

Brokering Strategic Partnerships between Asian and Western Biopharmaceutical Companies in the Global Biologics Market: Assessment of Capabilities of Asian Participants in the Biologics Contract Manufacturing Organization Marketplace

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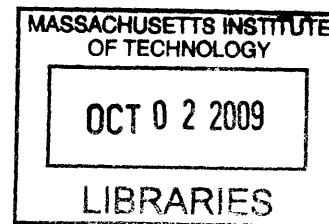
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ABSTRACT

It has become increasingly important for companies in the biopharmaceutical industry to maximize the clinical, commercial and economic impact of their products on a global scale. In this context, both Western and Asian firms have been engaging in international merger and acquisition (M&A) activities to improve global capabilities and competitiveness. The M&A activities in the sector are driven by near-term expiration of blockbuster drug patents and marketplace pricing constraints, resulting in a perceived need to attain improved economies of scale. Across the industry, one can see an increased emphasis on biotechnology medicines (or biologics).

Recent large business deals that have seen Pfizer acquire Wyeth, Merck acquire Schering-Plough and Roche complete the acquisition of Genentech all have some element of positioning around the exploitation of biologics for future growth. These trends are thought to put pressure on medium-/small-sized R&D firms to come up with competitive strategies in the global biologics market. Furthermore, the biologics market faces the threat of biosimilars (biogenerics or follow-on biologics). With the advent of expected changes in the US government healthcare policy, a number of companies will be facing competition from biosimilars in the near term.

Mitigating the impact of the threat of biosimilars, to some extent, is the fact that manufacturing of most non-vaccine biologics is challenging because of the structural and biological complexity of the commercial product as well as the significant differences in the manufacturing process from one product to the next. Technical capacity and the ability to respond to shifting demands are likely to be one of the critical determinants for the success of individual companies in the biologics (and biosimilars) market. To meet the perceived needs, companies have either expanded their manufacturing capacity and capabilities by building in-house facilities or by striking long-term supply deals through contract manufacturing organizations (CMOs). Utilizing highly efficient and cost-effective overseas biologics, CMOs could be a value-added business model for Western participants.

The most dramatic cost-saving strategy would likely result from outsourcing operations to firms in emerging Asian countries like India and China. However, intellectual property protection and quality control issues have been considered problematic in these countries. In this context, other relatively well developed Asian countries-Japan, South Korea (referred to as Korea) and Singapore, which have relatively strong intellectual property protection and sophisticated manufacturing environments, might be strategic partners for Western firms in the contract biomanufacturing markets.

In this research study, the current biopharmaceutical industry trends and global strategies of companies in Japan, Korea and Singapore were explored. As a sub-segment of the biopharmaceutical industry, the geographical features and defining characteristics of the biologics CMO market were examined. The framework for analysis was based on an assessment of the key contributing factors: capacity, capital and cost. The potential capabilities among emerging Asian participants in the global biologics CMO markets were assessed through

personal interviews with senior/executive corporate managers of Asian domestic biopharmaceutical companies (principally Japanese and Korean firms).

As the results indicate, the biopharmaceutical industry of each country has been influenced both by corporate strategy and government policy. The quantitative analyses show that the current biologics CMO market in these countries is underdeveloped with a few existing participants focusing on high-tech biomanufacturing of commercial products. In addition, the macro-and micro-environment of the biotechnology industry in these countries appears to be unfavorable for the development of a global biologics CMO market.

Through individual interviews, it was found that biopharmaceutical corporate managers believe that the opportunities for growth/development of an Asian emerging CMO at the global level are modest, expressing the view that their direct presence in the biologics markets as global-scale CMO participants was unlikely to take place because of financial concerns (high risk investment and profit margin sharing), absence of a global network (no proven track record) and existence of an R&D-intensive corporate culture.

In conclusion, while the capabilities of large and established domestic biopharmaceutical firms in these Asian countries certainly can meet regulatory, legal and technical requirements as emerging global CMO participants, the possibilities for development of a global CMO capability in these countries are likely to be small. Strategic considerations for the possible/likely development paths of the CMO market in these Asian countries are provided.

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1. STATEMENT OF PURPOSE AND OBJECTIVES

Recent large M&A deal announcements and legislative initiatives to change the US healthcare system have highlighted the rapid changes and increased activity that are likely to emerge in the biologics market. For more than 25 years, the market has enjoyed near-monopoly status due to underdeveloped regulatory and clinical evaluation protocols for biosimilars. However changes in US healthcare policy suggest this global marketplace will shortly become more competitive. Recent articles have suggested that partnering with a biologics-focused CMO could be a strategic solution for firms in the competitive biologics (and biosimilar) market place.

Specifically, it has been proposed that overseas contract biomanufacturing outsourcing can bring both innovators and biogenerics makers economic benefits by sharing financial and technological risks. While Western pharmaceutical companies have benefited from highly cost-effective Asian contract manufacturers in India and China since the late 90s (mostly for active pharmaceutical ingredients (APIs) intermediates, and contract research), several reports including those by Datamonitor (15, 54) have suggested that Asian countries with relatively developed infrastructures such as Japan, Korea and Singapore would be suitable regions for contract biomanufacturing. However, the current status of the biologics CMO markets in these Asian countries is relatively limited with few participants compared to the US and EU. Therefore, the objectives of this study are:

- To understand the biopharmaceutical industry trends and global strategies of three Asian countries
- To identify the most important contributing factors associated with development of the global CMO marketplace
- To explore the possible/likely development paths of the biologics (and biosimilars) CMO market in Asia
- To assess capacities and inclinations of emerging Asian participants in the global biologics (and biosimilars) CMO marketplace

2. BACKGROUND

2.1. Current Biopharmaceutical Industry Trends

Over the last two decades, the biopharmaceutical industry (the commercial sector resulting from the convergence of the biotechnology and pharmaceutical industries) has been highly profitable for firms with a therapeutic product orientation. The future for biopharmaceutical products appears promising, owing to the advent of human genome sequence information and the growing availability of new technologies for drug discovery and patient disease sub-typing and stratification. However, the need for increased productivity and efficiency in the drug discovery and development processes is widely acknowledged.

For almost a decade, biopharmaceutical firms have witnessed a declining trend of research and development (R&D) output, especially when framed in terms of new chemical entities, an accelerating cost for R&D advances and increased regulatory burden for new product introduction (25). The high price of drug development is a global headwind that all companies, with which large and small must contend. Multinational biopharmaceutical companies which mainly rely on revenue from small numbers of blockbuster drugs (defined as products with annual sales equal to or above US \$1 billion (bn)) are responding to the challenges of imminent patent expirations by a series of painful restructurings and alliances. They are attempting to devise new and cost-effective approaches to R&D, manufacturing, clinical trials, M&A activities and strategic partnerships to compete with other big participants in the global market.

In recent years, through a series of global acquisition deals, large biopharmaceutical companies have made an effort to expand their presence in the biologics market. Pfizer's growth-through-acquisition strategy has led it from the purchase of Rinat in 2006 (44) and the creation of

a small biologicals research center in South San Francisco to the purchase of Wyeth for \$68bn, giving it a major presence in vaccines and biologics as well as a large Cambridge, Massachusetts site for biological discovery that Wyeth retained following its acquisition of Genetics Institute in 1995 (80). When adjusted for inflation, the bid for Wyeth is smaller than the acquisitions of Warner-Lambert and Pharmacia in 2000 and 2003, respectively, which brought Pfizer the products atorvastatin (Lipitor) and celecoxib (Celebrex), respectively. In 2009, Merck & Co is acquiring Schering-Plough Corp., its marketing partner for Vytorin (the combination of simvastatin and ezetimibe), in a deal worth \$41.1bn (70). Swiss drugmaker Roche Holding AG concluded its purchase of the remaining shares of Genentech Inc that it did not control for \$40bn (35). Among industry professionals, the value of these mega-M&A deals are often questioned, even as the trend continues (71). Top Asian companies such as Takeda, Eisai, and Astellas have been participating in this process by buying US biotech firms such as Millennium, MGI Pharma, and Agensys to gain competitive advantages in the global market (13).

2.2. The Era of Biologics

Considered as a potential sustainable value-creation to these M&A participants, the biologics market has been growing steadily with \$125bn revenue in 2008 (56). Following the introduction of the first recombinant biological product, Humulin by Genentech in 1982, 633 biologics were put in development through 2008, and more than 125 of those made it to the market (43). Although typically expensive compared to small molecule drugs, the new therapies have offered breakthroughs in various diseases including cancer, autoimmune and orphan diseases (14, 37, 72). Market research analysts forecast that biologics will be major sources of revenue growth for large biopharmaceutical companies, with \$169bn in sales by 2014 and

particularly, that monoclonal antibodies (mAbs) will play a key role in this fast growing segment (19).

In contrast to synthetic small molecule drugs, biologicals are derived from living sources, and can be natural or recombinant proteins (e.g. insulin, antibodies), complex carbohydrates (e.g. heparin), complex mixtures of small molecules sourced from natural products (e.g. conjugated estrogens, herbal preparations) or more elaborate structures, such as mixtures of living and dead organisms, as exemplified by vaccines. In general, biologics have more complex characteristics than small molecules in term of size, structure, composition and biological activity. For a number of new therapeutic mAbs intended to be delivered at high concentration, safety concerns regarding a potential for immunogenicity have been raised (21).

Highly-controlled manufacturing, safe and efficient clinical verification, accurate and timely supply chain, and appropriate regulatory and legislative frameworks are required. The total capitalized pre-approval cost for development (R&D expenditure) of a new biologic was estimated to average \$1.24bn in 2006 (22). It is equivalent to or slightly higher than the average development cost for a small molecule, variously estimated at \$800 mn to \$1bn. From 1998 to 2006, the average cost of biologics has gone up 505 percent (31). The capital investment for building a new biologics manufacturing plant (typically about \$400mn) and its operating costs greatly exceed those for chemical drugs (34).

The manufacturing processes for biologicals are usually greatly different from those for chemical entities and the characterization of the final product is considerably more complex (Figure 1). The properties of biologics produced by cell engineering processes, which include

recombinant DNA technology with either microbial (bacteria/yeast) or mammalian cells, may vary depending on the nature of the manufacturing process. Mammalian cell manufacturing with a broader clinical application potential is at the stage of early development relative to microbial manufacturing (10). Additionally, the regulatory compliance framework in the U.S. is more complex regarding biologics manufacturing. Most recently, the US FDA is withholding their permission on Genzyme's request for larger scale manufacturing of Myozyme, because of differences in the chemical structure of material produced in its new Allston, Massachusetts facility, compared with material produced in its original small-batch plant in Framingham, Massachusetts (63).

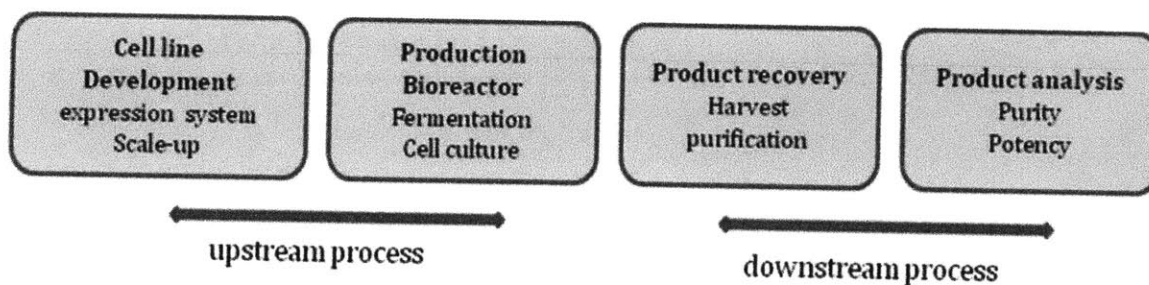


Figure 1. A simplified biomanufacturing process.

Biogenerics (called biosimilars in the EU and follow-on biologics in the US) are biologically equivalent or similar versions of first-to-market entities. According to IMS data (57), the global biosimilars market reached \$1bn in 2007, representing an increase of 5.9% over 2006. While there is no generic biologics market in the US, the biogenerics market in regions such as China and India has been flourishing with product introduction proceeding by an abbreviated process that does not require new clinical trials (52). Groundbreaking biogeneric regulation established by the European Medicines Agency (EMA) opened up the generics market in the EU which entered a new era following the approval of Sandoz's generic epoetin alfa in 2006.

However there remain case-specific safety concerns, requiring close regulatory oversight in the EU approval pathway.

In the US there are strong financial pressures due to medical care cost inflation and widespread failures of healthcare coverage (46 million non-insured residents, 7). In 2008, healthcare spending reached 16.6 percent of the US gross domestic product (GDP), and it is expected to surpass 17.5 percent of GDP in 2009 (71). The current administration has endorsed the development of federal legislation to support biogenerics for the potential savings for healthcare payers and consumers. At present, there is no legal pathway in the U.S. to approve biogenerics or substitute biological entities comparable to what exists for chemical generics. There have been ongoing conflicts between branded biologics developers and the US government authorities in regard to a variety of issues, especially, the length of market exclusivity for branded products (61).

The patents covering a number of novel biologics, especially mAbs such as Herceptin and Rituxan/Mabthera will expire in the short-to medium-term, with an estimated \$25bn worth of annual sales off coverage by 2016 (Table 1). Biosimilars should capture a significant portion of the market with a predicted 10-30% cheaper price in the US and EU with sales of \$16.4bn in 2011 (60). More competition in this sector is expected. Observers have suggested that initial efforts are likely to focus on non-antibody biologics (first-generation biosimilars) which fall into six classifications including erythropoietin, G-CSF, human growth hormone, interferon alpha/beta and recombinant human insulin (36).

Table 1. Upcoming expiration of patents on Biologics blockbuster drugs in the US market

Drug	Generic name	Drug maker	Major therapeutic area	Global Market size(\$bn)	Patent expiry (year)
Enbrel	etanercept	Amgen/Wyeth/Takeda	Rheumatoid Arthritis	5.0	2012
Epogen	epoetin alfa	Amgen/J&J	Anemia	5.3	2013
Remicade	infliximab	J&J/Schering-Plough/Centocor/Mitsubishi Tanabe	Rheumatoid Arthritis	4.4	2013
AVONEX	interferon beta 1a	Biogen Idec	Multiple Sclerosis	1.8	2013
Rebif	interferon beta 1a	Serono/Pfizer	Multiple Sclerosis	1.6	2013
Humalog	insulin Lispro	Eli Lilly	Diabetes	1.4	2013
Newpogen	filgrastim	Amgen	Neutropenia	1.2	2013
Cerezyme	imiglucerase	Genzyme	Gaucher disease	1.1	2013
Rituxan	rituximab	Genentech	non-hodgkins lymphoma	4.5	2015
Neulasta	pegfilgrastim	Amgen	neutropenia	3.0	2015
Lantus	insulin glargine	Sanofi aventis	Diabetes	2.7	2015
Humira	adalimumab	Abbott/Eisai	Rheumatoid Arthritis	3.0	2016
Herceptin	trastuzumab	Genentech	Breast Cancer	4.0	2019
Avastin	bevacizumab	Genentech/Roche	Cancer	3.4	2019
Lucentis	ranibizumab	Genentech/Novartis	Wet Age-related Macular Degeneration	1.2	2019

Source: Evaluate Pharma Company Reports, 2007

As suggested by the seemingly self-contradictory prediction by Claudio Albrecht, ex-CEO of generic group Ratiopham, that “innovative products are the future of generics”, the

challenging issues surrounding branded biologics overlap those of generic biologics. The development cost for biosimilars is expected to be between \$100mn and \$200mn each in contrast to those for small-molecule generic drugs, which are widely believed to range between \$1mn and \$5mn. Also, the biosimilar development process can be almost as lengthy (about 10 yrs) as that for branded drugs, albeit less risky (11). In addition, considering that the scientific and manufacturing technologies and processes of branded biologics are intellectually protected, manufacturing more complex biogenerics in the face of process exclusivity from innovators may pose a big hurdle for generic manufacturers.

There are also potential risks for biosimilars makers in terms of marketing and distribution channels, due to a lack of reputation and insufficient safety data compared to the innovators. Therefore, as Charles Cooney, a professor at MIT, has suggested, the concept of ‘bio-betters’ (or super-biosimilars, second-generation versions of biosimilars) is emerging as a competitive strategy for biogeneric manufacturers. Although biosimilars may appeal to many generic participants as an attractive and promising sector, it might not be favorable to the generic participants who lack financial capital, innovative biomanufacturing capacity, marketing position and distribution channels.

2.3. Potential Strategic Partners in the Biologics Market

One potential competitive strategy for innovators against rising threats of biosimilars will be focusing on developing more complex biologics with solid market and data exclusivity (usually, 5 years of data exclusivity in the US (10 years in the EU) from the day of registration of the drug, 48). Biosimilars manufacturers may have to contend with aggressive price competition for less complex biogenerics in the short-to mid-term and probably, more complex biogenerics in

the long-term. Even for biosimilars, it is widely expected that the establishment of functional equivalence by comparative clinical trials to ensure safety and efficacy will be mandatory to a certain extent in legally stringent regions such as the EU and US. Given these expected conditions, working with emerging participants with internationally acceptable and cost-effective biomanufacturing capacity, followed by clinical trials as well as efficient delivery systems using refrigerated supply chains, may be the foundation of a true value proposition for Western biologics and biogenerics participants.

Biologics outsourcing in the contract biomanufacturing arena appeared in the late 1980s and early 1990s. Biomanufacturing is the most rapidly growing contract manufacturing business, and it is estimated that 35% of biomanufacturers have outsourcing experience for their product(s) (20). According to a Deloitte Report (10), biomanufacturing is expected to grow steadily as the number of biotech drugs increases (projected 50% annual growth rate between 2005 and 2010).

Presently, it is estimated that 15~20% of global cell based-manufacturing capacity (by liters of fermentation capability) is held by CMOs and of that, 75% is controlled by only three CMOs: Lonza, Boehringer Ingelheim and Celltrion (17). Such a high degree of concentration suggests that there is room for market diversification, presenting an opportunity for manufacturers with biomanufacturing capacity and high-quality production. Industry figures see the contract biomanufacturing market in an optimistic light, predicting that the business model of biopharmaceutical companies may switch from FIPCO (Fully Integrated Pharmaceutical Company) to VIPCO (Virtually Integrated Pharmaceutical Company) (Figure 2. Burrill & Co).

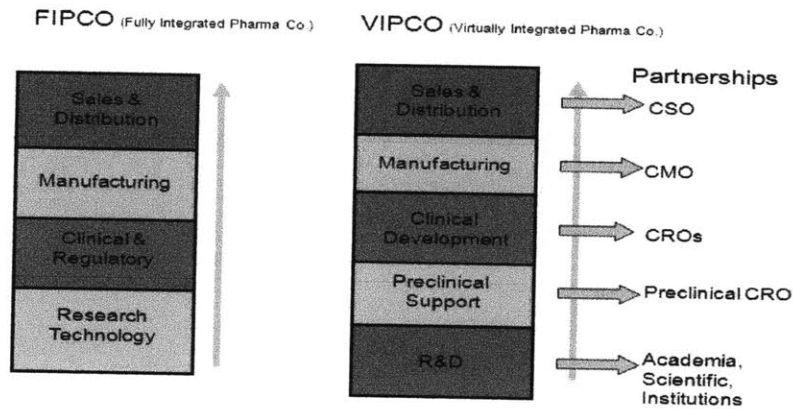


Figure 2. Changing business models

All sizes of firms can use CMOs rather than establishing their own in-house manufacturing facilities in order to minimize production risks. At the same time, CMOs can benefit from contract partnerships by developing and expanding their technical expertise. Global partnerships provide opportunities to overcome language barriers and to understand business culture differences between partners, which can serve as a stepping-stone for further business development. The contract biomanufacturing market is still in the growth/early mature phase compared to the contract pharmaceutical manufacturing business, and high technical capacities and a proven quality system are more important selling points than price (Figure 3, 83)

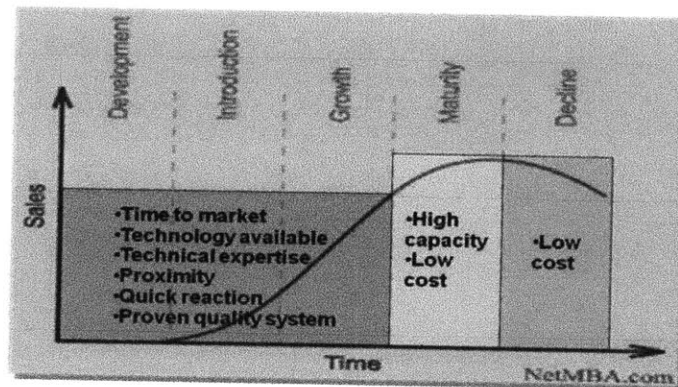


Figure 3. Product line cycle and competitive strategy of CMOs in each phase.

Source: presented by Yvon Tessier at ISPE Annual Meeting (2006)

According to a PriceWaterhouseCoopers (PWC) 2007 report 'Gearing Up for a Global Gravity Shift', 55 % of multinational companies (MNCs) strongly believe that Asia will be at the center of the global pharmaceutical market. After China and India, Singapore and Korea are the key countries in the sights of MNCs. Although the biologics/biosimilars manufacturing business in India and China is growing, some industry experts point out that there are challenges to overcome in these countries in terms of legal and technical infrastructure issues including intellectual property (IP) rights and quality control. In this context, other Asian countries such as Japan, Korea and Singapore may see opportunities. Korea and Singapore have begun to establish themselves as competitive centres for processing and development through the activities of CMOs like Lonza and Celltrion.

Although it is not a low labor cost hub, the US-New England area has been attractive to multinational and domestic biopharmas for biologics manufacturing because of the excellent labor force for R&D, and well-developed marketing and commercialization environment. Multiple high-technological mass-production level biologics CMOs are also located in this bio-cluster area. As one example, Momenta Pharmaceuticals (Cambridge, MA) has developed a practical route to low molecular weight heparin, potentially allowing them to compete with Lovenox, a naturally-sourced heparin product. The possibilities of alliances with academic institutes like Massachusetts Institute of Technology (MIT) or Harvard Medical School (HMS) has also created competitive opportunities in the New England area.

3. OVERVIEW OF THE ASIAN BIOPHARMACEUTICAL INDUSTRY

Like other high-tech industries, the biopharmaceutical industry has become more globalized as companies have become aware of country-specific advantages (CSAs) and business opportunities. Each country has its own biopharmaceutical landscape and global strategy influenced by a variety of components such as human resources, field expertise, financial capital, market size, IP rights and government policy.

3.1. Japan

As the second largest national pharmaceutical market after the US, Japan represents about 10% of the global market with an estimated market value of \$58.5bn in 2008. The modern Japanese pharmaceutical industry has a long history with Takeda, the largest Japanese drug firm, founded in 1781. Following the introduction of universal healthcare insurance coverage in 1961 and Japanese patent law reform in 1975, Japan grew rapidly from a manufacturing hub to an R&D center through the 1980s. However, during the late-80 and early-90s, the Japanese pharmaceutical industry market growth stagnated, amidst adverse economic and health policy conditions including a nationwide economic slowdown, the introduction of a National Health Insurance (NHI) serial drug price-cut policy in 1988, and attendant sluggish market growth for the prescription drug segment (53)

The sagging domestic environment motivated Japanese global participants such as Takeda (domestic-1st and worldwide-16th, 2008), Astellas (2nd, 20th), Daiichi Sankyo (3rd, 22nd) and Eisai (4th, 25th) to more actively explore global business opportunities in the late-90s, and to attempt to penetrate the global market with their own business strategies. Whereas Takeda

gained a foothold in the US by the formation of a joint venture with Abbott Laboratories (in the late-70s), Eisai entered the market by establishing overseas research and development operations directly. Astellas, formed by the merger of Yamanouchi and Fujisawa, (founded in 1894 and 1923 respectively), continued to pursue its strategy of monetizing Japanese innovation through marketing deals with multinational pharmaceutical companies.

A similar merger between Daiichi/Sankyo (Daiichi Sankyo) and Mitsubishi/Tanabe Seiyaku (Mitsubishi Tanabe) has led to the possibility that large consolidated Japanese firms may be thinking of developing sales and marketing capabilities in the US and EU. Corporate culture has shifted to some extent from traditional Japanese seniority-based models to more Western management, with a trend towards appointing young and innovative presidents for big corporations (for example, Yasuchika Hasegawa for Takeda and Takashi Shoda for Sankyo). So called triangular mergers have recently allowed foreign companies to use their stock to acquire or merge with Japanese assets (46).

The total sales of the top 10 firms account for approximately 45% of the overall sales of the Japanese biopharmaceutical industry in 2008 (4). A large portion of top four corporate sales come from the US market. Like other Western multinational biopharmas, they are also facing a “2010 crisis” of blockbuster drug patent expiration. Japanese firms have been expanding their pipelines through a series of acquisitions of US biotech firms, including the Takeda acquisition of Millennium (Velcade and potentially, biologics, \$8bn in 2008), Astellas of Agensys (biologics, \$387mn in 2007), and Eisai of MGI Pharma (biologics, \$3.8bn in 2007)/Morphotek Therapeutics (biologics, \$325mn in 2007) (13). In addition, the trading companies Kowa and Mitsui & Co

USA Inc have joined the trend by acquiring US firms ProEthic Pharmaceuticals and MED3000 Group, respectively.

Currently, there are approximately 1,660 biopharma companies (1062 pharmas and 600 biotech firms), of which about 416 are branded-name prescription drug manufacturers and approximately 70 are generics-related (4, 29, 33). Japan is at the forefront in terms of new drug innovation with a high-quality R&D environment (2nd rank in patents and annual publication record after the US in 2005) and clinical infrastructure (220 hospitals).

However, owing to accelerating national healthcare spending (6.8% of GDP in 2008 and 7.7% in 2013, 75) on an ever-increasing elderly population (27% of the population over 60 years old in 2007, WHO Statistical Database), the healthcare reforms promoted by the Japanese Ministry of Healthcare, Labor and Welfare (MHLW) have been driving the Japanese consumer to the generic drug segment. The government has encouraged doctors to prescribe cheaper generics to consumers as an attempt to overcome the patients' preference for branded drugs.

Consequently, the Japanese generic market share has shifted up from 4.7% in 1999 to 17% in 2008, although the share is still low compared to those of other countries (58% in US). In June, 2008, Daiichi Sankyo acquired Ranbaxy, the largest Indian generic manufacturer, in a \$4.6bn transaction to expand its generics pipelines in India, potentially leading to Japanese market introductions (77). In addition, Japan recently opened up the over-the-counter (OTC) sector to supermarkets and convenience stores (76). It appears likely that the trend towards increased consumption in the generics sector will continue.

While it is expected that the government biannual price-cut control system will intensify pressure on top Japanese biopharmas to increase overseas sales, the new wave of generics has

not made a significant impact on their global business strategies. Senior and executive managers in some of these companies believe that their R&D investment and innovation platforms have long-term value (anonymous, personal communication). It has also been reported that the Takeda R&D headquarters (located in Osaka, Japan) will be transferred to its US global R&D center (in Chicago) in the near term (74).

As seen in recent serial M&A deals, the rise in acquisition activity by top Japanese companies in the US has been associated with an expansion of their biologics R&D pipelines. This segment in Japan has seen substantial domestic growth, reaching total sales of \$680mn by 2007 (4) but lags far behind the US market. Recent data indicate that around 40 biologics were in some phase of clinical trial in Japan in 2007 and only 14 biologics in 2008, compared with 234 in the US (46). According to La Merie Business Intelligence, Chugai (\$1.3bn) Kyowa Hakko Kirin (\$51mn) and Mitsubishi Tanabe Pharma (\$264million) are the major biologics participants by sales in 2008. There are also several biologics contract manufactures such as Asahi Glass and TOYOBO Biologics.

With rising medical costs and a growing need for more complicated treatments, the Japanese biosimilars market will certainly grow. Regulatory structures and guidelines for biosimilars have been under development, and recently Japanese authorities have published guidelines for a national biosimilar regulatory pathway, based on a path analogous to that established by the EU approval process. As a result, in June 2009, Sandoz, a generic subsidiary of Novartis, received the first approval in Japan for a biosimilar, recombinant human growth hormone (66).

Industry experts point out that Japanese firms are disadvantaged by high costs for facilities, marketing, and central laboratories (approximately four times those in Korea and Singapore as well as twice those in US and EU) and by time-consuming regulatory processes and slow patient enrollment in clinical trials (8). There are more than 30 clinical contract research organizations (CROs) in Japan with the increasing demand by pharmaceutical companies (5). Thus, the clinical trial market in Japan, which was estimated to be approximately \$27mn in 2004, is expected to grow to \$180mn by 2010 (42). A significant portion of this growth has come from international CROs that have set up branches in Japan. Following a 2004 revision of the Pharmaceutical Affairs Law on research data requirements for drug registration, clinical data conducted in other countries can now be accepted in Japan.

Global Japanese firms are willing to establish clinical programs in foreign countries, and then bring the consolidated data to the Japan (Hiroki Yoshihara, CEO, Transpect Company, Yokohama, Japan, personal communication). In most cases, experimental medicines are required for clinical study with a certain number of Japanese participants to prove that efficacy and safety are not skewed by ethnicity. Some Japanese experts predict that Japan is unlikely to produce more than a handful of biosimilars domestically both because of the prevalent innovation-centric culture as well as the constraints of expensive manufacturing and clinical trials (23, 27).

3.2. South Korea

The Korean biopharmaceutical industry largely grew out of companies with fermentation and chemical manufacturing capabilities (40). Government support programs such as the Han Project and the BK 21 project were launched during the 1980s and 1990s, and chemical companies such as Lucky Goldstar Chemical (now LG Life Sciences) became interested in

exploring the sector (68). The recent government Biotech Vision 2016 program established in November 2006 and other incentive programs (e.g., tax incentives, cash grants, etc) for foreign direct investment (FDI), have helped the industry to grow to the 12th largest in the world with a market value in 2008 of \$9.8bn, representing a compound annual growth rate (CAGR) of 10.4% since 2004 (12)

With four regional bio-clusters including the Incheon Bio-Medical hubs, there exist approximately 1813 biopharmaceutical firms (553 drug manufacturers and 600 biotech firms). According to a Korean Pharmaceutical Profile 2006 provided by the Korean Drug Research association (KDRA), about 11% of biopharmaceutical companies such as LG Life Sciences, SK Life Science, Crystal Genomics and Cha Biotech are R&D focused. The top 10 companies account for 35% of the market by volume, and 39% by value in 2007 (12). While domestic companies dominate the volume market with generics, large biopharmaceutical companies such as Pfizer, Merck &Co and GlaxoSmithKline (CSK) hold a large portion of the total market share by price.

Like other Korean companies in high-tech industries, the major biopharmas mostly originated from large, family-owned multinational enterprises called as *chaebols*. Some biotech firms such as Cha Biotech are also family firms. Most Korean big biopharma participants still have conservative seniority-based management systems, partially due to their unwillingness to give up family-owned business strategies. Thus, mergers and acquisitions are not a prevalent practice in South Korea. However, potential M&A transactions might attend the globalization of Korean biopharmaceutical companies in a competitive market.

A driver of Korean market growth is an aging population (14% of total population over 60 yrs in 2006) with its related demand for treatment of chronic diseases such as cardiovascular disease (\$1.4bn of retail sales in 2007), cancer, and CNS disease. The expected liberalization of the over-the-counter (OTC) medicine sales is also expected to contribute to growth (58). Until recently, most Korean biopharmas have heavily concentrated on the generic-oriented domestic market. Compared to most developed markets such as the US and EU (17-30%), the generics market share in Korea has accounted for 34% of the total market in 2008 and is expected to increase by 35% in 2013 (59)

While there are potentially core capabilities in early drug discovery and development (world top 3rd in patents productivity, and 13th in annual publication record in 2005), financially insufficient investment activities from biopharmas, government and venture capital firms have limited innovative R&D and commercialization in the domestic and global market (38). Korean companies have mostly focused on preliminary studies and phase I trials; R&D spending as a proportion of sales (4-6% in 2004) is low compared to that of multinational biopharmas (10-25% in 2004) and government R&D investment in Korea (\$708.6mn in 2005) is low compared to that in the US (\$29.5bn in 2005).

However, the industry is changing. The Korea-US free trade agreement (KUFTA) talks initiated in 2005 have created momentum to spur Korean participants to leverage their economies of scope and scale to focus on global marketing. Proactive global R&D investments from major biopharmas (93 % R&D spending to net profit) and increasing interest in domestic and global funding mechanisms are emerging phenomena. Specifically, private and corporate investors such as Burrill & Co, MPM Capital and Novartis Venture Fund (NVF) have been

attracted to joint investment business opportunities with Korean government support. Recently, Korea's Ministry of Knowledge and Economy (MKE) has committed \$20mn each to Korean private equity STIC Investments and Burrill & Co for funding up to 35 private companies including biotech firms (18).

According to recent data from the Korea Drug Research Association (KDRA), seven new drug candidates developed by four Korean firms including LG Life Science *Factive* (antibiotics) have been approved by the US FDA for commercialization or clinical trials. In 2008, 45 out of 154 R&D projects from 34 major biopharmas in Korea are in the clinical phase (28). A recent focus in the new drug development industry in Korea emphasizes a shift from small molecules to biologics, although a number of companies still stay in the competitive small molecule sector for certain therapeutic areas. For example, SK has worked on small molecules for central nervous system (CNS) disease treatment (in general, biologics do not cross brain–blood barriers). Forty one of the 280 clinical trial approvals in 2007 were biologics; mainly recombinant proteins (12) and 12 out of 112 R&D projects were for biologics (28). However most of the biological market products developed by the Korean biopharmas are licensed biosimilars.

Historically the domestic sales environment had been highly protected from foreign pharmaceutical companies by restriction of access to the national health care insurance system. Regulatory transparency with regard to drug approval, pricing and reimbursement as well as patent rights appear favorable to domestic firms. There are 350 current CGP (cGMP), Korean GMP (kGMP), or behavioral GMP (bGMP) certified companies in Korea (41). The Korean government has implemented compliance policies and regulations including IP rights, GMP and

GCP to meet global regulatory standards. Under the circumstances, generics-dependent manufactures will face pressure to come up with new sustainable business strategies.

The Korean outsourcing segment has grown rapidly and most Korean CROs are clinical research organizations. The total contract research market size of Korea is estimated to be approximately \$50-\$100mn, with a \$30-\$50mn clinical CRO market (81). The attractions of a cost-effective territory, well-developed information technology (IT) and a good regional clinical trial infrastructure (most of the major hospital are located in the Greater Seoul area where about half of the Korean population resides) have attracted attention from top global biopharmaceutical firms such as Pfizer. Its clinical centers were transferred from Japan to Korea following a \$300mn investment in 2006 (47). Regulatory policies to accelerate Korea Food and Drug Administration (KFDA)'s investigational new drug (IND) approval timeline and to restrict unnecessary regulations associated with the conduct of global clinical studies have been implemented in 2008 (1). Korea now has similar timelines to the US for approval of a clinical trial application, within 30 working days (compared to the US 30 calendar days) and the Institutional Review Board (IRB) approval process can occur in parallel with the regulatory submission.

In the manufacturing industry, there are two CMOs in Korea, Celltrion and the Korean Biotechnology Commercialization Center. Celltrion, Asia's largest CMO for biologics, is located in the new Songdo City, a free economic zone near Incheon airport that opened in 2007, which provides significant tax incentives and convenient commercial transportation for its supply chain (2). Founded in 2002, Celltrion has a long-term contract with US Bristol-Myers Squibb (BMS) and deals with Sanofi-Aventis, MediGene, and CSL. As a top-ranked firm in the Korean

domestic stock market, it has been enjoying success with an increase of 258% in revenues (\$32.3mn) in the first quarter of 2009 compared to that of 2008, and 600% of growth of share price since the initial public offering (IPO) in 2007 (3).

Reacting to the dramatic growth of Celltrion, some large Korean biopharmaceutical companies have been planning to get into the biosimilars manufacturing segment. However some participants like CJ pharmaceutical withdrew from the market because of unmet expectations in terms of return on investment (ROI). To date, LG Life Sciences, Dong-A, Daewoong/Genexcell, Hanmi, SK, Hanhwa Chemical, Hanall, Green Cross and an electronics/semiconductor global giant, Samsung electronics/Isu Abxis have shown an interest in the biosimilars sector (the Korean Herald, June 2009) (70, 73). Together with a National Smart Project to invest \$300mn into the biosimilars sector, the Korean government is planning to set up its guidelines and regulations on biosimilars drug development in the next several months (79).

3.3. Singapore

Singapore is the 4th wealthiest country in the world in terms of GDP per capita (\$51,142 in 2008, World Bank). It is closely managed by its government, from macroeconomic policies to the supervision of government-linked companies (GLCs). Within a relatively transparent and free-market-oriented environment, it has been heavily dependent on outsourced manufacturing, IT and export-driven trading businesses. However, to adapt rapidly to the competitively changing environment in a highly interconnected world, since the beginning of the new millennium, Singapore has directed its efforts towards a knowledge-based economy (16).

In an effort to transform Singapore to a “Biopolis” of Asia, a biomedical sciences (BMS) and enterprise ecosystem integrated strategy was launched by the Agency for Science,

Technology and Research (A*STAR) of the Economic Development Board (EDB) in June 2000 (62). During the first 5 years (2001-5) of the BMS Initiative, promoting innovation through the accumulation of intellectual and industrial capital was the government's special focus with a budget of \$7bn. Recruitment from international scientific talent pools and educational joint venture programs with the top-notch academic institutes such as MIT (Singapore-MIT Alliance, SMA), Johns Hopkins and Wharton was actively initiated during this period (John Desforge, Executive Director, SMA, personal communication).

Located close to biomedical scientific centers such as National University of Singapore and the Singapore Science Parks, the Biopolis in One North Park established its presence as a major R&D center in various fields including genome and stem cell research. Based on its innovative culture, low language barriers, large workforce (16,000 employees in R&D and manufacturing), patent and data exclusivity protection (consolidated by the Singapore-US FTA signed in 2003), the biopharmaceutical industry has dramatically grown to the current status with approximately 130 biopharmaceutical companies in less than decade. According to the data from Singapore EDB, currently there exist five corporate R&D centers in Singapore, including those of Novartis, GSK, Lilly and Takeda.

According to BMI's Business Environment Rankings table for Q209, Singapore ranked 4th out of 15 key countries in the Asian region (after Japan (1th), South Korea (2nd) and Australia (3rd)), based on its urban market, aging population and predictable operating climate. Singapore and South Korea have shown great potential in the relatively low-risk manufacturing sector, ranked in the world top 1st and 2nd in the international manufacturing innovation index (32). As a high-value manufacturing hub, the biomedical manufacturing business in Singapore has grown

from about 5% in 2001 of total manufacturing output up to more than 30% with a record US\$14.8bn in 2008. Top biopharmaceutical companies' manufacturing facilities for active pharmaceutical ingredient (API) and biologics are located in Singapore, with more than 25 cGMP pharmaceutical plants in the Tuas Biomedical Park. For biologics manufacturing, Singapore has been building up capabilities since 1990. The Bioprocessing Technology Institute (BTI) funded by A*STAR and A-Bio Pharma Pte Ltd (A-Bio), a CMO owned by Bio*One Capital, a subsidiary of Singapore-based EDB Investments, are major domestic participants.

Having capabilities across the biologics value chain are a number of foreign biologics manufacturers such as GSK, Merck-Schering-Plough, Pfizer-Wyeth, Novartis, A-Bio, Genentech and Lonza. In the last few years, Singapore has attracted four major biologics investments totaling approximately \$1bn (57) including Genentech, GSK and Lonza. After forming a joint venture with Bio*One Capital in 2006, Lonza, a Swiss CMO, is building a third 80,000 liter cell culture facility in Singapore through 2011 based on internal financial investment (\$27mn). Lonza has 12 cGMP-certified cell therapy manufacturing suites in other locations, including New Hampshire, US. With its global presence and expertise in proprietary microreactor technology (MRT), Novartis recently entered into a partnership with Lonza to scale up its biologics pipeline (June, 2008).

In the BMS Phase 2 development project (2006-10), Translational and Clinical Research (TCR) is a major focus with a \$1.4bn investment. The clinical trial industry in Singapore has grown with the influx of multinational biopharmas. With diverse demographics to its population of 4.68 million (70% Chinese, 20% Indian and 10% others), developed infrastructure and good regulatory framework for ethical translational medicine and clinical trials including GCP

guidelines (established in 1998), Singapore is well-positioned to be a translational research center. The regulatory processes in Singapore, together with Korea, are said to be the most streamlined, quick, and predictable in the Asian region (50). The average regulatory approval period is approximately four weeks followed by an additional four to six weeks for site-level IRB/ethics committee (EC) approval.

Currently, early-stage clinical trials (phases 1 and 2) and late-stage clinical trials (phases 3 and 4) are conducted by Eli Lilly, Pfizer or Merck in partnership with local hospitals like National University Hospital and Singapore General Hospital. Through the in-house activities of biopharmaceutical companies as well as the operations of 14 clinical CROs, clinical trials conducted in Singapore focus on four key therapeutic areas: oncology, clinical pharmacology, gastroenterology/hepatology and cardiology, representing the niche areas with the prevalent Singaporean medical expertise (9). There is no legal framework in place for biosimilars in Singapore yet. The guidelines for biosimilars in development are expected to closely reference those of the EMEA (24). Recently, Teva (an Israeli generic firm) and Lonza established a joint venture approved by the European Commission, targeting the biosimilars market (Jan, 2009).

The domestic biopharmaceutical market in Singapore is limited by its small size (\$561mn market value in 2008). The local market is expected to grow modestly to \$660mn (2.08% CAGR) through 2013. In addition, the domestic academic and industrial R&D activities of Singapore-based biopharmas have been relatively low compared to other Asian countries by patent productivity (24th) and the number of domestic companies involved in drug discovery and development (82). However, with its strong government involvement, it has established a good international position as a science and technology R&D hub.

4. HYPOTHESES

While a large portion of the commercial biomanufacturing business is controlled by biopharmaceutical companies, there are substantial opportunities for biologics (and biosimilars) CMOs driven by the increasing number of biological products including mAbs in approval/development, upcoming blockbuster biologics patent expiry and cost pressures (34). Thus, the CMO industry is expected to continue to grow at a steady pace by providing competitive value to biopharmas, both large and small, and both innovators and biogeneric makers. While Western biopharmas are increasingly offshoring to Asian countries to obtain price advantages and other benefits, Asian CMO participants in the biologics sector might be greatly restricted to the countries whose biomanufacturing infrastructure capacity is well qualified. Within this context, the following major hypothesis was developed.

Asian participants, whose domestic environment is relatively well-developed and highly regulated such as Japan, Korea and Singapore, have sufficient capabilities to serve as strategic partners with Western participants in the global biologics CMOs markets.

In an attempt to test the hypothesis, several sub-questions were formulated as follows.

Question 1: What are the defining characteristics of biologics CMOs and geographical features of the biologics CMO industry?

Approximately 100 biologics contract outsourcing manufacturers were analyzed based on their location, manufacturing capacity and original expertise. Biologics CMOs were broadly divided into two groups-Western (US, Canada and EU) and Asian. With the intent of understanding the characteristics of the distribution of CMOs in terms of technological

manufacturing capacity, sub-classifications of CMO biomanufacturing capacity were defined as follows:

- A large-commercial-scale CMO has a cGMP facility (or facilities) equipped with bioreactor (s) (for cultivation of mammalian cells) or fermentor(s) (for cultivation of microbes) with a capacity greater than 5000 liters.

Question 2: What are the important contributing factors associated with the development of the biologics CMO market? What are the competitive advantages and disadvantages for biologics CMO market formation in three Asian countries, Japan, Korea and Singapore?

It has been reported that the contract biomanufacturing industry has been developed by external and internal forces within the framework of capacity, capabilities, capital and cost (17). According to a CIBC World Market report, a high initial capital cost of \$400mn and a four year engineering and commissioning time are required for a CMO to build a cGMP-compliant biologics plant. Through empirical analysis based on a firm's market cap and cash reserves, they concluded that the majority of US-based biotech companies, excluding the leading biotech firms such as Amgen, Genentech, and Biogen Idec, would not likely have the \$400mn cash reserves or be able to attract the financing to undertake such a capital campaign. Moreover it has been reported that 65 % of US biotech companies fall in the micro-cap (<\$250mn market cap) category and are operating with less than a year's cash in hand (6). Therefore, from a financial perspective, the following plausible assumption was made:

- Biotech firms who do not have minimally greater than \$250mn market cap are unlikely to make the investment to build a commercial scale-manufacturing facility.

Upon the assumption that capacity (technology and regulatory compliances), capital (financial management) and cost (labor costs) are the most important contributing factors to the development of the CMO market, comparisons were made among the three Asian countries in the area of biotechnology where a majority of biologics CMOs were originated.

Question 3: Are there Asian emerging participants in the global biologics CMO market? What are the possible/likely development paths of the biologics CMO market in these Asian countries?

To explore prospects and potential for growth for the global biologics CMO market in Asian countries, the capabilities of large and established Japanese and Korean biopharmaceutical firms in the biologics (and biosimilars) market were assessed with a special focus on their financial status, core portfolio, business transaction activities and corporate strategies. Based on the initial assessment of capabilities of these Asian firms in the biologics CMO marketplace (Table 6), individual interviews with senior/executive corporate managers among the Japanese and Korean biopharma companies listed in Table 6 were performed to investigate their capabilities for, and likelihood of participation in, the global CMO marketplace. To explore alternate views of the potential development of the biologics CMO market in Asia, the interview subjects also included non-corporate managers such as senior government officials and venture capitalists.

5. METHODS

Relevant data were collected through qualitative and quantitative methods, literature reviews and individual interviews.

5.1. Literature Reviews

Data for biopharmaceutical contract manufacturers and Asian biopharmaceutical companies were collected through various sources including the Windhover In Vivo publication, free directory data bases, company websites, press releases, news reports, journal reports and government data bases (26, 30, 39, 45, 49, 69). Since the global biologics CMO market as a sub-segment of the industry is relatively small, a sample of 109 currently active CMOs was identified and evaluated. Biologics CMOs were defined as contract manufacturing service organizations for both classes of biological products; large and complex protein products such as growth factors, vaccines, and mAbs as well as small and simple products such as peptides and naked DNA.

Each company in the cohort was studied to determine its defining characteristics for biomanufacturing capacity, geographic location and original industry background (history) through online resources. The use of bioreactors was taken to indicate the capability to cultivate animal cells and the use of fermentors was taken to indicate the capability to cultivate microbes. Several organizations did not disclose their manufacturing capacity. In such instances, the company was classified as a small-commercial-scale CMO. The European and North American pharmaceutical contract manufacturing sector was categorized into three tiers as follows.

- Tier 1. End-to-end service providers from clinical trials to logistics and marketing.
- Tier 2. Service providers from early stage project development to commercial level manufacturing.
- Tier 3. Service providers for the generics industry.

In this study, the global biologics CMO is considered a Tier 2 CMO equipped with regulatory compliant (cGMP) high-tech facilities. To evaluate emerging CMO participants in Asian countries, only domestic biopharmaceutical firms were regarded as potential candidates. For example, a majority of multinational biopharmaceutical companies in Singapore were excluded because of their foreign nationality.

5.2. Personal Interviews

Individual interviews through in person (on-site visits) or by telephone with biopharmaceutical industry associated professionals were conducted during spring and summer 2009. Interviews with Asian biopharmaceutical firms and CMOs were largely arranged by Asian government agencies including the Japan External Trade Organization (JETRO, New York, US), the Korea Trade-Investment Promotion Agency (KOTRA, New York, US) and Singapore's Economic Development Board (EDB, Boston, US).

On-site interviews were typically one hour in duration, and were conducted with senior /executive corporate managers at four major Asian (three Japanese and one Korean) and four major Western (three US and one EU) biopharmaceutical companies located in the US. The interview subjects (director-or executive director-level, strategy management and global business development) were selected because of their combined abilities of specialized industry knowledge and strategic decision-making position.

The major purpose of the on-site interviews was to explore competitive corporate strategy in the global biopharmaceutical industry. Through personal interviews with Western corporate managers, perceptions of the competitive outlook for Asian countries were investigated. The

capabilities and possibilities of Asian participants in the global biologics CMO markets were assessed by phone interviews (of average 15-20 minute duration) with five senior/executive corporate managers of major Korean domestic biopharma companies.

To explore the possible/likely development paths for the biologics CMO market in Asian countries, non-corporate groups-government and investment banking/venture capital professionals were interviewed with respect to their views of the multiple criteria associated with the development of CMO infrastructure: capital, cost and capacity. The group interviews were collected from four Asian venture capitalists and four Asian government officials at the partner (VC) or senior official (government) levels. Their common and country specific perspectives on the possible development of global CMOs in Asia countries were explored.

6. RESULTS

From the initial research, it was found that the biopharmaceutical industry of each country, Japan, Korea and Singapore, has adopted different global strategies. Singapore has served in the facilitation role as an excellent R&D and manufacturing base for multinational biopharmaceutical companies since the Biomedical Sciences Initiative (BMI), a national policy established in 2000. Japan still maintains a strong innovation culture although the biannual national healthcare pricing-cut policy (initiated in 1988) contributes to the momentum towards increased generic usage.

The Korean industry is slowly moving from generics-oriented manufacturing intensive business to R&D under pressure from a Korean-US Free Trade agreement (KUFTA) talk starting in 2005. Because of their long-standing presence in the domestic generics market, Korean biopharmaceutical companies have a relatively strong track record in manufacturing compared to Japanese and Singapore domestic firms (Figure 4).

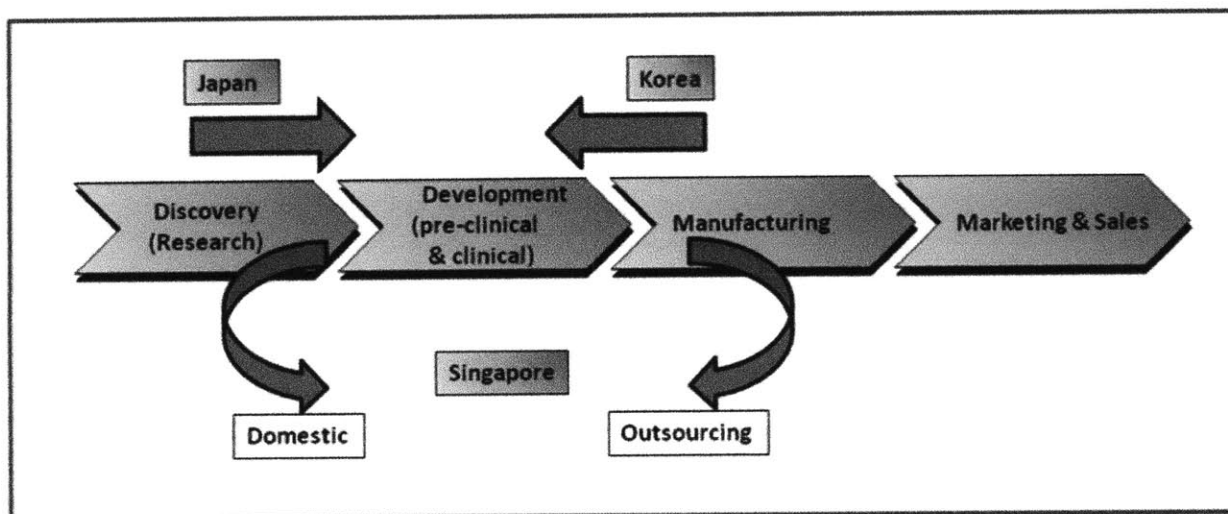


Figure 4. Current changing landscape in the biopharmaceutical industry by country.

Question 1: What are the defining characteristics of biologics CMO and geographical features of the biologics CMO industry?

One hundred and six contract biomanufacturers worldwide with GMP capacity were identified for this study. However, some CMOs like Lonza operate facilities in several different locations. The geographically distributed facilities of global CMOs were treated as independent CMOs for the analysis, creating a total of 109 CMOs. The data also included the projected production capacity for biopharmaceutical manufacturing to 2011. The biologics CMOs include 55 companies in North America, 35 in Europe and 19 in Asia-Pacific. The data show there are approximately four times more Western CMOs than Asian CMOs (Table 2).

According to a biologics CMO database held by Eden Biodesign, UK in 2007, out of 113 tracked companies, 61 are North American, 41 European and 11 Asian (17). Most of the large-scale mammalian production capacity of Chinese and Indian CMOs shown in Table 2 consists of projected (not existing) production capacity for three years (2009-2011). It can be seen that there is a small but growing number of emerging participants in the Asia-Pacific region, especially in China and India.

Interestingly, it was found that 80% of Western participants have been engaged in the small-or medium-scale commercial biomanufacturing business, which is different from the Asian CMO firms which focus on large-scale manufacturing production. The majority of CMOs in emerging countries such as India focus on high-yielding microbial expression systems, whereas three Asian countries, Japan, Korea and Singapore, are interested in utilizing advanced technological mammalian systems, holding 47% of the current and 33% of the projected (up to 2011) worldwide outsourced mammalian cell-culture manufacturing capacity.

It is not surprising that a majority of CMOs are biotechnology-related (Figure 5). As shown in Table 3, non-biotech-derived-major biologics CMOs such as Lonza have gained their capabilities and performances in the biologics CMO market through strategic deals such as alliances, acquisitions and joint ventures with biotech firms. This implies that firms with no or little biomanufacturing capacity can have a strong market presence through strategic partnerships in the industry.

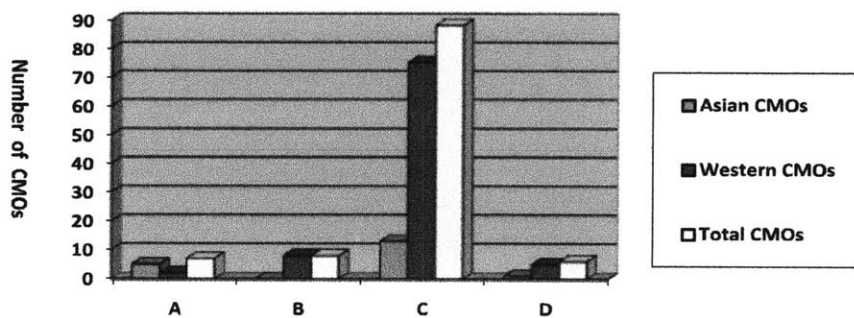


Figure 5. Characteristics of Asian and Eastern biologics CMOs based on historical origin. A: government-derived, B: Academia-derived, C: Biotech-derived, D: Non-biotech-derived.

Table 2. The number of biologics contract manufacturing organizations (CMOs); analysis of manufacturing capacity/expertise based on geographic location.

Manufacturing capacity	Total Western CMOs (US/Canada/EU)	Total Asian CMOs (Japan/Korea/Singapore)	Asian CMOs (China/India)	Total
Number of total CMOs	90 (47/8/35)	19 7(2/3/3)	7(3/4)	109
Number of CMOs with small-commercial-scale manufacturing capacity (<5,000 liters)^{1,4}	71 (38/6/27)	10 4(1/1/2)	3(2/1)	81
Number of CMOs with large-commercial-scale manufacturing capacity (>5,000 liters)⁴	19 (9/2/8)	9 3(1/1/1)	4(1/3)	28
Mammalian cell culture capacity (liters)^{2,4}	256,262 (198,090/32,000/26,372)	250,100 165,200 (5,200/80,000/80,000)	36,600(20,500/19,100)	499,362
Microbial production capacity (liters)^{3,4}	130,566 (23,266/3,100/104,050)	646,920 3,500 (3000/500/----)	552,800(----/552,800)	777,336

1. Several organizations did not disclose their manufacturing capacity. In these instances the company was classified as small-commercial-scale. 2. Bioreactors are used to cultivate animal cells. 3. Fermentors are used to cultivate microbes. 4. Data includes production capacity for biopharmaceutical manufacturing projected to 2011

Table 3. Characteristics of Non-biotech-derived biologics CMOs.

Biologics CMO name	Nation (founding year)	Size (market cap, 2009)	Original Industry Background	Business transaction activities
Lonza Group AG	Switzerland (1897)	\$5.2bn	Fine Chemical	Acquisition of Celltech Biologics (1996); Acquisition of microbial biopharma divisions from Cambrex Co (2006)
Akzo Nobel (Diosynth)	Netherlands (1923)	\$13.15bn	Industrial chemical	Acquisition of Covance Biotechnology (2001)
Celltrion	Korea (2002)	\$1.4bn	Electronics engineering	Joint venture with VaxGen, a US biotech firm(2002)
DSM N.V.	Netherlands (1902)	\$4.7bn	Coal mining and fine chemical	Acquisition of Andeno, a biotech firm (1887)
Asahi Glass Co	Japan (1907)	\$10bn	Fine chemical and glass manufacturing	Strategic Alliance with DSM (2000)
Wacker Chemie AG	Germany (1914)	\$4.8bn	Silicon and Fine chemical	Acquired German biotech firm, ProThera GmbH (2005)

Question 2: What are the important contributing factors associated with the development of the biologics CMO market? What are competitive advantages and disadvantages of the biologics CMO market formation in three Asian countries-Japan, Korea and Singapore?

As a result of biotechnology-infrastructure analysis of three countries based on capacity, capital, and cost (Table 4), there are competitive advantages and disadvantages of these countries for the biologics CMO market (Table 5). While Japan has a more developed biotechnology industry, high-manufacturing labor costs (4% higher than the US) could pose a challenge for the development of the CMO market. It has also been reported that 90 % of biomanufacturing is production-related, with only 7% devoted to R&D (64). Contract manufacturing investment is not followed by high-margin commercialization activities, which is different from R&D

investment. Thus, to traditional R&D-oriented Japanese domestic biotech firms, a biologics CMO model whose focus is entirely on low-cost and high-yield manufacturing may not be attractive.

Although Korea turned out to be the most cost-effective of the three countries in terms of labor (40% of the US/Japan and 60% of Singapore), most Korean biopharmaceutical firms have kGMP and bGMP manufacturing facilities and operation abilities, i.e do not meet international GMP standards. According to the Korea pharmaceutical manufacturing association, 65 biopharmaceutical firms have invested or planned to invest a total of \$1.7bn for GMP upgrade by 2010. In Singapore, the biotech strategy has seen heavy investment into biotech R&D and education. Singapore has produced a highly specialized workforce for government-associated biologics service organizations and foreign biologics CMOs, however there is a small number of domestic companies in this area so far.

Upon the assumption that biotech firms with greater than \$250mn market cap are more likely to make the high upfront investment required to build a commercial scale-manufacturing facility, the financial capacity of Asian IPO biotech firms were evaluated. Among more than 62 Asian IPO biotech firms, only a few firms such as Takara Bio (Japan, \$658mn), Sewon Cellontech (Korea, \$333mn) and Cha Biotech (Korea, \$481mn) had market caps greater than \$250mn (Table 4). However, this value may not accurately reflect the costs of establishing a CMO. Considering the net present value (NPV) including operation, sunk and opportunity costs (3-4 years), the capitalization requirement is likely to be much higher than \$250mn. According to a recent Deloitte report, assumed average NPV for a biotech companies self-manufacturing its own biologics was approximately \$570mn with several different scenarios depending on the

expected rate of return on investment (ROI). Not surprisingly, this macro-and micro-environment of the biotech industry in these countries appears to be unfavorable for the development of the biologics CMO market.

Table 4. Comparative assessments of three Asian countries by the framework-capacity, cost and capital in the biotechnology sector (the US is used as a standard). Foreign currencies were converted using foreign exchange data obtained on August 1st, 2009.

Framework	Criteria	US	Japan	Korea	Singapore
Capacity	Size of domestic biotech market (2006)	\$53.5bn	\$17.6bn	\$2.9bn	\$540mn (biotech+pharma)
	Number of domestic biotech firms (2006)	1,452	586	794	<22
	Size of workforce (number, 2006) (% of total population)	180,000 (0.06%)	40,000 (0.03%)	17,316 (0.03%)	9,225 (0.18%)
	Compliance to international standards (cGMP)	FDA GMP Yes	MHLW GMP Yes	KGMP/BGMP No	GMP Yes
	Number of biotech drugs in pipeline (2006) ¹	269	27	12	----
Cost	Average annual wage ² (2009) (US =1)	\$71,000 (1)	\$74,199 (1.04)	\$ 28,622 (0.4)	\$ 50,400 (0.7)
Capital	IPO biotech firms (2008) ¹ (>250mn, market cap)	414 (103)	25 (1)	42 (2)	----

Sources: Japanese External Trade Organization (JETRO), 2006 report on the pharmaceutical and biotech industry, Scrip Executive Briefing (2008), the Korean Drug Research Association (KDRA) 2005 /2008 Korean Pharmaceutical Industry profile Invest Korea website (http://www.investkorea.org/InvestKoreaWar/work/ik/eng/bo/content_print.jsp?code=102021801), MEST, 2007 White paper on biotechnology (Dec. 2007), BIO website (<http://www.bio.org/speeches/pubs/er/statistics.asp>) Biotechnology, Drugs & Genetics business statistics provided by Plunkett Research (2006) and Takatori (2007)

1. The R&D and IPO status of Singapore-based biotech companies is unknown. 2. Annual salaries in 2009 are estimated by current foreign exchange rates.

Table 5. Competitive advantages and disadvantages of Asian countries for Biologics CMO market.

Nation	Japan	Korea	Singapore
Comparative advantages	More developed biotechnology Industry	Cost-effectiveness	Highly specialized workforce
Comparative disadvantages	High manufacturing costs	Regulatory compliance	Limited biotechnology industry

Question 3: What are the possible/likely development paths of the CMO market in Asia? Are emerging participants likely in the global biologics CMO market in Asian countries?

From quantitative observations of the biotech industry in these countries, the commercial scale-contract biologics manufacturing business model more likely is suitable for companies that have access to sufficient amounts of capital (>\$570mn) as well as cost-effective and highly-skilled labor pools. In this context, among the large and established biopharma players in these countries, eight Japanese and nine Korean domestic companies were identified as existing or emerging participants in the biologics (and biosimilars) market (Table 6). Multinational biopharma companies in Singapore were excluded because of their foreign ownership structure.

While Japanese companies ranged in market cap from around \$4bn to \$31.5bn (large-cap), Korean biopharmas had small-market caps between \$780mn and nearly \$1bn except for one non-biopharma firm, Samsung Electronics, with a \$87.2bn market cap. Some of the biopharmaceutical firms were identified as subsidiaries or business units of their parent companies. Thus, it is assumed that their financial position might be overestimated based on their parent corporate' market cap. Among seventeen Japanese and Korean firms that were considered to be qualified to become a biologics CMO, personal interviews with senior/executive managers

with eight out of 17 companies were conducted. All corporate respondents showed their unwillingness to be involved in the global biologics market as emerging CMO participants because of financial issues (high risk investment and low profit margin), the absence of an established global client base-network, and the presence of an R&D-intensive corporate culture. However, one out of eight respondents expressed that there might be a possible CMO development path, if Western partners were to take the initiative, to commercially exploit business opportunities together.

Eight non-corporate respondents consisted of government officials and venture capitalists. They shared similar views with corporate respondents on the biologics CMO market development in these countries, expressing the view that there would be an opportunity, but not a huge one. They also expressed opinions that a CMO would be required to establish credibility based on quality of work and significant cost savings, requirements that would limit potential participants to a small number of firms with the necessary capital/facility/management team (scientific/technical/regulatory/business development (BD) skill set).

Table 6. Assessment of capabilities of existing and emerging Asian domestic companies in the biologics/biosimilar sector (ordered in terms of market cap size)

Company Nationality	Financial Status (Market cap, 2009)	Core Portfolio	Major Business Activities (M&As/Strategic Alliances)	Corporate Strategies
Samsung Electronics. Korea	\$87.2bn	Consumer electronics IT industry	Strategic alliance with ISU ABXIS, a Korean biologics biotech firm (2009)	Entering biosimilars business (2009)
Takeda Pharmaceutical. Japan	\$31.4bn	Biopharmaceuticals (NCEs/biologics)	Acquisition of Millennium, a US NECs/biologics biopharma (2008)	Enbrel, co-marketing with Wyeth in Japan NCEs/ Biologics (mAbs)
Astellas Pharma. Japan	\$18.8bn	pharmaceuticals (NCE)	Acquisition of CV Therapeutics (2009) and Agensys (2007), US biologics biotech firms; Merger of Yamanouchi and Fujisawa (2005)	NCEs/Biologics (mAbs)
Daiichi Sankyo co. Japan	\$12.5bn	Biopharmaceuticals (NCEs/ biologics)	Acquisition of Ranbaxy, a Indian generic firm (2008); Merger of Daiichi and Sankyo (2006)	NCEs (generics)/ Biologics (mAbs), possibly, Biosimilars
Eisai Co. Japan	\$10.5bn	Biopharmaceuticals (NCEs/biologics)	Acquisitions of MGI pharma (2008) and Morphotek (2008), US biotech firms	Humira, co-development with Abott NCEs /Biologics (mAbs)
Chugai pharmaceutical. Japan	\$10bn	Biopharmaceuticals (Biologics)	Acquisition of Roche Japan for biologics firms (2008)	Actemra, co-development with Roche Biologics
Kirin Kyowa Hakko Co. Japan	\$6.7bn	Biopharmaceuticals (biologics)	Merger of Kirin and Kyowa Hakko (2008)	Biologics
Mitsubishi Tanabe Pharma. Japan	\$6.6bn	Biopharmaceuticals (NCEs/ biologics)	Merger of Tanabe and Mitsubishi (2007)	(Ramicade, co-development)NCEs/Biologics (mAbs)

Dainippon Sumitomo Pharma. Japan	\$3.9bn	Biopharmaceuticals (NCEs/ Biologics)	Merger of Dainippon and Sumitomo (2005)	NCEs/Biologics (mAbs)
*Hanwha Chemical-dream pharma-Hanwha business unit. Korea	\$1.6bn	Oil, Fine chemical, Biopharmaceuticals (NCEs/Biologics/Biosimilars)	Acquisition of Med-tech (2006)	Biologics/Biosimilars
*CJ Pharma-CJ business unit. Korea	\$1.6bn	food, entertainment, pharmaceuticals (NCEs/Biosimilars)	Acquisition of Hanil Pharmaceutical (2004)	NCEs, Cell therapy, possibly, Biosimilars
*Yuhan Pharma-Yuhan business unit. Korea	\$1.5bn	Biopharmaceuticals (NCEs/Biologics/Biosimilars)	Strategic alliance (co-development) with a biologics CMO Celltrion and Viomed	NCEs/Biologics/Biosimilars
Green Cross. Korea	\$965mn	Biopharmaceuticals (Biologics, especially, vaccines/blood plasma-derived, Biosimilars)	Merger of Sang A pharma and Green Cross LS(2003)	Biologics/Biosimilars
Hanmi Pharmaceutical. Korea	\$857.1mn	Biopharmaceuticals NCEs(generics)/Biologics	Acquired German biotech company ProThera GmbH (2005)	Generics/Biosimilars
SK Life Science-SK subsidiary. Korea	\$839mn	NCEs (CNS therapeutics)	Acquisitions of Dong Shin pharma (2006) and In2Gen, a biotech (2007)	NCEs, possibly, biosimilars
LG Life Sciences-LG Subsidiary. Korea	\$818.9mn	NCEs/Biologics/Biosimilars	Strategic alliance (co-development) with BioPartner (EU)	NCEs/Biosimilars
Dong-A pharmaceutical. Korea	\$787.5mn	NCEs (antibiotics)/ Biologics/Biosimilars	Strategic alliance with Otsuka, a Japanese pharma (2009)	NCEs/Biologics/Biosimilars

* These organizations are subsidiaries or business units of their parent companies. Their current financial status is indicated based market cap of parent corporate.

7. DISUSSION

7.1. Conclusion

With the clear prospect of biosimilars emerging as a major industry in the near future, and with the equally obvious sustained enthusiasm by major biopharmaceutical firms for development of future innovative biologics, the prospect for contract manufacturing and/or standalone biosimilar companies appears bright. The major goal of this research study was to help determine if business conditions in Asian countries would allow Asian domestic companies to participate in the global biologics marketplace.

In this context, contract manufacturing outsourcing in Asian countries whose domestic environment is relatively well-developed and highly regulated was considered a potential strategic approach for Western biopharmas, to create branded and generic biologics for growth and sustainability in the global market. Thus, the following hypothesis was advanced: ‘Asian participants such as Japan, Korea and Singapore have sufficient capabilities to serve as strategic partners for Western participants in the global biologics CMOs markets’ However, the quantitative and qualitative findings did not support the hypothesis. There are several reasons for these findings.

First, it was found that the contract manufacturing industry in these countries is very limited (or underdeveloped) with relatively few key industrial (non-government-derived) participants. Although existing firms such as Lonza, Celltrion and Toyobo biologics have capabilities to meet the global customer demand in manufacturing more sophisticated and highly innovative complex products, there are not many smaller competitors with an active interest in the sector.

Because the current underdevelopment of the sector in Asian countries might be a transitory characteristic, key contributing factors for biologics CMO development were explored. The causes of underdevelopment of the biologics CMO market have country-specific and common constraint factors. In addition to country specific issues (cost in Japan, regulatory compliance system in Korea, size of biotech industry in Singapore), a common drawback for biologics CMO developments is the scarcity of biotech firms with sufficient capital to establish themselves as a biologics CMO. In contrast to other industrialized countries, financial investments through government and private resources in domestic biotech firms in these countries remain relatively small. So from a financial standpoint (based on the estimated NPV to construct a standard biologics plant), the domestic biotech industry in Asian countries shows little potential for participation in the global CMO market.

Thirdly, as the outcomes of interviews with eight senior/executive corporate managers among of some the financially more secure and larger companies in the biologics/biosimilars sector showed, all interview respondents exhibited negative opinions on the possibility of their participation in the CMO market. They perceived the biologics CMO business model as a high-risk upfront investment, with uncertain global market (client) demand, low profit margins and less R&D intensive manufacturing processes. Only one out of eight respondents expressed a possible consideration for such a development, and only if the actions to create strategic partnerships would be taken at the initiative of Western participants.

Fourth, personal interviews with non-corporate management group (venture capitalists and government officials) showed that although the emerging market opportunities could exist in Korea and Singapore, the practical opportunities would be limited to only a few domestic and

foreign participants with sufficient capital accessibility, innovative biomanufacturing capacity, effective management execution and credible global customer base. Interestingly, none of the participants mentioned IP as a factor. It is believed that a combined analysis of all data disproved the initial hypothesis. These findings also show that there is an apparent gap in terms of the perspective of supply and demand in this sector which differs from the predictions of several major reports (15, 67) that have noted that Korea and Singapore are well suited for contract biologics manufacturing from a biopharma perspective.

It can be concluded that under the current circumstances, Asian participants in Japan, Korea and Singapore have either little capability or little inclination to become major participants in the global biologics CMOs market. This must be considered surprising in light of the well-validated success of Celltrion in Korea. It is possible that corporate cultures do not favor the kind of risk-taking that is required to launch a new venture.

7.2. Strategic Considerations

The one possibility left open by one interviewee was that a CMO could be established in an Asian country if a Western partner were to take the initiative. From the initial research results, it was expected that Korea domestic biopharma companies with labor cost advantages could be strategic partners for Western participants in the CMO marketplace. However, through interviews with Western biopharma managers, it was found that compared to Japan and Singapore, Korean capabilities were not well recognized by Western counterparts in the biopharmaceutical industry. Thus, the absence of brand name recognition and of an established global marketing presence might be a big hurdle for emerging Korean participants to attract high-profile global clients for a CMO business. Even if they have state-of-the-art facilities that

offer significant advantages, they might end up securing only a small number of clients and might not be able to realistically consider the biosimilars sector of the emerging market. It was concluded that for emerging Korean participants, it would be critical to focus on branding strategy and marketing execution which might be accomplished by through active overseas strategic partnerships.

If existing biopharmaceutical companies are unwilling to embrace the opportunities, could other firms replace them? As shown in several successful CMO cases (Table 3), non-biotech origin companies can establish a strong position in the biologics CMO market by leveraging strategic partnerships with appropriate partners. For example, in 2002, a non-biotech (electronics) management group entered the market through a joint venture with VaxGen, a California-based biotechnology company with a technical expertise and marketing channel, to form Celltrion. They successfully raised capital through the initial public offering (IPO) of VaxGen in the US stock market and through Korean private and government organizations, cumulatively estimated at \$200-300mn (in about 2002) to initiate the biomanufacturing business (30). The Celltrion example suggests that the opportunities are most obvious to those outside the industry. This is puzzling, but points to a conservatism among existing managers that is, more than any other single factor, the greatest explanation for the failure of the hypothesis.

Outside of the companies studied in this thesis are a fast growing number of biologics CMO participants in India and China. In the next five to ten years as the industry become more mature, it is expected that they will become the primary Asian biologics CMO vendors for Western biopharmas, offering significant cost advantages and advanced biomanufacturing practices.

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9. STATEMENT ON CONFLICTS OF INTEREST

There are no conflicts of interest.