



## Open innovation: An opportunity for Pharmerging countries to close the technology gap?

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**Abstract:** The pharmaceutical industry is entering a critical phase in its history, with declining profits and patent cliffs fallouts awaiting their former blockbuster drugs. Several hypotheses have been formulated to explain the causes of this downfall whether it is the drought in their R&D pipelines, the rising competition of generics or the ever-increasing pressure from healthcare providers such as governments seeking to curb their health expenditures thus causing price erosion. However, rather than striving to find the root causes of the issues the industry is facing, the major players in the Pharma field should focus on implementing measures to transform the very structure of the pharmaceutical companies and change the drug discovery and commercialization processes. These core changes that the pharmaceutical sector has to undergo could be achieved through several methods. One of the most suggested solutions to this R&D bottleneck could be shifting from the traditional “closed model” towards a new “open innovation” model based on collaboration of Pharma companies whether it includes working together with a biotech company, CROs, Academia or local Pharma manufacturer. This open innovation model is believed to foster innovation and invigorate the agonizing R&D Pharma sector as it proved itself to be effective resulting in innovative projects and ideas in the IT sector. It is in this context that this paper will address the opportunity emerging pharmaceutical markets could benefit from when this open innovation model is applied to the pharmaceutical industry. Mainly, we will discuss the integration of this strategy within big Pharma companies in their efforts to enter what is designated as “Pharmerging countries” in general with a special focus on one key global health market: China. We will discuss the impact of this innovation strategy could bring in terms of both tangible and intangible benefits and potential drawbacks.

**Keywords:** Pharmaceutical Industry, R&D, Open innovation, China

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## INTRODUCTION

Current Pharma industry situation is critical according to most industry analysts, this new decade marks the start of a the dramatic yet predictable patent expiration wave for major drug blockbusters such as the anti-thrombosis drug Lovenox manufactured by French SANOFI-Aventis or Swiss Roche’s anti-cholesterol drug: Lipitor. The latter drug generated \$10.7billion in 2010 only, illustrating the crucial role these blockbuster drugs play in the big Pharma’s so far unprecedented profitability, peaking in the eighties and nineties ,a golden era for the Pharmaceutical industry worldwide where few Pharma Multinationals (Big Pharma) had a quasi monopoly on the global drug market.

(Fig1)

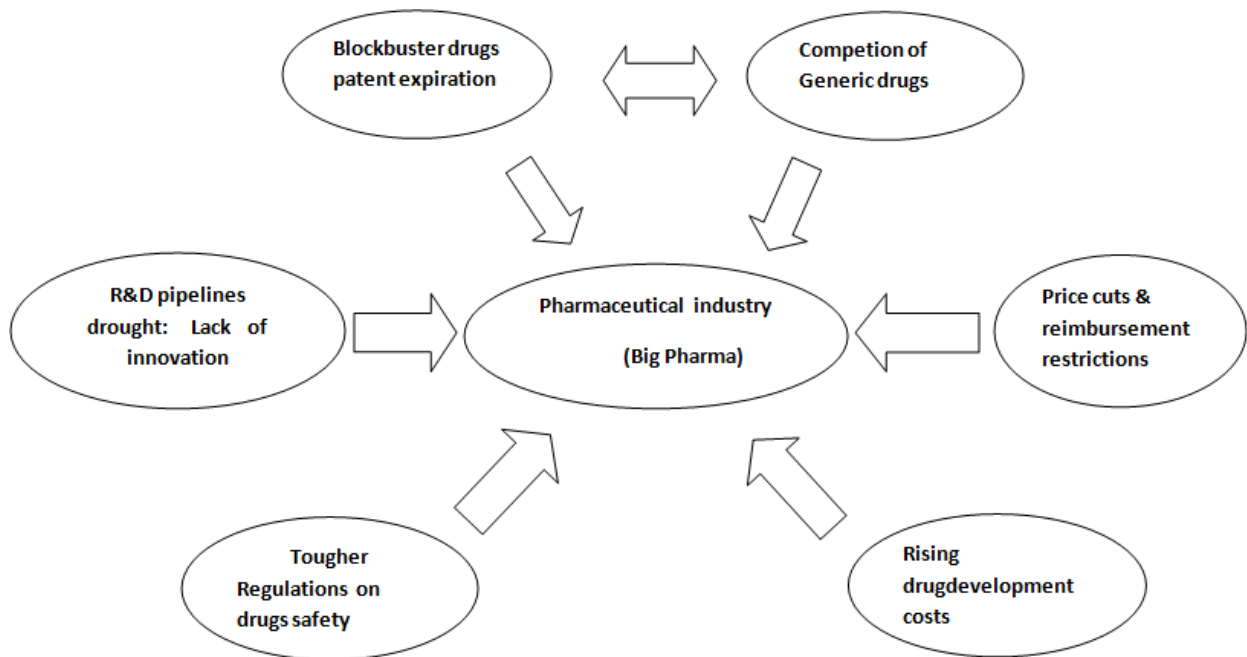


Fig 1.Challenges hampering the growth of the Pharmaceutical Industry

Today’s Pharma market is still one of the most profitable, with \$600billion in 2011 and a 6.5 percent CAGR essentially driven by a strong near-term growth in the U.S market and the rise of new drug markets in developing countries like China or India, where the size of the drug market is making Big Pharma salivate over colossal future profits. Nevertheless, we are currently far from the golden age of Pharma industry with Big Pharma ruthlessly dominating the market and earning astronomical return on investments with a few powerful patented drugs, namely the blockbuster drugs treating widespread conditions: Coronary diseases, Hypertension, Diabetes, Cancer...Etc. This clear blue sky is now threatened by the drug patent expiration storm and the generic drugs competition which are usually 30-80 percent cheaper than the original drugs and set to generate \$129.3 Billion USD in 2014 with a double-digit expected growth especially in Pharmerging countries (15-17 percent CAGR), also the constant pressure of price cuts governments are imposing now on the healthcare expenditures illustrated by Austerity plans in EU countries affecting the healthcare reimbursement schemes & social security in many countries: France, Spain, UK or the Obama’s Medicare plan in the US to curb health spendings. Add to that the rising pressure of what some Pharma executives already qualify as an “over-regulated” industry. This refers to an increasing set

of laws and regulations passed by governments through regulatory organizations such as FDA in the US and AFSSAPS in France. These organizations impose more control and transparency for clinical trials and new drug approval.

In the UK, the pharmaceutical industry faces tougher legislation on the disclosure of adverse events in clinical trials following the MHRA's thwarted attempt to prosecute GlaxoSmithKline for allegedly withholding information about risks of suicidal behavior in children and adolescents taking its antidepressant Seroxat (Paroxetine). Another example is the bill enforced by the congress in the USA allowing FDA new authority to impose safety requirements on medicines once they go on the market, including restrictions on consumer advertising. The bill also would require registration of clinical drug trials and their results in public databases. The FDA Amendment Act of 2007 has forced the FDA to increase the standards for approvals of new drugs introducing mandatory risk evaluation and mitigation strategies (REMS).

Another major issue that the Pharma players need to address is the constant increase in the bill to develop a new drug, Pharma companies have been spending more to develop drugs but with an attrition rate of 999/1000. These costs are starting to weigh on the Pharma companies budget especially when they will not necessarily lead to the next Blockbuster drug. A study conducted in 2003 in the Health Economics Journal showed that the cost of developing a new drug for Pharma companies average of \$802 million apiece to produce in 2000, or \$1 billion in 2011 dollars when accounting for inflation. Even if there has been some controversy about the validity of these results, an independent study has been conducted to verify the accuracy of these claims and it concluded that the costs are more or less accurate with 5 percent error rate for the 2003 estimated numbers. Yet, Pharma industry remains a profitable business when conducted well and based on a promising innovative drug R&D project. Hence, Pharma companies have been trying to figure solutions out to these rising R&D costs by outsourcing some of their operations in regions where operating and labor costs are cheaper: India, China, Brazil...etc.

Despite all the aforementioned challenges the industry is facing, the most critical factor that would seal the industry's fate is the adoption of a new R&D Innovation approach that would ensure the Pharma industry's sustainable growth. Developing promising drugs is a complex equation in which consequent human and material resources are combined to result into a new drug or therapeutic approach for a given disease. So far, this has been achieved throughout a closed model in which all stages of the drug development from the discovery of the potentially active molecule or compound to its commercialization in the market were handled in-house by the same Pharma company. This generated the highly innovative and jealously protected patented drugs; these blockbuster medicines yielded considerable benefits to their manufacturers who invested considerable financial & Human resources to develop these products yet yielded colossal profits after it was out in the market. Unfortunately for the industry players, this single or multiple blockbuster drugs based model could not indefinitely provide sustainable growth and profits. This conundrum justifies the deep rooted restructuring the pharma industry is undergoing at various levels: organizational structure, operations, production processes, supply chain and most importantly the R&D model. The latter restructuring of R&D processes has been influenced by the ascension of a new innovation model, called 'Open Innovation', which has 3 key objectives throughout the process of its implementation within an R&D structure:

- Sharing the risks (and profits) associated with the drug development process
- Reduce time & costs related to a new drug development
- Provide a sustainable growth strategy for an industry facing a drying R&D pipeline

## OPEN INNOVATION IN PHARMA

### The open innovation concept

The concept originally dated back to the 1960's with a special focus on inter-firm cooperation in the R&D departments. However, the open innovation and its applications in today's fast-paced business landscape is a model promoted by Henry Chesbrough, a professor and executive director at the Center for Open Innovation at the University of California, Berkeley, in his book *Open Innovation: The new imperative for creating and profiting from technology*. The concept is related to user innovation, cumulative innovation, Know-How Trading, mass innovation and distributed innovation. "Open innovation is a paradigm that assumes that firms can and should use external ideas as well as internal ideas, and internal and external paths to market, as the firms look to advance their technology". The boundaries between a firm and its environment have become more permeable; innovations can easily transfer inward and outward. The central idea behind open innovation is that in a world of widely distributed knowledge, companies cannot afford to rely entirely on their own research, but should instead buy or license processes or inventions (i.e. patents) from other companies. In addition, internal inventions not being used in a firm's business should be taken outside the company (e.g. through licensing, joint ventures or spin-offs.)

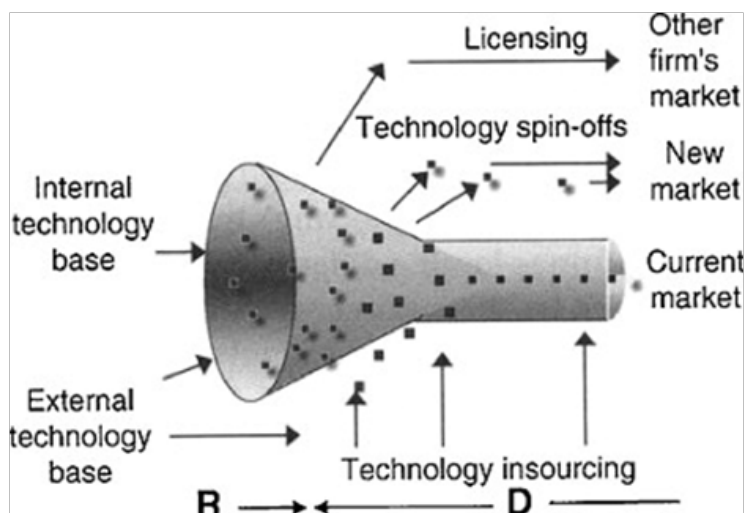


Fig 2.The open innovation model (Chesbrough, 2006)

### Open innovation in Pharma industry-The necessary transition from closed to open model

Open innovation is more than just a trend for the pharmaceutical industry. Indeed, the sector is undergoing a critical phase in its history, with R&D pipelines desperately dry with R&D departments either unable or not dynamic enough to produce an innovative, safe and profitable drug. The Pharma sector is an industry where R&D is the core business unit within the organization and the rest of the departments' organization and size depend on how innovative and time efficient the research unit is. Until recently, the drug makers were solely operating on a very efficient "closed model" where all stages from research of active components, identification of the targets, pre-clinical, clinical trials and finally the registration and marketing of the drug were exclusively handled by the Pharma company, this would start off with consequent human and capital investment in the potentially successful compound or molecule, which eventually would

yield a considerable return on investments due to its patent protection.

This patent would guarantee the exclusivity of the new drug ,extending the protection from the active compound itself called “Princeps”to its adjuvants, its production processes and its therapeutic use all property of the Innovative Pharma company which discovered the drug for a duration that would vary from 10 to 20years.After the expiration of this patent, the drug would experience what we call a patent cliff ,illustrated in a steep drop in sales due not only to declining unit numbers ,but also because of price erosion up to 70% within months mainly due to the introduction in the market of cheaper substitutes, with the same active ingredient, but with different adjuvants and/or methods of manufacturing.(Fig3)

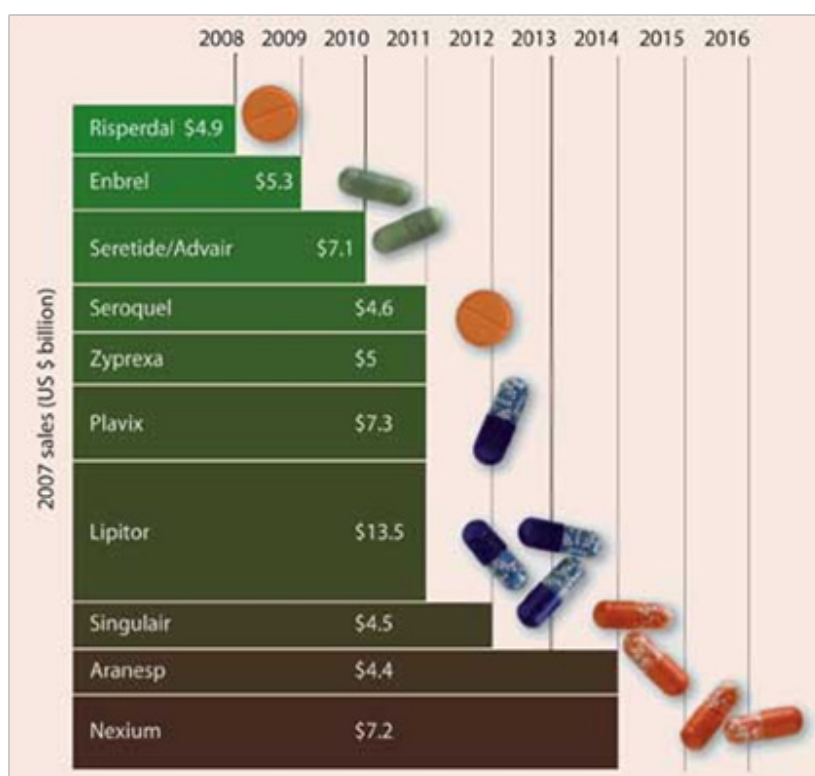


Fig 3. Illustration of Patent cliff of blockbuster drugs (Royal Chemistry Society, 2009)

Patent cliff would essentially impact individual Pharma companies in the mid-term future within the period 2010 - 2014, the revenues of drugs whose patents will expire is around \$89.5billion USD. In 2011, Lipitor, the bestselling drug of Pfizer will go off patent as will Plavix (anti-thrombosis drug), Actos the anti-diabetic drug as well as Sequel and Zyprexa, which are used to treat schizophrenia and bipolar diseases. The loss induced by patent cliffs could only be compensated by the launching of new products, for example, new indications such as osteoporosis, cancer, multiple sclerosis or respiratory illnesses. Hence, the urgent need for new drugs and treatments to limit the losses induced by these patent cliffs. Another way to minimize the damages of patent cliffs is to sell branded generics, which are the authorized version of the patented drugs as a mean to maintain the bigger market share even when the latter drugs would no longer be protected by their patents.

In a bid to retain as much revenue as possible from its Lipitor cholesterol pill, which lost

patent protection in the US in May 2011 and now faces generic competition, the US Pharma giant, Pfizer is undertaking several unusual strategies. These include offering incentives to health plans and pharmacy benefit managers to favor its brand-name drug, providing consumers a co-pay card that lowers their cost significantly and partnering with a specialty pharmacy to mail Lipitor directly to patients. The gambit is being closely watched by other drug makers, payers, pharmacies and regulators for the implications as numerous best-selling meds also encounter generic rivals. Lipitor generated \$10.7 billion in sales last year: capturing even a small slice of ongoing sales is important to Pfizer. To gain some insight, Reimbursement Intelligence's recent market research showed that Pfizer would lose 54.5 percent of the market after 6 months and 75 percent after a year. Pfizer's aggressive strategy towards pharmacy retail stores and healthcare providers is a pioneer model, that if proved to be successful could be applied by other Pharma companies willing to stop the brand erosion they are facing and to some extent considerably slow down the roaring success of generic drugs in the global market. This latter strategy shows how desperate Pharma firms are in retaining as much revenue as they can from their star drugs.

The biggest issue in Pharma remains the lack of innovation. Where the long-term forecast is merely 1 new drug per company per year, productivity in the sector has declined by 20 percent from 2001 to 2007. This phenomenon could be the combination of many factors: after the M&A fever in 2009 that had resulted in a series of acquisitions of smaller biotech companies by Big Pharma trying to penetrate new markets by purchasing smaller generics manufacturers in this field USA leads the pack with over 114 deals made in 2010 including 8 worth more than \$500 million USD. These deals represent 50 percent of the deals made in 2008-2010 such as SANOFI-Aventis who boosted its presence in China in the OTC market by acquiring BMP Sunstone in 2010 for \$520 million USD. Although these M&A activities might have their perks, it seems that it has become a brick in the "R&D wall" Pharma industry is hitting: several experts argued that the M&A might keep its promises in terms of market penetration and strengthen a firm's position in a new market. However, in terms of innovation it had to some extent failed to produce tangible results, the explanation could emanate from the fact that by merging and acquiring new firms Pharma companies simply lost in efficiency what they gained in size. The lack of inter-firms synergy between the mother company and the newly acquired ones, as well as the vertical structure of the decision making processes is affecting the R&D more than any other department, hence shifting the focus of these companies from innovation to deal with integration issues within the organization. Over time, complexity becomes a drag on the quality and speed of decision making and there is a need to shift towards leaner models such as Virtual development which have been proven to be successful for Eli applying Chorus virtual model molecules through candidates identification and Phase I at median cycle times that were 40 to 60 percent faster than the industry average.

Another issue hindering the development of new drugs is the heavy focus on biotechnology and small molecules, though they are promising for the future. So far, however, Pharma companies who acquired these firms have failed to translate these discoveries into concrete drugs or clear therapeutic indications. A recent analysis showed that out of 6,000 biotech projects available for late-stage licensing; only about 200 are likely candidates for larger Pharma companies and fewer than 100 have the potential to become top-sellers. Combined, these projects would account for \$30 billion USD in potential revenues.

Another example of promising projects with so far meager results is the Human

Genome Project, while undeniably a huge scientific achievement; results have fallen far short of expectations. The project simply has not yielded the sort of immediate benefits in terms of therapeutic treatments and diagnostics that had been hoped. New models for “data-driven” public/private collaboration are poised to transform industrial drug discovery. Pharma is then set to enter a new era: The open innovation era, based on what seems to be at first the very notion the industry has been jealously avoiding: data sharing and collaboration. This shift towards a pre-competitive era is a necessity to foster creativity and ideas on a global scale and from this paradigm; it should profit everyone from drug makers, healthcare providers to patients desperate for new and efficient therapeutic solutions. This open collaboration has many forms, we can see it in the growing number of private-public consortiums of various kinds such as Merck`s SAGE initiative. This acknowledges the common need to develop tools and frameworks able to analyze and integrate data from multiple sources and across disciplines (for interest in chemistry, biology and agriculture etc), fostering the innovative ideas from industry, academia and NGOs.

This SAGE initiative would rather account as an exception in the open collaboration field as it has non-profit purposes. But we have seen an increasing number of projects involving Pharma companies either with each other or with biotech firms to boost the drug discovery process and yield tangible results within shorter deadlines. Another case of this new model is illustrated by Lilly`s new open innovation platform designed to help build its pipeline and to identify new treatments for multi-drug resistant tuberculosis, which builds on the success of Lilly`s Phenotypic Drug Discovery Initiative (PD2), launched in 2009 to facilitate research on molecules around the world that have the potential to ultimately be developed into medicines. The Open Innovation Drug Discovery platform utilizes a secure website that offers Lilly`s proprietary computational and informatics tools to aid scientists in the design and selection of molecules. Once a scientist submits a molecule to the website and it meets certain specified requirements, Lilly tests it – free of charge – in a series of biological assay panels that evaluate it for its uniqueness and potential to be further optimized into a drug candidate. Comprehensive data reports are then provided to the submitting scientist. In the case of the cancer, endocrine, cardiovascular and neuroscience screenings, Lilly receives first rights to negotiate a collaboration or licensing agreement with the submitter in return for the data`s provision. If no such agreement is reached, the external scientist retains “no-strings-attached” ownership of the data and can choose to use it in publications, grant proposals or to further refine their hypotheses about the molecule`s potential as a medicine. In the case of the MDR-TB screening, promising data could result in collaboration between the submitting organization and the Lilly TB Drug Discovery Initiative. Lilly`s R&D operations, through this project recognized the “many untapped sources of ideas and molecules” outside the company. The initiative is part of Lilly`s wider goal of raising R&D productivity with faster development times and lower costs. Another Lilly R&D project entitled Chorus, focuses on leaner development processes, and aims to reach decisions about 12 months earlier and at about half the cost of the current industry model. Novartis is another big Pharma company who believes in the potential of open innovation to thrive and sustain its growth strategies on a global scale. GlaxoSmithKline, the UK based Multinational Pharmaceutical company, is putting thousands of possible malaria-treating drugs into the public domain in a move that the Wall Street Journal calls a ‘Linux approach’ to pharmaceutical screening. Of course, synthesis or discovery of new chemicals is cheap compared to efficacy and qualification studies, but this is a refreshing change

from the current practice of providing no information at all until after all patents have cleared. J&J executives see the appeal of this new R&D model to enhance intellectual entrepreneurship and multidisciplinary collaboration to find solutions for healthcare problems. It has lately signed a deal with GE the powerhouse of medical imagery and diagnostics to joint their efforts in the Alzheimer disease research. Terms of this collaboration have not been disclosed but it would essentially combine the two companies 'expertise in data integration, imaging, informatics and genomics in order to find a set of biomarkers as a way to diagnose people with higher risk of developing the disease as they grow older. Also worthy of note is GE's efforts to advance breast cancer treatment through the open innovation platform in which they invested \$100million USD in collaboration with private Pharma companies, venture capital entities Kleiner Perkins Caufield & Byer venture capitals with a special focus on data. So whether it is competitors teaming up together for the research phase or Pharma collaborating with Academia like the collaboration announced in 2011, where 37 US universities and colleges were announced as the recipients of the British Council's New Partnerships Fund which would enable George Washington University to work with Oxford University and Tata Memorial Centre, Mumbai, India on cancer research), these partnerships whether for profit or non-profit motives are set to be the new way to perform research work in healthcare field at least for early stages research efforts to respond more proactively to the growing demand for innovative, ad-hoc therapeutic solutions. This paradigm enables Pharma companies and Academia research institutions or other partners to use each other's forces and combine them, with Pharma finally acknowledging that all talents are not necessarily part of their organizations, hence providing their expertise and financial support to those who might nurture promising ideas but fail to translate them into concrete drugs due to lack of funding or their inadequate infrastructures.

## **Open innovation impacts on the Chinese pharmaceutical industry**

### **Overview of Chinese Pharmaceutical industry**

With an absolute GDP of \$91trillion USD in 2009 and a pharmaceutical market that is estimated to drive \$40billion USD in growth through 2013, China is leading the pack of Pharmerging countries. Driven by aggressive government spending on healthcare and an increasing demand for drugs to treat chronic illnesses such as: Diabetes, Arthritis...etc. China's pharmaceutical market expanded at an astonishing 20percent in 2009. A landmark \$125billion USD incremental government funding is at the heart of the healthcare sector's transformation, targeting substantial improvement to the nation's healthcare infrastructure, a move which is set to double the size of China's pharmaceutical market by 2013. Nevertheless, the operating environment remains complicated and a challenge along with local competition, government intervention on drug pricing and uncertainty of healthcare reforms. Due to all these factors, big Pharma see China as their saving grace whether to increase their sales volume in the Asian region with the two ascending Pharma giants China and India injected \$180billion USD in the global drug market through drug sales; or to boost their research departments through collaboration with Chinese counterparts. Bayer's incremental growth is mainly attributed to investments in China and Turkey and its capacity to adapt to the local market environment by investing in products highly sought by these markets such as Glucobay for Diabetes and Adalat for hypertension, the company has



achieved a dominant position in these high-growth therapy areas and now derives 3percent of global revenues from China and this number is likely to rise in the next five years.

**Table2.Chinese government policies to build an innovation-driven Pharmaceutical industry**

<b>Innovation promotion policies</b>	<b>Goals</b>
Increase direct investment in the Pharma industry	Combine industry, Academia and partner industries' innovation capacities
Tax credits or concessions speed up depreciation of R&D facilities & equipments	Encourage & support enterprises in setting up R&D centers with favorable measures
Establish and/or renovate Public technical support platform for Pharma industry	Help firms reach their innovation goals
Government purchasing of domestically produced drugs	Encourage local firms to provide effective and marketable drugs by demand encouragement measures
Investment in the renovation of TCM research facilities	Promote TCM drugs research to capture value

Another consequent advantage for China is the cheap labor and operating costs,as it requires 40percent less investment to develop a drug or to run a clinical trial in China than in Western countries which explains the booming number of CROs in China operating for Big Pharma laboratories and the investment in these structures is forecasted to rise in the next five years.

Another segment on the rise is theAPI production which makes up more than 50% of the export value of China's pharmaceutical trade.As a result, the Chinese market for APIs is rapidly growing and is estimated to witness a compound annual growth rate (CAGR) of 18% from 2010 to 2017. Ingredient suppliers in the Chinese API market will be keenly following the events in the pharmaceuticals industry, which is in the midst of integration. Apart from the sustained and rapid growth of the pharmaceuticals industry, the long-term use of multiple specialized drugs for an aging population and the reform of the Chinese medical system have also given a shot in the arm to the Chinese API market.As drug administrations in China put more effort into the supervision of the pharmaceutical industry, safety and environmental protection issues have become the areas of concern for the API producers. API producers in China are required to follow the guidelines such as the good manufacturing practice (GMP), which was revised by the Ministry of Health of the

People's Republic of China in 2010. These manufacturers are also required to reach higher levels of standards and certifications, which are similar to the Japanese and European standards. These measures have resulted in interdisciplinary joint research projects between universities, research institutes and industry's local players which foster innovation and creativity in the country. All these efforts are designed to overcome major challenges still hampering the sector such as the counterfeit drugs scandals that are plaguing China's Pharma industry's image with the last one to date involving Colgate. The scandal follows the discovery of a shipment of Chinese-made contaminated with DEG toothpaste in the US. The US Food and Drug Administration (FDA) said DEG, which is sometimes used as a low-cost but potentially deadly substitute for Glycerine sweetener in cough medicines, posed a "low health risk" but did not belong in toothpaste. Palmolive-Colgate company's executives were quick to distance themselves from what turned out to be Chinese imitation destined to be exported to South American market. As a result, Two-thirds of multinational drug companies shared that they remained concerned about both IP protection and corruption in China. But drugmakers have found some allies in the Chinese courts. Pfizer won a landmark trademark-infringement case in 2011 when a Chinese court ordered a domestic company to stop using Pfizer's logo on its website and fined the offender \$25,000. Novartis CEO Daniel Vasella, for one, cites China's "enlightened" patent laws as the reason the Swiss drugmaker will continue to invest in China vs. India, where a court recently rejected the company's attempt to protect a patent on a leukemia drug. Therefore, Chinese Pharma industry has to work hard on polishing its image by tightening controls for the manufacturing and distribution process and quality control to make sure the products are high quality and safe to use for the consumer on both the local and global market. Adding to that the relatively poor input in medical biotechnology research which accounts for 1/500th of China's foreign counterparts investments and input, with 20 million patent applications for the US between 1985-2005 are still from China's reach with a meager 90 thousands applications. The lack of collaboration between domestic research institutes and drug companies, is also one other challenge the Chinese pharma industry has to overcome. Moreover, China's pharmaceutical industry still lacks independent and efficient research and development capabilities, with poor corporate support for new drug research. The sector is also challenged by a lack of intellectual property rights to effectively protect domestic innovation, contributing to destructive competition in the field illustrated by the Vitamin C case where a Chinese scientist discovered an innovative manufacturing process: the two-step fermentation but due to the lack of legal knowledge he did not patent his discovery and only published in a paper, a foreign firm acquired the rights for this method and patented it abroad with paying the scientist only few thousands of USD instead of the several millions this new technology was worth. That affected the Vitamin C exports of China as foreign firms were already using the same techniques and that resulted in huge losses for Chinese manufacturers of Vitamin C. Add to that the serious threat India is posing to China, with the huge pool of English speaking qualified staff and scientists the country is producing, the cheap labor and operating costs it provides for both local and domestic firms, and the aggressive M&A strategies implemented by Indian Pharma companies to go global such as the recent acquisitions by Ranbaxy laboratories in Germany, for all the aforementioned factors, India will constitute the biggest threat, especially if the Indian government pushes toward a tighter control of IP and patent rights in the country reinforcing the existing Patent Act.

**Table 3. SWOT analysis of China Pharmaceutical industry**

<b>Strengths</b>	<b>Weaknesses</b>
<ul style="list-style-type: none"> <li>-Government's support: "863" plan, healthcare system renovation, Biotech parks: Shanghai, Beijing &amp; Tianjin</li> <li>-Solid patent protection system for drugs</li> <li>-Rapid growth of bio and natural extract patents</li> <li>-Cheaper labor &amp; operating costs in comparison to the Western countries.</li> <li>-API booming market</li> <li>-Tax incentives for biotech &amp; Pharma industry players</li> </ul>	<ul style="list-style-type: none"> <li>-Poor outcomes &amp; poor inputs in medical biotechnology research compared with USA or EU</li> <li>-Lack of management skills and entrepreneurship of Chinese R&amp;D staff</li> <li>-Weak innovation capacity from firms and lack of synergy between academia and industry</li> <li>-Counterfeit drugs and quality control issues (Fake Insulin, Melamine contaminated milk scandals)</li> <li>-Out-of-date infrastructures &amp; Low level of technology in drug patents</li> </ul>
<b>Opportunities</b>	<b>Threats</b>
<ul style="list-style-type: none"> <li>- New collaborative R&amp;D model in Pharma industry through open innovation schemes</li> <li>-Growing and ageing population</li> <li>-Growing interest of Pharma MNCs in Chinese market</li> <li>- Growing interest in TCM integration &amp; Modernization</li> </ul>	<ul style="list-style-type: none"> <li>-Increase in patent applications by Foreign Pharma in China</li> <li>-Outflow of HR &amp; output in Pharma and high turnover rate</li> <li>-Competition: India and other Pharmedging countries</li> </ul>

Despite all these challenges one huge opportunity looms ahead of the Chinese Pharma industry, following its entry to the WTO Chinese Pharma industry could benefit from international alliances and foreign investment opportunities. These goals would be achieved mainly through open innovation setting that could be carried out throughout the entire Pharma industry value chain. China is becoming a destination of choice for R&D outsourcing thanks to the several advantages the Chinese Pharma industry's landscape offers (see figure 4).

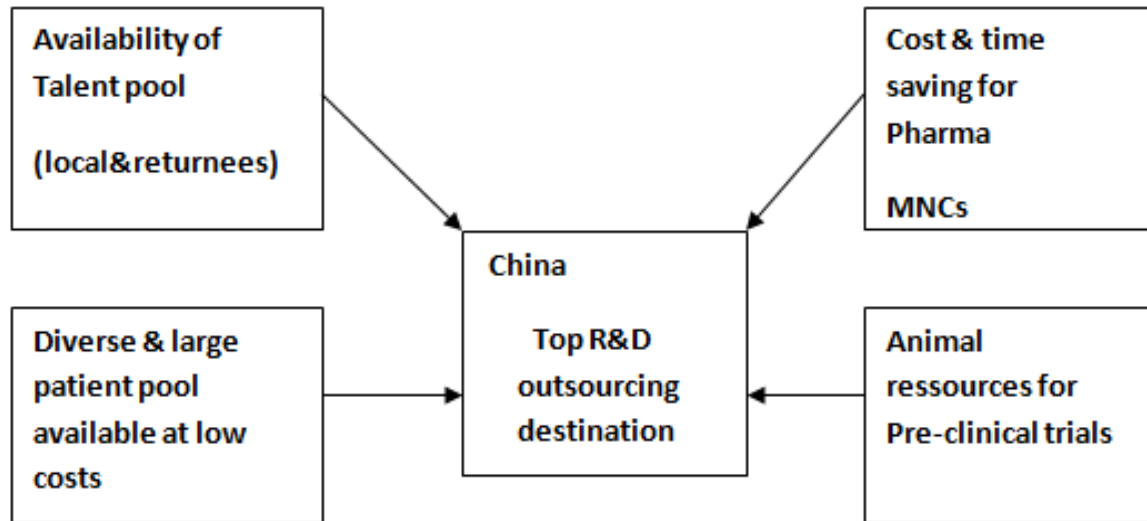


Fig4.China: An R&D outsourcing destination of choice

#### OPEN COLLABORATION SPEEDING UP INNOVATION IN CHINA

China is becoming a destination of choice for foreign firms to establish their R&D headquarters, considering the size of the population which has not been heavily medicated especially in villages; making clinical trials even more efficient and accurate when carried out in the Mainland. Adding to that the availability of various mammals for the clinical trials and the cost savings from operating in a low labor cost environment, constituting the main reasons why the industry in China is and will continue to flourish. The drought in Big Pharma R&D pipelines along with the attractiveness of the Chinese drug market is changing the dynamics of the drug research and development processes through open innovation model. Whether through the collaboration with Academia, independent or government sponsored Research institutes or partnerships with CRO's or with domestic Pharma companies in China, all these strategies would benefit the involved parties. Various collaborations projects are to be carried out between China and foreign Pharma companies or universities in several fields. Notably, the recent healthcare research partnership between the Dutch Imagery giant Phillips with West China hospital in Chengdu affiliated to Sichuan University. The project is designed to develop new medical imaging procedures for diagnosis and monitoring of certain types of cardiovascular diseases, cancer and mental diseases involving MRI (Medical Radioactive Imagery), CT (Computed Tomography), PET (Positron Emission Tomography), SPECT (Single Photon Emission Computed Tomography) scan images. This project would eventually benefit both parties, as it will allow the Phillips strengthen its position inside the Chinese market, especially in smaller provinces and villages where it lacks local market knowledge and adequate distribution channels. It permits them to produce innovative therapeutic solutions and devices to launch in the global market, if proven to be successful, with keeping development costs in control by carrying them out in a favorable R&D outsourcing country like China. As for the Chinese hospital in the Sichuan Province, the open innovation setting would allow them to use the industry leading imaging capabilities of Phillips and use it to leverage its outdated imaging system in these hospitals, another third party constituted by patients would reap the benefit from this open collaboration by accessing better

diagnosis tools and thus better therapy approaches towards the diseases affecting them.

In June 2011, J&J opened a medical device & diagnostics R&D center in Suzhou, Zhejiang province in China focused on market-appropriate innovation with new product development & marketing as well as clinical research and regulatory and quality assurance and operations. This is a perfect example of the open innovation dynamics, where a multinational (J&J) opening its doors and sharing their know-how for marketing, management and legal framework in China and providing access to their database to advance research in specific fields such as Cancer which is the leading cause of death in China with just over 450 “cancer villages” spread across the Chinese territory. It is not a coincidence that R&D is and will be more focused on Asian specific diseases such as Cancer: Stomach, liver and lung and also cardio and cerebrovascular diseases considering the size of the Asian market and the incremental incidence of environment related affections worldwide. That would result in the acceleration of the development of more specific drugs by combining the experience of foreign firms in the treatment of these ailments and their technical & financial capabilities to nurture the innovation abilities and data provided by Chinese research institutes and hospitals which would be part of these strategic partnerships.

The French Pharma multinational Sanofi-Aventis has chosen the path of strategic partnerships with Chinese counterparts instead of the classical M&A strategy to enter the Chinese drug market by collaborating with the Institute of hematology and blood diseases hospital academy of medical sciences in Tianjin to carry out a study on stem cells in order to isolate acute myeloid leukemia stem cells and develop monoclonal antibodies. Sanofi-Aventis didn't establish collaboration or acquired CROs in China, but is relying instead on strategic alliances with universities and state-sponsored research institutions with a special focus on cancer and Rheumatoid arthritis drugs. Thus, the company provides its experience shepherding drugs through regulatory processes and nurture the already existing innovative ideas of their Chinese partners to speed up the development and marketing of new and more efficient drugs for an increasing number of patients worldwide.

Recently, GSK the UK Pharma giant reaffirmed its commitment to China; with a total R&D investment in China has exceeded RMB1 billion in the past 20 years. Research focus adheres to the disease control priorities set by Chinese government, such as infections, diabetes, oncology and respiratory diseases. Along with economic development and increased healthcare core transformation in the Mainland, GSK is planning to develop a more comprehensive and robust R&D strategy to bring China into a key strategic center for GSK global R&D in near future. Including Clinical Research Centers in China with over 200 drug development projects conducted in collaboration with over 30 leading medical universities/hospitals focusing on hepatitis, asthma, diabetes, oncology and mood disorders in China. With also a substantial investment still dedicated to drug discovery and genetic research in leading medical universities and the Chinese Academy of Science. The latest to date open collaboration scheme is illustrated by a partnership program in the field of combinational chemistry with the Shanghai Institute of Materia Medica (SIMM). One year ago, Novo Nordisk committed up to \$100 million to expand its Beijing R&D center. As much as \$40 million of that will go to build new labs for diabetes research. The company also said it will add 200 new jobs by 2015. The Beijing center will become the company's largest R&D facility outside of its native Denmark.

Another project is set to deliver promising outcomes in the cancer research field, with

the United States and China being international leaders in nanotechnology research, they have both launched national programs to support nanotechnology efforts. The accelerating trend of co-authorship among US and Chinese nanotechnology researchers demonstrates that individual scientists already recognize the potential for cooperation, providing a strong platform for creating additional partnerships in pre-competitive research areas. Mechanisms that could help to enhance US–China cancer nanotechnology partnerships include: developing new programs for bi-directional training and exchange; convening workshops focused on specific scientific topics of high priority to both countries; and joint support of collaborative research projects by US and Chinese funders. In addition to the accelerating scientific progress, expanded cooperation will stimulate important dialogue on regulatory, policy, and technical issues needed to lay the groundwork for US and Chinese scientists to move greater numbers of cancer nanotechnology applications into the clinic.

These various open innovation collaboration projects between Pharma International players and Chinese Partners would eventually benefit the Chinese Pharmaceutical industry in several ways:

- It will increase the financial investments whether governmental or private to further boost the industry. Also, the budget allocated to this industry is likely to rise in the near future considering the demographic data in the country allowing China to be competitive on a global scale.

Both governments and private partners see the opportunity of these open collaboration projects could bring to the local players and thus will encourage the Chinese partners by supporting them financially and making them able to constitute qualified partners for Pharma partners.

- It also allows the research to shift its focus from the traditional chemistry-based techniques to more modern tools: Genomics, Biotechnologies, Nanomedicine...etc. The lack of focus on the latest technologies lie on the fact that most research centers in China do not have the necessary R&D tools and technologies to nurture their potential drug discoveries. By building R&D state-of-the-art facilities in China, Pharma MNCs make their technology available for Chinese scientists to carry out their research efforts.

- Improve the industry's image through more international exposure when cooperating with prestigious international organizations: Big Pharma, Harvard university, Swiss Federal Institute of Technology, MIT, GE...etc.

- Benefit Chinese patients who could not afford the treatments under non collaborative circumstances, especially in secluded rural areas such as the sinister "cancer villages" and tailor the drug development to the specificities of the Chinese population

- Provide the Chinese scientists with the necessary legal and management knowledge lacking in the Chinese research.

- Finance innovative and promising small Chinese biotechnology firms in drug research who would be carried out in a low-labor & operations costs environment.

- Help the promising TCM research sector thrive and modernize its structure through the TCM integration with Western Medicine and the update of TCM products R&D techniques.

- Set the right environment for the transition from "Made in China" to "Discovered in China" such as the Academy of Military Medicine which helped develop artemether-lumefantrine, considered the most effective antimalarial drug on the market. One example among a rising number of other Chinese drug manufacturers operate in state-of-the-art production facilities and supply the U.S. market with high-quality products.

The open innovation strategy can also be carried away domestically between Chinese pharma firms and universities or research institutions. Lately, inter-collaboration between the public and private organizations in the healthcare sector to share data and encourage “domestic innovation” illustrated by the strategic partnership concluded between Simcere Pharma group, a leading manufacturer and supplier of branded generics and innovative pharma in China, with Sun Yat Sen University cancer center in order to develop innovative anti-cancer drugs that would benefit the University hospital patients with innovative therapeutic solutions and at the same time enhance Simcere R&D capabilities through this open collaboration.

The foreign firms or organizations participating in these open innovation projects can benefit from these initiatives in various ways:

- Cut their research and development costs through operating in a country where cheap, competent labor and APIs are available and where clinical trials cost 4times less of what they would cost in western countries.

- Fill up their R&D pipelines with external ideas and techniques instead of relying on in the house research from scratch that would take longer and cost more with a high attrition rate.

- Improve their position within the Chinese market profiting from their partners knowledge of the market needs, specificities and effective distribution channels especially deeper into tier 2& 3 cities alongside with rural areas.

- Speed up the drug discovery process by funding late stages clinical trials in innovative research areas that would yield lucrative therapeutic solutions.

## **CONCLUSIONS & FUTURE RESEARCH PROSPECTS**

Open innovation is becoming an obligation rather than an option for out-of –ideas Pharma industry, with the new “innovate or dissipate” imperative the healthcare industry needs to join forces in order to accelerate the drug discovery pace. We have seen that through these strategic partnerships, the industry could achieve faster and more probing results while keeping R&D costs from soaring when operating in pharmerging countries especially in China, where the government is deeply committed to broaden healthcare coverage to the entire population and make the innovation a national priority both to be achieved by 2020.

China is so far an outsourcing destination of choice for some Big Pharma companies whether through partnering with CROs or with academia through open innovation settings to achieve tangible results faster and at lower costs.

Throughout this paper, we have seen that this open-collaboration model is set to yield benefits for both parties through scientific data sharing, their management skills and regulatory expertise in the research process provided by foreign partners combined with the innovative research projects carried out by Chinese scientists from both public and private sectors. Such as GSK’s global R&D Center set in Shanghai in 2007 focusing on research into neurodegeneration to create new medicines for profound medical needs as multiple sclerosis, Parkinson’s disease, and Alzheimer’s disease. The center will eventually direct the global discovery and development activities within its therapeutic area, from drug-target identification to late-stage clinical studies, while collaborating with research institutions elsewhere in China.

Nevertheless, the sustainability of Big Phama’s strategy in China is questionable. So far,

Chinese domestic Pharma industry is unable to contend with its foreign counterparts due to lack of financial assets, management and regulatory skills crucial in the industry. It is so far mainly focused on the production of generics, the “imitation” of patented drugs. But these companies are growing at a fast pace, they receive more governmental support through favorable policies and financial support, they see the benefits of collaborating with research institutions and universities in China which are the epicenter of innovation in the country, all these factors will provide China with the necessary experience and know-how to become an innovative powerhouse in the pharma industry and therefore rely less on the foreign expertise in its research projects. Or at least capture much more value from this open collaboration model which is so far mainly beneficial for the multinational pharma companies at least when it comes to financial returns on investments.

A major issue is looming ahead when implementing these pre-competitive strategies in China or elsewhere. We will see a rising number of IP disputes that would result from the discoveries made through this open innovation framework. Indeed, when a collaboration project yields discoveries that could result in blockbuster drugs the issue would then rise on the party who would have the right to market the drug discovered especially if the terms of the initial collaboration which lead to the discovery did not clearly address the intellectual property right attribution terms and conditions and this could lead to more delays in the drug development processes and new costs would be allocated to trials and legal fees for the two parties in case of disagreement.

Because of the length of the drug R&D processes, we cannot measure the impact this pre-competitive model in the pharma industry just yet.

But what will be apparent by then is whether open innovation and precompetitive collaborations and consortia, as applied to drug discovery, are just a passing fad or an alternative (and perhaps better) way of structuring and managing pharmaceutical R&D. The myriad of ‘open’ initiatives are only going to be impactful if they make drug discovery innovation system more efficient and equitable.

Open innovation has a long way to go when it comes to transparency and inclusivity which are the main issues to address when implementing this open innovation model whether in Pharma or any other sector. So far, all of the precompetitive initiatives between pharma/biotech companies and academia remain distinctly early stage, if not exploratory. So the main problematic in the future is to see how the industry will shape these new models of cooperation into more efficient ways of developing drugs and. What’s more, open innovation, within the pharma industry at least, has been invoked to describe widely varying and often inexactly defined undertakings. Therefore, some pharma companies remain skeptical on the potential of this pre-competitive model as it might lead to projects where long-term cost is small but [where the outcome is also] unproductive.

The solution to make this collaboration model a sustainable R&D strategy, the solution might relate on the level at which this paradigm is applied to avoid conflict of interest, for the Pharmaceutical industry it would be translated in the collaboration with drug screening partners that would not have the ability to be involved in further research on the potentially active compound and could benefit from pre-existing data Pharma MNCs could provide for them, or with clinical trials organizations that would not be involved in the drug development process.



The other solution to the IPR war that would be triggered by the open innovation paradigm would be the inter-industry collaboration where the knowledge-transfer and exchange will benefit without overlapping both parties strategic goals prior to this collaboration. Further research is critically needed to assess the different impacts the open innovation would have on specific industry sectors, as the R&D outsourcing to cheaper operating countries is on the rising trend this model would likely become an imperative rather than an option, therefore, making it urgent to define the scope in which the open innovation model could be used at to what extent by tailoring it to a specific industry's characteristics.

To conclude this paper I would quote Mr.Werner Lanthaler, CEO of Hamburg, Germany-based drug developer Evotec which shared his thoughts on the open collaboration model in the pharma industry” “Let’s give it time—but not too much time,”As the projects using this paradigm are on the rise,only time will tell whether it will reshape the R&D structure permanently rather than just a temporary phenomenon.

Initiative	Participants	Description	Website
Open Innovation Drug Discovery	Eli Lilly	Academic and industry researchers submit novel structures for free assessment in Lilly-developed assays. Lilly retains first right of first negotiation on resulting leads. Focused on cancer, cardiovascular disease, endocrine disorders, neuroscience and tuberculosis	<a href="https://openinnovation.lilly.com/dd/">https://openinnovation.lilly.com/dd/</a>
Centers for Therapeutic Innovation	Pfizer; University of California (UC) San Francisco; UC San Diego; Beth Israel Deaconess Medical Center Boston; Boston University, Children's Hospital Boston; Harvard University; Partners Healthcare; Tufts Medical Center and Tufts University in Boston; University of Massachusetts Medical School in Worcester, Massachusetts; Rockefeller University in New York; New York University; Memorial Sloan-Kettering Cancer Center in New York; The Mount Sinai Medical Center in New York; Columbia University Medical Center in New York; Albert Einstein College of Medicine of Yeshiva University in New York; Weill Cornell Medical College in New York; and the Sanford-Burnham Medical Research Institute in La Jolla, California	Pfizer and academic researchers work together to develop new biologics programs in jointly owned and managed laboratories with access to Pfizer technologies and expertise	<a href="http://www.pfizer.com/research/partnering/centers_for_therapeutic_innovation.jsp">http://www.pfizer.com/research/partnering/centers_for_therapeutic_innovation.jsp</a>

Initiative	Participants	Description	Website
WIPO Re:Search	WIPO; BIO Ventures for Global Health; Alnylam Pharmaceuticals; AstraZeneca in London; Eisai in Tokyo; GSK; Merck in Whitehouse Station, New Jersey; NIH; Novartis in Basel; Pfizer; Sanofi in Paris; and 11 other unnamed academic and not-for-profit research organizations	Participants provide access to patents and expertise to qualified researchers working on drug discovery for 19 neglected tropical diseases, malaria and tuberculosis. Any resulting drugs, vaccines or diagnostics to be sold on a royalty-free basis in 48 "least-developed countries"	<a href="http://www.wipo.int/research/en/">http://www.wipo.int/research/en/</a>
Tres Cantos Open Lab Foundation	GlaxoSmithKline (GSK)	Not-for-profit initiative established by GSK to provide academic researchers with support and access to GSK resources and facilities for drug discovery research directed against diseases of the developing world	<a href="http://openlabfoundation.org/gsk.aspx">http://openlabfoundation.org/gsk.aspx</a>

## ABBREVIATIONS

API: Active Pharmaceutical Ingredient

Big Pharma: Group of top multinational pharmaceutical companies: Roche, AZ, Sanofi-aventis, Merck, J&J, Lilly...etc.

CAGR: Compound Annual Growth Rate

CRO: Contract Research Organization

FDA: Federal Drug Administration

GDP: Gross Domestic Product

GE: General Electric

IPR: Intellectual property Rights

IT: Information Technology

J&J: Johnson& Johnson

MNC: Multi National Companies

Pharma: Pharmaceutical

Pharmerging: Emerging Pharmaceutical Markets: China, India , Brazil, Russia, Poland, Turkey, Venezuela, Vietnam...etc.

R&D: Research & Development

TB:Tuberculosis

MDR-TB: Multi Drug Resistant Tuberculosis

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