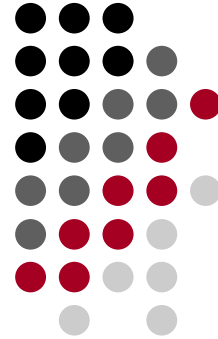




Centre interuniversitaire
de recherche sur la science
et la technologie

Note de recherche
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Is China Catching up Human Health-related Applications of Biotechnology ?

Petr Hanel

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Abstract

Biotechnology is still in the early stage of development. It offers a window of opportunity for emerging developing countries catching up. Scientific research and industrial applications of biotechnology in China have been rapidly developing. The paper examines whether Chinese biotechnology is catching up leaders in the field. The approach follows the conceptual framework of Malerba's Sectoral System of Innovation and Production (Malerba and Nelson, 2012), complemented by Mathew's (2002) insight into strategies for latecomer firms. The data for the empirical analysis are mostly from China's Science and Technology and High Technology Industry Yearbooks and bibliographic data on Chinese scientific publications and patenting. Brief case studies of outstanding organizations complement the statistical analysis. The results of the study show that China is fast catching up in scientific research, and more moderately in industrial production of biotechnology-based manufacturing of drugs and medical devices.

This research note was carried out in collaboration with Groupe de recherche en économie et développement international (GREDI) from the University of Sherbrooke and was published as a working paper 2014-07.

Table of contents

1. INTRODUCTION	1
2. THEORETICAL FRAMEWORK AND EMPIRICAL APPROACH	3
2.1 The technological regime	3
2.2 The principle actors and institutions	4
2.3 Empirical approach and data	5
3. INSTITUTIONAL REFORMS AND THEIR IMPACT ON RESEARCH IN HEALTH-RELATED BIOTECHNOLOGY	6
3.1 Reforms	6
3.2 Evolution of Scientific Resources and Capabilities in Biotechnology	12
3.3 Is Biotechnological Research in China Catching up with the Scientific Frontier?	16
4. INDUSTRIAL APPLICATIONS OF BIOTECHNOLOGY	21
4.1 Manufacturing of Medicines by Biotechnology-based Processes	23
4.2 The Size and Performance of Industries Manufacturing Biotechnology-based Medicaments and Medical Equipment & Appliances	27
4.3 Enterprise Investment in R&D	30
4.4 Catching up on the Global Scene? – The Evidence from Patenting in China and the US.	35
5. DISCUSSION AND CONCLUSIONS	38
5.1 Recapitulation of main findings	39
5.2 New niches and strategies	41
5.3 Challenges ahead	43
6. BIBLIOGRAPHY	45

1. Introduction

The emergence of biotechnology opened a window of opportunity for a few large emerging developing countries to catching up with the leaders in the field. This paper focuses on the case of China's catching up in scientific research and principal biotechnology applications in manufacturing of pharmaceuticals and medical equipment and devices.

Modern biotechnology is a science-based technology. Its development, use and applications are closely associated with the high level of scientific education and public research. Most dedicated biotechnology firms are small and at the beginning of their existence; R&D activities are often more important than production of goods and services. They require highly specialized personnel and their industrial development is dependent on appropriate public policies and regulation. Government funding and venture capital are important sources of financing during the long process to commercial success.

China's planners believe that the modern biotechnology will help resolve the pressing need for affordable human health services by introducing new, cost-effective pharmaceuticals and diagnostic methods and medical devices. They earmarked biotechnology for accelerated scientific and technological development in the Bio-industry 'Eleven-Five' development Program in 2007. The announcement in April 2009 of the long awaited China's health care reform with a budget of 850 billion Yuan promising affordable universal health care by 2020, will give Chinese biotechnology further impetus. The Health Reform that started in 2011 has increased the demand for and investment in health care including in pharmaceutical and medical device research and production. It has created huge solvent demand and opportunity for development of pharmaceuticals and medical devices.¹

¹ The funding is part of China's stimulus package: <http://www.chinabusinessreview.com/chinas-healthcare-reform-how-far-has-it-come/>

The objective of the paper is to assess whether China has been catching up in biotechnology research and industrial production of human health-related applications during the last ten to fifteen years, the early growth period, well covered by the Science and Technology statistics for up to about 2010.²

The structure of the paper is as follows. The next section presents the theoretical framework, references to the literature and the methodology for an empirical approach and the data.

Section 3 focuses on reforms after 1978. The first part presents the reforms of principal institutions framing the Chinese biotechnology system. The second part deals with their impact on the evolution of resources and performance of the Chinese biotechnology scientific research as measured by the rapid growth of scientific articles related to biotechnology.

Section 4 focuses on the industrial applications of biotechnology in manufacturing of pharmaceuticals and medical equipment & devices. It underlines the structural and performance differences between the incumbent chemical manufacturing of medicines and the ascending biological and biochemical medicine both in production and in R&D as revealed by Chinese statistics of high technology industries. It also examines the striking differences between the domestic private, state-owned and the foreign-invested enterprises. The evolution of patenting by domestic biotechnology enterprises in China and the U.S. and short case studies of several leading enterprises complete the text.

The last section discusses the principal findings and concludes with a brief section on challenges facing China's biotechnology catching up.

² Coincidentally, the China's National Bureau of Statistics introduced a significant change in statistical data classification which breaks the High Technology data series in 2011 and makes them difficult or impossible to compare with previous years. Thus, except for some more recent data from other sources, the effects of the Health reform-related investment could not be included in this paper.

2. Theoretical framework and empirical approach

The literature on catching up originated with Genschekron (1962). The latecomer firms (LCFs) have to be able to absorb more advanced technologies (Abramovitz, 1986).

The catch up process is typically sectorial. The Sectorial System of Innovation and Production (SSIP) (Malerba and Orsenigo, 1997; Breschi et al., 2000) provides a theoretical framework for the analysis. The resource-poor LCF has to adopt a strategy for learning the dynamic capabilities needed to compete in the technology-intensive markets and catchup with the forerunners (Mathews, 2002, Lee and Lim, 2001). Two collections of studies on catching up by developing countries appeared recently: Malerba and Mani (2009) and Malerba and Nelson (2012).

As its name and nature suggest, biotechnology is not a sector, or even an industry. It is more akin to Perez and Soete's (1988) technology system (or in SSIP jargon, technological regime). The present main industrial application of biotechnology is manufacturing of medicines by biological and biochemical processes and, to a lesser extent, other health care-related products and services.

2.1 The technological regime

The technological regime of biotechnology is a combination of four components (the knowledge base, technological opportunity, appropriability of innovations and cumulativeness of technical advances that describe the chief traits of the technological environment in which take place innovation and industrial applications of biotechnology (Breschi et al., 2000).

The knowledge base

Applications of modern biotechnology in manufacturing of drugs, medical equipment and devices and related services are closely related to the progress of the scientific research. The sciences underlying biotechnology and life sciences are progressing

rapidly, and their results are highly uncertain. Owing to its multidisciplinary character and public impact, the product cycle of biotech drugs is long and expensive.

Technological opportunity

Since biotechnology is still in the early stage of its development, especially in China, it provides technological opportunities which may provide a “window” allowing developing countries to catch up (Perez and Soete, 1988; Niosi and Reid, 2007).

Appropriation regime

Empirical studies are unanimous in indicating that patents and trademarks are the most useful and frequently used statutory instruments to protect against imitation and provide a means to appropriate innovation-related benefits in chemical, pharmaceutical and special equipment industries. A strong patent signals to prospective partners, lenders, investors and funding agencies the technological prowess of the patentee and may serve as collateral for financing (Levin et al. 1987; Baldwin and Hanel, 2003; Hanel, 2006).

Cumulativeness of technical advances

The original innovators, Genentech, Amgen and few others are still leaders of manufacturing of biologic drugs – the biotechnological knowledge is still very cumulative. The capacity of a new technology to generate new technological opportunities declines over time; c.f. the decreasing returns to the chemical-based “small molecule” drug research, illustrated by the falling number of new chemical drugs, the declining productivity and increasing cost of R&D.

2.2 The principle actors and institutions

The three main actors of the biotechnology system are public research organizations (PRO), universities, and industrial enterprises. The evolution of the pharmaceutical SSIP and its biotechnology using component are evolving in an institutional environment

determined by government institutions and policies. Some of them are sector specific like the Chinese State Food and Drug Administration (SFDA). Others are national, like the financial system or the intellectual property regime, within the rules governing international economy, such as the WTO's TRIPS agreements which determine the mandatory international standards of intellectual protection.

Catch up strategies by latecomer firms

In contrast to “start-ups or spin-offs” in a developed country, latecomer firms (LCF) often do not have the advantage of access to knowledge and technology resources of the parent firm, university or public research organization (PRO), existing market, linkages and supporting institutions. The successful LCFs overcome their competitive disadvantages through repetitive application of linkage, resource leverage, and learning in an international environment dominated by leading incumbent foreign firms. These CU strategies are suggested in the context of globalization with inter-firm networks and abundant financial resources on the one side and technological solutions on the other (Mathews, 2002; Lee and Lim, 2001).

2.3 Empirical approach and data

The paper is data-driven, based mainly on Chinese official statistics. The principal sources are High Technology Industry (HT) and Science and Technology (ST) Statistical Yearbooks (Ybk). These statistics are exceptional in many ways. The data reflect the government's priority to catch up with the technologically advanced western countries. This may put in question their reliability. The statistics also have problems that make them for some purposes incoherent and their use often frustrating. Despite these potential and real shortcomings, the statistics provide a wealth of information on the development of biotechnology in China.

The nomenclature of H-T industries includes the pharmaceutical sector, constituted by three branches defined by their technologies: ‘Manufacture of chemical medicine,’ ‘Manufacture of traditional Chinese medicine’ and ‘Manufacture of biological and

biochemical chemical products,' i.e. biotechnology-based production of "biopharmaceutical" medicines. The other health care-related industry also using biotechnology is 'Manufacturing of medical equipment and appliances.' Original bibliometric analysis of scientific publications and patenting in China and in the US PTO and references to trade literature and our interviews of biotechnology organizations in Guangdong province complete the study.³

3. Institutional Reforms and Their Impact on Research in Health-related Biotechnology

A series of reforms reoriented the Chinese economy from the rigid planning to an increasingly market-oriented private enterprise sector framed by policies of reformed and new institutions progressively integrated into globalized international environment. The first part of this section presents an overview of reforms of institutions framing the Chinese biotechnology system (science and technology policy, state support of science and technology, the financial system, State Food and Drug Administration (SFDA) and intellectual property protection system). The second part deals with the impact of reforms on the evolution of resources and performance of the Chinese biotechnology-related scientific research in PROs and universities.

3.1 Reforms

Before 1978, Public Research Organizations (PRO) were practically the only institutions conducting scientific research. The best were affiliated with the Chinese Academy of Sciences. Their role was to conduct mission-oriented projects and provide R&D services to industry. Universities trained the scientific manpower and industry executed projects conceived by PROs. There was a gap between what the PRO did and what firms needed. Industry relied mainly on imitated and imported technology (OECD, 2009, Liu and White, 2001).

³ Highlights of the survey are presented in more detail in Hanel *et al.*, (2013).

A series of market-oriented reforms drastically reduced the funding of PROs, introduced competition and encouraged research institutes, as well as universities, to set up spin-off companies and run enterprises. Later reforms abolished most industry specific ministries and transformed their research institutes into technology-based enterprises and technology service agencies. Closures of institutes and reductions of R&D personnel followed until the adoption of the China's Medium & Long Term Scientific and Technological Development Plan (MLP) Guidelines in 2006. The share of scientific research performed by PROs has been falling while increasing in universities. Enterprise sector started rapidly to conduct R&D activities.

The budget cuts and staff reductions created a leaner, more efficient PRO system as indicated by the increasing share of Scientist and Engineers in total employment of PROs from 52.9% in 1998 to 69.2% in 2008. Despite the reduced percentage of government appropriation for S&T, owing to Chinese fast economic growth the funding of PROs increased in constant prices six-times from 1987 to 2008.

The inflation-adjusted Chinese total R&D intramural expenditures increased from 1995 to 2010 annually by an average rate of 21.6%. The R&D expenditures as the proportion of GDP increased from 0.57% in 1995 to 1.76% in 2010 and it is approaching 2% in 2014. The R&D personnel surpassed 2.5 million persons in 2010.

Due to the pruning of PROs and rising R&D activity in the private sector, the proportion of China's R&D personnel employed in basic research has been declining steadily from close to 10% in the late 90s to 6.8% in 2011. Moreover, contrary to their original mandate to concentrate on basic research, PROs still spend more than half of their R&D budget on development and only 11% on basic research. In comparison, Universities allocated to basic research about 40% of their R&D budget in 2010. Industrial enterprises are almost exclusively pursuing development; their scientific research activities are minimal. The Chinese scientific research system is not yet sufficiently oriented toward

basic research needed to support the innovation-based economy, the publicized goal of Chinese planners.

Government Support of Scientific and Industrial Research in Biotechnology

Development of biotechnology and modern research-based pharmaceutical industry were among the top priorities of the “Eleven five” year plan (2006-2010) and the national 'Medium to Long Range Program Outline for Scientific and Technological Development (2006-2020).' The Government ‘plans,’ among other things, China to have three Nobel laureates by 2020. The ‘162-Drug development program’ and the \$12 billion New Mega Drug Development Program allocates impressive funding for the development of innovative drugs and large scale bio-enterprises (Scott (2012); ChinaAccess4EU, 2012). It is not clear whether these initiatives include projects included in ongoing programs such as the National High Technology R&D Program 863 (allocating to biotechnology about 20-25% in the past), the Basic Research program, Program 973 and others (OECD, 2007).

The three levels of Government are the principal source of funding of scientific research in PROs (85%) and universities (59%) in 2009. Direct government support for R&D executed in enterprises is, however, relatively modest. Government funded 8% of intramural R&D expenditures of manufacturing of Biological medicine, 5% of Chemical medicine and only 4% of medical equipment and appliances industry.

In addition to direct grants, a vast program of various fiscal and other incentives supports R&D and innovation activities, especially in medium and large enterprises. Against economic logic, the Governments subsidize small firms less than the large ones.

The three levels of government endeavor to create biotechnology innovative clusters by creating ‘Bioindustry bases’ and building all over the country high-and new technological development zones for biopharmaceutical research organizations and industry (Prevezer (2008; Zhang et al.,2010; Hanel et al., this volume).

Financial System

The Chinese financial system is highly regulated and opaque. The badly needed reforms are slow, and ineffectual. Banks's priority is to fund large state-owned enterprises. Banks are reluctant to finance the privately-run small and medium size high-tech companies. Investment in real estate and infrastructure is more profitable than uncertain long-term private high-tech projects.

Both local (mainly government-funded) and international VC investments are increasing in China. But since biopharmaceutical projects need a longer commitment and are riskier than non-innovative projects, VC invests mainly in the export-intensive consumer electronics and computers.

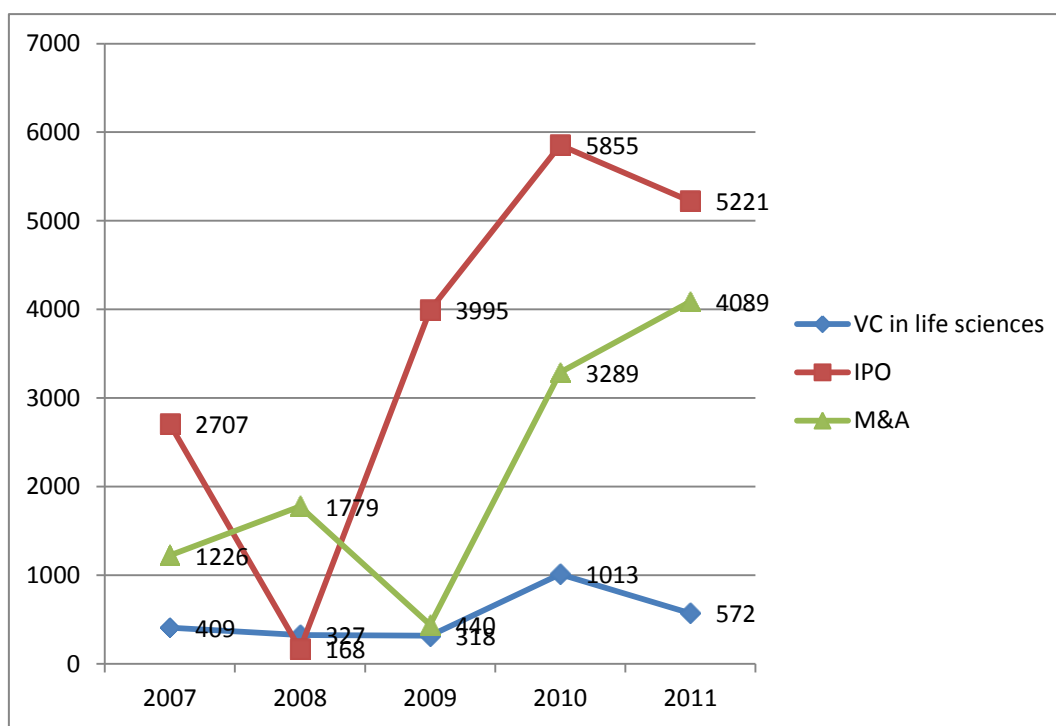
A recent study of Life sciences venture capital investments in Brazil, China, India and South Africa found that VC activity in biotechnology-related projects was muted; only 10.4% of their dollar weighted portfolio was invested in sciences, and a mere 0.3% in innovative biotechnology (Chakma et al., 2013).

VC investment in life sciences (both innovative and non-innovative) has been fluctuating widely since the global financial crisis. First, it fell to \$318million in 2009, then it more than tripled to over one billion the following year before falling again by more than 40% in 2011.

After investing in promising projects and developing them, VC has to find a profitable "exit" to recoup their investment. The most popular exit strategy is selling the new VC supported company on the stock market. An increasing number of larger, successful biopharmaceutical firms, clinical research organizations and medical equipment manufacturers had successful IPOs in Shanghai, Shenzhen, Hong Kong and New York. The stock market is, however, not a solution for the small start-ups and medium size firms at the stage when they have difficult access to funding.

The total value of initial public offerings (IPOs) of drug companies (including an unknown share of the VC invested ones) has fluctuated even more than the VC, albeit with an increasing trend, as did mergers and acquisitions, many of them with foreign companies. Cross-border partnering deals were also on the rise (Figure 1).

Figure 1. Investment activity in Chinese life sciences, VC, IPO and M&A. (Millions of US dollars)



Source: China Bio, China Life Sciences 2010: A giant Leap Forward (2011). and China Bio, China Life Sciences 2012: From Local to Global (2012).

China Food and Drug Administration

Created 1998, reorganized and renamed several times, the CFDA is responsible for the approval and regulation of drugs, cosmetics and food. The Administration introduced in 2003 good laboratory practice (GLP) standards and stipulated that clinical research organizations (CROs) could conduct clinical trials for their clients in China (Zhou, 2007). Since 2004, all pharmaceutical manufacturers have to obtain CFDA certificate of good manufacturing practices.

The approval process is similar to procedures of the U.S. FDA, with which CFDA has close ties. The U.S. FDA's 13-person staff in China has trained more than 1,600 manufacturers and regulators on United States safety standards (U.S.FDA, 2014). The principal CFDA's handicap is the lack of competent human resources resulting in a complicated and slow regulatory system. It takes Chinese CROs 10 to 18 months to obtain approval for clinical tests. In India it takes only four months, in Singapore two and the U.S. a single one (Christie, 2012).

Patent System

Effective protection of intellectual property is of utmost importance for the development of new drugs. Before the mid-nineties, like in many industrialized countries earlier, patenting of chemical and pharmaceutical inventions in China and other developing countries was limited to production technologies. Product inventions such as new medicines were not patentable. The IP regime was designed to encourage import substitution as a means to develop the national pharmaceutical industry.

The creation of the World Trade Organization fundamentally changed the rules of international trade. The WTO adopted the Agreement on Trade-related Aspects of Intellectual Property Rights known as TRIPs that imposed minimal standards of IP protection to all countries. Product patents became mandatory in all fields, including food,

chemicals, pharmaceuticals and biotechnology products. Patent protection was universally extended to 20 years.

China joined WIPO in 1980, signed Paris Convention and adopted its first-patent law in 1984. It adopted a TRIPs patent regime in 1995 and achieved full compliance in 2000. The next amendment in 2009 improved IP protection in China and at the same time addressed some Chinese concerns (Li, 2010; Hanel et al., 2011).

According to Pricewaterhouse Coopers (2009) protection of intellectual property in China's pharmaceutical industry has improved significantly. According to their survey, half of the multinational pharmaceutical companies were “quite optimistic” and some “very optimistic” regarding the intellectual protection in China. The positive impact of IP reforms on patenting by Chinese biotechnology inventors is presented in Section 4.3.

3.2 Evolution of Scientific Resources and Capabilities in Biotechnology

The essential factor of the research system is the qualified scientific and engineering personnel trained by the higher education system in China and abroad.

Education in Chinese universities

The number of students newly enrolled in biochemistry and drugs programs undergraduate and junior colleges reached 76 758 in 2011, the total enrollment was 237 580 and 85 344 students graduated. While the numbers are there, the quality of training in Chinese universities is less impressive. In response to specific questions in our survey regarding human resources for the biotechnology R&D, it was often mentioned that it is difficult to find and hire competent personnel capable of doing innovative research. The Chinese education system is blamed for not adequately training students for research. There is lot of imitation and sometimes falsification of research results by researchers impatient for glory and riches. In contrast to the foreign practice, the Chinese system does not

tolerate failure in research. The long gestation of biotechnology research projects, their high cost and uncertain results encourage promising graduates to study abroad or accept employment in foreign firms. Several respondents recognized the importance of training their employees.

Evolution of personnel engaged in biotechnology scientific research

The evolution of pharmaceutical research personnel in (1) Public Research Organizations, (2) universities and (3) in the industry is presented in Table 1. The number of research personnel increased faster in industry than in PROs and universities. R&D in enterprise is, in fact, almost exclusive development (see details in the Industry section below).

The top public research institution is the Chinese Academy of Sciences (CAS) with most research institutes concentrated in Beijing. After an initial decline, R&D employment increased from 2007 to 2010 by about 15% annually, adding more than one thousand R&D positions in the three years. By 2010, the scientific personnel engaged in medical and pharmaceutical research at PROs and universities is about equal (Table 1.).

Table 1. R&D Personnel Conducting Pharmaceutical Research in Public Research Organizations, Higher Education and Industry

(full time equivalent person years)				
	Public Research Org.	Higher Education	Industry	Total
Year	Medical & pharmaceutical products	Pharmacy	Manufacturing of medicines	
	1999 (2000)	2 336	1 523	16 750
2005	n.a.	2 174	26 910	n.a.
2007	2 047	2 422	34 380	38 849
2008	2 441	2 728	55208	60 377
2009	2 886	2,625	70 065	72 954
2010	3 086	3093	81766 *	87 945

Sources: China Science and Technology Yearbook, 2010 and earlier years and High-Tech. Industry Yearbook 2011 and earlier years.

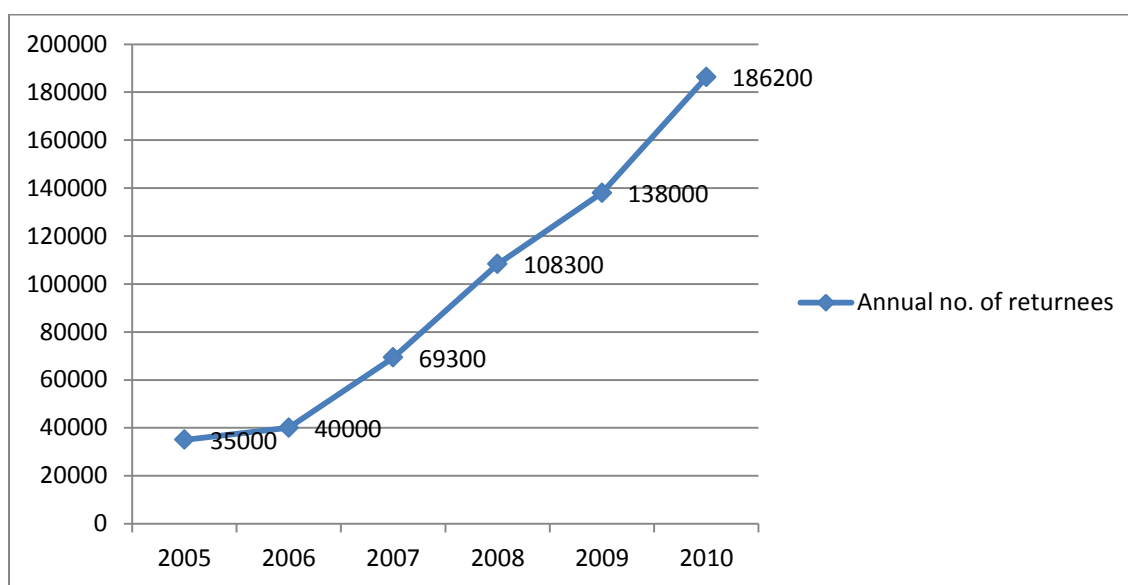
Notes: The allocation of R&D to broadly defined pharmaceuticals is only approximate.

The designations are those used in Science and technology Yearbook for each of the three organizations, PRO, HE and HT industry.

Returnees

A fundamental component of the Chinese biotechnology knowledge base is the large and growing number of highly qualified and experienced scientists, engineers, managers and other professionals returning to their homeland after studies, university research, teaching and professional business career abroad (Figure 2.).

Figure 2. Annual Number of Returnees



Sources: China Bio LLC, (2012) China Life Science 2012: From Local to Global, and <http://biotechine.blogspot.ca/2013/08/pharma-r-in-china-role-of-returnees.html>

Their contribution to the nascent biotechnology industry has been widely recognized (Prevezer, 2008, 2006; Baeder and Zielenziger, 2010 pp.3, 17). Like in the corporate sector, returnees also constitute the majority of senior positions in China's top scientific and academic institutions. Studies of biology and health related sciences are popular among the Chinese students, and they are returning to they are homeland in increasing numbers.

According to our survey, biotechnology enterprises founded by returnees are more likely to conduct R&D than the other ones. They tend to collaborate more with their foreign scientific and business contacts than with the local ones for two reasons: (1) the technical level of the former is more advanced, and they can access tacit information, and (2) they are not well integrated with the local business networks, where they have more to gain from building contacts with the local party and government officials because these are key to success in China (Rowen et al. 2008).

Some entrepreneurs maintain a hybrid company; one part in the U.S., Canada or EU and another one in China and circulate between the two.

3.3 Is Biotechnological Research in China Catching up with the Scientific Frontier?

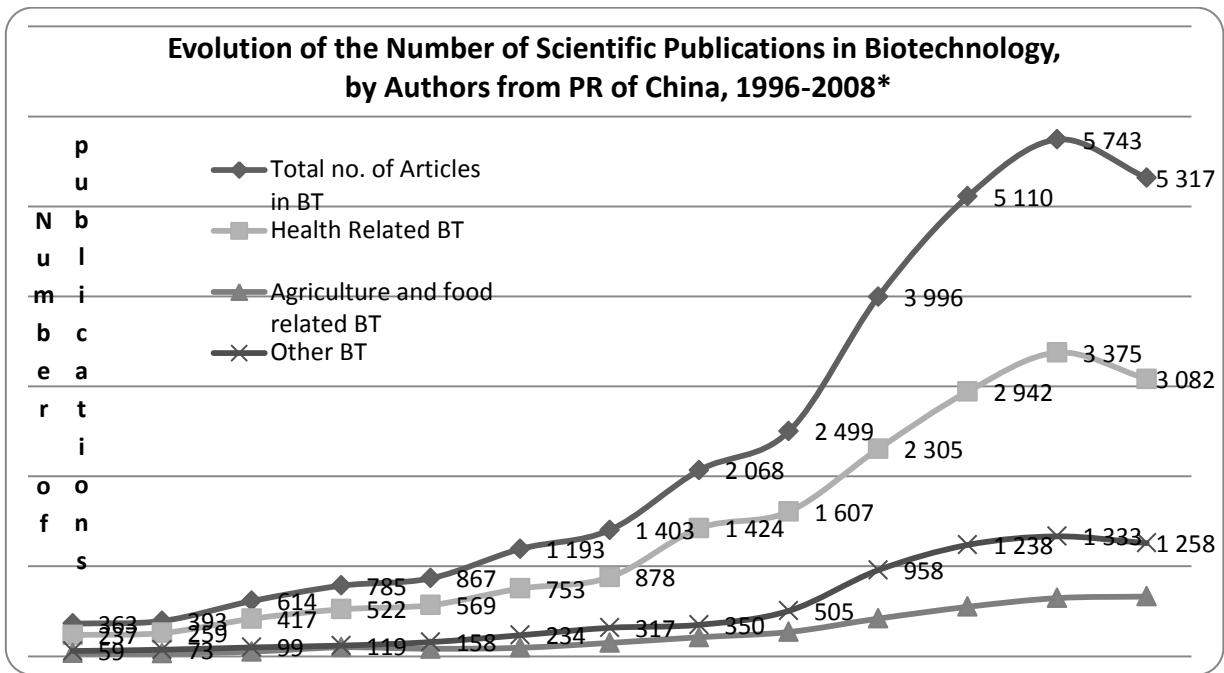
Given China's position as a latecomer, the first objective of its scientific research is absorbing, assimilating, replicating and applying the current state of biotechnology used by the leaders of the field. Biotechnology scientific research is often a "use-inspired" basic research as illustrated by the conceptual model of the Pasteur's Quadrant, contributing to both basic understanding and applied innovation. (Stokes, 1997; Hermhans et al. 2008). Results of basic and applied Chinese biotechnology research are diffused by scientific publications in Chinese and increasingly in English.

Publications of Chinese Scientific Research in Biotechnology

The number of scientific articles in biotechnology authored by Chinese scientists and engineers in PROs and Chinese Universities has increased exponentially from 1996 to 2008. Almost two-thirds of BT publications were related to health-related issues (22 423). The remaining third of articles deals with BT in agriculture and food (3 374) and in other biotechnology subjects (7 336). The residual (2378) deals with unidentified, biotechnology related subjects. Altogether, Chinese researchers published 35 110 publications from 1996 to 2008 (Figure 3.). However, Chinese articles are not yet widely cited and their impact,

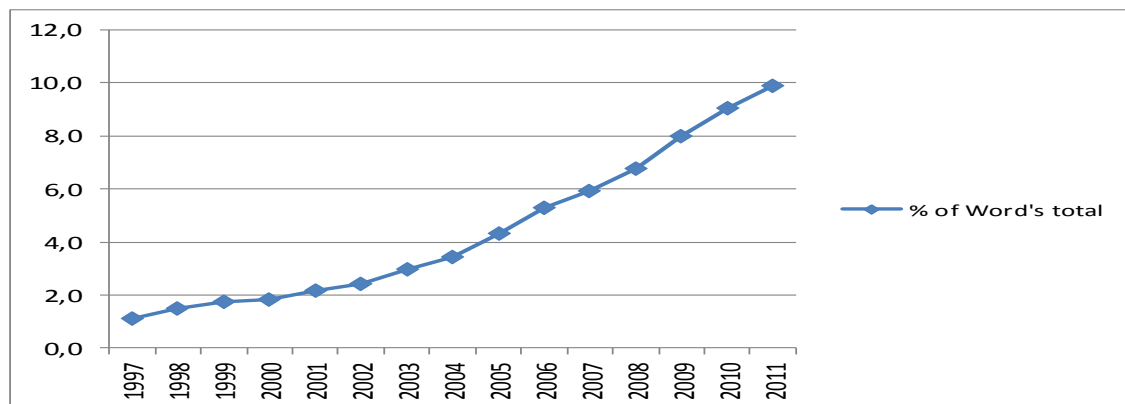
even though improving, is limited. China's share of world's scientific publications in biology has increased from 1.1% in 1997 to 9.9% in 2011 (Figure 4).

Figure 3. Evolution of the Number of Scientific Publications in Biotechnology, by Authors from PR of China, 1996-2008



Source: Tabulation of Scopus data by SCIENMETRIX

Note: * The count for Year 2008 is incomplete- that explains the change of the trend in 2007.

Figure 4. Chinese Share of World's Total Number of Scientific Publications in Biotechnology

Source, U.S. National Science Foundation, Science and Engineering Indicators 2014, Appendix, Table 5-50

Researchers from the twelve best universities authored two-thirds of the total number of articles in health-related biotechnology published worldwide from 1996 to 2007 by the top 15 Chinese institutions, compared to one-third published by authors affiliated with PROs i.e. the Chinese Academy of Science and Academies of Agricultural and Medical Sciences as shown in Table 2. Universities appear to be contributing more than PROs to advancement of biopharmaceutical knowledge and training of qualified personnel.

Table 2. Number of articles in health-related biotechnology

Organisation	1996-99	2000-2003	2004-2007	% of total	
				1996-2007	biotechnology
1 Chinese Academy of Sciences	309	613	1171	2093	52,0
2 Fudan University	53	303	559	915	65,9
3 Chinese Academy of Medical Sciences	164	207	374	745	65,3
4 Zhejiang University	31	145	542	718	78,2
5 Peking University	41	203	393	637	70,9
6 Sichuan University	4	103	435	542	70,8
7 Huazhong University of Science and Technology	19	85	431	535	62,6
8 Peking Union Medical College	97	132	281	510	84,3
9 Sun Yat-sen University	7	47	358	412	60,1
10 Tsinghua University	44	108	258	410	68,7
11 Shanghai Jiao Tong University	1	37	356	394	73,5
12 Wuhan University	22	97	264	383	65,6
13 East China University of Science and Technology	47	61	199	307	60,7
14 China Agricultural University	15	34	170	219	45,0
15 Chinese Academy of Agricultural Sciences	18	23	125	166	35,5
Total	872	2198	5916	8986	average % 64,9

Source: Tabulation of Scopus data by SCIENMETRIX

Chinese scientists are increasingly publishing with co-authors from abroad. The number of internationally co-authored articles has been growing fast, but slower (19%/year) than the growth of articles by Chinese authors (25%/year), see Table 3. Hence, the rapid growth of the total number of Chinese biotechnology publications cannot be attributed to collaboration with foreign co-authors as suggested by Yu (2007).

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Table 3. Number of health-related biotechnology publications with international collaboration

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008*
With collaboration	95	104	120	140	125	114	147	290	346	467	568	646	638
All articles	368	379	568	710	767	919	1 072	1 502	1 797	2 599	3 368	4 124	3 849
Collaboration %	26%	27%	21%	20%	16%	12%	14%	19%	19%	18%	17%	16%	17%

Source : Computed by Science-Metrix; data Scopus (Elsevier)

* Data for 2008 incomplete.

The comparison of the explosive growth of BT publications with the slower growth of R&D personnel active in biotechnology scientific research suggests a significant increase of research productivity. Part of it may be attributed to capital deepening. The other part of the explanation is improved organization, incentives and increased domestic competitive pressure, especially in universities.

In the ranking of articles published in Nature Journals, China is the top Asia-Pacific nation in five Nature journals in 2012. Its strongest showing was in Nature Genetics. The Beijing Genomic Institute- Shenzhen was the top-ranking Chinese institution from the Asian-Pacific region publishing in Nature biotechnology in 2012.

BGI-Shenzhen sequencing “factory” in Hong Kong

The joint venture between BGI-Shenzhen and the Chinese Hong Kong University (CHKU) created the largest gene sequencing capacity in the world. BGI-Shenzhen is partnering with research laboratories all over the world. It has created a network of affiliates in the U.S., BGI Americas and BGI Europe, in Denmark, to be close to potential partners and customers. In March 2013, BGI acquired the U.S. Complete Genomics, a leader in human genomic sequencing which became a separately run wholly owned subsidiary of BGI-Shenzhen.

The short and impressive history of BGI-Shenzhen is a typical example of the Chinese strategy of overcoming of competitive disadvantage – or in this case, creating a competitive advantage- through linkage, resources leverage, and learning as argued by Mathews (2002).

There can be no doubt that the productivity of the Chinese biology and biotechnology–related scientific research has been improving. Chinese scientists are rapidly catching up with the world biotechnology leaders.

4. Industrial applications of biotechnology

According to a mandatory survey of biotechnology firms, manufacturing of biomedicines and human health applications in China accounted for between two-thirds and three-quarters of sales revenues of modern biotechnology in 2003 (OECD, 2006). This paper centers on human health-related applications of biotechnology in manufacturing of medicines and medical equipment & appliances.

The Pharmaceutical Sector and its Biopharmaceutical Component

The Chinese Pharmaceutical sector (or manufacturing of medicines) has three components using distinct knowledge bases and technology regimes:

- (1) Manufacturing of medicines by chemical processes,
- (2) Manufacturing of Chinese traditional medicine, and
- (3) Manufacturing of biopharmaceuticals and other health care related products by biological and biochemical processes.

Each of the components has its own, distinct, but interrelated knowledge base reflecting successive stages of understanding of human life, starting with the traditional Chinese herbal medicine, followed by manufacturing of chemical medicines and the most recent one based on modern biotechnology. They are essential parts of the health care system, evolving within the common institutional environment, subject to similar constraints, market forces and policies.

The question is whether the nascent Chinese manufacturing of bio-pharmaceutical medicines has laid foundations for a sustained catch up process. More specifically, is there evidence (1) that the Chinese biotechnology industry is more dynamic than local manufacturing of chemical medicines – how do they compare? (2) Is it catching up with the forerunners?

Manufacturing of medical equipment and devices

Some medical equipment and devices use biotechnology in addition to other technologies (electronics, information and communication, electro-optic and fine mechanics, etc.). Both manufacturing of biopharmaceuticals and medical equipment & devices are new components of the life sciences complex.

4.1 Manufacturing of Medicines by Biotechnology-based Processes

The majority of Chinese biotechnology firms are manufacturing bio-similar products based on imitation, production under license or under contract for foreign firms. Some also collaborate with foreign MNC in drug discovery R&D (Zhou, 2007). They are in intensive competition among themselves and with the brand name products of leading MNC firms that dominate some segments of the Chinese pharmaceutical market. Foreign brand medicines command higher prices, often in spite of not being protected by patents.

Bioplan and Associates (2008) classified the 60 top ranking manufacturers of biotechnology-based medicines into two groups:

- (i) Recombinant DNA (rDNA) and Monoclonal antibodies (MAbs) products
- (ii) Manufacturers of Vaccines and Blood Products.

Recombinant DNA (rDNA) and Monoclonal Antibodies (MAbs) Products

About half of the companies in this group specialize in rDNA products; one-quarter is combining manufacturing of rDNAs with production of chemical medicines. Only three companies are producing (MAbs) products. The rest are producing various combinations of the above. The dedicated biotechnology firms are mostly medium or small size. The low concentration of the industry and the modest average size of the firm typical of entry stage of a new technology regime suggest ample technological opportunities.

The history of the leading biopharmaceutical company 3SBio Inc. is typical of the strategy of latecomer firms leveraging their advantages. In in this case the knowledge of the regulatory process, established presence on the Chinese pharmaceutical market and low cost qualified scientific personnel, in exchange for the access to advanced knowledge, value and distribution chains of foreign partners or acquired foreign subsidiaries (Mathews, 2002). It also illustrates the contribution of returnees to China's nascent biotechnology.

Two cofounders, father and son, established the company in 1993, under the name Shenyang Sunshine. The father graduated from the Third Military Medical University, one of China's leading medical research universities. His son received the Ph.D. from Fordham University in the U.S. for work on interferon and completed his post-doctoral study at the U.S. National Institute of Health. Prior to joining Shenyang Sunshine Pharmaceutical Company Limited, the son founded Lifegen, Inc., a Maryland Corporation involved in optimizing the manufacturing processes for EPIAO and TPIAO. Lifegen is an investee company of Shenyang Sunshine. Two other two top executives of 3SBio also studied and practiced abroad, in the U.S. and Canada.

3SBio Inc. received the New Drug Certificate for the bio-similar recombinant human Interferon INTEFEN and INLEUSIN in 1995 and started large scale production. In the same year, it initiated the R&D program that developed EPIAO (bio-similar to AMGEN's EPO) and TPIAO (bio-similar to TPO) with support from the National 863 project. EPIAO obtained New Drug Certificate in 1997, production license in 1998 and three years later it became the best-selling EPO in China. After longer development, TPIAO gained the New Drug Certificate and good manufacturing practices from the SFDA in 2005.

The company incorporated in 2006 in Cayman Islands and had a very successful IPO on NASDAQ raising \$135 million in 2007. In 2013, it delisted from Nasdaq and went private.

The employment of the company increased from 320 persons in 2006 to 891 persons in 2013. Its operations consist of bulk manufacturing and formulation of drugs used in cancer treatment and viral diseases. It distributes their products in 31 provinces, and its drugs are used in more than 3 500 hospitals (General Biologic, 2009)

To expand their market and competence in new fields, 3SBio partnered with and acquired from AMAG (U.S.) the exclusive license for obtaining SFDA's approval for AMAG's principal nephrology and oncology product Feraheme and its commercialization in China. Later 3SBio also partnered with and invested in a smaller cash-strapped Canadian company ISOTECHNICA, to develop and commercialize in China its 'next generation' drug complementary to FERAHHEME, used in the prevention of rejection of transplanted organs and treatment of autoimmune diseases. Both partnerships provide complementary knowledge, and they were instrumental in establishing 3SBio in the nephrology and oncology field.

In addition to these first two North American partners, 3SBio has collaboration agreements with several Chinese companies, and one from Hong Kong. Lastly, 3SBio formed a joint venture with a leading U.S. dialysis services provider Da Vita, a Fortune 500 company. The agreement will enable 3SBIO to enter the dialysis service market, starting in Jilin and Lianing provinces (Bioplan Associates, 2008 and Annual reports to the U.S. Securities and Exchange Commission).

Manufacturers of Vaccines and Blood Products

This branch is dominated by large firms established before the 2nd WW. The largest, the China National Biotech Group (CNBG) with eight regional subsidiaries controls 90% of China's vaccines included in the National Immunization Program (NIP) and about 50% of type II vaccines. More than half of enterprises in the second group are specialized producers of vaccines, 20% specialize in hematologic products, and the rest are combining vaccine manufacturing with recombinant products. The average size of the firm in this group is twice as large (472 employees) as the firms in the recombinant protein group. (Bioplan Associates, Inc. 2008). The expanding state-subsidized NIP drives the development of vaccines and blood products. Domestic producers control completely the planned immunization market (Yezhou, L., 2010).

The CNBG became in November 2013 the first ever Chinese vaccine manufacturer to receive the WHO pre-qualification certification of approval for quality, safety and efficacy that allows CNBG to sell globally its vaccine against Japanese encephalitis, a mosquito-borne disease, that kills 15 000 children each year. China now has the largest vaccine manufacturing capacity in the world, producing more than 1 billion vaccine doses annually. The WHO approval opens the door for China's entry into the global vaccine market.

The growing affluence of the urban population provides a market for vaccines of foreign origin, which are more trusted than the local products. Most novel vaccines are marketed by foreign MNC. For example, Sanofi launched an influenza vaccine production in Shenzhen in 1996 and expanded the production in 2012. GSK also started production of influenza vaccine in Shanghai in 2004.

Innovative biotechnology-based medicines

The first Chinese successful modern biotechnological therapeutic product 'Recombinant human interferon' was developed by Shenzhen Kexing Biotech Co. and commercialized in the early 90s. By 2007, there were about 200 modern, innovative biotech firms that launched 35-biotech drugs in the domestic market. Among them the world's first-gene therapy product "Gendicide" for treatment of solid tumors, developed and manufactured by Shenzhen Sibiono Gene Tech (Bioplan Associates, Inc., 2008).

The Chinese State Drug and Food Administration (SFDA) approved between 2003 and 2010 (29 for marketing and 196 for clinical trials) developed by Chinese domestic companies. Both categories include only original chemical and biological drugs not yet approved anywhere in the world. Out of the 187 investigational new drug applications 70 are protected by Chinese patents, 23 by U.S patents and 16 are patented in Europe. (Jingzong Qi et al. (2011).

4.2 The Size and Performance of Industries Manufacturing Biotechnology-based Medicaments and Medical Equipment & Appliances

The rapid growth of the pharmaceutical sector is driven by the strong demand generated by the acceleration of the Chinese health-care. By 2013, medical insurance has covered 95% of the population, and another 3% should be added by 2015.

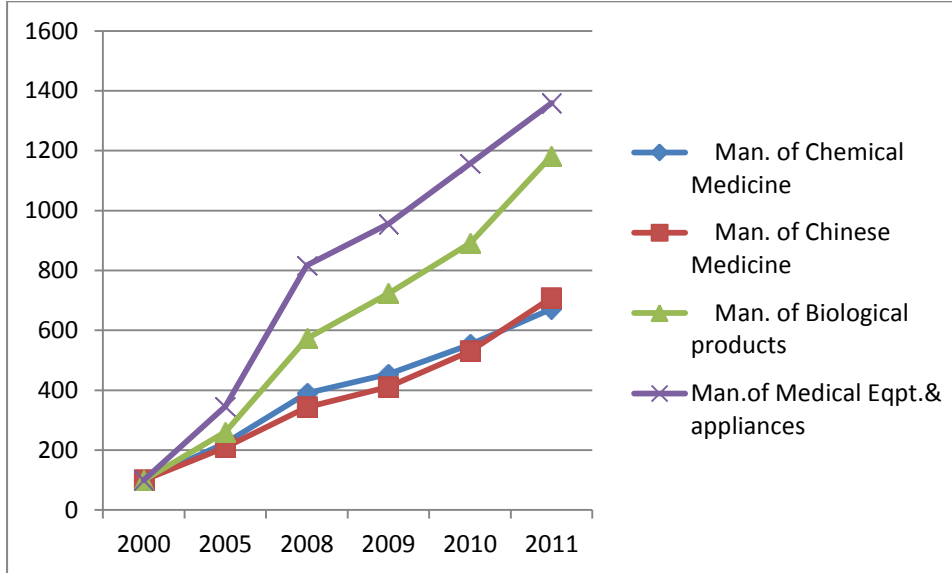
In 2010, China counted 862 enterprises manufacturing biopharmaceuticals, employing about 142 thousand persons and generating sales revenue of 152.5 billion Yuan (23 US\$ billion). They represent about 11% share of sales of the whole pharmaceutical sector, compared to 6.7% in 2000. In comparison, the share of sales of manufacturing of chemical medicines declined in the same period from 59.5% in 2000 to 49%.

Medical equipment was manufactured in 1310 enterprises, employing 233 thousand employees, reporting 136 billion Yuan (US\$20.6 billion) of annual sales in 2010, compared to US\$11.5 billion in 2000.

A comparison of the growth of the principal industries of the pharmaceutical sector is in Figure 5. The two 'new industries' BBM and MEA are in the early phase of the life cycle of their technology systems. Their growth rate of output, sales and profits surpassed the two incumbent industries, manufacturing of chemical (CM) and traditional Chinese (TC) medicines.

Figure 5. Index of Gross Output of Chemical pharmaceuticals Chinese medicines, Biological products and Medical Equipment & Devices

(Enterprises with annual sales over 5 million Yuan, Const. prices 2000=100)



Source: High Technology Yearbook, 2012, Table 1-1-3.

Exports

An increasing share of biological products and medical equipment & devices production was exported, respectively about 11% and 30% in 2010. However, relative to Chinese exports of electronic and computer products, the combined value of exports of biotechnology and medical equipment products is still minuscule, accounting for about 1.5% of total exports by the high-technology sector in 2011, i.e. less than a half percent of China's total exports.

Performance of foreign-invested enterprises

More than thirty years after China opened to foreign investment, two-thirds of China's high-technology production is manufactured by foreign-invested firms. Big Pharma multinationals have been selling their brands in China since the early 90s, some even much earlier. Even though the top ten MNCs hold between 10% and 20% of Chinese

drug market, the world's top 15 pharmaceutical firms derived just 0.9% of their combined revenues from the Chinese market and 2.9% from the combined markets of Brazil, India and Russia (IMAP, 2011). By now, most Big Pharma have established in China joint ventures or whole-owned subsidiaries manufacturing mainly high quality, low cost active pharmaceutical ingredients (APIs), for their own use in China and their home countries.

In comparison with other Chinese high-tech industries such as manufacturing of electronics or computer equipment where foreign-invested firms produce respectively 63% and 92% of industry's output, their share of production of biopharmaceutical and medical equipment & devices industries is respectively 25% and 40%, well below the average of all high-tech industries (66%) in 2011.

The rapidly growing personal income, the ongoing health reform and improving health services, improving protection of intellectual property, and regulatory system are making the Chinese pharmaceutical market increasingly attractive for Big Pharma multinational companies (Baeder and Ziegenziler, 2010).

Foreign-invested enterprises (FIE) are the most productive segment of the biopharmaceutical and medical equipment industries. They export significantly more than their local counterparts. Their average labor productivity of FIE is higher by a third than in the non-state owned firms and those invested from Hong Kong and Macao, and two and half times higher than productivity in the state-owned enterprises (SOE). SOEs stand out as being the largest employers producing the smallest output per person.

The source of higher productivity of FIE is not only their technological and administrative superiority. They are also significantly more capital intensive than their undercapitalized local competitors.

The more efficient FIEs accelerate the desirable consolidation of the pharmaceutical industry and enhance efficiency of local competitors. But in the process foreign firms may eliminate promising but undercapitalized small local competitors poorly served by the Chinese inefficient capital market. Multinationals also compete successfully for the scarce human resources.

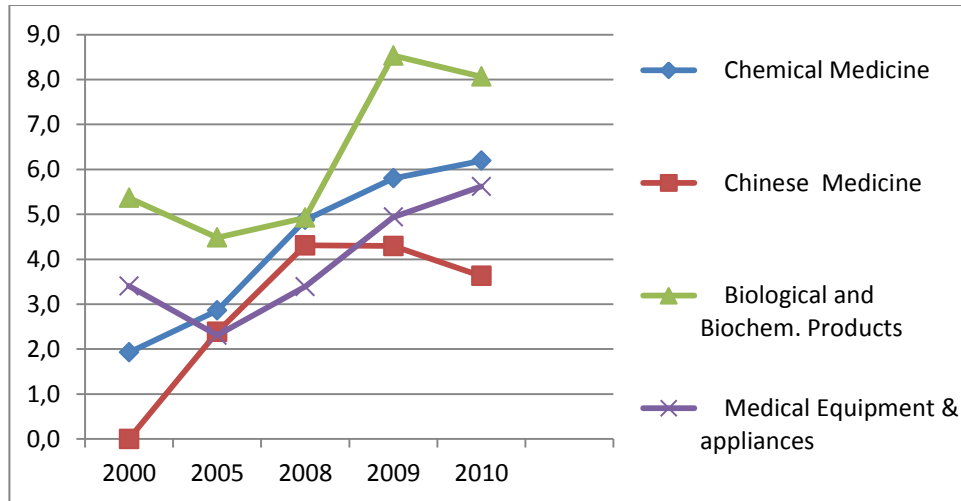
4.3 Enterprise Investment in R&D

Enterprises manufacturing biotechnology-based drugs were from 2000 to 2010 on average more profitable by about 3 percentage points than other pharmaceutical firms and more than twice as profitable as all high-technology industries.

Despite their profitability, still only about 40% of biopharmaceutical enterprises invested in R&D in 2010; i.e. more than firms manufacturing chemical medicines (35%) and medical equipment enterprises (28%), but insufficient to sustain an innovation-based growth. The R&D expenditures of the Chinese pharmaceutical sector were less than 2% of the Gross industrial output value (GIOV), compared to 26.6% in the U.S., 25% in the UK, 16.4% in Japan and 8.3% in Germany. Chinese pharmaceutical companies' R&D and innovation activity are still lagging far behind the leading industrial countries. Even most of those enterprises that conduct R&D are developing 'me too' imitations of foreign products and technologies rather than more original drugs.

It can be argued, however that owing to the low cost of Chinese R&D personnel and the large percentage of firms that do not conduct R&D, the research intensity measured by the percentage of sales spent on R&D underestimates the actual R&D intensity of innovating firms. Therefore, research intensity in this paper is measured by the R&D personnel's share of total employment in large and medium size enterprises (Figure 6).

Figure 6. Evolution of the Share of R&D in Total Employment in Large and Medium Size Enterprises (% of Full-time equivalent person-year)



Sources: China Statistical Yearbook on High Technology, 2012, Tables 1-1-4 and 2-1-3

Structure and performance of R&D

Exceptionally, for 2009 exist R&D data for all firms with annual sales over 5 million Yuan, classified by size (Large, Medium and Small). The data provide a more comprehensive comparison of the structure of the two “new industries” with the much larger incumbent manufacturing of chemical medicines. The four ratios in the right-hand part of the Table 4 illustrate the structures and compare the performance of the three industries, by small, medium, large size and ‘all’ enterprises in 2009.

Ratio 1. The propensity to engage in R&D activities varies among the three industries and even more among firms of different size. Biological and chemical medicine manufacturing lead with respectively 39% and 35% of enterprises of all size engaged in R&D, compared to only 28% in medical equipment manufacturing. In chemical drugs and medical equipment manufacturing large enterprises are more likely to engage in R&D than

the smaller ones. Not so in the nascent biopharmaceutical industry, where only one of the two large enterprises was conducting R&D in 2009.

Ratio 2. Small biopharmaceutical firms are more R&D intensive. The intensity of R&D in small firms manufacturing biological drugs was in 2009 almost twice as high (6.3%) as in small chemical firms (3.5%) and about as high as in large chemical firms. On the other extreme, the R&D intensity of the only two large biopharmaceutical manufacturers was only 1.3%.

Ratio 3. The lower the number of R&D person-years per patent, the higher the productivity of R&D. R&D productivity is higher in both new industries than in the incumbent manufacturing of chemical medicines. As predicted by the SSIP model, technological opportunities are more abundant at the early stage of the biotechnology system than in the mature stage of the chemical technology (Perez and Soete, 1988). It is yet another evidence of the declining productivity of the drug research in incumbent chemical technology-based innovation model.

Ratio 4. Finally, the last column shows labor productivity, i.e. the value of output per unit of labor, in each industry by firm size category. On the one hand, it shows convincingly, that under the existing prices, irrespective of the firm size category, biotechnology-based drug manufacturing is more labor-productive than the incumbent manufacturing of chemical medicines. The low labor productivity in the medium and small size medical equipment firms may be due to a combination of low-technology products and high proportion of unqualified, low-cost labor employed mostly in assembly activities. A micro-econometric analysis of enterprise data could explain the sources of industry differences in innovation and productivity more completely. Unfortunately, the enterprise data are not publically available and could not be used in this paper.

The simple ratios analysis above suggests that biotechnology-based drug manufacturing is more R&D intensive, innovative and labor productive than the incumbent chemical drug manufacturing.

Table 4. Number of Enterprises, Employment, Output, R&D Employment and Patenting

Enterprise Size	Enterprises no.		Employment		Output	Patents	Ratio 1	Ratio 2	Ratio 3	Ratio 4
	Total	with R&D	Total	R&D	GVI0	count	Enterprise with R&D/Total	Employment (RD/Total)	R&D productivity R&D _{emp} /PAT	Labor productivity GVI0/EMP _{yuan/emp}
Column no.	(1)	(2)	(3)	(4)	(5)	(6)	(7)=(2)/(1)	(8)=(4)/(3)	(9)=(4)/(6)	(10)=(5)/(3)
Chemical Medicines										
Large 2009	50	41	207 826	13 781	1 341	795	82.0	6.6	17.3	64.5
Medium 2009	507	335	334 458	17 676	2 119	967	66.0	5.3	18.3	63.4
Small 2009	1 937	505	225 312	7 788	1 431	691	36.0	3.5	11.3	63.5
All 2009	2 494	881	767 596	39 245	4 891	2 453	35.0	5.1	16.0	63.7
Biological products										
Large 2009	2	1	6 265	80	63.4	10	50.0	1.3	8.0	101,2
Medium 2009	89	61	54 507	5 106	391.1	284	68.0	9.4	18.0	71,8
Small 2009	724	257	68 264	4 283	526.0	464	36.0	6.3	9.2	77,1
All 2009	815	319	129 036	9 469	980.5	758	39.0	7.3	12.5	76,0
Medical Equipment & appliances										
Large 2009	7	5	21 596	1 718	111.1	122	76.4	8.0	14.1	51,4
Medium 2009	132	64	90 208	3 805	372.0	322	48.5	4.2	11.8	41,2
Small 2009	1 123	283	121 218	3 669	490.4	922	25.2	3.0	4.0	40,5
All 2009	1 262	352	233 022	5 523	973.5	1 366	27.9	2.4	6.7	41,8

Sources : China Statistical Yearbook on High Technology (2008,2009; Tables 1-2-3; 2-5-3; 2-20).

R&D activities of the Big Pharma

After setting up distribution channels and local manufacturing, often in joint ventures with local drug companies, ‘Big Pharma’ companies are increasingly off-shoring to China some of their R&D and clinical trials. According to a survey, pharmaceutical multinationals invested in their laboratories in China more than 8 Yuan billion /year (about 1.25 US\$ billion) in R&D, representing 57% of China’s pharmaceutical industry’s total R&D expenditure in 2012 (Christie, 2012). Their R&D expenditures are about 10% of revenues, compared to the China’s local industry’s average of 2%. Their firms created 210 partnerships with universities, hospitals and academic institutions, including graduate degree programs. They were employing in 2012 about 3 000 R&D personnel of which 21% are returnees.

The effects of spillovers from MNC's production and R&D activities on the locally-owned segment of the industry are expected to be very positive. However, the studies of the effect of foreign-invested firms on the performance of their locally-owned competitors in Chinese manufacturing industry do not support these expectations (Fu and Gong (2011). Foreign firms have few interactions with local firms that could promote technological learning, and they do not share the latest technologies (Wang, 2006).

Contract research organizations

As Big Pharma companies in developed countries are being challenged by the manufacturers of generic and bio-similar medicines, escalating R&D costs, patent expirations, increased scrutiny from regulatory agencies and institutional procurement of pharmaceuticals and medical devices, they seek to increase efficiency and reduce costs by outsourcing an increasing number of research activities to Contract Research and Manufacturing Organizations (CRO and CMO) abroad.

The first few CROs established in China were foreign multinational companies (MDS, Quintiles, Covence, PPD and others) and joint ventures (Kendle Wits, Venture Pharm, Rundo, Pharmaron). The domestic CROs entered the market after 2000, many of them providing contract services to generate revenues needed for their own R&D projects (Louet, 2004). In 2011, China's total CRO market was approaching US\$ one billion, growing more than 20% per year and ranking third in Asia, behind India and Singapore (Christie, 2012).

Among the 22 major CROs, only six had biotechnology capabilities in 2004-2005 (Zhou, 2007). Since then the share of CROs providing biotechnology services increased to 40% in 2011. Foreign-invested CROs dominate all phases of clinical trials and share the market with the two largest domestic CROs, WuXi and Shang Pharma (Ma, 2012). Their development has been based on expanding expertise by mergers and acquisitions abroad and in China.

After a very successful IPO on NYSE in 2007 that raised \$185 million, WuXi PharmaTech merged in 2008 with AppTec Laboratory Services Inc., a U.S. company with expertise in medical-devices, biologics testing and cell therapy. That opened WuXi the U.S. market and extended its capabilities from chemical to biological medicines and medical device expertise. It now provides the full range of R&D services in China and the U.S. Three-quarters of its revenue of \$578 Million in 2013 originated in laboratory services (21% in the U.S.) and the rest in manufacturing services (\$147 Million). It is one of rare Chinese U.S. listed health care companies with a growing stock price.

The foreign and top Chinese CROs are the principal beneficiaries of the Big Pharma's strategy of reducing the cost and sharing the risk by outsourcing to China, some of their R&D activities, including drug discovery.

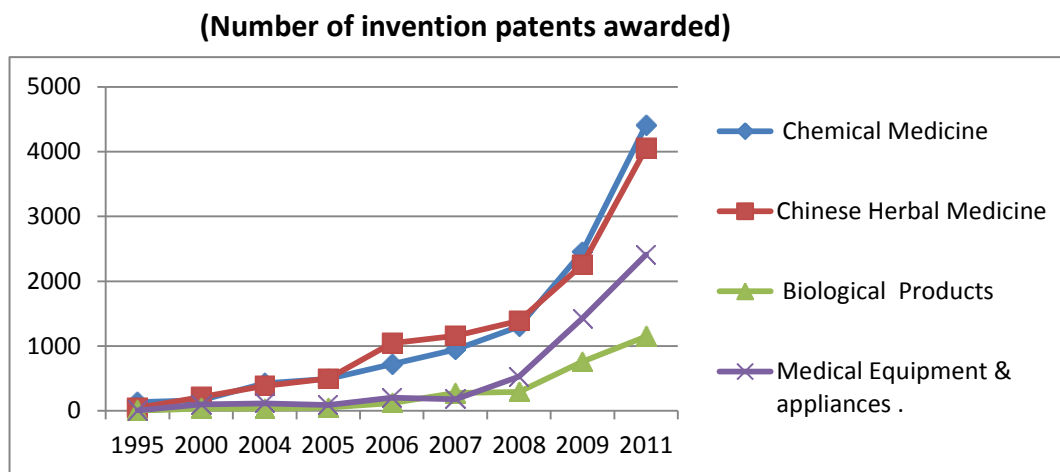
4.4 Catching up on the Global Scene? - The Evidence from Patenting in China and the US.

Like the rest of the high-tech industry, after introduction of TRIPs compliant patent regime, Chinese biotechnological and medical equipment companies started patenting aggressively.

Patenting in China

The average annual growth rate of the number of patents awarded by the Chinese State Intellectual Property Office (SIPO) from 2000 to 2011 to biopharmaceutical enterprises in China reached 33% (Figure 7).

Figure 7. Number of patents granted by the Chinese Patent Office to Biopharmaceutical, Chemical, Chinese and Medical equipment industries



Source: China Statistical Yearbooks on High Technology, 2008 (Table 2-20) and 2010, 2012 (Tables 2-5-1).

Note: Includes enterprises over designated size, i.e. Large, Medium and Small size with annual sales over 5 million Yuan 1995-2010 and over 20 million Yuan 2011.

Patent statistics shows that small firms play an essential role in the development of an innovative Chinese biopharmaceutical industry. The share of biotechnology patents owned by small firms is larger (54%) than their share of industry's output (46%) and employment (42%). Obviously, biotechnology provides abundantly technological opportunities that attract new firms.

The contrast with small firms manufacturing chemical medicines is telling. Their share of patents for chemical pharmaceuticals is only 25%, compared to employment and output share (both about 29%). Patenting by small firms in medical equipment and appliances industry is slightly lower than their share of output and employment.

The foreign-invested biopharmaceutical firms are the most innovative. Their share of the total number of patents awarded to China's bio-pharmaceutical industry is 36%, more than their share of output (31%) and employment (27%) and also more than the patent share of foreign-invested producers of chemical drugs (31%).

The surge of patenting in China in the last decade is an evidence of the growing awareness of the importance of intellectual property and increasing innovation in manufacturing of biopharmaceuticals. It is, however, not a good benchmark of China's biotechnology catching up with the world biotechnology leaders. This purpose is better served by the share of biotechnology patents obtained by Chinese patentees in the U.S., the first, most advanced country in biotechnological research and its industrial applications.

Patenting in the US

The cumulative number of U.S. patents for biotechnological inventions listing a Chinese inventor or co-inventor increased notably after 2000, reaching 740 patents in 2013. Patentees from the U.S., Eu, Japan and few other countries own almost half (354) of them. The inventors were presumably Chinese nationals studying and working in U.S, EU or Japanese organizations in the given period.⁴

Since the purpose of the analysis is to assess whether Chinese biotechnology is catching up with the biotechnology frontier, Table 5 includes only 386 USPTO patents assigned to organizations and individuals with an address in P.R of China. Their number has been growing exponentially.

The composition of patentees has dramatically changed. Before 2004, the majority of US biotechnology patents were awarded to Chinese universities, public research institutes and individuals; only very few to enterprises. Considering 2005 as the first year of full Chinese compliance with TRIPS, the share of US patents awarded to Chinese

⁴ It is recognized that after their return to China, some of them may have contributed with their subsequent inventions there to USPTO patents assigned in later periods to Chinese entities or individuals.

enterprises has significantly increased from 17% in 1989-2004 to 38% in 2005-2013. This suggests that TRIPs have provided powerful incentives for local innovation and patenting to which Chinese universities, research institutes and especially enterprises responded vigorously (see Table 5 for details). More recent data on Chinese international patenting of biotechnology inventions under the Patent Cooperation Treaty confirm the increasing trend. The upward trend supports the hypothesis of a catch up, but the gap separating China's biotechnology industry from the leaders in the field is still very large.

**Table 5. US patents to Chinese inventors assigned to Chinese entities and individuals
(Patents to Chinese assignees only)**

Year	Enterprises	Universities & Research Institutes	Individuals	Co-ownership within China	Total
1989-1994	1	2	1	0	4
1995-2000		7	4	5	16
2001-2004	9	13	5	11	38
2005-2009	41	33	8	18	100
2010-2013	85	79	35	29	229
Total	136	133	53	63	386

Source: Author's tabulation of patents from the U.S.PTO.

Methodology. The selection criteria: (1) Patents in international patent classes listed as biotechnology by the OECD (2003), awarded to inventors and co-inventors with address in the P.R. of China. Patents to inventors from Hong Kong, Macau or Taiwan are not included. Each patent is counted only once.

(2) Slightly more than one half (386) of the total of 740 patents with Chinese inventors or co-inventors assigned to Chinese organizations and individuals are classified manually by the type of assignee in one of the five categories above.

5. Discussion and conclusions

The paper examines how far China has advanced in its goal of catching up with leading industrialized countries in modern biotechnology. The Sectoral System of Innovation and Production (SSIP) complemented by strategic considerations of latecomer firms appeared to be the best suited approach. The first views the catch up as a learning process; the second considers the strategies by which the latecomer firms are overcoming competitive disadvantages through linkages, resource leverage and learning; learning being the common denominator of both perspectives.

5.1 Recapitulation of the main findings

Scientific capabilities

The first empirical part of the paper examines (1) the effects of reforms on building a sustainable knowledge base for the development of the biotechnology regime and (2) whether the radical restructuring of the Chinese scientific infrastructure is reducing the gap separating China's scientific research from biotechnology forerunners.

China's higher education system is already training more scientists and engineers at the doctorate level than any other country in the world as befits her scientific ambitions. The education is, however, reflecting the top-down thinking proper to China's political system. It prizes memorizing more than free individual initiative, and it does not tolerate failure, a quality indispensable for bold innovation. The government has been underinvesting in basic research and to make things worse, PROs do more development than scientific discovery-oriented research. The statistical system pays insufficient attention to small firms, the most likely and dynamic source of radical innovations. Small firms are also treated less generously by R&D incentives than the large ones.

The growing numbers of highly qualified personnel returning from the U.S. and Europe to China help to improve and accelerate the development of Chinese biotechnology

research base and encourage R&D and innovation. Their continuing active links and collaboration with their former foreign professional networks is the best channel for learning and diffusion of new ideas, technologies and market opportunities. It certainly helps to reduce the gap between Chinese and Western biotechnology research and applications.

The reorganization of the scientific infrastructure improved its quality and productivity. Despite the low level of basic research, the number and quality of Chinese scientific publications in biotechnology have been increasing much faster than the scientific personnel employed in biotechnology research. The knowledge base of the SSIP of human health-related applications of biotechnology in China is well advanced in the catch up process. The rapidly growing world's largest 'genomic research factory' BGI-Shenzhen exemplifies the Chinese strategy of creating a competitive advantage through linkages, resource leverage and learning from incumbents.

Industrial applications of biotechnology

The majority of enterprises in the biotechnology-based component of the pharmaceutical sector are manufacturing APIs and biosimilar drugs often under the license or contract from foreign firms in China and abroad. An increasing number of Chinese biotechnology firms are engaging in discovery and development of innovative APIs, incremental innovation and some world-first ones. Most of these innovative products are still in the approval process of the SFDA and not yet on the market. The other, even faster growing 'new industry,' *Manufacturing of medical equipment and devices* has been benefiting from the symbiotic relationship with the ITC and electronic enterprises and research laboratories co-located in the same clusters.

Foreign invested firms are more export as well as research-intensive and more labor-productive than their local competitors. Even though most Big Pharma companies are present, their sales in China still account for less than 1% of their global sales, a suboptimal situation which their strategy of outsourcing to emergent markets is trying to correct. The rapid introduction of universal health insurance, ambitious plans for the development of biotechnology and pharmacology, as well as improvement of intellectual property protection and regulatory process, explain why most of the Big Pharma companies continue establishing or expanding R&D centers and CMOs in China as part of their global value chain.

5.2 New niches and strategies

New niches

While most Chinese biotechnological companies pursue either the bio-similar or innovative strategy described above, some organizations are aggressively developing more specialized niches in biotechnology and related scientific disciplines. One outstanding example is GBI-Shenzhen's drive to transform gene sequencing from a piece-meal expensive laboratory research procedure into a factory-like large-scale low-cost operation and open the way to personalized medicine (Spencer, 2014).

Another is the active embryonic stem cell research which has been severely constrained or banned in many Western countries, including the U.S. More relaxed regulations have opened a window of opportunity for Chinese researchers who are now recognized leaders in the field that may revolutionize the regenerative medicine (Murray and Spar, 2006).

Biotechnology's share of the pharmaceutical sector's sales, investment and R&D has significantly increased; an evidence of a shift from chemical to biotechnology-based drug manufacturing. Their patenting, not only in China but also in the US and elsewhere abroad, has significantly increased. In contrast to very little patenting by the large,

incumbent manufacturers of chemical medicines (Niosi J., S. Reid and J. Zhao, 2013), new, mostly small biotechnology companies, responded to TRIPs-imposed international standards of protection of intellectual property by patenting aggressively in China and abroad. Even though the cumulative number of patents owned by Chinese entities pales in comparison with the patent chest of the U.S. biotechnology giants, their ascending trend may be interpreted as an early sign of catching up with the leaders in the field.

Strategies

The strong drive of MNCs establishing proprietary R&D centers and partnerships with Chinese universities, PROs and enterprises, is not only part of the Big Pharma's new global cost cutting and risk sharing strategy. It is also a means to expand their share of the large and growing Chinese drug market. The close cooperation between the U.S. FDA and their Chinese counterpart aimed at improving the safety and quality of the 'Made in China' APIs, generics and biosimilars are part of this globalizing strategy.

Whether the short benefits exceed the future costs for the society in terms of increasing Big Pharma's penetration of the Chinese drug market is less clear. It is obvious that it is not a zero-sum game. A comprehensive study of the long run effect of foreign-invested firms on their local competitors, the development of pharmaceutical industry, life sciences and the welfare of the Chinese population does not yet exist.

Several recent international deals described in the text show a new strategy of China's foreign direct investment abroad. Chinese enterprises invest increasingly in High-Tech sectors like pharmaceuticals (Niosi J., S. Reid and J. Zhao, 2013). Financially strong Chinese companies are 'buying-in' the new knowledge, technological capabilities and access to foreign distribution channels in exchange for facilitating their partner's products or services entry on the Chinese market, or licensing it and distributing it on their own distribution networks.

Further development of the Chinese biopharmaceutical sector is likely to proceed by a combination of three strategies “borrowed” from the world of music:

1. Becoming a part of a global music scene by playing in a cosmopolitan orchestra directed by a foreign director (a Big Pharma company) and striving to increase the number of concerts given in China by adjusting its repertoire to Chinese needs and taste.
2. Pursuing the goal of becoming a well-known chef of one of China’s excellent orchestras by hiring impoverished foreign musicians when the local talent is not good enough or not available. Play Chinese and foreign music, especially the compositions or arrangements of its foreign members.
3. Becoming a world-renown virtuoso and composer for its own instrument and give concerts on the domestic and international music scene.

5.3 Challenges ahead

Like in Western countries, further development of Chinese life sciences-related biotechnology will be increasingly integrated in the pharmaceutical sector rather than developing more independently. To become more innovative and bring own original drugs on the market, Chinese research in biotechnology will have to focus more on basic research. It has to aim at discovering original, ‘me first’ medicines, devices, services and procedures rather than continue to rely on ‘me too’ imitation and incremental innovation of foreign discoveries.

The R&D support policies will have to concentrate on supporting rather than discriminating against small companies, the most likely fertile source of radical innovations. To properly manage the public support of small firms, better statistical coverage of these enterprises is necessary. Despite a concerted effort to improve the quality of regulatory procedures, the approval procedures are still too slow and their quality not always to international standards. Without an improvement of SFDA services quality and

timeliness, China's attraction as a partner integrated with the global value chain of foreign multinational pharmaceutical companies will not fulfill its potential. Given the importance of the pharmaceutical sector for China's huge drug market, the stakes of closer integration with Big Pharma are high and merit an in-depth study.

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