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Title	Big Pharma's internationalization of R&D to China
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Publication Date	2015-04-18
Publication Information	Grimes, Seamus, & Miozzo, Marcela. (2015). Big Pharma's Internationalization of R&D to China. <i>European Planning Studies</i> , 23(9), 1873-1894. doi: 10.1080/09654313.2015.1029442
Publisher	Taylor & Francis
Link to publisher's version	<a href="http://dx.doi.org/10.1080/09654313.2015.1029442">http://dx.doi.org/10.1080/09654313.2015.1029442</a>
Item record	<a href="http://hdl.handle.net/10379/6440">http://hdl.handle.net/10379/6440</a>
DOI	<a href="http://dx.doi.org/10.1080/09654313.2015.1029442">http://dx.doi.org/10.1080/09654313.2015.1029442</a>

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**Grimes, S, and Miozzo, M (2015) 'Big Pharma's Internationalization of R&D to China'.  
European Planning Studies, 23 :1873-1894.**

**Introduction**

China's emergence as a significant force in the global pharmaceutical value chain coincides with what appears to be a critical juncture in the global pharmaceutical industry, dominated by "big pharma", with falling revenues and competitiveness and a possible need to reinvent the global pharmaceutical R&D model. One of the main reasons for falling revenues among big pharma companies is the so-called "patent cliff" with the period covering the patents of former high revenue blockbuster drugs about to expire and competition from generic drug manufacturers, many of which are in less developed countries like India and China, becoming increasingly intense and impacting negatively on revenues. These pressures on the competitiveness of big pharma are also some of the reasons why emerging regions like China hold out significant hope for reducing costs, for market expansion and for reconfiguring the drug development model.

This paper addresses two main issues. First, the paper examines the factors explaining the process and nature of R&D offshoring by large pharmaceutical firms from developed countries in China. Although less developed countries, including China and India have already experienced significant inward R&D investment by big pharma, the long-term success of these strategies must be evaluated within the context of significant challenges. Indeed, offshore R&D by multinational corporations has become an important element of the globalization of innovation. Many contributions explore the sharp increase and change in the nature of internationalization of R&D activities of multinationals, with offshore R&D investment designed to augment rather than replace home-base technological competence (Kuemmerle 1999, Florida 1997). Much of the literature examining this process is based on developed countries' multinationals offshoring R&D in other developed countries. More recently, however, offshore R&D of multinationals has shifted towards less developed countries, and India and China in particular (Chen 2004; Niosi and Tschang 2002; Dossani and Kenney 2007; Massini and Miozzo 2012). Less is known about the nature of the process of R&D internationalization by multinationals from developed countries in less developed countries (Reddy, 2011). Also, less is known about how this process is evolving in science-based sectors, in the context of relatively weak local science and technology infrastructure and important institutional changes, including transformations in regulations and intellectual property rights.

Second, the paper establishes a link between the literature of R&D internationalization and that of innovation in less developed countries. There is wide agreement that upgrading in the context of globalisation requires a combined effort by both domestic and foreign firms, both aimed at increasing capabilities of local firms and adapting borrowed foreign technology to host markets. A literature on innovation systems emphasises the role played by the interaction among different institutions in public and private sectors whose activities and interactions initiate, import, modify and diffuse new technologies (Freeman, 1987; Lundvall, 1992; Nelson, 1993). As a growing number of less developed countries are being drawn into the global landscape of R&D

internationalization, it is essential to understand the responses from less developed countries, to enrich the current understanding of R&D internationalization.

Having reviewed the literature relating to the internationalization of R&D activity by multinational companies, the more limited academic research on China's recent integration into the global value chain of big pharma is also examined. This is supplemented by a wide range of reports and evaluations by industry consultants and other specialists of China's potential contribution to big pharma's attempts to reconfigure its business model and to increase R&D productivity. The senior management of a small number of big pharma R&D centres, together with a US clinical trials startup company was interviewed in Shanghai in 2011. The interviews provide detailed insights into the early stages of big pharma R&D in Shanghai, which has become a major concentration of such investment in China.

### **Offshore R&D and innovation in LDCs**

The literature on R&D internationalization tends to concentrate on the trends (Cantwell 1995, Patel and Pavitt 1991, Gerybadze and Reger 1999, Guellec and van Pottelsberghe de la Potterie 2001) and on the multinationals' strategies, organization and location choices in deploying offshore R&D (Kumar 2001, von Zedtwitz and Gassman 2002, Zander 1999). This literature tends to acknowledge two main R&D internationalisation strategies. One is often called home-base exploiting R&D (Kuemmerle, 1999) or asset-exploiting R&D (Dunning and Narula, 1995). This is mainly concerned with exploiting firm-specific capabilities in foreign environments. As firms establish manufacturing facilities abroad and assign increasingly complex products to them, locating R&D sites in close proximity to factories to adapt products to local conditions becomes a necessity (Chiesa 1996, Medcof 1997).

A second strategy is often called home-base augmenting R&D (Kuemmerle 1999) or strategic asset seeking R&D (Dunning and Narula, 1995). This involves monitoring or acquiring competitive advantages which are complementary to those possessed by the firm, to augment its stock of knowledge. This strategy requires the development of links with host-country R&D organisations and systems to enhance the knowledge base at home and to connect more closely to the foreign R&D environment and access local knowledge (Florida 1997). Specific nations or regions might be particularly attractive locations for R&D facilities because of potential knowledge spillovers from existing and productive local R&D organisations, such as research universities, publicly funded research institutes and innovative competitors (Cantwell 1991).

Similarly, a number of contributions contemplate different roles and behaviour for overseas R&D units in multinationals. For example, Pearce and Papanastassiou (1999) discern two roles: a first is to develop new products, or particular product variants, for key segments of the global market. These labs have a very close operative association with other localized functions such as marketing, engineering and management. A second is to take part in the global programmes of precompetitive research coordinated by their parent, in which they carry out specialized pieces of basic research that reflect particular areas of expertise within the host country. In turn, von Zedtwitz and Gassman (2002) develop a classification of types of international R&D organization which differ in organizational structure and behavioural orientation. They discern a number of

structures: ethnocentric centralized R&D, geocentric centralized R&D, polycentric decentralized R&D, R&D hub model and integrated R&D network.

Cantwell and Santangelo (2000), drawing on US patent data, show that multinationals are now more likely than in the past to expand their R&D activities beyond their home base, but they also find that the technologies they develop abroad are less science-based and less dependent upon tacit knowledge than those developed at home. However, within the science-based industries, firms may generate abroad some technologies that are heavily dependent on tacit knowledge, but in areas outside their own core technological competencies. The study by Le Bas and Sierra (2002) confirms this view. Based on a study of the multinationals firms with the greatest patenting activity in Europe, they found that the large majority of the firms locate their R&D activities abroad in technological areas where they are relatively strong at home, with home-base augmenting R&D being a more prevalent strategy than home-base exploiting R&D.

There is also evidence that the offshore R&D strategies of foreign R&D facilities vary across host countries. Diez and Berger (2005) compare the R&D activities of multinationals in Europe and Southeast Asia. They show that multinationals in Europe tend to be involved more in home-based technology augmenting, whereas in Southeast Asia they are more oriented towards home-based technology exploiting. Multinationals in Europe do more product innovation and devote significantly more resources in terms of R&D expenditure and personnel to their innovation activities than do local companies. The picture in the Southeast Asia is just the opposite. Innovating multinational affiliates in Europe cooperate more often with regional partners and less often directly with partners in the rest of the world. On the other hand, multinational subsidiaries in Southeast Asia are much more outward looking, as a response to insufficient local S&T infrastructure.

As a number of less developed countries are being drawn into the global landscape of R&D internationalization, it is essential to understand their responses to enrich our understanding of the offshore R&D process. There is wide agreement that upgrading in the context of globalisation requires a combined effort by both domestic and foreign firms, both aimed at increasing capabilities of local firms and adapting borrowed foreign technology to host markets. A group of contributions combine insights from innovation systems literature with the importance of the creation of inter-firm linkages and networks and the development of national technological and organisational capabilities. These emphasise the role of interaction among different institutions in public and private sectors whose activities and interactions initiate, import, modify and diffuse new technologies and argue that the quality of these relations explain differences in national and sectoral patterns of innovation (Freeman, 1987; Lundvall, 1992; Patel and Pavitt 1993; Malerba, 2005). The innovation systems concept has been applied to less developed countries (Nelson, 1993), but its application to these is not straightforward because of differences in innovation processes from developed countries (emphasis on incremental rather than radical innovation, emphasis on learning, insufficient science and technology infrastructure, and importance of foreign technology) (Pietrobelli and Rabellotti, 2011; Breznitz and Murphree, 2011).

Within this context, industrial development is argued to require a broad range of technological and organizational capabilities, which can only be acquired through a long process of deliberate

accumulation of resources, including skills, knowledge and production-enhancing institutional structures (Lall, 1992; Bell and Pavitt, 1993; Kim, 1998). The learning processes of firms is seen as partly tacit, cumulative and path dependent (Nelson and Winter, 1982; Rosenberg, 1982; Cohen and Levinthal, 1989), highly technology-specific, with capabilities built up in one activity not easily transferable to another. The costs of technological exploration, the importance of basic technology and science, and the institutions supporting knowledge accumulation, are different in each case. Different technologies have different potential for further technological advance, including knowledge leakages for other sector or technologies. The building of firm capabilities occurs at all levels – the shop floor, process or product engineering, maintenance, inventory control, logistics and R&D. R&D is at one end of the range of technological activities and it becomes more important as more complex technologies are used (Lall, 2001). The roles of imitation and technology acquisition, however, may be even more important than R&D and innovation as a basis for learning and catching up (Bell and Pavitt, 1993; Katz, 1986). Industrialization is argued to take place in latecomers through incremental improvements in foreign products and process innovation. The model of technological acquisition for East Asia is described by Hobday (1995) as a move through rapid technological advances from original equipment manufacture agreements (to supply electronic products and equipment to Japanese firms) to own-design manufacture and original brand manufacture.

Because of the complexity in developing national capabilities, industrial latecomers can not simply tap global markets and technology by opening up to foreign investment and markets. This literature shows clearly that technology imports are not a substitute for domestic capability development. But both the absorption of imported technology and the success of local technological efforts depend on the nature of the supporting national innovation infrastructure as much as they do on the capabilities of individual firms. Amsden (1989) shows how the outstanding economic growth of Korea was explained as the result of three particular set of institutions: the developmental role of the government, the competitive focus on enterprises, which concentrated on shopfloor incremental product and process improvements in ‘mid-technology’ industries (based on foreign technology), and the strategy, structure and operation of leading firms, with diversified business groups operating in technologically unrelated areas. Although there are no simple rules for innovation and industrial policy in less developed countries, research shows that there is a crucial role for public policy in less developed countries in supporting dynamic technological capability formation in local firms (Lall and Teubal 1998, Teubal 1996).

This paper explores why and how pharmaceutical firms are establishing R&D laboratories in China or outsourcing their R&D to local firms and the role played by local R&D capabilities in this process. This can offer insights on the process of R&D offshoring in less developed countries in science-based industries, in the context of relatively weak science and technology infrastructure and important institutional changes, including important transformations in regulations and intellectual property rights.

### **China’s integration into global pharmaceutical value chain**

While both India and China have experienced considerable offshoring of multinational R&D activity in the past ten years particularly in the ICT and pharmaceutical sectors, this paper

focuses on big pharma R&D investment in China, seeking to explain its expansion in the context of China's increasing integration into the global pharmaceutical value chain (Bruche, 2009). The specific nature of the pharmaceutical value chain involves a development of cycle of ten years or more and a range of activities from drug discovery and development to identifying promising candidates, animal testing and later trials with humans to ensure safety and effectiveness of drugs (Wadhwa et al., 2008). The composition of the value chain, with 10 or more parallel processes in the manufacturing process alone, allows for the splitting of that process with early stage activities in low cost locations and later stages in locations with high quality standards (Mullin, 2013). With the emergence of molecular biology and of genomic sciences in recent years, together with technological developments particularly in combinatorial chemistry, the innovation process in biomedicine has become more modular, allowing for increased outsourcing of activities (Reddy, 2011). Whereas previously big pharma companies carried out the whole range of processes in the value chain, more recently small biotechnology firms specialising in particular services at different stages of the value chain have emerged. The increasingly modular nature of R&D activity also makes it possible to segment it into particular sites, which helps avoid significant intellectual property (IP) loss in locations like China (Bruche, 2009, 278).

While the modular nature of pharma's value chain make it a suitable candidate for offshoring some of its activities from developed regions in which big pharma, which dominates the value chain, has concentrated its activities to date, to lower cost locations in the emerging regions, there are a number of converging reasons why big pharma has been increasingly offshoring activities to these regions. Industry consultants, for example, have been highlighting how big pharma's traditional business model based around very significant R&D investment to produce blockbuster drugs has entered a period of crisis for a number of reasons (Kandybin and Genova, 2011). According to them the recent period has been characterised by declining profits and rising costs which is adding to increased pressure on the competitiveness of the traditional model. This fall in competitiveness is partly related to growing competition from generic drug companies which have been eating into the market share of big pharma, exploiting the 'patent cliff', as more blockbuster drugs come to the end of the period covered by patents Davidson and Greblov, 2005). In addition to external pressures, big pharma has also been experiencing its own internal problems associated with declining R&D productivity and an anemic pipeline of new drugs.

### Reconfiguring the business model

Big pharma, therefore, faces a major challenge in reconfiguring its overall business model and despite the significant challenge from generic drug companies, particularly in emerging markets, it is precisely in markets such as China that big pharma sees significant opportunities for reducing production costs, expanding market share and bringing about major changes in the overall drug development model. According to one venture capitalist, part of big pharma's strategy includes developing generic versions of previously successful drugs either independently or through collaborating with generic companies (Kessel, 2011). Kessel claims that big pharma is too bureaucratic to be innovative and it should leave the early stages of R&D to the more nimble biotech companies which are often under-funded. Part of the reconfiguration of big pharma's model, therefore, involves a global search for intellectual property from small biotech companies for potential products during the various stages of clinical trials (Salter, 2009, 68). This search can proceed through mergers and acquisitions or through joint ventures.

Industry consultants point out that different aspects of R&D can be allocated to particular locations because of the modular model of biotech development (Goodall et al., 2006). A significant loss of IP can be avoided in locations like China by segmenting R&D into particular slices (Bruche, 2009, 278). It is within this context, therefore, of both challenges and opportunities that this paper will analyse the increasing shift of big pharma R&D activity to China.

The share of foreign R&D being invested in emerging markets is still relatively small compared with developed regions. In 2010, for example, US foreign affiliates invested only 3.7% of all US R&D invested overseas in China. Despite this, however, there is growing concern in countries like the UK in which there was a loss of 6000 pharmaceutical R&D jobs in 2011, including 2400 which were lost from the closure of Pfizer's R&D centre at Sandwich (Jack, 2011). Pfizer recently reduced its R&D budget from \$9 billion to \$3 billion, and despite the closure of its 2400-person research lab in Ann Arbor, Michigan in 2007, the overall effect to date has been a greater concentration of R&D activity in the US. Since its merger with Wyeth, Pfizer has only four major R&D sites globally, down from 20 sites at the time of acquisition in 2009 (Kessel, 2009). Such closures are explained by management as being a result of the need to free up fixed assets in old plant, providing opportunities for a more flexible approach in new locations, but it is more widely interpreted as one of the consequences of the failure of the current big pharma R&D model more generally and also a failure of policymaker awareness of what very well could be a significant shift in this R&D model. Part of the new approach could be a move away from the traditional in-house laboratory approach towards greater reliance on outsourcing research to universities and small biotechnology companies both in developed and emerging regions. Rather than a fundamental shift in the paradigm of drug development, Kessel (2009) argues that many of the cost-cutting measures being adopted by big pharma are more related to short-term efforts to increase earnings.

#### Attractions of China

With their generally lower costs for particular areas of activity, and also because of their potential market growth, both India and China have emerged as important offshoring centres for preclinical R&D, large clinical trials and contract manufacturing (Wadhwa et al., 2008). While China has an abundant supply of science and technology graduates of varying quality, because its pharmaceutical/biomedical ecosystem is still in the early stages of development there is a scarcity of leadership and management skills. In fact the head of Astra Zeneca's R&D in Asia pointed out that since it takes 10 to 15 years to bring a drug to market from its initial development stage and because China's shortage of experienced toxicologists, pathologists, statisticians and clinicians, it could take several decades before China's pharmaceutical ecosystem was fully developed (McKinsey, 2012).

One of the areas in which both China and India already play a significant role in the global pharmaceutical supply chain is as providers of Active Pharmaceutical Ingredients (APIs). Between 2007 and 2011, Asia's portion of the world API market went from 24 to 28% and is expected to reach a value of more than US\$50 billion by 2017 (Gross, 2103). A 2010 consultancy report on the API sector in China stated that the sector was worth US\$31bn in 2010 and despite some recent high profile quality issues, improvements were underway with the help

of western companies, so that the sector was expected to expand to US\$65 billion by 2015 (JZMed, 2010). A particular regulatory loophole the Chinese Food and Drug Administration (CFDA) has been battling against in recent years, which affects China's credibility globally, is the ambiguous definition of 'chemical entities', which allows industrial-grade factories to produce and export intermediaries or chemicals which eventually end up in APIs intended for human use (Bioassociate, 2012). Despite China's efforts to attract investment in high-end API and finished drug dosage manufacturing, Western pharma companies were reluctant to outsource these activities to Chinese contract manufacturing organisations (CMOs) because it constitutes the last step in the production process and also because of the difficulty of monitoring the quality of regulations in China (Dierks et al., 2013).

Yet with its huge population of potential participants in clinical trials, China presents opportunities to big pharma for reducing the cost of this essential aspect of drug development. Salter (2009, 138) argues that China can exploit its advantages including its large pool of human subjects for clinical trials in exchange for access to basic science and venture capital. Since China is still in the early stages of providing wider access to health services for its huge population, it provides in the words of Salter and Waldby (2011, 288) 'an interesting case study of relationships between health, medicine, market and politics.' Part of the response of China's hospital system to the huge pressure on its services is to enrol poor patients in international clinical trials which are profitable for hospitals. Cooper (2011) identifies such arrangements as a new form of nonskilled risky labour, by which nonpaying patients gain temporary access to medical checks and drug treatment in return for bearing the experimental risk involved.

According to an industry consultant, with people earning between \$7,000 and \$27,000 expected to grow to 75% of China's population by 2020, the rapidly increasing numbers of patients with ability to pay present both a challenge for China's healthcare system and opportunities for big pharma companies in China (Forchielli, 2013). Since many diseases not previously treated or misdiagnosed, the numbers with chronic conditions such as hypertension and cancer are rapidly expanding. For example, recent estimates suggest that China has 114 million diabetics and perhaps as many as 493 million prediabetics (Huang, 2013). The projected programme of urbanization on an unprecedented scale in the coming decades will increase these numbers significantly together with the rapid ageing of China's population which is estimated to have 223 million 65 years and over by 2030, will put increased pressure on the health system.

The huge growth in demand for healthcare together with China's expenditure in biomedicine, estimated to be \$71 billion in 2011, partly explains the increased focus by big pharma in establishing manufacturing and R&D centres in China. According to a recent consultancy report, because of the uniqueness of the genomics and metabolomics of the Chinese population, this will demand a new R&D investment by multinationals in Asia and will also give competitive leverage to domestic R&D entrants (Bioassociate, 2012). While China presents obvious opportunities for a global shift in big pharma, Dierks et al (2013) also to the unique complexity which western companies face in China, particularly its fragmented market with 3,700 domestic companies accounting for 75% of annual sales, of which 95% operate in the low value generics market. They also highlight the negative effects of a three to four year time lag between drug registration in Europe and in China because of the critical regulatory issue requiring foreign pharma companies to conduct clinical trials in China prior to their product launches. With 40%

of China's healthcare budget being spent on medicine compared with 10-12% in western countries, it is not that big pharma companies in China are experiencing political pressure to reduce prices (KnowledgeWharton, 2013).

It is not surprising therefore that the *Financial Times* reports that although in a small number of cases, China has already become an important market for big pharma companies, it contributes only 1-3% of global revenue for most foreign companies (Table 1). McKinsey's 2012 report 'Healthcare in China' advise companies for a number of reasons to think twice about investing in China. Because of various government restrictions, foreign pharma companies opt for partnerships and while increased collaborations between big pharma and contracting companies in China often entail sharing of knowledge about how to run long-term projects, they rarely involve the transfer of core intellectual property (Engardio and Rissing, 2008). Failure on the part of Chinese policymakers to create a more effective regulatory infrastructure, to reform education and to allow public-private partnerships to drive research are, according to industry consultants, among the factors slowing the development of a more innovative environment in China for drug development (Baeder and Zielenziger, 2010). Yet, because of the growing significance of the Chinese market, some multinationals like GSK, LILY and Novartis were already moving into a more mature phase in the R&D space in China, shifting from late-stage drug development and R&D outsourcing to setting up a second wave of more fully integrated R&D capabilities (Li., et al., 2008). The level of investment in China by big pharma companies to date reveals significant commitment to this market (Table 2). The strategy of developing China as a major pharmaceutical R&D hub, however, is likely to be a long-term one with a view to developing significant market share in the coming 10-20 years, as growth opportunities in other markets decline.

Already some foreign companies have faced significant fines for being associated with the common practice of offering poorly paid Chinese doctors incentives for promoting the use of their drugs. Unlike in developed countries drugs in China are dispensed primarily by doctors in the main hospitals, which can create an environment in which corrupt practices may flourish. The anti-corruption push to date has been focused primarily on foreign companies, with GSK in particular suffering significant reduction in sales because of negative publicity. Although many acknowledge that illegal practices are widespread within the pharmaceutical sector generally, some suggest that foreign companies are more easily targeted as part of the anti-corruption push of the new regime in power. While some have interpreted the crackdown on corrupt practices as a growing hostility to foreign companies, others suggest that it is a relative easy way to give a wider message to the sector more generally, including local companies, and also to put pressure on companies to reduce costs.

### China's ambitions and limitations

While China presents a range of opportunities and challenges for big pharma investors, China's increasing integration into the global pharmaceutical value chain must also be evaluated within the context of China's ambitions to develop its own pharmaceutical and biotechnology capacity (Goodall et al., 2006). Thus, while acknowledging China's definite aspirations to become a global biopharmaceutical innovator, and to develop molecules in China for its own population in place of big pharma drugs, some commentators suggest it will take five to ten years to duplicate

developments similar to those of the US (KnowledgeWharton, 2013). Some suggest that China's recent push for 'indigenous innovation' could negatively affect its innovative capacity if it were to focus too much on domestic applications (Salter, 2011). This domestic orientation is reflected in the fact that its share of biotechnology patents has remained at the same level as its overall United States Patent and Trademark Office share, which is one percent.

Thus while Indian and Chinese firms increasingly occupy higher-value segments of the pharmaceutical value chain, few of these firms engage in the discovery and development of new-concept drugs because of the high costs involved and also because of their high failure rates (Wadhwa et al., 2008). Most domestic companies are engaged in producing low-cost generics or copycat versions of existing drugs for which there is a significant market in both countries. Because of the need to balance drug innovation with the challenge to deliver healthcare to its huge population, there is not the same emphasis in China on inventive science as in the US. Salter (2011) argues that China needs to invest in basic science and to ensure that innovation is not constrained by a bureaucracy that limits autonomy. A major challenge facing China is gaining ownership of intellectual property through a judicious use of national and international patenting systems. In the view of one industry consultant, China will continue to rely on foreign companies to provide necessary expertise because pharmaceutical innovation lags considerably behind that of the west and that this dependency presents multinationals with an opportunity to leverage their position in the Chinese market (Forchielli, 2013).

The US and the UK remain in a very dominant position in life sciences generally, with China making little impact to date in terms of foreign patents and particularly the US market (Salter, 2009). While Fangzhu et al (2011) believe that China has considerable potential to become a laboratory for biotechnology development, the low patent ratios of Chinese companies show the limitations of a state-sponsored model in generating knowledge for value added. China's biotechnology sector is highly internationalized with 50% of biotechnology inventions owned by either foreign companies or co-inventors compared with 12% in the US. Most state funding was diverted to building physical infrastructure than actual research, while multinational companies were more effective in exploiting China's large and relatively low-cost talent pool in science. Fangzhu et al (2011) also note that biotechnology multinationals in China, particularly contract research organisations (CROs), interact mainly with their headquarters and thus have weak horizontal linkages with local companies. Not surprisingly therefore, although pharmaceutical exports from China average US\$67 billion annually, virtually none of this revenue comes from innovative products, since few Chinese companies are involved in developing drugs (Bioassociate, 2012).

### Big pharma R&D in China

Despite China's apparent ambiguities about the role of FDI, an interviewee manager of one of Shanghai's biggest foreign-owned R&D centres claimed that the government was doing its best to attract big pharma multinationals to China, offering all forms of incentives, and that there was considerable competition between cities to attract R&D investment, because of the benefits in terms of GDP, knowhow and technology. In his view the government's approach was now more even-handed treating both foreign and local companies in the same way, and he emphasised that foreign companies were expected to have the same high standards in areas like environmental

protection as in developed countries. At this stage there were no local companies capable of competing with big pharma because of the high risks associated with drug development. It might be possible in the longer term for some of the Clinical Research Outsourcing companies to compete when they acquired sufficient knowledge, but at this stage, with the plentiful business available in providing services to other companies, they were happy to maintain their profit margin (Company Interview1, 2011).

This interviewee explained that Shanghai, with the most concentrated cluster, is the top choice location for pharma multinationals to begin R&D activity in China, with much fewer in Beijing. Pharmaceutical companies cannot survive in isolation and thus the presence of major Chinese Clinical Research Organisations (CROs) like Wuxi and Shanghai Pharma, both listed on the New York Stock Exchange, was important for forming joint venture partners or as collaborators. The Shanghai region had a pharmaceutical legacy, with several dozen companies run by returnee Chinese who were educated abroad, and who therefore had a strong background in the pharma industry. Big pharma companies invested heavily in cutting edge science while the CROs provided services, not just to local R&D centres but to big pharma globally. By facilitating the process they were an important component of the emerging ecosystem in China. The situation was somewhat similar to what happened earlier in Japan when multinationals set up R&D centres, but because of cost factors they had relocated their operations to China. Contract manufacturing, on the other hand, which was more mature in India and other regions had yet to emerge in China (Company Interview1, 2011).

While lower costs may be a factor for a big pharma company in establishing an R&D centre in China, it was more an additional help than a driver, since labour costs formed only a small proportion of the total cost of drug production, and the top 10 senior scientists in the centre earned salaries equivalent to those in the west. The main driver was the expectation that the new research group would be more productive, that it would think outside the box and that it would develop a new way of doing innovation in China, somewhat different than the western model. This interviewee marvelled that three of the top global pharma companies in terms of revenue had already established R&D centres in Shanghai's Zhangjiang High Tech Park, and doubted that such a cluster was to be found in any other global location. Over time, it was expected that each of these companies would develop their own separate campus facilities in different locations (Company Interview1, 2011).

The primary factor bringing pharma multinationals to China was the market, which was still at an early stage of development. They were currently testing the water to ensure that they could have a legitimate presence when the market was more mature, since they could not just jump in at the last minute. As part of its open door policy, in existence for 30 years, China had encouraged young people to study abroad and now they were being encouraged to return, which together with local science graduates, though of variable quality, created a large talent pool. With the large numbers of graduates, companies could choose the top graduates from the best universities. Companies were also attracted by the entrepreneurial spirit in China, thinking 'if it is so hard to push innovation in well-established western companies, maybe we can have an experiment in another world region'. Executives from company headquarters, visiting Shanghai were generally impressed with the infrastructure and with what they saw, and thus Shanghai was growing in popularity as an investment location (Company Interview1, 2011).

When questioned about the issue of intellectual property protection (IPR), which has been an ongoing issue of controversy for many foreign companies in China, this interviewee manager said that it was not an issue in their case. Although there were some cases where Chinese copycat companies made generic versions of foreign drugs and tried to export them to western markets, in most cases these companies copied drugs whose patents had already expired. If foreign companies have not filed patents in China for their drugs, it was legitimate for local companies to make copies and sell them in China, but not for export to countries where the IP was protected. While big pharma brand names are gaining popularity among the growing Chinese middle class who can afford them, they faced considerable competition from lower priced generics (Company Interview1, 2011). Between 1992 and 2008 pharmaceutical patents could be violated in China and marketing approval was provided in cases where minor structural differences were made to existing drugs (Bioassociate, 2012). Although China finally adopted comprehensive patent protection regulations in 2008, the implementation of IP regulations needs to be improved.

In relation to the significance of the Shanghai R&D centre, the interviewee explained that from the beginning it was established as an end-to-end R&D centre, focused on alzheimers, which had not been researched by any of the company's other R&D centres, and that while there was a small centre in Singapore with 50 people, this was the company's main centre for the Asia Pacific region. Unlike other big pharma companies, it had no research facility in India. The centre had significant autonomy about what to research and how to do it, but as part of a global corporation it was necessary to follow guidelines on key issues such as the care of animals and issues to do with compliance. Explaining why the centre was assigned the task of focusing on alzheimers research, the interviewee explained that in seeking a senior pharma scientist in China who spoke Chinese as a director for the centre, the company selected a Chinese scientist who already had an established record of research in multiple sclerolosis. Although the company had been thinking about working on infectious diseases that were common in China, they were sufficiently flexible to change their focus to the area of expertise of the selected director. The interviewee was impressed with the company's open attitude in building a research centre from 'ground zero' and recruiting the best talent worldwide (Company Interview1, 2011). Since the interview in 2011, however, this company has faced two major upheavals in China, one in relation to offering incentives to doctors to promote their drugs and the second has been the dismissal of the director of their R&D centre because of misrepresenting data in a 2010 scientific paper. The first issue has had an immediate impact on the company's revenues in China and the second is seen as presenting a more general problem for the future of multinational R&D research in China in the pharma sector (Tremblay, 2013). Because this particular scientist had been assigned huge responsibilities with the management of research in an entire disease area, his sacking was seen to have wider implications for the credibility of Chinese scientists in pharma R&D in China.

China's policy push for greater indigenous innovation since 2006, not only sought to pressure foreign companies to file patents in China, but also to compensate local investors, something that was not always easy to do within the global R&D model of many corporations. Interestingly, however, the Chinese-born interviewee manager of this R&D centre was very much in agreement with the new Chinese policy, stating that the approach of western companies was that

‘you work for me and everything you invent belongs to the company’ (Company Interview1, 2011). His view was that if he was involved in developing a drug that turned out to be worth billions, he was entitled to some compensation, and this view may reflect possible tensions between the traditional global R&D model of multinational companies that seek to acquire knowledge inputs from different global locations, and the aspirations of an emerging country like China which seeks to push for greater indigenous innovation within its own borders. He did say, however, that China’s patent office in Beijing interacted with foreign companies like his to get some feedback about policy developments.

While some interviewees commenting on the work being carried out in the foreign-owned R&D centres in China claimed that they were beginning to bridge the link between drug discovery and development, one interviewee emphasised that in most cases multinationals were only beginning to test the water in relation to R&D, since China was still in the early stages of building local capabilities. The company of this particular interviewee, like some others, was adopting a collaborative approach with local scientists, since they did not have any laboratory in China as yet. The company did not have any facilities for toxicology work in China, and it outsourced early stage work to local supplier companies while focusing on later stage work themselves, which was supervised by expatriate personnel from headquarters. In some cases while working with a local company that already had developed a chemical compound, it was necessary to redo the work because of quality issues. The cost and availability of senior skills was a factor, with high turnover levels among personnel, and issues in relation to the training of graduates, affecting the quality of their work, were also raised. Continuity in relation to senior management was an issue because of the tendency for expatriates to spend only a few years in China, and while returnee-Chinese filled many senior positions, issues related to compliance required a continued reliance on expatriates (Company interview3, 2011).

#### Clinical Research Outsourcing (CRO)

Although a number of big pharma companies have established some elements of R&D activity in China already, some suggest that the greatest potential for developing a partnership platform between China and multinational companies is in clinical trials (Forchielli’s, 2013). Because Clinical Research Organisations (CROs) assume none of the risks associated with drug development, and are paid a fixed amount for performing specific stages of drug development and testing, this sector is particularly suitable for the early development of the pharmaceutical sector (Wadhwa et al., 2008, 13). Domestic CROs focus on specific segments of the pharma R&D value chain such as standardised chemistry research (Dierks et al, 2013). The rise in this sector in emerging regions like China is revealed in a recent Reuters report (2011) based on data from the Tufts Center for the Study of Drug Development (Tufts CSDD) which noted that the North American share of clinical trials had declined from 83% in 2001 to 53% in 2009, while Western Europe’s share increased from 9% to 14% and that of the rest of the world had increased from 5% to 33%. While China presents considerable attractions for CRO investment, there are also a number of obstacles to its growth, such as low level of English language ability, ethical challenges and the fact that Chinese regulations require clinical trials with Chinese patients before a new drug can be sold in the local market. Before trials can commence in China compounds must be tested in Phase II trials elsewhere, creating a considerable time lag before approval is granted (Schulz, 2012).

A complementarity exists between the innovation resources of big pharma, who increasingly lack the necessary capital for the further development of potential candidates in the molecular pipeline and China's wealth of early and late-stage clinical trial resources such as extensive animal facilities which are likely to have less cumbersome regulatory hurdles than in the west. Clinical trials can account for between 40-60% of total costs of drug development, and estimates of savings in China vary from 67% to 80% of the costs in the US or Japan (Forchilli, 2013). China also has an enormous and willing patient pool that could gain some access to free healthcare, and could lead to faster and cost-efficient recruitment. Under current Chinese laws, however, first-in-human investigations are prohibited in China for foreign-developed molecules, which necessitates either late stage animal studies or earlier R&D stages taking place in China. For big pharma companies seeking to penetrate what is likely to be a significant future market, it makes sense to conduct international, multicentre clinical trials in China (Forchielli, 2013). Some commentators, however, referring to the recent GSK bribery investigation and to other incidents of corruption in China have suggested that this could have a seriously negative impact on the more than 3000 clinical trials by foreign companies in China, with consumers being concerned about the integrity of these trials, and that participating doctors are not unduly influenced by monetary compensation (Brinded, 2013). It has also been suggested that drug companies outsourcing clinical trials to China will continue to have problems such as 'sloppy data and misconduct' if they did not provide better oversight for these trials (Armstrong, 2013).

Another company interviewee, who was charged with establishing clinical trials in oncology for an American company explained that CRO outsourcing was a specific inward investment category that China was seeking to attract, because of its perceived potential contribution, and because of that policies and regulations in this area were improving for inward investors with some preferential treatment being offered to companies. Lower tax rates for the first three years were among the incentives offered, but there was little support to date for companies that had reached a more advanced level in their operations. This interviewee noted that generally there was a lack of knowledge among officials about the processes and that big pharma companies had to educate them gradually. Despite this companies involved in outsourcing were placed in a special category for preferential treatment (Company interview2, 2011).

The fact that Phase 1 clinical trials of foreign company drugs were not permitted in China was a source of serious dissatisfaction for one of our interviewee company managers, whose main goal was to establish a Phase 1 oncology centre. This interviewee emphasised the importance of Phase 1 research as the first important step in establishing a new potential medicine in a human, and without this step drug development cannot move forward. The interviewee explained that China's State Food and Drug Agency (CFDA), known as the State Food and Drug Agency (SFDA) before 2013, does not allow foreign companies to test drugs on Chinese patients because of safety concerns. This agency has had its own turbulent history, with its former head being executed in 2007 for taking bribes from companies in exchange for licences. The policy is that foreign companies can get involved in China only after they have completed phase 1 trials elsewhere, since the risk at this stage is lower, and the agency does not want to take on the responsibility of managing earlier risks. This interviewee felt that not allowing Phase 1 trials ten years ago in China was acceptable as China had not developed any innovative product and the developed product was just imported, but now with so many foreign-owned and domestic R&D

centres in China the situation has changed. Yet, foreign companies were not allowed to put their product into Chinese patients for phase 1 trials. You must do it outside China and then come back for further development. ‘This is really an historical legacy from ten years ago that does not make much sense’ (Company interview2, 2011).

## Conclusion

This paper attempts to explain the offshoring of big pharma R&D activity to China within the context of China’s increasing integration into the global pharmaceutical value chain. This offshoring can be seen within the broader context of multinational R&D offshoring to newly emerging regions as part of their augmenting strategies to enhance their global knowledge base and to develop new products. Within the context of the globalisation of the pharmaceutical value chain, the offshoring of big pharma R&D to China needs to be evaluated in relation to the convergence between big pharma’s growing needs to reconfigure its traditional business model based on deriving major blockbuster drugs from significant R&D investment and the increasing attractions and opportunities associated with China’s emergence as a major market for pharmaceutical products as well as a potential centre for drug development. In addition to understanding China’s increasing significance as an R&D centre for big pharma, it is also important to appreciate China’s interest in attracting big pharma investment in relation to China’s own ambitions to develop its pharmaceutical sector.

Although China has major ambitions to become a significant pharmaceutical innovation hub, its pharmaceutical ecosystem is still in the relatively early stages of development, with little or no innovative drug development to date and an absence of senior specialist research and management skills. Despite significant state investment in recent years, China is under significant pressure to provide for its huge healthcare requirements with increasing large numbers of people suffering from untreated or misdiagnosed diseases such as cancer, diabetes and hypertension. Thus despite the recent policy push in China towards ‘indigenous innovation’, China continues to rely heavily on attracting big pharma investment to help develop its own pharmaceutical ecosystem and to provide medication for a rapidly growing middle class with an ability to pay. China’s growing healthcare needs provides big pharma with an ideal opportunity to expand its markets at a time when markets in more developed regions are experiencing little growth.

In addition to China’s healthcare needs, big pharma is also looking to China and other emerging regions to help reconfigure its traditional business model which has become increasingly uncompetitive in recent years. A major reason has been the ‘patent cliff’ with many blockbuster drugs reaching the end of their patent period and facing significant competition from generic drug companies, particularly in countries like China. It must also be acknowledged that big pharma’s own R&D productivity in recent years has declined significantly, with few major innovative drugs being developed despite huge investment. In order to both reduce the costs of drug development and to seek new forms of innovation, big pharma has been increasingly integrating China and other emerging regions into a more globalised value chain. Because of China’s relatively early development of its ecosystem, much of big pharma’s offshoring to date has related to the early stages of drug development. China in particular has become a major centre for developing Active Pharmaceutical Ingredients (APIs) and also for clinical trials for big

pharma. Despite its growing significance in the API sector, it is noteworthy that concerns about the early stages of its regulatory environment and associated safety and quality issues, big pharma has been reluctant to offshore the high end of this activity to China.

Concerns about China's developing regulatory environment has also affected the development of clinical trials in China, which is regarded by many as showing significant cost-saving potential for big pharma. The insistence by Chinese regulations that Phase I trials must be conducted outside China adds a considerable time lag to the process of approving new drugs for the local market. With big pharma's growing need to reduce the cost of drug development, China, with its huge population of patients willing to become involved in clinical trials presents particular attractions as a location for expanding this investment. An important aspect of big pharma's growing investment in R&D in China relates to the specific needs of the local population in relation to the prevalence of particular diseases. While, on the one hand, China provides significant opportunities for increasing the market share of existing blockbuster drugs for major diseases such as diabetes, even in generic form, big pharma is also researching solutions for diseases that are more prevalent within the local population.

Despite the considerable investment by a number of big pharma companies in R&D centres in China to date, this investment is still in its very early stages, with big pharma aware that its success in the Chinese market depends on a long-term investment. With China accounting for less than 3.0% of the global revenue of most big pharma companies to date, the complexity and fragmentation of China's market is creating a significant challenge for big pharma companies. With much of the local market dominated by generic drugs and with the Chinese state determined to reduce the cost of its burgeoning health budget, which is largely made up of the cost of pharmaceuticals, China presents considerable challenges for big pharma together with many opportunities. The significant problems faced by one big pharma company to date, relating to the provision of incentives to local doctors for promoting their products, together with the sacking of a major Chinese pharmaceutical scientist as director of their R&D centre in Shanghai, indicates some of the thorny issues which big pharma companies may have to negotiate before achieving significant success in the local market. As with other sectors in which foreign investment plays a significant role in China, most big pharma companies are likely to adopt a patient and long-term strategy to eventually reap the benefits which China offers both in terms of providing considerable market expansion and also contributing to reduce the costs of drug development.

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Table 1 China as a % of global sales

AstraZeneca	2.7
Pfizer	2.4
Sanofi	2.2
Roche	2.0
Glaxosmithkline	1.6
Merck & Co	1.4
Novartis	1.1
Johnson & Johnson	0.9

Source Mathurin (2013)

Top 10 MNCs in China by investment (US\$ billion)

Pfizer	9.4
Roche	9.2
Merck Sharp & Dohme	8.12
Novartis	8.08
Johnson & Johnson	6.84
GlaxoSmithKline	6.09
Sanofi	5.94
AstraZeneca	5.3
Eli Lilly	4.88
Bristol-Myers Squibb	3.56

Source: BioMed Tracker (Bioassociates, 2012)