REVIEW ARTICLE

Models for accessing biomedical innovation in Asia

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Abstract: Asian countries are striving to transition into innovation-driven economies, and healthcare is a key sector on government agendas. Strong funding at academic institutions, high-impact publications, state-of-the-art clinical infrastructures, vast talent pools, increasing start-up activities and strengthening intellectual property regimes, all aligned with coherent government policies, is creating an evolving innovation ecosystem in countries such as China, South Korea, Singapore, Taiwan and India. Such factors have fuelled a desire from global pharmaceutical companies to seek innovation in Asia. In this article, we review the varied strategies of large multinationals using two key aspects—the capital investments and operational model—to understand such diverse approaches. Based on a qualitative and quantitative analysis, we have classified these strategies into four distinct approaches—"Captive", "Partner", "Service" and "Open" models—and discussed case studies that fit into each of these clusters. The model may provide global pharmaceutical companies with a framework to evaluate their respective approaches for sourcing innovation and align them with the operational, financial, business and strategic needs of their organizations in Asia.

Keywords: biomedical innovation, capital investments, operating models, Asia, in-licensing, joint ventures, research collaborations, open innovation

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1. Introduction

The United States, Europe and Japan have dominated biomedical innovation over the last several decades, with the majority of research and development (R&D) funding and the ensuing innovation being localized to these regions[1,2]. However, in recent years, the rest of the Asia region, specifically China, South Korea, Singapore, Taiwan and India are increasingly recognized as key centres of pharmaceutical R&D with the potential to deliver future innovative drugs[3,4].

Unlike the stagnating or declining investments by the public and private sectors in the United States and Europe, the government and industry investments in biomedical research are continuously increasing in Asia, most notably in China, Singapore and South Korea[1]. The change in biomedical R&D expenditure as a percentage of nominal gross domestic product of Asian countries like China, South Korea, and Singapore[1] further points to strong innovation focus in the bioscience sector. An increasing number of start-up companies, high-impact publications, state-of-the-art clinical infrastructures, a robust contract research organization (CRO) industry and vast talent pools[4–6] in these countries are fuelling scientific breakthroughs, positioning the region as an attractive location to tap innovation.

Asia also presents unique disease and genetics landscape for pharmaceutical companies[7]. The region

has been at the forefront of clinical studies of diseases such as gastric cancer, hepatocellular carcinoma, hepatitis B and tuberculosis. The advances in personalized medicine that utilize molecular understanding of diseases to optimally select and treat patients have also resulted in innovative breakthroughs for the Asian region, including drugs such as gefitinib and erlotinib targeting lung cancer mutations that are much more highly prevalent in Asian patients as compared to the US or Europe[8]. Such advances provide unique R&D strategies for pharmaceutical companies to target specific diseases in Asia.

The confluence of these factors has led large multinationals to focus more R&D efforts in the Asia region over the past decades. The companies have utilized a range of strategies to tap into this innovation landscape, such as internal R&D units, innovation centres, virtual research networks, joint ventures and open innovation platforms. Such strategies take into account the opportunities and challenges of each market, the extent of R&D capabilities, language and cultural barriers, and operational alignment with the multinational pharmaceutical companies' headquarters.

In this article, we analyse the various strategies of the multinational companies in Asia to understand the diverse approaches for accessing biomedical innovation. We utilize data on two key aspects—capital investments and operational model—to classify such strategies into four distinct models being implemented by these companies. The capital investments and operating model parameters were defined using a qualitative and quantitative approach. For example, a model that requires in excess of $20 million in investments, such as R&D units or innovation centres, is classified as a high capital investment. An integrated model would be one with significant portions of R&D pursued at internal labs versus a dispersed model where a loose network of external alliances is used to push the projects toward. Of course, any single model does not preclude pursuing an alternate model in parallel—for example, an internal lab could also use external collaborations—but for simplicity we have classified the approaches into clearly defined groups to facilitate a comparison between the models. The framework is presented in Figure 1 with illustrative cases, and an extensive list of examples is included in Table 1.

2. High Capital, Integrated Operations: "Captive" model

Since Roche opened its Shanghai R&D centre in the Zhangjiang Hi-Tech Park in 2004, most of the large multinational companies have established an integrated research unit in China[9]. Within Asia, China is the preferred location for R&D units with 8 of the top 10 pharmaceutical companies establishing their R&D centres in China, mostly in Beijing or Shanghai. Singapore is also an attractive destination in Asia[9] although the focus has increasingly been on manufacturing of biologics.

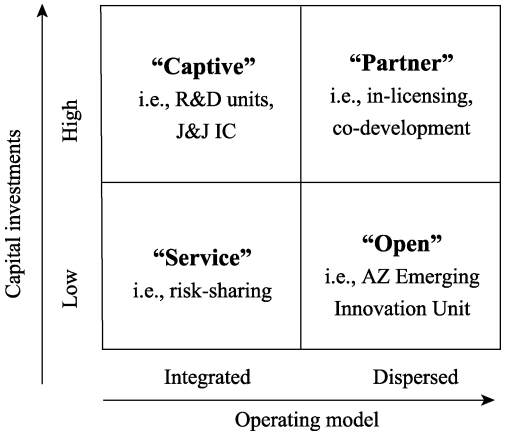

Figure 1. Framework for models to access biomedical innovation in Asia. The capital investments and operating model were used to assign the illustrative cases shown into one of the four cells shown in the 2 × 2 matrix.

The "Captive" model provides several advantages for accessing local innovation. The science unit can tap into local talent pool, develop deep local disease knowledge, and in parallel, establish research and translational networks with academic labs, medical centres and CROs. Lilly's China Research and Development Center (LCRDC) in Shanghai, which aims to discover innovative diabetes medicines with novel mechanisms of action that can be tailored specifically for the Chinese patients, is one such example. The center employs approximately 150 scientists and staff[10]. Another example is Johnson & Johnson's Asia-Pacific Innovation Center (J&J IC) in Shanghai, China. With science and business experts, the centre focuses on building relationships with academia, government and non-profit organizations as well as entrepreneurs and investors across the Asia Pacific region. Having a centralized company culture under such a model also allows employees to collaborate internally so that complex projects can be advanced rapidly. A tight portfolio alignment with global units and IP risk-mitigation are added benefits of this model. An entrepreneurial culture without multiple decision layers typical at headquarters of large companies can further

Table 1. Different models for accessing biomedical innovation in Asia

Description	Examples in Asia	Pros	Cons
"Captive" model (high capital investment, integrated operation)			
Stand-alone in-house R&D center	• AstraZeneca Innovation Centre, China (2007) • Biocon's Syngene and Bristol-Myers Squibb Research Centre (BBRC), India (2009) • GSK Global R&D Centre, Shanghai, China (2007) • Johnson & Johnson's Asia-Pacific Innovation Center (J&J IC), China (2014) • Lilly China Research and Development Center in Shanghai, China (2012) • Merck Beijing R&D center, China (2011) • Novartis Institute for Tropical Diseases (NITD), Singapore (2002) • Novartis Institute of BioMedical Research in Shanghai, China (2007) • Novartis Pharmaceutical Development organization in Shanghai, China (2009) • Roche R&D Centre in Shanghai, China (2004) • Roche's Pharma Development Center in Shanghai, China (2007) • Sanofi's China Clinical Research Unit in Shanghai, China (2005) • Sanofi's Biometrics Center in Beijing, China (2008) • Pfizer China R&D Center (CRDC) in Shanghai, China (2005) • Pfizer China R&D Center in Wuhan, China (2010)	- Tap local talent and disease knowledge - Ease of collaboration with local academic labs, medical centers, and CROs - Ease of internal collaboration - Strategic alignment with global portfolio - IP risk-mitigation	- Higher operational cost - Potential for sub-optimal portfolio prioritization - Model not flexible for changes
Acquisition	• GlaxoSmithKline's acquisition of Nanjing MeiRui Pharma Co., the China-based pharmaceutical company (2010)		
"Partner" model (high capital, dispersed operation)			
Co-development	• AZ-Hutchison MediPharma in China (2011) • Eli Lilly-Hutchison MediPharma in China (2013) • Eli Lilly-Innovent in China (2015) • GSK-Hanmi in Korea (2012) • Merck-Serono-BeiGene in China (2013)	- Rapid set-up - Access partner asset - Control of the work quality	- Low availability of partners with assets in Asia - Trust building takes time - Potential IP risks
Joint venture	• Pfizer-Hisun Pharmaceutical joint venture in China (2012) • Samsung Biologics - Biogen Idec joint venture in Korea (2011)		
"Service" model (low capital, integrated operation)			
Lean resources	• AstraZeneca and Wuxi AppTec alliance in China (2012) • Sanofi and SIBS for China Discovery platform (2008)	- Cost and risk sharing - Usage of existing local infra-structure and capability - Flexibility in capacity management	- Potential IP risks - Cross-company contamination of intelligence - Management of work quality
"Open" model (low capital, dispersed operation)			
Open innovation	• AstraZeneca's Open Innovation Portal (2013) • AZ–NRPB Drug Repurposing Program in Taiwan (2013) • Bayer Grants4Targets (2009), Grant4Leads (2013), Grants4Apps (2013) • Eli Lilly's Open Innovation Drug Discovery Program (2009)	- Low cost and low risk - Test diverse ideas	- Organizational and cultural changes may be needed - IP protection and quality of work are hard to control - Need strong innovation eco-system

provide an ideal innovative environment. However, higher operational costs and sub-optimal portfolio prioritization are potential risks to be considered and mitigated.

3. High Capital, Dispersed Operations: "Partner" Model

Such a model of accessing innovation includes, amongst others, co-development and licensing deals between multinational and local companies. One such example is AstraZeneca's global licensing agreement with Hutchison MediPharma, for joint development and commercialization of Savolitinib, a c-MET receptor tyrosine kinase inhibitor for the treatment of cancer. Another example is Merck-Serono's licensing, co-development and commercialization agreement

with BeiGene for a portfolio of cancer molecules. Eli Lilly recently announced[11] a partnership with Innovent Biologics in China to co-develop at least three experimental cancer drugs including one from Lilly's research labs and two from Innovent. GSK and Hanmi's co-development and co-marketing deal[12] for evidence-based drug formulation for multiple therapeutic areas allows GSK to tap into not only Hanmi's expertise in formulations but also Hanmi's marketing network in Asia, especially in South Korea. In India, Sanofi and Eli Lilly partnered with Glenmark on pain molecules[13]. Each of the deals above included upfront payments, and downstream milestones[14] and royalties, and is often a mix of either pure in-licensing and/or co-development partnerships.

The "Partner" model provides rapid, flexible access to external innovation and has been utilized by many of the multinationals in the Asia region. The model leverages on the partner's complementary capabilities such as local development knowledge to not only accelerate clinical development in a specific country but also secure attractive opportunities for the multinational's global portfolio. As compared to the "Captive" model, this model provides a faster ramp-up and access to innovation while still allowing the quality of work to be controlled with tight management oversight. However, there needs to be a critical mass of companies and enough substrate available to implement such a model, and thus has been most successfully used in China, South Korea and India where there is increasing venture capital and start-up activities[3]. In contrast, there have been few such partnerships in Taiwan and Singapore, for example, where the local ecosystem has not produced a strong pipeline of drug candidates. To implement a successful "Partner" model, a pharmaceutical company needs to develop deep networks within the biotech community, strong "Partner of Choice" communication and mutual trust with local players.

Joint ventures between the multinational pharmaceuticals and a local company are other examples of the "Partner" model. Pfizer and Hisun formed a joint venture in 2012[15] with USD 250 million invested by Pfizer and USD 295 million invested by Hisun respectively to make both branded and low-priced generic drugs. It is a mechanism for Pfizer to get better traction in the China market as well as for Hisun to build the capabilities to tap Western markets. Earlier in 2011, Merck established a joint venture with Simcere, a Chinese company with a track record in drug development, to combine resources and expertise for development and commercialization of a combined portfolio of medicines from both companies in the areas of cardiovascular and metabolic diseases. However, in February 2015, it was announced that Merck is pulling out of the joint venture citing the change in the market prospects in China, hence highlighting the inherent risks of such models in Asia.

4. Low Capital, Integrated Operations: "Service" Model

The "Service" model is centred around lean resources where the bulk of R&D activities are outsourced to CROs or are done through collaborative R&D partnerships with local companies. This allows the multinational pharma to share costs, risks, and decision-making with the partner company while the majority of R&D activities are carried out locally using the local partner's existing infrastructures and capabilities. Unlike the above "Captive" and "Partner" models, the "Service" model also allows flexibility for the global company to easily adapt to changes in market situation and strategy. However, intellectual property protection should be carefully devised and a robust mechanism to monitor and address quality of work needs to be put in place. An example is AstraZeneca/MedImmune and WuXi AppTec's collaboration to develop MEDI5117, a novel antibody for rheumatoid arthritis, in China. WuXi brings its capabilities in preclinical and clinical services, as well as the capital investment for manufacturing, while AstraZeneca/MedImmune contributes the molecule and technical expertise. Although the partnership is structured as a joint venture, we have classified this under the "Service" model given the focus on a single asset and the resource contributions from the partners. The Eli Lilly–ChemPartner research collaboration in China is another such example as is Sanofi's strategic partnership with Shanghai Institute of Biological Sciences (SIBS) as a part of the China Discovery platform involving long-term relationships with top local institutions.

5. Low Capital, Dispersed Operations: "Open" Model

Open innovation platforms are key examples of this model and have been tested by various pharmaceutical companies in the Asian region. There are various levels of "openness" with Eli Lilly's Open Innovation

Drug Discovery Program[16] initiated back in 2009 and AstraZeneca's Open Innovation Portal launched in 2013[17] being completely open, online platforms. In contrast, GlaxoSmithKline's Tres Cantos Open Lab Foundation is limited to select partners or diseases of interest. For multinationals, these open innovation platforms allow the company to spread a vast net across diverse set of ideas, thereby diversifying risks and testing multiple hypotheses in parallel. These open initiatives are also attractive to academia and small businesses with novel ideas that can access the multinational pharmas' resources and expertise, and collaborate with international pharma scientists to progress the science[18]. To implement an "Open" model, the multinational companies need to tailor the processes and organizational structure for speedy decision making and adopt flexible deal structures. An agile and risk-taking culture is also a key for a successful "Open" model. There are, however, significant hurdles to an "Open" model in Asia. The key aspects remain a lack of funding for early-stage projects at academic centres, ownership of new intellectual property, and sharing on downstream economics. Based on our own experience in rolling out AstraZeneca's pharmacology toolbox in Asian countries[17], lack of funding seems to be one of the biggest hurdles preventing many investigators in Asia from participating in this initiative. An effective way to drive open innovation in Asia is public–private partnerships and one such example is the collaboration between AstraZeneca and the National Research Program for Biopharmaceuticals (NRPB) in Taiwan. AstraZeneca has opened its portfolio of preclinical and clinical molecules for the clinicians and translational researchers in Taiwan to explore alternative mechanisms and diseases for the candidate molecules, while NRPB provides the funding for the research projects. "Open" models work well where an innovation ecosystem is well-established, primarily the existence of strong academic and translational centres that can test novel hypothesis and ideas, such as the example in Taiwan.

6. Looking Forward

A key structural change in R&D has been the pharmaceutical industry's trend toward externalization over the past several years, in part driven by R&D productivity and budget pressures[19,20]. More than half of recent new drugs have originated from outside of the global pharma labs and the focus on accessing the best science will continue to push the pharmaceutical industry to more active externalization. Although a majority of scientific collaborations are still focused on the US and Europe biotechs, Asia is a fertile ground for future innovation and we have presented various models to help access such breakthroughs.

The models here provide a toolbox for global pharmaceutical companies—if capital investments are restricted, a "Service" or "Open" model can be used to pursue innovation. If capital is not a constraint, a "Captive" model might allow the organization to tap into the local talent pool and capabilities to pursue innovative science. As global companies seek biomedical innovation in Asia, it is important to pick the appropriate operational model given the resource and strategic considerations, and find an ideal partner best suited to the company's objective. However, it is also important to consider the overall country's strength and weakness[4], which also explains why an "Open" model works better in South Korea and Taiwan, a "Partner" model in India, and a "Captive" or "Service" model in China.

However, significant challenges remain. Although there have been many new activities in Asia in recent years, there has also been reduction or re-distribution of efforts in Asia due to various strategic or financial reasons. Examples include the dissolution of the Merck–Simcere joint venture in China, Lilly's exit of the Singapore Centre for Drug Discovery in 2010, and Pfizer's exit from Singapore in 2013[21–23] with the closure of the clinical research centre which had been established in 2001. In 2012, Pfizer also exited the Asia Research Unit which was established in 2006 in Shanghai based on a virtual biotech model aimed to "seed, seek, source, and spark" innovation across Asia. Tapping Asia's innovation can also seem daunting given language and cultural barriers, paucity of efficient partnering forums, business practices and regulations, and quality of the assets. Finally, alliance management can pose operational challenges because of the need to work across multiple time zones, relative inexperience of collaborations between the local and multinational partners, and often different expectations of the outcome. Nevertheless, we believe that regardless of the chosen model, local presence with knowledge of the R&D landscape, business and cultural aspects is critical for efficient scouting and access to the right opportunities in Asia.

Finally, an interesting aspect is that although many multinational companies operate venture investment

arms globally, only a few of them, such as Eli Lilly, Novartis and J&J seem to be active in Asia. Lilly Asia Ventures was established with investment resources of USD 100 million in 2008 and invests in companies with the potential to grow rapidly as well as those that are developing innovative products with potential impact in China and around the world. As per publicly disclosed information, Lilly Asia Ventures is currently managing 16 portfolio[24] companies and investments in the life sciences and healthcare sectors, with several portfolio companies in Asia. Novartis Korea Venture Fund, also established in 2008, planned to invest for novel therapeutics and platforms with a focus on diseases prevalent in Asia and, as per public information, it is currently managing three portfolio[25] companies in Korea. Furthermore an increasing trend, at least in countries like China, is local venture capital funds seeking earlier stage investments, in contrast to the trend in established markets such as Europe and the United States, positioning Asia as an important ground for investing in new innovative start-ups.

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References

1. Chakma J, Sun G H, Steinberg J D, *et al.* 2014, Asia's ascent—global trends in biomedical R&D expenditures. *New England Journal of Medicine*, vol.370(1): 3–6. http://dx.doi.org/10.1056/NEJMp1311068.
2. Moses H III, Matheson D H M, Cairns-Smith S, *et al.* 2015, The anatomy of medical research: US and international comparisons. *Journal of the American Medical Association*, vol.313(2): 174–189. http://dx.doi.org/10.1001/jama.2014.15939.
3. Chakma J, Sammut S M and Agrawal A, 2013, Life sciences venture capital in emerging markets. *Nature Biotechnology*, vol.31(3): 195–201. http://dx.doi.org/10.1038/nbt.2529.
4. Gautam A and Yang S, 2014, Market watch: a framework for biomedical innovation in emerging markets. *Nature Reviews Drug Discovery*, vol.13(9): 646–647. http://dx.doi.org/10.1038/nrd4413.
5. Gautam A, 2015, Market watch: Evolution of Chinese bioclusters as a framework for investment policies in emerging markets. *Nature Reviews Drug Discovery*, vol.14(1): 8. http://dx.doi.org/10.1038/nrd4516.
6. Xia C and Gautam A, 2015, Biopharma CRO industry in China: landscape and opportunities. *Drug Discovery Today.* http://dx.doi.org/10.1016/j.drudis.2015.02.007.
7. Ma Q and Lu A Y H, 2011, Pharmacogenetics, pharmacogenomics, and individualized medicine. *Pharmacological Reviews*, vol.63(2): 437–459. http://dx.doi.org/10.1124/pr.110.003533.
8. Mitsudomi T, 2014, Molecular epidemiology of lung cancer and geographic variations with special reference to *EGFR* mutations. *Translational Lung Cancer Research*, vol.3(4): 205–211. http://dx.doi.org/10.3978/j.issn.2218-6751.2014.08.04.
9. 2010, Evolving R&D for emerging markets. *Nature Reviews Drug Discovery*, vol.9(6): 417–420. http://dx.doi.org/10.1038/nrd3204.
10. *Lilly's Commitment to global innovation reinforced with opening of new diabetes-focused research and development center in Shanghai* n.d., viewed April 6, 2012, <https://investor.lilly.com/releasedetail.cfm?ReleaseID=678375>
11. *Lilly and innovent biologics announce a strategic alliance to bring oncology therapies to patients in China and around the world* n.d., viewed April 6, 2015, <https://investor.lilly.com/releasedetail.cfm?releaseid=902643>
12. *Hanmi enters into a co-development/marketing agreement with GSK* n.d., viewed April 15, 2015, <http://www.pipelinereview.com/index.php/2012032847506/More-News/Hanmi-enters-into-a-Co-development/Marketing-agreement-with-GSK.html>
13. *Sanofi-aventis and glenmark pharmaceuticals sign license agreement on novel agents to treat chronic pain* n.d., viewed April 7, 2015, <http://www.sanofi.se/l/se/sv/layout.jsp?cnt=BF7B30E1-28EA-4625-A932-6B735E48C242>
14. *Lilly and Glenmark Pharmaceuticals announce license agreement* n.d., viewed April 7, 2015, <https://investor.lilly.com/releasedetail.cfm?ReleaseID=271993>
15. *Pfizer and Hisun announce launch of Hisun-Pfizer*

Pharmaceuticals Co., Ltd. n.d., viewed April 10, 2015, <http://press.pfizer.com/press-release/pfizer-and-hisun-announce-launch-hisun-pfizer-pharmaceuticals-co-ltd>

16. *Lilly open innovation portal* n.d., viewed April 10, 2015, <https://openinnovation.lilly.com/dd/>
17. AstraZeneca *open innovation portal* n.d., viewed April 10, 2015, <http://openinnovation.astrazeneca.com/>
18. Robertson M N, Ylioja P M, Williamson A E, *et al.* 2014, Open source drug discovery – a limited tutorial. *Parasitology*, vol.141(1): 148–157. http://dx.doi.org/10.1017/S0031182013001121.
19. Khanna I, 2012, Drug discovery in pharmaceutical industry: productivity challenges and trends. *Drug Discovery Today*, vol.17(19–20): 1088–1102. http://dx.doi.org/10.1016/j.drudis.2012.05.007.
20. Paul S M, Mytelka D S, Dunwiddie C T, *et al.* 2010, How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Review Drug Discovery*, vol.9(3): 203–214. http://dx.doi.org/10.1038/nrd3078.
21. *Merck hands over China joint venture to partner Simcere Pharma* n.d., viewed April 10, 2015, <http://www.fiercepharma.com/story/merck-hands-over-china-joint-venture-partner-simcere-pharma/2015-02-09>
22. *Lilly to close Singapore Discovery Center* n.d., viewed April 10, 2015, <http://www.bio-itworld.com/2010/10/15/lilly-singapore.html>
23. *Pfizer to lop off Asian research unit and amid major R&D downsizing* n.d., viewed April 10, 2015, <http://www.fiercebiotech.com/story/pfizer-lop-asian-research-unit-amid-major-rd-downsizing/2013-02-08>
24. *Lilly asia ventures* n.d., viewed April 10, 2015, <http://www.lillyasiaventures.com/en/home.asp?lm_id=12&lm_id_2=14>
25. *Novartis venture fund* n.d., viewed April 10, 2015, <http://www.nvfund.com/#OurPortfolio>