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editorial

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China's drug innovation and policy environment

China will be the fifth largest pharmaceutical market in 2010 and the third largest in 2020 [1]. Its pharmaceutical industry has developed rapidly concomitant with its booming economy. Since China's reform and opening-up in 1978, pharmaceutical industrial output value has been increasing at an average annual growth ratio of 16.6%. To gain a competitive edge in the global market, the current national strategy of China forcefully pushes for independent drug innovations. Drug innovation is central to China, at both the individual firm level and national level. First, the pharma industry is knowledge-intensive and companies rely on innovation to improve performance and gain competitive advantages over rivals. Second, the government needs the pharma industry continuously to conduct research and development (R&D) to discover affordable new drugs to counter emerging diseases and maintain public health. Given the strong influence of the centralized power in China, drug R&D is inevitably constrained and facilitated by government policies. Therefore, a discourse of the historical, legal and regulatory contexts in which China's drug R&D has evolved will help to understand the impact of national policies on drug R&D, which can be used to inform decision-making on investments in China or conducting technology trade and international cooperation with Chinese partners.

Evolution of China's drug R&D

Since the People's Republic was founded in 1949, China's drug R&D has evolved through four phases: (1) pure imitation, (2) innovative imitation, (3) imitative innovation and (4) independent innovation. As drug R&D and the IP policies have co-evolved in China, the enforcement dates of different patent laws can be used as anchors to delimit the four phases. In Phase I (1949–1985), there were no laws to regulate pharmaceuticals and the pharma companies fully depended on copying from foreign companies to synthesize and manufacture drugs to meet domestic needs. China's first patent law entered into force in 1985, indicating the beginning of Phase II (1985–1993). This patent law protected only the production process of drug synthesis and did not allow pharmaceuticals and substances obtained by chemical processes to be patented. In this phase, drug R&D was mainly based on modifying delivery methods and preparation formulations of existing drugs without changing the molecular structure. Phase III (1993–2009) started in 1993, when the patent law's first amendment was enacted. Because the amendment granted full patent protection to drugs, pharma companies could no longer imitate existing drugs without modifying their molecular structures. Drug R&D

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in this phase was thus focused on chemical modifications of the structure of existing drugs, such as changing acidic or basic groups, altering optical configuration and developing isomers of original drugs to develop 'me-too' drugs. Phase IV started from 2009, when the patent law's third amendment entered into force. In this phase, drug patent protection is becoming stricter, stronger and more comprehensive, making it very difficult to imitate existing drugs. The Chinese government has been trying to transform the pharma industry into an innovation-centric industry through a series of national policies since 2006. The third amendment symbolically signified that the primary basis of competition in China's pharma market became independent innovation, although innovative imitation and imitative innovation could still be some companies' principal strategies.

R&D input and output

Current investments on drug R&D are highly insufficient in China. The R&D to sales ratio for Chinese pharmas is merely 2.7% [2], much lower than the 17.4% ratio of their US counterparts [3]. In view of this small R&D input, China has a disproportionately large R&D output. The numbers of new drug applications (NDAs) filed to the State Food and Drug Administration (SFDA) in 2005 and 2006 were both over 12,000. This number dropped to over 4000 in 2007 after the SFDA tightened drug registration. Compared with the number of NDAs in the US, mostly below 100 per year, it is still a huge number. This is, however, due primarily to China's loose standard for new drugs. Before 2007, the SFDA defined any drug not in the Chinese market as a new drug. Imported drugs and any new way of using existing drugs could obtain the new drug status like new chemical entities (NCEs). If only considering NCEs, China's drug R&D level is far behind the US. From 2000 to 2008, the US had 193 NCEs, whereas China had only two – the world's first gene therapy product for head and neck cancers, Gendicine, by Shenzhen Sibiono GeneTech [4] and the world's first oncolytic viral therapy for cancer, H101, by Shanghai Sunwei Biotech [5].

National strategies

Two fundamental national strategies have substantially influenced China's drug innovation: building an innovative nation and establishing IP rights. In 2006, the 17th National People's Congress announced that enhancing independent innovation capabilities and constructing an innovative nation are the core of China's national development strategy and crucial for improving China's comprehensive national power. This is the first time that China had included the concept of innovation in its national development strategy. In 2008, the Chinese State Council issued 'National Intellectual Property Strategy Compendium', asserting that China would be transformed into a country with a high level of creating, utilizing, protecting and administrating IP rights by 2020. Given China's centralized power structure, these strategies have effectively spurred drug innovations by creating a facilitative policy environment and mobilizing R&D resources.

IP protection

The IP legal system in China includes patent, trademark and copyright laws, of which patent law is the most influential with respect to drug innovation. The State IP Office (SIPO) and its local branches are the main executing agents of the patent law. The patent law was first enacted in 1985 and amended three times in 1992, 2000 and 2008 (entered into force in 1993, 2001 and 2009, respectively). Under the first patent law, pharmaceuticals were not patentable. Owing to the pressure from the Sino-US trade negotiation, the 1992 amendment was implemented to allow for pharmaceuticals to be patented, setting a milestone for China's drug R&D. To prepare for China's accession into the WTO, the 2000 amendment was passed to comply with the TRIPS agreement. A noticeable revision was to remove the non-infringing exemption which stipulated that the act of use or sale of a patented product without knowing that permission was not obtained from the patentee was not an infringement. This exemption has made it impossible to stop patent violations effectively and its removal strengthened effective patent protection.

Whereas the previous two amendments were due to external pressures, the 2008 amendment was driven by the 'build an innovative nation' strategy, intending to create a safe IP environment to encourage R&D and attract foreign investors. It adopted the international standard of absolute novelty which only issues patents to innovations that are new worldwide. Previously, China's relative novelty standard allowed a drug to be patented as long as it was new in China. The amendment introduced several changes to deter patent infringements. For example, administrative penalties for patent violations were increased from three times the illegal income to four times. The new patent law also caused concerns [6], however. For example, compulsory licensing may be issued if the patent owner has not adequately practiced the invention for three years, and patented products can be legally manufactured if the purpose is to obtain regulatory approval. Foreign pharma companies might feel that these changes put them in disadvantage.

Drug regulation

Besides the IP regime, drug R&D in China is influenced by drug regulation policies. China's drug regulation is charged by the SFDA and its objective is to ensure drug safety, efficacy, quality and accessibility. China's drug regulation used to be highly problematic, overemphasizing quantity and ignoring innovation and quality. Consequently, many low quality drugs sneaked into the market. Several high profile drug accidents in 2006 resulted in a crisis of trust in domestic drugs. For example, nine patients died from injection of Armillarisin manufactured by Qiqihar Second Pharmaceutical Factory and another 11 patients died after receiving injection of Clindamycin Phosphate manufactured by Huayuan Pharmaceutical Factory. These accidents put enormous pressure on the government. The former SFDA director, Zheng Xiaoyu, was executed for corruption and dereliction of duty. To correct the flaws in the past regulations and strengthen drug control, in 2006 the Chinese government started to create a new drug regulatory regime. A new 'Provisions for Drug Registration' was enforced in 2007 and a series of supplemental rules were implemented subsequently. The current drug registration regulation heightens the standard for new drug and discourages the 'short, simple and fast' drug development model used to be popular among domestic pharmas, seeking to optimize resource allocation within the industry and steer it to a more innovation-oriented path. The industrial structure is being transformed so that only the strong innovators have chances to succeed.

The Chinese government has traditionally regulated pharmaceutical pricing. At present, about 60% pharmaceutical sales occur at regulated prices [7]. The State Development and Reform Commission (SDRC) has issued a series of policies on drug pricing since 2000. In 2006, it drafted the 'Drug Pricing Measures' which proposes higher prices for patented drugs than generic drugs to help companies get return on investments in drug R&D. Besides, the government allows new drugs with high cost-effectiveness to be added into the national essential medicine list to compensate for the innovative companies.

Other national policies

The Chinese government has implemented a series of policies in various areas such as science and technology input and tax preference to encourage innovation in the pharma industry. To accelerate implementing the innovative nation strategy, the NDRC specified that the focus of the Eleventh Five-Year Plan (2006–2010) was to improve China's fundamental capacity of independent innovation. The plan proposes that via the development of supporting systems of independent innovation, the position of domestic enterprises as the main agency of technology innovation should be fully strengthened, and the research condition and innovative environment for enterprises should be significantly improved, so that a group of advantageous enterprises possessing independent IPR, well-known brands and relatively strong international competitiveness are developed.

As an important special national project under the Eleventh Five-Year plan, Major New Drug Creation aims to develop a series of innovative drugs for treating ten major diseases such as malignant tumors and cardiovascular diseases with a budget of about $1 billion. The project was officially started in May 2008 and includes three phases: 2008–2010, 2011–2015 and 2016–2020. The goal of the first phase is to develop independently 30 new drugs. The government input into this project will possibly increase from $1 billion to about $4.3 billion by 2020 [8].

Parting remarks

As China continues to transform its policy environment for technology innovations, foreign pharma companies will find many opportunities for drug R&D. They can use different business models, such as collaborating with local contract research organizations or establishing their own research facilities in China, to conduct discovery and preclinical research [1,9]. Inexpensive local research staff will help to reduce R&D costs. Besides, China's rich genetic resources and traditional knowledge can be exploited for drug discovery. To achieve R&D success in China, foreign companies should be aware that they need a deep understanding of China's policy systems so that their R&D activities can be smoothly carried out.

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