**Cross Border Alliances in the Asian Biopharmaceutical Industry**

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**Abstract:**

In recent years there has been an increase in cross border alliances in the Asian biopharmaceutical industry where cost, time and innovation are of the essence. This paper studies the motivations of firms for cross border collaborations from the exploration-knowledge seeking and exploitation-market seeking perspectives. There are evident explorative alliances across borders that entail forming a synergy of unique and complementary assets between transnational partners, contract manufacturing and situating in optimal locations that give strength and competitive edge to the R&D, manufacturing and clinical trials part of the value creation activity as well as exploitative alliances that warrant a fast and efficient commercialization of new drugs. Included in the paper are value added case studies of how Asian biopharmaceutical firms pursue these cross border alliances to increase their market valuation and improve long-term performance.

**Keywords:** cross border alliances, explorative alliance, exploitative alliance, biopharmaceutical industry, Asia

**Introduction**

The development of the pharmaceutical and the emergence of the biotechnology industries provide valuable insights into the role of alliances and networking that shaped the synergy between both industries. For example, Powell found that biotechnology industry analysts explicitly examine the alliances of individual firms and ascribe market value based on the quality and quantity of those relationships.

Thus, firms with a higher quality constellation of alliances generally enjoy higher market valuations, a reflection of the market belief that they will perform better in the long run. All Goldman Sachs analyst reports on biotechnology firms devote time to exploring alliances,
and Goldman Sachs publishes a comprehensive listing of biotechnology alliances. Both biotechnology and large pharmaceutical firms compete in an industry characterized by rapid technology change, in particular, these firms depend on the creation of new knowledge. Alliance competencies should be prevalent in any market characterized by fast changing intangible assets, given the difficulties inherent in trading intangibles. Moreover, in industries with very high rates of technology change, technologies can be introduced that create new market segments, obsolesce existing product lines, and create substantial competitors from previously little known firms. Under such conditions, few firms can afford to conduct research in enough directions to build sufficient R&D options.

Alliances offer opportunities for firms, in essence, to outsource R&D efforts, creating options on knowledge developments without requiring mergers or acquisitions.

Many pharmaceutical firms are under pressure to improve productivity and to maintain their leadership. Asian pharmaceutical firms receive some of their revenues from the production of generic drugs or in-licensed products. But as recent developments show, the dwindling of new products in the pipeline and with patents of blockbuster drugs soon to expire, they are much concerned about their long term profitability. The cost of developing innovative drugs is very high and the rate of success from development to commercialization of the drug is rather low, so pharmaceuticals firms have to review their business strategies. On the other hand, biotech firms, most of them small, are gaining ground in the health care sector competing with established pharmaceuticals. In this light, there are now consolidations in the bio-pharmaceutical sector characterized by more partnerships and alliances between pharmaceutical and biotech firms that transcend national borders to rationalize their activities and bring together complementary competences and assets, which each of the company lacks, facilitate entry into a foreign market and increase market presence and spread and reduce costs and risks in the costly development of new drugs.

Maximization of the prospects of financial gains has prompted firms in the bio-pharmaceutical sector to build horizontal and vertical collaboration networks, domestically and across borders. Alliances are formed to share complementary resources and competences. Recent breakthroughs and innovations have become interdisciplinary and inter-industry such that capabilities and resources do not come from a single firm. Hence it is more practical to form synergies with firms having complementary skills to avoid duplication of any capital and knowledge intensive and time consuming value creation activities. In high-tech industries, where knowledge required is ever changing and very complicated usually and one firm does not have the expertise nor the resources to internalize operations by itself but rather need to collaborate with other firms in the industry. This Chang-referred to as network of
learning. His research revealed that new biotech firms, usually small research oriented biotechnology firms (NBF), some of them spin-offs from universities or public research labs, that are involved in in-depth research and develop of new drugs have more partnerships to survive. Firms have core competences, certain skills that they are good at and which other firms can not match and these competences can be utilized in the value creation activities. Leveraging on these core competences, the firms can offer products or services which they can produce in a more efficient way. Put simply, the firm can exploit the opportunities that its value creation competence can bring, and the resulting product or service can and in an alliance, each partner can leverage on their respective comparative advantages. The value creation for instance in the case of the bio-pharmaceutical industry covering activities from research, product development, pre-clinical testing, clinical trials and manufacturing and marketing is a long, risky and costly process and supporting this value creation are the pool of manpower, logistics, information systems and company infrastructure (e.g. organizational structure, corporate culture) without which it can not proceed effectively and these value creation events are composed of upstream activities (R&D to manufacturing) or downstream activities (marketing and sales). Roethaermel and Koza and Levin refer to alliances that pertain to that upstream portion of the value creation activity concerned with the pursuit of know-how or technology as exploration alliance and the part that deals with commercialization (downstream activities) as exploitation alliance. According to Koza and Levin for firms to realize and sustain profitability in the long run they pursue explorative alliances and seek innovation by acquiring new resources and expertise externally or exploitative alliances to improve the utilization of capital and assets that can also increase profitability. In this rapidly changing global environment cross border alliances are on the rise for economical viability which have either market orientation Hladik or knowledge seeking orientation. Firms form transnational alliances to acquire technology from other international firms for example R&D alliances to get new and complementary technologies to speed up innovation. In the study of chemical-pharmaceutical industry, Kim and Inkpen found out that technological learning among cross border alliances is strong as firms learn more from the technology that comes out of this international R&D partnership specially when countries offer their distinct technological foundation and opportunities and when combined can bring the best possibilities for both partners. They further indicated that key for an effective alliance to source external technology is firm’s absorptive capacity which Cohen and Levinthal defined as the company’s ability to value, assimilate and utilize external knowledge.

In this paper we will study the motivations for cross border alliances in the emerging
biopharmaceutical industry in Asia in the context of exploration, knowledge seeking, and exploitation; market seeking; and alliance formation. First, a brief overview of the trends in the biopharmaceutical industry in Asia will be presented followed by an added value of specific case studies of how biopharmaceutical firms in the Asian region pursue different sources of competitive advantages through transnational strategic alliances for their long-term success in an industry where cost, time, and innovation are of the essence.

**Trends in the Biotech Industry in Asia**

The biotech industry in most Asian countries is lagging in development, share, and size to that in the US and Europe. It is relatively small in terms of revenues and expenditures on R&D. But governments of some countries like Japan, Taiwan, Singapore, South Korea, India and China strategize that the biotech sector would be one of the next engines of growth for their economies. New biopharmaceuticals for the treatment of diseases common in Asia such as respiratory and infectious diseases, cancer and cardiovascular ailments are the focus of many biotech firms. Expensive and novel medicines may still be unaffordable to the majority of the population in India and China where health insurance system is poor or nonexistent and price is very important for consumers; hence generic drugs are in great demand.

So it is left to Japan, South Korea, Singapore and Taiwan, the more advanced countries in Asia that have advanced health care systems, to serve as important research-based lead markets for innovative but costly medicines. India has a strong bulk and generic manufacturing of vaccines, recombinant therapeutics, and diagnostics most of which are to meet the domestic health needs such as hepatitis B, typhoid, diabetes, cancer, cardiovascular, malaria, cholera, encephalitis, HIV of the billion population. The same is true for China where most of the drugs for sale are generics used for treatment of hepatitis, cancer, stunted growth, diabetes and cardiovascular diseases. With China intensifying its efforts in genomics and stem cells, they have also developed biomedical products for the treatment of hepatitis B, SARS, cancer, anemia, cardiovascular ailments and hepatitis B, the more common diseases in the country. According to Ernst and Young, there have been close to public and private biotech firms in the Asia Pacific market, most of them small, emerging and some being used for offshoring to top Western pharmaceutical firms. A reverse flow of Western educated Chinese nationals has the potential of building a new generation of biotech startups in their home country. In some countries such as South Korea and Japan much of biotech has been conducted within the conglomerates and by firms in
related but established industries – pharmaceutical, chemical, food, beverages and others.

Though the biotech sector in the more advanced Asian countries started decades ago it has remained lagging vis-a-vis their Western counterparts. Most R&D in biotech are still done in public laboratories and national universities, some headed by first class scientists that have access to state-of-the-art research facilities and infrastructures and these institutions often own the patents. In most Asian countries, with a partial exception of India and South Korea, there has been an almost complete lack of science-technology entrepreneurship. Indian biotech entrepreneurship was partly initiated by Indian expatriates mainly from the US, some of whom lately have been returning to their country to start biotech ventures. The other part resulted from spin-offs of well-established pharmaceutical firms, or IT related corporations such as Infosys and Tata expanding to biotech areas as in bioinformatics.

The governments’ role to develop the biotech sector comes in many form and for a different motivation. For one, public research institutions, laboratories and universities are known for their leading roles in R&D, usually in line with the government’s overarching goal of safeguarding the basic needs and health of the local people. Some of the research centers are arms of the government ministries and some small biotech firms are spinoffs from these public and university laboratories. The main purpose of the collaboration between the public institutions and the biotech firms is to find solution to diseases prevalent in the country or region.

The biopharmaceutical industry has become more global where competition has become intense and the pressure to bring down costs and come up with novel drugs posthaste are resolute. In spite of the sluggish growth in the past decades, Asian biopharmaceutical firms are now seeking multiple sources of competitive advantages alongside the government support and guidance. The industry is characterized as risky due to the low rate of success of the R&D reaching the commercialization stage given the large investment in R&D.

**Cross Border Alliances**

In recent years there has been an escalation in cross border alliances in the biopharmaceutical industry which have either a market-orientation or know-how seeking orientation. Firms ally with firms in other countries for various reasons to maintain their global competitiveness in a fast changing global biopharmaceutical market. To substantiate the interdependent science and technology which characterize the biophar-
maceutical sector to get new and complementary technology to quicken innovation and to hasten the commercialization of new products. Why is cross border alliance on the rise? The Heckscher-Ohlin theory explains comparative advantage based on the differences in the nations factor endowments which also explain the differences in cost. Porter on the other hand explains that factor endowment is just one factor that explains the differences in national competitiveness and there are also local demand condition, related and supporting industries and firm strategy, structure and rivalry. These four factors shape the environment of a nation where the local firms compete thus promote the firm’s competitive advantage. Dunning on the other hand offers the location specific advantages theory which states that some resources or assets are linked to a particular foreign location and firms can make use of them in combination with their own unique capability. Cantwell has indicated that competence and technology that a firm may need to have competitive advantage are found and ingrained in some specific countries. This is why firms’ cross border R&D alliances for example seek alliance partners who have not only the firm specific technology but also whose home country has intrinsic capability and technology to offer the alliance that at the end will give the firm global strength. Further to this, Gomes and Casseres posited that transnational R&D alliances allow the firm to acquire what skill another firm has as well as the technological capability that are rooted in the country of the alliance partner and they further stressed that there are natural variations in comparative advantages with regard to technology and this offers the firm a more broad window of opportunity to learn from this natural differences.

Given this rationale for cross border alliances in the Asian biopharmaceutical industry we can detect the prevalence of technology seeking explorative alliances in R&D, manufacturing and clinical trials by forming a synergy of unique and complementary assets for firms, outsourcing of production contract manufacturing to countries that offer innate capability and cost advantage rather than the market seeking exploitative alliance which basically pertains to the fast and efficient commercialization of the new product as exemplified by the following case studies.

Synergy of unique and complementary assets

Learning-by-doing economics suggests that the more the firm produces it can exploit the benefits of the accumulated knowledge as it moves down the experience curve resulting to more efficiency and cost reduction. There will be more specialization and creation of dedicated assets and systems giving the firm competitive advantage. Hence, small biotech firms who want to develop global scale medicines, can share and leverage on their unique
strengths and capabilities or core competences with other firms by forming horizontal alliances across national borders. Merlion Pharmaceutical is a small home-grown pharmaceutical company in Singapore which was a spin off from a public institution, Centre for Natural Product Research (CNPR), a unit of Singapore’s Institute of Molecular Biology. The core assets of Merlion include the world’s largest and most diverse natural product sample library with potential pharmaceutical applications not to mention the high throughput (HTP) screening of natural product samples to discover an array of new bioactive compounds and natural product chemistry, skills for which reason many biotech foreign firms would like to collaborate with Merlion. Banking on these prime competences Merlion has formed strategic alliances with foreign pharmaceutical and biotech firms capitalizing on its collection of natural compounds. Genome Therapeutics (US) Discovery of anti infectives using natural occurring compounds. Abbott Laboratories (US) Drug discovery for therapeutics in the fields of oncology, antiviris, immunology and neuroscience using natural compounds. NovImmune S A (Switzerland) Discovery and development of drugs for immunosuppression and immunomodulation using natural products. Merlion formed only in sought quick expansion by acquiring stocks of two German biotech firms, Combinature and Athelas. Merlion expertise is in screening microbial, fungal and plant sources for new compounds but does not possess its own internal drug pipeline and clinical development capabilities for biopharmaceutics. Rather than allocating substantial time and resources in conducting in-house drug development, the acquisition of Combinature have provided them outright two novel antibiotics that were about to enter clinical trials already.

Japanese pharmaceutical firms would rather invest in foreign biotech firms abroad to invigorate their dwindling pipeline of new drugs. Takeda, Japan invested in Xoma, an American biopharmaceutical company for it to take the lead in the discovery of therapeutic antibodies for Takeda, and Astellas put in US into FibroGen, a biotech company in the US to develop drugs candidates for anemia. For another, Kirin Brewery has invested around US into Merix Bioscience (now Argos Therapeutics) of the US, to do joint activities from research to commercialization of dendritic cell vaccines. With competition in the home market getting severe with foreign multinationals’ market share in the increase due to the deregulation of the pharmaceutical market as well as their aggressive marketing strategies Japanese firms are collaborating with Western biotech firms. In Yamanouchi, Yamanouchi has inked an agreement with Phytopharm, UK, and Takeda with Evotec, Germany for drug discovery alliance for Alzheimer and in Mitsubishi Pharma signed a deal with Vertex Pharmaceuticals to develop and commercialize Oral HCV
Protease Inhibitor VX for Hepatitis C in Japan and the Far East.

Biocon, a leading biotech company in India has partnered with American drug development company Nobex to develop oral insulin for the global market and with a biotech company based in the US, Vaccinex. The Biocon-Vaccinex tie-up involves a joint R&D on therapeutic antibody products for the treatment of cancer, inflammation and autoimmune diseases, combining Biocon’s strengths in clinical research and biologic production and Vaccinex’s expertise in human monoclonal antibodies, a move that would allow them to identify the antibody candidates and proceed with the clinical development posthaste and introduce the new anti-body products in India and in America and Europe. Not only Biocon but other biotech firms in India notably Avesthagen, Serum Institute of India, Biological E have taken the same business model of collaborating with foreign biotech or pharmaceutical firms to strengthen their positions in the biopharmaceutical industry and achieve their financial targets.

Contract Manufacturing

For a considerable number of years now, outsourcing production across borders or what is referred to as contract manufacturing of chemical-based pharmaceuticals to low cost countries in Asia has been a common practice but not biopharmaceutical production although this tendency is already changing. The biopharmaceutical industry in Asia is still in its infant stage and biopharmaceutical firms are still finding their niches but in no time some are proving their track records in terms of capability, cost and quality. In dire need of more resources to fund future R&D activities speedily, firms in Asia resort to contract manufacturing which is more concentrated in technology generation side of the value creation exploration alliance. Moreover, government regulations in Asia such as the revisions of IP protection laws in India and China serve as incentives for outsourcing. In Biocon India launched a low cost human bio-insulin, the recombinant insulin Insugen. Diabetes is a chronic disease worldwide and in India alone it is affecting people in and is forecasted to reach people in years so there is the urgent need to offer insulin at affordable prices. The pressure to meet these local demands worked to the advantage of Biocon. Now it possesses the largest insulin manufacturing plant in India that gives it economies of scale and enables it to sell insulin as low as US international unit per milliliter. Cognizant of Biocon’s insulin product and manufacturing capability, the company has agreed to supply Bristol-Myers Squibb its low priced recombinant insulin requirements. Under this partnership, Biocon can also benefit from the economies of scope when Bristol-Myers Squibb markets the insulin in foreign markets.
Recombinant DNA or Genetic Engineering is an umbrella term for a set of experimental techniques that enable individual genes and DNA sequences to be manipulated. Production of therapeutic products using the rDNA technology has several advantages such as provision of drugs that could not be produced by conventional methods, manufacture of sufficient quantities of drugs and provision for manufacture of safe drugs.

In the global sale of recombinant pharmaceutical products was approximately US $ b. In India, the commercialization of nine recombinant products has been approved - insulin, diabetes drug, alpha interferon, cancer drug, hepatitis B vaccine, GMCSF, G-CSF, blood clotting factor, erythropoietin, a drug used in kidney failure, streptokinase, a drug administered in heart attacks, and human growth hormone. All these products except Hepatitis-B are being imported at a cost of Rs $ crores US $ m. The four major recombinant products with high market potentials in India are human insulin, alpha interferon, and erythropoietin. Domestic and foreign pharmaceutical firms are vying for the rising niche market for recombinant DNA. Erythropoietin in India. With the prevalence of kidney failure and anemia in the country, there is a big market for EPOs estimated at Rs $ crores US $ m. The first to develop EPO was Wockhardt in under the brand name, EPOX and then in after spending Rs $ crores US $ m. Shanta Biotechnics launched its own version under the name, Shanpoietin. Other competitors and their corresponding EPO brand names are LG Life Sciences, Espogen, Ranbaxy, Ceriton, Johnson and Johnson, Eprex, Emcure Pharmaceuticals, Vinter, Intas, Epoft, Zydus Biogen, Zyrop, and Hindustan Antibiotics. Most of these r-EPOs are rather expensive hence their usages are limited. To make the drug more available to treat cancer and kidney ailments, Wockhardt is now selling it at a lower cost of Rs $ US $ ml. and for its part, to compete in the EPO market, Janssen-Cilag CRF, the Indian division of J&J successfully introduced, Eprex by staging a different kind of competitive strategy by contacting the patients directly, educating the nurses and scientific marketing. Competition in the EPO market in India is very severe but in spite of the presence of several biopharmaceutical firms that offer EPOs, prices of the product has not gone down. Cognizant of this, Hindustan BioSciences (HBSL) has a manufacturing contract to produce lower priced Eposino recombinant human erythropoietin at the Shandong Kexing BioProducts Co. facility in China. This is another case where price pushes one low cost country India biopharmaceutical firm to buy from a lower cost country China biopharmaceutical to get a bigger share of the EPO market, targeting people in the middle and low income echelon.
Location Specific Advantages

Firms perform value creation in optimal locations to achieve location economies. Thus firms will locate in areas where there are relatively cheap and high quality factor inputs to reduce the cost of value creation. One advantage of Asia aside from the skilled manpower relates to cost. It costs around US $500m to develop a drug. The innovation and manufacturing costs as well as biotech services in India are less costly by international standards. For example, the price of Shanvac B, a hepatitis B vaccine produced by a local company, Shantha Biotechnics costs only 5 cents close while the imported vaccine costs US $12. Biotech services are being outsourced to biotech firms such as Syngene and SIRO Clinpharm in India which can offer cheap and yet highly skilled labor force. Costs of R&D in India for Streptokinase is US $1m whereas in the US it is over US $20m clinical trials Phase II for Rotavirus cost US $4m in India and over US $10m in the US development and production of Gmp tablets of new molecule-malaria cost US $1m in India and more than US $5m in the US Bharat, Chinese scientists with doctoral degrees get a yearly salary of US $12,000, a mere percent of what scientists earn in the West. Hence complicated R&D such as biological testing can be performed less expensively in China since salaries account for percent of total R&D costs. The savings then can be used to expand their pipeline of potential blockbusters. The screening process of compounds with medical application to novel drugs which has to be verified many times over is very labor intensive. To save on cost Roche inaugurated an US $3m laboratory in Shanghai to screen different compounds that have potential use in anti virus and cancer drugs, and at the same time access to the big Chinese market. For labor intensive services and yet requiring high level skills, China can offer low cost bioservices such as nucleotide sequencing and synthesis, protein expression and library construction. Multinational pharmaceutical firms conduct clinical tests in China where recruitment of patients is not difficult and the related hospital fees are cheaper. For these reasons, Germany’s Mologen is having Starvax of Beijing test the efficacy of a certain compound for a colon cancer drug now undergoing clinical trials in Europe for the treatment of other forms of cancer. WuXi Pharma Tech Co. China was approached by TargeGen, a US pharmaceutical company that is developing small-molecule drugs for cardiovascular ailments to perform chemical screening of various compounds that can be used for further development.

Fast Access to Local and International Markets

Firms can choose either to internalize some downstream activities or collaborate with another company who can distribute the products for them vertical alliance based on
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efficiency gains. The reason behind the formation of across the border vertical alliances among biotech specially biopharmaceutical firms is to secure fast and reliable access to the global market or to previously closed markets utilizing the partners distribution expertise and established network. This is what we refer to market oriented or exploitative alliance. LG Life Sciences of South Korea develops and commercializes new anti-infection drugs, medicines for cancer, diabetes, etc. Some of its well-known drugs are Euvax-B for the treatment of Hepatitis B and LG HCD for Hepatitis C. In Sinovac Biotech of China and LG Life Sciences of Korea have agreed on a sales and distribution alliance. LG Science’s known prowess is its knowledge of overseas market development and its international marketing network. It already has well-developed global sales and distribution networks for its HepB vaccine, including UNICEF programs and distribution to countries. Sinovac Biotech Ltd. specializes in the research, development, commercialization and sale of human vaccines for infectious illnesses such as hepatitis A and hepatitis B, influenza, SARS and avian flu. The two vaccines of Sinovac approved for commercialization are Healive for Hepatitis A and Bilive for Hepatitis A and B combined both seen to have big market potentials in China. Given this, LG Science will sell Sinovac’s Hepatitis A vaccine Healive and for its part of the deal Sinovac will introduce LG’s HepB vaccines in the Chinese market. Sinovac and LG believe that there is tremendous potential for selling LG’s HepB vaccine in China. LG will register its HepB vaccine in China through Sinovac. They will also work together on Sinovac’s influenza vaccine Anflu. Sinovac is the global forerunner in the research and development of SARS vaccine which is already awaiting approval. LG thus seeks to collaborate with Sinovac in the development of the vaccine cognizant that it is a novel drug with worldwide medical application.

Summary

The growth and development of the biopharmaceutical sector in Asia have been quite unique in a way. For one, government support and initiatives were imperative for it to develop to where it is now. Many R&D activities in biotech were done in universities and public laboratories the results of which could not be commercialized that rapidly. Most of the researches have been done in public institutions and laboratories, and researches were focused on the treatment of local regional diseases due to immense political, social and economic implications of not doing so. The biotech firms were either small new biotechnology firms which were spin-offs from university or public laboratories and start ups as well as large firms that have long been doing biotech R&D e.g. Mitsubishi Kasei and Kirin,
Japan. Due to the rapidly changing global business environment and the need to come up with blockbuster drugs and considering the factors affecting the profitability of firms in the biopharmaceutical industry like patent expiration, widespread usage of generic drugs, and escalating costs of R&D to come up with a new drug and yet not knowing whether the new drug will reach the commercialization stage or not, have put a lot of pressure for alliance formation between the biotech and pharmaceutical firms. Biopharmaceutical firms in Asia form cross border explorative knowledge seeking or exploitative market-seeking strategic alliances in an industry where cost, time and innovation are of the essence to increase their market valuation and improve long term profitability. Asian biopharmaceutical firms engage in explorative cross border alliances for the upstream activities of their value creation e.g. R&D, manufacturing and clinical trials which involve forming synergies of unique and complementary assets between partners, contract manufacturing and locating in optimal locations to keep product portfolio flowing, as well as exploitative alliances to bring new drugs to the market before competitors do.

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