one is a new 5 year, $75 million scheme called the Biotechnology Industry Partnership Program (BIPP) for the high-risk technologies and "breakthrough" research projects. This alliance will award 40 early career fellowships to Indian citizens working in India or abroad (and possibly to non-Indian citizens who wish to pursue research in India), 20 intermediate fellowships, and 15 senior research fellowships annually, with the first awards to be handed out in May 2009. A major goal of this alliance is not only to woo Indian researchers working overseas to return to their home-land and to set up independent labs, but also to excite the biomedical research and bio/pharma industry in India (Singh, 2009).

To encourage young people to think about science as a long-term career, Indian government has implemented some fellowship programs, such as the Young Entrepreneurs Scheme, a collaboration with the UK's Biotechnology and Biological Sciences Research Council, and the Bio-design Program, a collaboration between Stanford University and the All India Institute of Medical Sciences in New Delhi. The Stanford Bio-design Program aims to train the next generation of medical technology innovators in areas such as diagnostics and imaging and has resulted in several patents. On the other hand, in November last year, Prime Minister Singh launched a 5 year $480 million scholarship program for one million 10- to 15-year-old Indian students, whose funding will continue through graduate school as long as they pursue a science career.

This year, DBT will start an Ignition Grant scheme in collaboration with MIT to fund postgraduates, who have ideas that could lead to products but do not have a registered company or the infrastructure to put their ideas into action (Singh, 2009).

In addition, since India has a large pool of treatment-naive patients, that is, those who have not taken any other medicine, it would be a good opportunity for India to train medical professionals to conduct clinical researches. Global consulting firm McKinsey (as cited in Iype, 2004) also estimates that by 2010 there will be 700,000 specialty hospital beds and 221 medical colleges in India. Combined with the modern infrastructure in technology and transportation, as well as its various types of diseases, India would be a hot bed to conduct non-core clinical trial activities on a broad spectrum of drugs for many multinational bio/pharmaceutical firms.

Human Capital in Taiwan

Over the past two decades, Taiwan has concentrated on the development of high-tech industries such as electronics, information technology, computer and semiconductors. Through the example of the Silicon Valley and the Bay Biotech Cluster in San Francisco, California, Taiwanese government attempted to integrate the innovative success in high-tech industry and the vigorous biomedical research to revolutionize the bio-pharma industry in Taiwan (Efendioglu, 2006). Currently, Taiwan has 164 universities with more than 80 incubation centres within the campuses; 18 medical centres; a growing number of science-based industrial parks; and government and private non-profit research institutes such as Academia Sinica, the Development Centre for Biotechnology (DCB), the Industrial Technology Research Institute (ITRI), and the National Health Research Institute (NHRI), all of which are involved in biotech-related research activities. The

main strengths of Taiwanese bio-pharma industry are the energetic basic research in life science and the sound system of clinical trials. According to the recent statistic from Ranking Web of World Research Centers, Academia Sinica (the Taiwanese National Academies) lists as the 16th of Top 2000 Global R&D Institutes and as top one in Asia (Ranking Web of World Research Centers, 2009). To build up the foundation of biotechnology and cultivate young scientists in Taiwan, Academia Sinica and National Health Research Institutes (the Taiwanese Institutes of Health) not only has frequently collaborated with the domestic preeminent universities, such as National Taiwan University, National Yang Ming University and National Tsing Hua University, but also established the Taiwan International Graduate Program to attract young talents from other Asian countries and worldwide (Scholarshipnet, 2008). In addition, Academia Sinica has held regular Academician Convocations to keep the tight connection with the science societies in other countries, particularly in the United States, Japan and China (Academia Sinica, 2009).

Research articles published in the peer-reviewed international scientific and technical journals represent quantifiable research outputs of academic research institutes. According to the statistics, the number of papers that were published in SCI/SSCI Journals by National Taiwan University has been increased over seven times during the past three decades (Chen, 2008). In addition, as shown in Table 4.1, the 189,337 filed patents from 1995 to 2005 makes Taiwan list as number nine of the top innovative countries in the world, and following Japan and Korea as the third among Asian counties (Table 4.1; Liu & Lin, 2009). "Innovation in biotechnology here is growing, but the challenge is to connect the local with the global," says Chung-Cheng Liu, general director

of Biomedical Engineering Research Laboratories (BEL) in Taipei, the largest non-profit R&D organization in Taiwan and part of the Industrial Technology Research Institute (as cited Aldridge, 2009).

Table 4.1 World's most innovative countries by the number of patent submission and approval[ii]

Rank (Patent no.)	Country	Patent submission	Patent approval	Approval rate
1	Japan	5,218,096	2,067,674	39.63%
2	United States	2,850,957	1,467,758	51.48%
3	Korea	1,044,868	381,344	36.50%
4	Taiwan	252,777	189,337	74.90%
5	Israel	49,885	18,494	37.07%
6	Ireland	18,411	7,561	41.07%
7	Singapore	9,414	3,809	40.46%

Source: Science & Technology Policy Research and Information Centre, NHRI, Taiwan; as cited in Liu & Lin, 2009.

Besides the intense basic research of life science, Taiwan also owns a pool of well-trained medical professionals. Coupled with the first-class healthcare quality and a large number of patients (because Taiwanese patients prefer large-scale hospitals), medical professions usually can conduct quality clinical researches efficiently. The well-developed medical systems also ensure the safety and quality of clinical researches that are conducted in Taiwan. In the study about the clinical trials in Asian countries, Taiwan, Singapore, Hong Kong and South Korea are listed as tier two, whereas India, China and Southeast Asia are tier three. The report shows that the quality standards for clinical trials in Taiwan adhere to the accepted international standards of International Conference on

[ii] Including United States Patent and Trademark Office (USPTO), Japan Patent Office (JPO) and State Intellectual Property Office of the P.R.C. (SIPO)

Harmonization/ WHO Good Clinical Practice (ICH/GCP). GCP guidelines has been implemented by Taiwanese Department of Health since 1997 and then further revised in 2002 to be consistent with ICH standards. THE DOH conducts GCP inspections on nearly all clinical trials to ensure their quality and credibility and is equivalent to the FDA. Taiwan also offers the option of Joint Institutional Review Board Approval (JIRB), which allows for multi-centre approval as opposed to individual IRB approval for each hospital. More than 40 hospitals have participated in the joint IRB, and JIRB has helped Taiwan attract more multi-centre trials (Drug Delivery, 2007). The clinical trials reviewed by the DOH in 2002 were shown in Table 4.2. The proportion of multinational trials in Taiwan is 49.79% (71/143) in 2002. Taiwan has demonstrated its ability to conduct increasing number of early phase clinical trials and to participate in multi-national clinical trials. These efforts are essential in creating a favourable environment for domestic research and development of new pharmaceuticals (Wang & Chen, 2005).

Table 4.2 Multinational and domestic clinical trials reviewed by Taiwanese DOH in 2002

	Multinational trials	**Domestic trials**	**Total**
Phase I	0	4	4
Phase II	12	14	26
Phase III	52	49	101
Phase IV	7	5	12
Total	71	72	143

Source: Wang & Chen, 2005

Human Capital in Singapore

As the full government supports and vigorous foreign investment, Singapore is now a city of imported scientific talents -- currently about one third of all scientists in

Singapore are foreigners (Epps, 2006). With this advantage, Singapore has developed strong connection with the first-class university and research institutes in the world. In addition, to maintain a critical mass of scientists, as well as to breed its own scientific workforce, the government has revamped the education system -- from overhauling the primary school curriculum to offering scholarship programs that fund undergraduate and Ph.D. science training either locally or abroad. As a result, the National University of Singapore was ranked as the 30th out of top 100 universities in the world last year, and following the other three universities in Japan and Hong Kong as the fourth in Asia (QS Top University, 2008).

Because of the sound healthcare system, Singapore is also viewed as a good location for conducting clinical trials in Asia. It owns high-quality medical facilities and highly educated doctors, many of whom went to school in the United States or Europe, especially England. Therefore, it is listed as the tier two of Asian countries for conducting clinical researches. However, one of the drawbacks of doing clinical trials there is its small population (about 4.3 million people), and thus sometimes trials in Singapore can encounter difficulty recruiting enough patients (Drug Delivery, 2007).

4.1.4 Expertise in regional diseases

In addition to the prevalent studies of cancer therapies, developing countries have been increasing their expertise in this field and possess other resources, such as indigenous materials, important for health biotech development (Melon, et al., 2009). Hepatitis B and C, for example, has caused epidemics in parts of Asia and Africa, and it is endemic in China. Therefore, several hepatitis research centres in Asia countries have fruitful discovery in both basic pathology and clinical therapy. Taiwan, for example, has

dedicated itself in study of hepatitis for a long time and fostered many outstanding academic and clinical research talents for studies of liver disease. Aiming to stand in a key position as a ruling research centre for liver diseases, Taiwanese government is integrating both excellent academic results & industrial strength in Taiwan with international research institutes & drug firms related in liver diseases. Genelabs Technologies Inc. (NASDAQ:GNLB), for example, announced the collaboration on hepatitis C research with Taiwan National Health Research Institutes and Genovate Biotechnology Co., a biopharmaceutical company in Taiwan (San Jose Business Journal, 2008).

Another example is Tuberculosis (TB), which distributes not uniformly among the world. About 80% of the population in many Asian and African countries testing positive in tuberculin tests, while only 5-10% of the US population test positive. While one third of the world's current population has been infected with Mycobacterium tuberculosis, the pathogenic virus of TB, most of these cases will not develop the full-blown disease; asymptomatic, latent infection is most common. As a result, it is estimated that the US has 25,000 new cases of tuberculosis each year, 40% of which occur in immigrants from countries where tuberculosis is endemic (Kumer, Abbas, Fausto, & Mitchell, 2007). To ensure the widespread availability of affordable, faster and better TB drug regimens that will advance global health and prosperity, the TB Alliance, a global non-profit organization, was formally launched in October 2000, at the International Conference on Health Research for Development, in Bangkok, Thailand.

The TB Alliance is operated as a product development partnership (PDP), working to develop new, simpler, faster-acting TB treatments. As less than three percent

of global funding for health R&D is dedicated to diseases of the developing world, such as TB, it is unlikely for a pharmaceutical company (even a Big Pharma) to develop drugs by itself. However, through partnering globally with the public, private, academic, and philanthropic sectors, the TB Alliance functions as a virtual R&D organization, minimizing costs, and optimizing the speed of drug development. Over the past decade, global health PDPs, like the TB Alliance, have advanced dozens of potential new diagnostics, drugs, vaccines, and microbicides through the development pipeline, toward registration and launch. Recent news also shows that many global pharmaceutical companies, such as Tibotec Inc. (Tibotec), have collaborated with TB Alliance to identify new compounds for the treatment of TB, and on the other hand, to gain the access to the vast developing market (TB Alliance, 2009).

4.1.5 Low-cost

It is not a new challenge for multinational companies that competition from generics and pricing pressures in the healthcare market continue to create pressures for reduction in costs in all parts of the pharmaceutical value chain. “Cost has always been a driver of outsourcing decision,” says Mike Keech, director of PwC’s advisory services group in the pharmaceutical and life science sector (Drakulich & Arnum, 2009). As a result, outsourcing to lower cost but highly effective companies in Asia has become a common response to these pressures. For example, generics make up the majority of China’s biopharmaceutical market, accounting for >90% of the $3 billion market in 2006. China’s population size creates a significant need for low-cost products. For both multinational and domestic generics producers, China’s low-cost manufacturing, huge work force and less stringent regulation have been the major elements that make

companies profitable (Frew, et al., 2008). However, according to a survey conducted by PwC, a majority of both the Asian-based domestic and multinational companies interviewed (56 percent) thought that most of the industry still does not see outsourcing in a sufficiently dynamic way and is missing opportunities for shared development, learning and improvement. In addition, studies showed that both the cost of American scientific talents and the price of typical R&D projects are 3-5 times higher than that of Asian ones (Wang J. , 2006). At present, much of the focus has been on outsourcing drug manufacturing, but increasingly, because of maturing knowledge and technology of the basic and clinical research in the Asian countries, Western pharmaceutical companies have been turning their attention to R&D and clinical trials (Schooler, 2007).

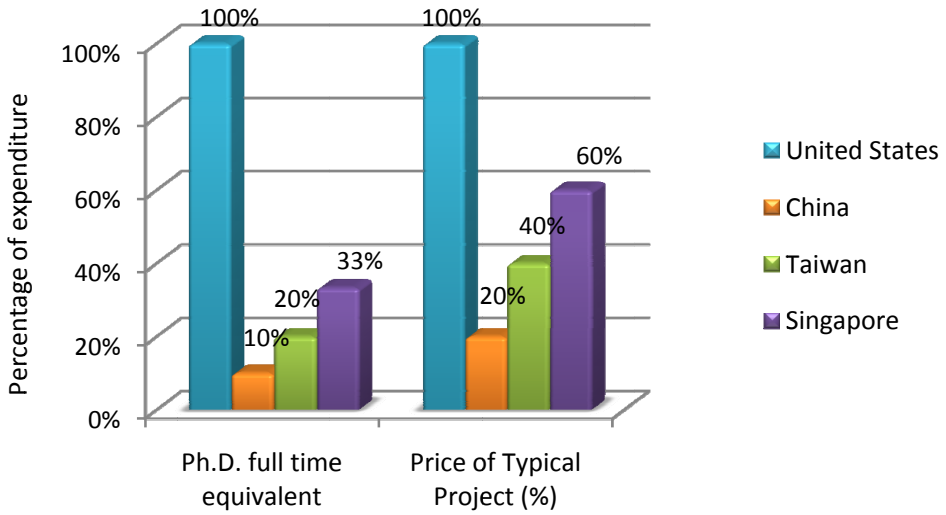


Figure 4.3 Preclinical R&D cost comparison between Asia and U.S

Source: Wang J. , 2006

Indeed, Asian countries' cost advantages lie in the hiring of skilled labour with its clinical trial costs comparable to Eastern Europe, while medical and research standards

are on par with those of the United States and Western Europe. As the comparison shown in Figure 4.3, the cost of PhD full time equivalent in the United State was about ten times in China, five times in Taiwan, and three times in Singapore; the price of typical project in the United States is five times in China and about two times in Taiwan and Singapore. Recent news also shows that pharmaceutical companies outsource the clinical research or set up clinical R&D centres in Asia countries, such as Singapore and Taiwan.

4.2 Threats:

4.2.1 Safety and quality of products

Although the low-cost production, a pool of scientific talent and maturing public infrastructure make Asian countries become more important in the pharmaceutical supply chain, one of the major concerns to Western bio/pharma companies is the safety and quality of products.

One key event was that Baxter International (Deerfield, IL) recalled thousands of vials blood-thinner heparin that has been linked to hundreds of allergic reactions and possibly 81 deaths in the United States. Baxter and FDA later traced contamination (oversulfated chondroitin sulfate) to the product's active pharmaceutical ingredient (API), which was supply by Scientific Protein Laboratories' Changzhou SPL plant in Changzhou City, China (Freking, 2009). The FDA has increased inspections and product testing efforts in response to the melamine contamination problem which originated in Chinese dairy products, such as flavoured drinks, milk and milk-based products in China. The widespread contamination made several Taiwanese food producers recalled a large number of products (U.S. Food and Drug Administration, 2008).

At the beginning of this year, the FDA announced that the Paonta Sahib facility owned by India-based Ranbaxy Laboratories falsified data and test results in approved and pending drug applications. In fact, since the fall 2008, the FDA has issued two warning letters and instituted an Import Alert barring the entry of all finished drug products and active pharmaceutical ingredients from three Ranbaxy's facilities, including Dewas, Paonta Sahib and Batamandi Unit facilities, due to violations of U.S. current Good Manufacturing Practices requirements. That action barred the commercial importation of 30 different generic drugs into the United States and remains in effect (U.S. Food and Drug Administration, 2009).

Because of the recent events, many Western bio/pharmas state that some Asian manufacturing is no longer as profitable to the companies as it used to be, even though the cost could be reduced to 50-60% by doing so (Drakulich & Arnum, 2009). As a global Big Pharma, Pfizer emphasizes that adherence to quality standards are a prerequisite for working with any supplier. By further asked the questions about the consideration to the suppliers in India and China in a recent interview with Pharmaceutical Technology, Natale S. Riccardi, the president of Pfizer Global Manufacturing and senior vice-president of Pfizer, said, “Special considerations when working with suppliers in emerging markets are numerous, obviously the first and foremost is product integrity and safety. Any potential supplier is evaluated on its ability to produce material in a manner that is fully compliant in all regulatory procedures,” as cited in Ricciardi (2008).

4.2.2 Intellectual property right

Intellectual property protection is essential for bio/pharma industry because while the cost of innovation is high, the cost of imitation is relatively low. Unlike commodity-based industries, where access to cheap materials, labour, or markets can provide a competitive advantage, knowledge- and innovation-based industries, such as commercial biotechnology, rely on the ability to generate and exploit knowledge to gain a competitive advantage. Intellectual property protection therefore plays an integral role in enabling bio-pharma research by establishing a barrier to competition that permits pioneers to sustain lengthy research efforts and recoup their R&D costs. That is to say, to get a drug to market, a pharmaceutical company needs at least three pieces of intellectual property -- one is for the target, one is for the product, and one is for the manufacturing process (Friedman, 2006, pp. 79-106).

Government incentives fuel the growth of bio-pharma industry in Asia countries, but intellectual property risk remains a concern to many of Western pharmaceutical companies. By interviewing with 93 senior pharmaceutical executives from multinational companies with operations across nine different territories in the region, including China, India, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam, PricewaterhouseCoopers (PwC) report that three-quarters of interviewers said they are worried about intellectual property rights and legal risks, and concerns about intellectual property protections are cited by them as the biggest reason to consider leaving Asia countries (Schooler, 2007).

However, since the awareness that assurance of intellectual property rights protection has been an important incentive for multinational companies' investments, many Asian countries have recently introduced rules ensuring greater protection to

intellectual property rights, in compliance with World Trade Organization (WTO)'s Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS; Thomas, 2008). In the same survey that was conducted by PwC, it is also highlighted that nearly the same amount (74 percent) of multinational companies saw an improvement in intellectual property right protections during the past five years, primarily as a result of the introduction of new intellectual property laws, underpinned by a stronger government emphasis on intellectual property protection and more rigorous application of existing laws (Schooler, 2007).

4.2.3 Political, social and economic stability

In pursuit of business opportunities in developing countries, the biggest challenge to executives is the uncertainty and security of economic environment. Indeed, national security is a critical factor that determines the level of investment, both domestic and foreign, along with favourable business environment, positive policy matrix and return on investment. Global investors apply these parameters diligently while making their decision on investment destinations.

In the case of Asian countries, political turbulence is usually the major influence of financial markets. Taiwan's stock market, for example, generally responds dramatically to new information regarding political decisions that may affect domestic and foreign policy. However, because of the complicated relationship between Taiwan and China, and, regretfully, the democratic reform of Taiwan, the political condition in Taiwan has been restless all along. In a recent study about the congressional effect between the pre- and post- democratization on the stock market, Wang and Lin (2009) show that the congressional effect and the democratic effect are negative on stock returns,

and the democratic effect even increases the volatility of stock market. Considering both the slippery investment market, many Western companies show the indifference toward the bio/pharma industry in Taiwan. On the contrary, the tranquil political condition in Singapore indeed has drawn many Western pharmas' favour.

Because the series of conflicts between India and Pakistan since 1947, India was the focus of numerous attacks from both externally based terrorist organizations and internally- based separatist or terrorist entities, said the State Department's annual report on global terrorism (Kumar, 2009). The 2008 Mumbai attacks devastated India's financial capital and its largest city, and made India become one of world's most terrorism- afflicted countries. As a result, the business confidence that was weakening due to current global turmoil will now bear the heat of this terror attack, with sentiments further going weak. As to the bio/pharma industry, where the quality and safety of products is the essence of the business, terror attacks caused several Western companies to rethink their strategies in India (Drakulich & Arnum, 2009).

4.2.4 Distance & Business transparency

Considering the requirement of the unobstructed communication and business transparency to build mutual trust, distance would be a critical threat to performance of strategic alliances between Western and Asian bio/pharma firms. Distance between two countries can manifest itself along four basic dimensions: cultural, administrative, geographic and economic. The types of distance influence different businesses in different ways. In the case of R&D collaboration between Western and Asian bio/pharma companies, geographic and cultural distance is most likely to disrupt the mutual

understanding and the transparency of management, and thus affect the efficiency and productivity of the collaborated activities.

Geographic distance

In general, geographic distance affects the costs of transportation and communications, so it is of particular importance to companies whose cooperation requires a high degree of coordination among highly dispersed people or activities. This is one of the reasons why bio/pharma companies form as local clusters.

However, as the modern information and communication technologies are developed, it becomes easier to connect disseminated R&D activities and thus makes distributed R&D organization possible (Howells, 1990). More importantly, as I discussed above, both the market and R&D skills of biopharmaceutical industry are globalizing. Companies that pursue business opportunities from emerging markets should balance between the risk of geographic distance and the possibility of profit.

Cultural distance

A country's cultural attributes determine how people interact with one another and with companies and institutes. Differences in religious beliefs, race, social norms and language are all capable of creating distance between two countries. Indeed, they can have a huge impact on trade: All other things being equal, trade between countries that share a language, for example, will be three times greater than between countries without a common language.

Moreover, the study also shows that colony-colonizer links between countries boost trade by 900%, which is perhaps not too surprise given Britain's continuing ties with its former colonies in the commonwealth. As a result, because of the greater

predominance of English as second language and the stronger historical links with the UK, Singapore, India, Hong-Kong may collaborate more with developed countries. Through the globalization and the development of Westernizing education systems, the barrier of language is getting lower. In the article entitled “Biotech Vision Taiwan”, for example, Cyranoski (2003) reports that Western researchers generally find that Taiwan’s research environment fosters a fruitful, open exchange of ideas in which language is not a problem. In everyday life, too, English works well enough at supermarkets and hospitals for researchers and their families to feel comfortable without having to learn Chinese.

4.3 Opportunity & threat analysis of strategic alliances with firms in China, India, Singapore and Taiwan

While the North American and European bio/pharma industry has been developed for several decades, the sector is just newborn in Asia. In light of the regional growing market, several Asian governments have actively promoted the bio/pharma sector, providing considerable sum of financial and administrative support to cultivate the human resources in basic research and clinical R&D and improve research facilities and technical infrastructure. In addition, they have heavily invested biotech-related business and offered special tax incentives to foreign bio/pharma firms to bridge the Western-Asian R&D alliances. In the previous sections, I detail the biotech-encouraging policy and financial programs and identified the potential risks in four Asian countries: the two biggest countries -- China and India, and two biotech-capable countries -- Singapore and Taiwan -- and provide the comprehensive view of Asian bio/pharma industry. Figure 4.4 presents the opportunity and threat analysis of Western bio/pharmas’ strategic alliances with firms in these Asian countries from the following aspects: size of domestic market,

government support, quality of human capital and healthcare, innovative ability, expertise in local diseases, cost, safety and quality of products, protection of intellectual property, political, social and economic stability, bio/pharma related regulation and infrastructure, cultural familiarity and business transparency.

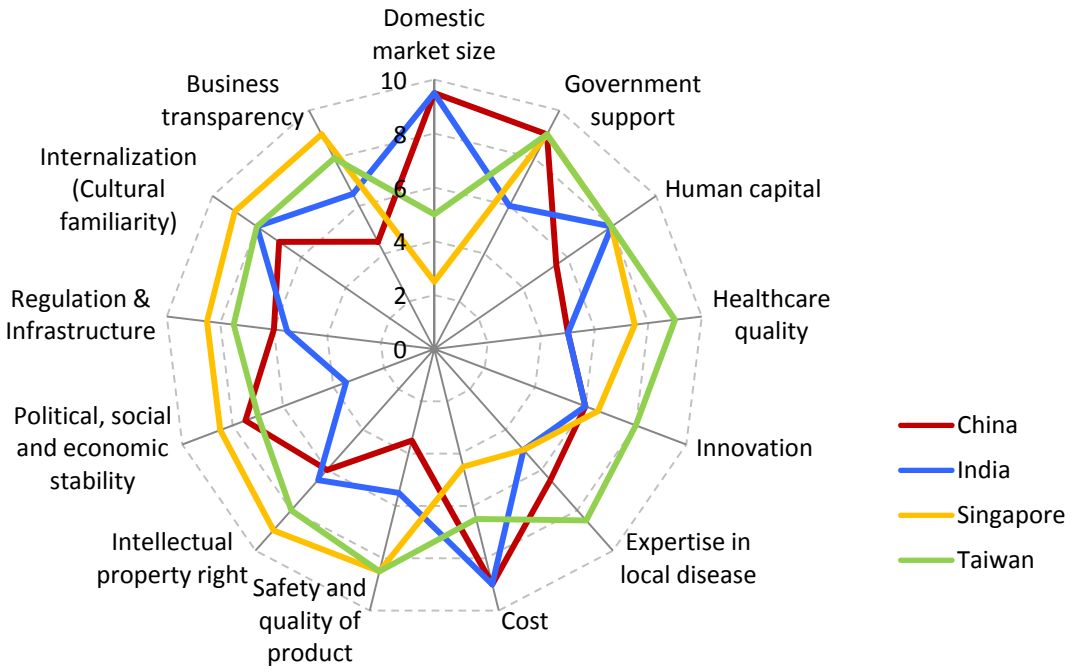


Figure 4.4 Opportunity and threat analysis of Western bio/pharmas' strategic alliances with firms in China, India, Singapore and Taiwan

The distinct strength and weakness of these countries provide various options of collaboration for Western bio/pharma companies. Generally speaking, the considerable strength of China and India is the immense marketplace and the low-cost labours and facilities, whereas the strength of Singapore and Taiwan would be the soft skills, infrastructure and regulations. In the study entitled "Strategies and achievement of

bioscience industry development in Israel, Ireland and Singapore", Liu and Lin (2009) analyze the competitiveness of bio/pharma sectors in China, India, Singapore and South Korea, and also suggest that while Taiwan and Singapore do not have the advantages of marketplace and cost benefits, other circumstances, such as the healthcare quality, regulations and infrastructure, actually make these two small countries a better environment of biotech industry than China and India. Considering the functional difference in each phase of drug development process, as well as the strength and weakness of these countries, Western bio/pharma companies have the opportunities to find partners with proper function to reinforce their core strategies and avoid the potential risks. As shown in Table 4.3, I categorize the types of collaboration in terms of the different specialties of these countries. Manufacturing small-molecule drugs, for example, needs less technique or R&D and the cost would be the major concern to bio/pharma companies. Thus, as long as Western companies establish optimal quality control systems, it would be most profitable by collaborating with manufacturers in China and India. However, manufacturing biotech drugs requires advanced R&D and strict control for the quality and safety of products. Therefore, Singapore and Taiwan would have better performance of manufacturing biotech drugs. Bearing in mind that clinical trials require a large number of volunteers and competent healthcare systems, Taiwan could offer great profit to Western bio/pharma partners by conducting high-quality clinical research. The requirement of collaboration in basic research is stringent, especially in terms of intellectual property right, innovation and expertise of local diseases. However, considering that the advanced life science is still concentrated in North America and

European, Western bio/pharma firms could only benefit from the collaboration of local disease study.

Table 4.3 The options of Western bio/pharma companies' collaboration with firms China, India, Singapore and Taiwan in terms of countries' specialties[iii]

Countries / *Collaboration*	*China*	*India*	*Singapore*	*Taiwan*
Manufacture of small-molecular drugs	5	5	1	2.5
Manufacture of biotech drugs	3	3	4.5	4
Clinical trials	2	2	4	4.5
Basic research	3	3.5	3.5	3.5

[iii] On a scale of 1 (poor) to 5 (excellent)

Chapter 5 Conclusion

In respect of the rising concerns in health care and the matchless significance of medicine, many countries have heavily invested the bio/pharma industry. Through the introduction of the value chain from drug discovery to FDA approval, it is evident that the steady exchange of knowledge and technology for companies are essential to run business in the bio/pharma sector, regardless of the companies' economic scale. The constant interchange of R&D resources motivates companies' strategic alliances in the bio/pharma industry. This report concludes four factors that encourage companies to build partnership: 1) the fulfilment of the early-stage pipeline by external R&D recourses; 2) the reducing financial resource from the expired blockbuster drugs; 3) the tendency toward personalized medicine; 4) the rising hurdle of FDA examination.

While the complex nature of bio/pharma business, as well as the growing global market and competition, make strategic alliances an essential element of bio/pharma firms' productivity and competitiveness, the partnerships do not always give company equivalent payoffs. This report further discusses about how bio/pharma firms manage the different transactions to acquire external resources and analyses the advantages and disadvantages of strategic alliances, providing a comprehensive view to the bio/pharma firms that are seeking external resources to sustain their business. Moreover, in light of the globalizing bio/pharma industry, a conceptual framework is applied in this report to illustrate the motives of strategic alliances in the broader circumstances (p. 36).

Unlike the United States with widening budget deficit, many Asian countries are actively investing bio/pharma industry. The cases of the bio/pharma sectors in some Asian countries (China, India, Singapore and Taiwan) analyzed in Chapter 4 reveal that Western bio/pharma firms should think over the R&D alliances with those in Asian. The result shows that in addition to the immense Asian market and low cost, which are definitely the most important factors, those countries have provided substantial financial resources and biotech developing plans to support their domestic bio/pharma sectors. In addition, as the capability of life science knowledge and R&D is progressing in Asia, the larger pool of scientific talents and advanced facilities also provides Western bio/pharma firms opportunities of strategic alliances. On the other hand, the potential risks in these Asian countries and the problems caused by remote collaboration should also be taken into consideration. The risks include the product safety issues, the protection of intellectual property, the stability of business environment and the business transparency resulting from geographic and cultural distance. Finally, this report analyzes the opportunities and threats of Western bio/pharmas' strategic alliances with firms in these Asian countries and provides the detailed comparison of countries' specialty to companies that look for collaboration in different stages of drug development process.

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