



The Internationalization Challenge: Where to Access Innovation

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“There will come a time when breakthrough innovation occurs in China on a regular basis. . . . I don’t think there’s anything innate in the Chinese that would prevent them from innovating.”

Joe Jimenez,
CEO, Novartis

7.1 Trends in R&D Internationalization

As a science-driven endeavor, the pharmaceutical industry is inherently global. One the one hand, the fundamental science—biochemistry, molecular biology, genetics, etc.—follows the same natural laws regardless of location on the planet. Especially during the early stages of pharmaceutical innovation, when R&D is mostly a numbers game, the more input there is into the research machinery, the greater the chances of success. On the other hand, the costs of R&D have become so huge that they can be recouped only if they are marketed to as large a population as possible. Drugs sold to twice the number of people cost each patient only half, assuming the same fixed ROI. With governments in most countries having a strong say in the pricing of drugs sold locally, this is an important driver for globalization of R&D as well.

The impetus for globalization is even more acute for pharmaceutical companies from small countries, such as the Netherlands, Sweden, or Switzerland, as they cannot rely on the benefit of domestic homecourt advantage. It is therefore no surprise that the pioneers of R&D internationalization are high-tech companies operating in small markets and with little R&D resources in their home country, as it is the case for Novartis, Actelion, Serono and Roche (Switzerland), Janssen or Solvay (Belgium) or Astra, Pharmacia or Ferring (Sweden). These companies increasingly conducted R&D in foreign research laboratories. Overall, Swiss, Dutch and Belgian companies carried out more than 50% of their R&D outside their home country by the end of the 1980s. Companies such as Pfizer and Eli Lilly

in the U.S., Takeda in Japan, and Bayer in Germany had large home markets and a substantial domestic R&D base, and hence had less pressure to internationalize their R&D activities.

Only in recent years, starting in the mid-1990s, increased competition from within and outside their industries forced companies from large countries to source technological knowledge on a global scale. Global mergers ensued, expanding the research of R&D organizations quickly into new territories. The rise of China as an emerging market for health care and pharmaceuticals has attracted much pharma R&D investment in the mid-2000s. As a result, the top pharmaceutical companies today have R&D locations in all major markets, not just for the coordination of local clinical development projects but also for discovery research.

Drivers and Barriers to R&D Internationalization

The management of cross-border R&D is characterized by a significantly higher degree of complexity than local, single-site R&D management. The extra costs of international coordination must be balanced by synergy effects such as decreased time-to-market, improved effectiveness, and enhanced learning capabilities. Top corporate managers are confronted with the task of finding the optimal R&D organization based on the type of R&D activities, the present geographic dispersion of subsequent value-adding activities such as production and marketing, and the coordination between a multitude of contributors to the R&D process.

The case for R&D internationalization is not unchallenged. Besides the ubiquitous cost argument, foreign R&D units are more difficult to manage, and control, and may be less efficient due to missed scale effects. Table 7.1 summarizes some of the most cited arguments against international R&D.

What drives R&D internationalization? Most factors are due to either science & technology-related issues or sales & output efficiency (Table 7.2). Science and technology-related factors are concerned with R&D personnel qualification, know-how sourcing and regional infrastructure. These factors are largely outside the direct influence of R&D but necessary for its fundamental operations, such as the proximity to universities or the R&D environment. Proximity to markets and customers, improvements of image and collaborations are notable sales & output efficiency-related factors. Efficiency-related criteria focus on the costs of running and the critical mass of R&D units, as well as efficient hand-over processes between R&D and other corporate functions. Direct cost advantages (such as the often-publicized labor costs) rarely influence the internationalization of R&D in the long run, but other efficiency-oriented factors such as costs of coordination and transfer, and critical laboratory size do have an even bigger impact on international R&D organization. Direct costs may become more important in the coming years as the other factors improve in low labor cost countries.

Political and socio-cultural factors such as local content rules, technology acceptance and public approval times, all play an important role in locating R&D abroad. Protectionist, legal and cultural constraints imposed by national governments,

Table 7.1 Barriers to R&D internationalization

Factors in support of central R&D	Obstacles to international R&D
<ul style="list-style-type: none"> • Economies of scale (critical size) • Synergy effects • Higher career potential • Minimal R&D costs and development time • Better control over research results • Communication intensity • Legal protection • Global product standards • Common R&D culture • Harmonization of regulatory environment • Improved information and communication technologies 	<ul style="list-style-type: none"> • Immobility of top-class personnel • Critical mass (for start-ups) • Redundant development • Language and cultural differences • Effective communication difficult • Much of scientific and technical information worldwide available by Internet • Specific know-how easily lost when support not present • Political risks in target country • Establishment and running costs • No wage advantages in triad nations • Coordination and information costs

Source: Boutellier et al. (2008)

Table 7.2 Reasons for locating R&D abroad

Science & technology	Sales & output efficiency
<ul style="list-style-type: none"> • Availability of scientists and engineers • Tapping into local scientific community • Proximity to universities • Recruiting local talent • Better R&D environment • Higher quality of life • Lower R&D costs • Higher acceptance for pharmaceutical research 	<ul style="list-style-type: none"> • Smooth hand-over with local marketing and sales organization • Easier coordination with local hospitals during the clinical phases • Compliance with local regulatory requirements • 24-h-Laboratories • 'Good citizen' argument • Local content rules • Protectionist barriers • Tax optimization

Source: von Zedtwitz and Gassmann (2002)

however, often require a company to establish local R&D units. R&D-external forces such as a business unit's striving for autonomy and the build-up of local competence alters the original mission of a local R&D unit. This evolution may take place without HQ's knowledge, particularly in strongly decentralized companies.

In the pharmaceutical industry, mergers and acquisitions have significantly contributed to the internationalization of R&D, particularly with recent cross-border mergers. Even though small size is a driver for internationalization, the global marketing reach of large firms facilitates the leverage of global R&D and innovation. For instance, when Pfizer acquired Wyeth and Merck acquired Schering-Plough in 2009, on paper the two merged firms would have accounted for 51% of the total U.S. pharmaceutical R&D spending and 39% of total world-wide spending (Comanor and Scherer 2013). Subsequent cost reduction programs eliminated R&D units in the combined companies, but since both domestic and foreign units were closed down, this had little effect on their new extent of R&D internationalization. Rather, we

observed a centralization of R&D in certain internationally leading regions of innovation (centers of excellence). However, mergers are rarely driven by scientific or technological reasons. Access to new markets and economies-of-scale effects are primary drivers for mergers. Nevertheless, the resulting R&D conglomerate must somehow come to terms with a new and more international organization.

The development of local products requires the early involvement of market and customer application know-how, which is more likely to be found in regional business units. Companies with local R&D exhibit an inclination towards over-emphasizing different local market specification in order to support local autonomy and independence from the parent company. Host country restrictions, such as local content requirements, tolls, import quota, and fulfillment of standards, can attract R&D into key market countries (pull regulations): Both the U.S. and China have plenty of such regulations attracting inbound R&D investments from overseas. On the other hand, home country restrictions may induce companies to move R&D abroad (push regulations): European regulations caused biotechnology R&D to be transferred to the U.S., and lack of homegrown talent forced Swiss pharma companies to set up R&D centers abroad.

Locations of Pharmaceutical R&D Around the World

A study of 9452 R&D sites across various industries (including automotive, engineering, electrical, IT, software, food, chemical and pharmaceutical companies) produced the following overall results concerning international R&D locations (see also von Zedtwitz and Gassmann 2016):

- R&D is concentrated in the triad regions of Europe, the United States, Japan, as well as major regional centers in South Korea, Singapore and other emerging economies in Asia-Pacific, such as India and China. China has seen a particularly strong increase of inbound R&D investments in recent years, but domestic companies are also conducting more and more R&D. Compared to China and India, the other frequently mentioned BRIC countries—Brazil, Russia, and sometimes also South Africa—are far behind. They lack economic and institutional attractiveness, and their domestic high-tech ecosystem is still underdeveloped, comparatively speaking.
- Over 70% of all research sites are in the five regions of the Northeastern USA (New Jersey, New York, Massachusetts), California, the United Kingdom, Western Continental Europe (in particular Germany), and the Far East (Japan, South Korea). China (especially Shanghai and Beijing) and India (especially Mumbai and Bangalore) are catching up as locations for research, too. The trend of research concentration is even more apparent when only foreign research locations are considered: almost 90% are in the triad regions of the U.S., Europe, and Japan.
- Although the main regional centers for development largely coincide with the regional centers for research, development is more evenly distributed among European countries and the Northeastern United States, and extends into



Fig. 7.1 Locations of 821 R&D labs of 45 pharmaceutical firms. Source: GLORAD Database 2016

Southeast Asia, Australia, Africa, and South America. Only slightly more than half of all development sites are located in the eight most development-intensive countries.

Moreover, research and development sites of the same company are not necessarily co-located. This is especially true in the pharmaceutical industry, where development mandates differ so much from research. Since the late 1990s many large companies have made multiple efforts to consolidate their activities in order to realize synergy and coordination potential in international R&D. Transnational R&D projects are managed more easily if the R&D network consists of competence centers (pharmaceutical firms tend to be ahead in reorganizing themselves around competence centers), given that complementary competencies are provided locally. With increasing complementarities of resources, competencies, and knowledge bases, as well as the division of labor and specialization of work, synergy potentials in R&D projects can be exploited.

Figure 7.1 shows a subset of 821 pharmaceutical R&D centers of the 9452 R&D locations. It presents the R&D locations of 45 pharmaceutical companies, including Abbott, AstraZeneca, Boehringer Ingelheim, J&J, Eli Lilly, Eisai, GSK, Pfizer, Merck, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Sinopharm, Takeda, or Teva. The distribution of these R&D sites shows a similar pattern to global R&D dispersion across all industries but differs in the following observations:

- There are very few R&D centers outside the globally most attractive countries (the Triad countries, as well as China).
- In the US, R&D is focused more on the North-East, in particular the Tristate area, North Carolina, Massachusetts, and a few centers in the Mid-West. Relatively

speaking, there is less R&D in California, but the Bay Area, San Diego and Los Angeles are catching up also as hosts for pharma and biotech R&D.

- In Europe, R&D is concentrated in the U.K., France, Germany and Switzerland, mirroring the relative strength of these countries as homes of big pharma (Novartis and Roche are from Switzerland, Sanofi and Servier are French, AstraZeneca and GSK are from the U.K., and Bayer and Merck KG are German).
- Despite what some call Japan's lost two decades, there is a strong representation of R&D in Japan, led by the many Japanese pharmaceutical firms, although most of them are smaller compared to their Western competitors (e.g., Takeda or Eisai).
- Emerging new centers of pharma R&D are Shanghai, Beijing and Singapore, but also India (Mumbai and Bangalore), and Israel.

Given this data, the pharmaceutical industry is one of the most internationalized in terms of R&D locations. Pharmaceutical companies also seem to internationalize research as fast as development (albeit for different reasons). Most other industries tend to keep research at home and localize development. Although not obvious from location data alone, pharmaceutical companies also tend to organize R&D as competence-based networks, as opposed to R&D hubs (e.g., automotive and chemicals), polycentric networks (e.g., local market-dependent companies such as Royal Dutch/Shell) or centralized R&D (e.g., dominant design industries). In competence-based R&D networks, each R&D node has a clearly defined competence—and responsibility!—which it brings into the network of other R&D centers. The coordination and management of such R&D networks is more demanding and costly than rather centralized and directive R&D hubs, or the *laissez-faire* style of polycentric R&D networks. As a consequence, pharmaceutical companies (and many electrical and IT companies, who also favor this type of R&D organization) try to coordinate R&D activities across multiple levels, including the deployment of transnational project teams, platform management, informal as well as formal network techniques.

Examples of Global Pharma R&D: Novartis, Chugai, Ferring

The history of **Novartis** has been documented in detail by Zeller (2001). We will focus here only on some of the more recent developments as they are representative of big pharma. In 2002, about 3000 scientists worked in 10 research centers worldwide in several therapeutic areas. Only 1400 of them were employed in research centers in Switzerland, along with a comparable number in pre-clinical and clinical development: More than half of the R&D workforce was located outside Switzerland. Novartis had 67 drug candidates in clinical development at that time.

In May 2002, Novartis announced it would move its global research headquarters to Cambridge, Massachusetts. Over the following 15 years, the Cambridge-based center has grown by 2000 people in R&D alone and now occupies multiple sites. In 2003, it opened a research center focused on dengue and other tropical diseases (the NITD Institute for Tropical Diseases) in Singapore. It closed its Palo Alto-based

SyStemix R&D and moved it to East Hanover, New Jersey. In 2006, Novartis opened a R&D center in Shanghai, being one of the first of the big pharma to do so.

Over the next few years, Novartis would continue to consolidate R&D in its preferred research hubs. In 2013, Novartis closed its Horsham, U.K., respiratory research center, its center for topical dermatology treatments in Vienna, and a biotherapeutics development unit in La Jolla. It also relocated oncology R&D from Emeryville in California to its Cambridge R&D center.

In 2016, Novartis closed its Schlieren, Switzerland-based ESBATech R&D center, and moved its Institute for Tropical Diseases from Singapore to Emeryville, although Singapore remained a major R&D hub for Novartis in Asia-Pacific. It also shut down its biologics group in Shanghai. However, it opened a brand-new US\$1 billion research center in Shanghai, to become its third largest research center behind Cambridge and Basel. As of 2016, Novartis employed 6000 scientists in its global R&D organization, almost half of them in Cambridge alone. Novartis's headquarters remained in Basel, Switzerland.

Chugai is one of Japan's pharmaceutical pioneers. It was acquired by Roche in 2002 but continues to operate independently. Founded in 1925 in Tokyo, it had established R&D centers in Ukima, Kanagawa, and Shizuoka. With new ambitious research targets in the early 1980s, it started to establish overseas offices in the mid-1980s, and to invest or acquire U.S.-based biotech firms. In 1992 it set up its first international research center in Korea, and expanded its London office into a fully-ledged pharma center in 1995. In the same year, it founded a research center in Ibaraki, and 6 years later one in Tsukuba and in Singapore. With the alliance with Roche in 2002, global R&D was reorganized as well. The Tsukuba and the Takada centers were both closed, but the Forerunner Pharma Research company formed, as was a new Clinical Research Center organization, which eventually also opened a base in Singapore in 2011.

An interesting case of internationalization is **Ferring Pharmaceuticals**. Founded in 1950 in Malmö, Sweden, it later moved its headquarters to Copenhagen, Denmark, and then to Saint Prex, Switzerland. It established R&D centers in San Diego in 1996, Tokyo in 2001, Mumbai in 2007, as well as Glasgow and Beijing in 2011. In the U.S., Ferring opened a drug development center in Parsippany in New Jersey in 2008. It also acquired an R&D lab in Israel in 2005. Its main R&D hub is in Copenhagen. In Switzerland, it has an R&D center in Allschwil near Basel.

These examples are typical for the changes in global R&D in the pharmaceutical industry (see Fig. 7.2 for Takeda). We see three major trends:

1. Consolidation in hubs with abundance of talent and technology.
2. Acquisitions of smaller competitors and biotech firms expand the geographic dispersion of R&D.
3. Increased presence in Asia-Pacific, especially China.

The last trend is also observed for global R&D in other industries, which nevertheless requires an explanation, as China is not known to be a place in which

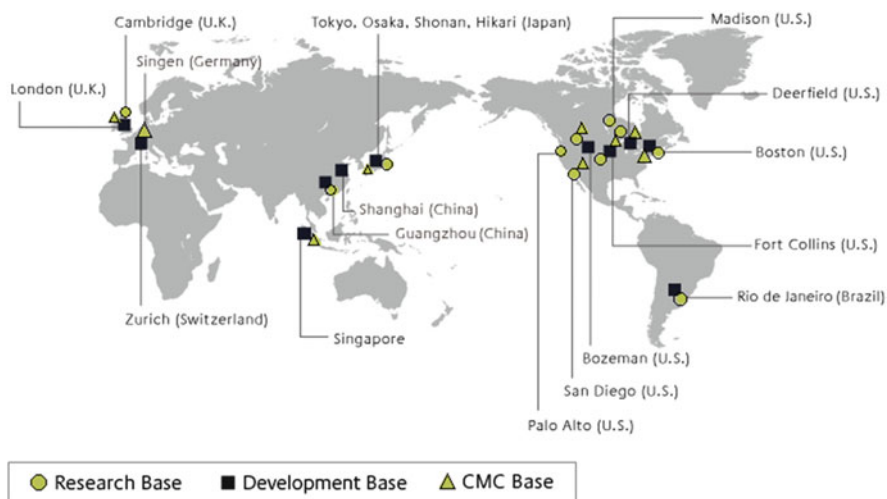


Fig. 7.2 The global R&D network of Takeda. Source: Takeda website 2015. CMC (Chemistry, Manufacturing and Control) research supports compound characterization, process development, pharmaceutical manufacturing, and analytical testing

R&D is conducted easily, nor is it a country in which intellectual property—the main result of R&D work—is well protected.

7.2 New Opportunities for Drug Development in China

The Healthcare Context in China

China is no longer a mystique country closed off to foreigners, but it is still very much misunderstood. Under almost constant reform mode, the China's economy was opened up in the 1980s, picked up speed in the 1990s when it became a major destination for manufacturing investments, excelled at growth rates beyond 13% and 14% in the 2000s, when it also became attractive for R&D, but in the wake of the economic crisis of 2008 it slowed down to what is now called a “new normal” economic growth of 6–7%. It passed Japan as the second largest economy in the world in 2010, and in 2015 its GDP was US\$11 trillion, behind the U.S. at about US\$18 trillion.

Despite a growing middle class (whose definition is ambiguous in China), most of China is still a developing country, which translates into great tensions about healthcare services needed and wanted, and what role the pharmaceutical industry can play in this context. Improved living conditions further mean that China's population is aging fast, with the share of the population aged 65 or older to double to about 13% by 2025. China's one-child policy, although relaxed to a two-child policy in 2015, led to wealth being distributed among fewer children and family

members, which means that more earnings are disposable for life-style and health-related products. Furthermore, as China westernizes, its disease profile will become more and more comparable with the Western world, including afflictions such as hypertension, cancer, diabetes, etc., for which multinational companies already have developed drugs and therapies.

With a population of more than 1.3 billion, China presents a huge market opportunity as it is. A rapidly aging population (in 2015, an estimated 131 million people are aged 65 or over), coupled with new afflictions resulting from air and water pollution, pushes the emerging healthcare system to the brink, and the solutions required will need to concerted effort of government, pharmaceutical industry, and healthcare institutions. Administrative hurdles, low healthcare spending, the lack of intellectual property protection and the poor distribution network infrastructure remain the biggest challenges.

Major pharmaceutical companies pursue aggressive growth strategies and try to benefit from the Chinese market in the longer term. They invest in the sourcing of active ingredients, research and development, and the production and selling of generic and proprietary drugs. In 2002, China was still a low-tiered market of about US\$6 billion in total. Pharmaceutical sales grew at a CAGR of 26% between 2007 and 2010, exceeding overall growth in GDP and overall healthcare expenditure (Deloitte 2011). It passed US\$100 billion in 2015 and is estimated to grow to US\$200 billion in 2020. China has the world's fastest-growing over-the-counter (OTC) drug market and is already the second largest pharmaceutical market worldwide.

Chinese Pharma

Pharmaceutical sales amounted to 17% of total health expenditures in 2015, or US\$78 per person. Generics accounted for 64% of total sales, patented drugs only 22% (ITA 2016). The generics market is dominated by low cost domestic producers. Webber (2005) put their number at approximately 6800 Chinese pharmaceutical companies, of which 5000 produced medicines (small-molecule generics and biotech products, i.e. not including herbal medicines or traditional Chinese medicines) and the remainder were involved in pharmaceutical-related activities such as packaging and equipment supply. A large share of them are merely producers of raw materials (Wang and von Zedtwitz 2005). By 2015, this market was still highly fragmented, with 5000 domestic companies in operation, of which the top 100 accounting for only one third of the total market (ITA 2016). Government and Chinese FDA (CFDA) policies have been expected to weed out those not in compliance with GMP (good manufacturing process) practices, but have made only limited progress. The 2010 Strategic Emerging Industries initiative plans to create national champions, and policies are being put in place that seem to favor domestic over foreign companies (Prud'homme 2016; ITA 2016).

Chinese manufacturers are very strong in their ability to copy foreign drugs, sometimes selling them under foreign labels. The vast majority of the 3000–4000

pharmaceutical products manufactured in China are copies of foreign products, either legal generics or illegal counterfeits. They serve a worldwide counterfeit market estimated to exceed US\$24 billion in 2014 alone (Philipp 2014), with 79% of counterfeit pharmaceuticals seized by U.S. authorities in 2008 coming from China. The situation is complex to control: In addition to the almost 5000 Chinese companies involved in medicine manufacturing, there are 400,000 retail pharmacy shops, and 29,000 firms involved in shipping medical products (Philipp 2014). China lacks effective regulatory control over the manufacture and distribution of active pharmaceutical ingredients (APIs). Chemical manufacturers only need to register with the CFDA if their product is intended for medical use. The CFDA has no authority to regulate them if they declare otherwise, and the CFDA does not monitor or inspect APIs intended for export (ITA 2016). For many Chinese companies, the term ‘R&D’ refers mainly to the production of additional generic products particularly for China—in terms of strengths, dosage forms and even specific compounds (Webber 2005). As of 2016, what constitutes a “new drug” was still of unclear definition and subject to policy debates (ITA 2016).

In 2015, Tu Youyou won the first Nobel Prize awarded to a Chinese in Physiology or Medicine for her discovery of a novel Malaria therapy, artemisinin. While Traditional Chinese Medicine (TCM) has been a staple in China for a long time, it put the spotlight on the uneasy relationship between western and Chinese approaches to medicine (many Chinese doctors prescribe TCM side-by-side with western ethical drugs). More than 8000 (including different dosage forms) traditional Chinese medicines (TCM) are manufactured and sold. With few market entry barriers, there were over 2500 TCM companies in China. TCM accounts for more than 20% of sales and is particularly strong in rural areas. TCM drugs make up 39% of the Essential Drug List (EDL) and 46% of the National Drug Reimbursement List (NDRL) (Export 2016).

In the Chinese view, TCM has already proved itself to be effective in curing many kinds of diseases, having “gone through thousands of years of clinical trials” (Guo 2016, quoting Wang Guangji, a deputy to the National People’s Congress (NPC) and former vice president of China Pharmaceutical University who specialized in western medicine): “But important terms like Yin (substance) and Yang (energy), whose balance are essential for harmonious operation of the body, according to traditional Chinese medicine, would hardly be accepted by foreigners.”

Western pharmaceutical firms shy away from TCM R&D, as it is difficult to isolate single, scientifically testable compounds (Waldmeir 2015). According to Ye Yang, deputy director of Shanghai Institute of Materia Medica, “to get a single compound out of a single plant, like in the case of artemisinin, took so many years. In traditional herbal medicine [you might have] 500–600 compounds working together. We don’t have the technology to follow all of them to see how they are working individually and together.”

The Chinese government promotes TCM, and several government departments are guiding the TCM industry’s attempts to modernize. According to Webber (2005), the Chinese authorities have identified two tracks for developing TCM R&D. The first is through purification and standardization to meet global standards

and remove impurities such as pesticides and heavy metals. The second track is to utilize TCM as a starting point for producing *novel* medicines. This may be through the identification and purification of the active element(s) (often complex molecules) or the discovery and development of small molecules which mimic the activity of the original TCM. Liu and Xiao (2002) found that about 140 new drugs have originated directly or indirectly from Chinese medicinal plants by means of modern scientific methods.

The Chinese government has also set clear focus on certain areas of biotech research, especially genomics research. In 1998, the Ministry of Science and Technology established the Chinese National Human Genome Centre based in Beijing and Shanghai, and the Beijing Institute of Genomics, as centers of excellence for genome sequencing and analysis, thus enabling China to join the International Human Genome Sequencing Consortium in 1999, in which China played a significant part. China now is on par with major international research leaders in areas such as gene mapping, transgenic technology for animals and plants, gene therapy technology, stem cell research, gene chips and gene research of some major diseases (Webber 2005). The country has several world-class scientific biomedical institutions—the North and South Genome Centers, the Institute of Materia Medica, Tsinghua and Beijing Universities, for example. China also has some 200 research institutes for biotechnology and more than 30 of the 150 key state laboratories in biopharmaceutical-related areas.

In China, the domestic pharmaceutical research and development environment is still dominated by universities and scientific institutes rather than pharmaceutical enterprises. The industrialization of pharmaceutical research and biotechnology still lags the Western world, but is catching up quickly as well (Shi et al. 2014). For instance, **Beijing Genomics Institute** (BGI) was founded in 1999 in Beijing as a non-governmental independent research institute in order to participate in the Human Genome Project as China's representative. It moved to Hangzhou when the local municipal government picked up the expiring HGP funding. In 2002, it sequenced the rice genome, and in 2003 it decoded the SARS virus genome and developed a detection kit. It moved to Shenzhen as the first citizen-managed, non-profit research institution in China in 2007, and in 2008 published the first complete human genome of an Asian individual. In 2010 it established offices in Cambridge (Mass.), and Copenhagen. In 2013 it worked with 17 of the top-20 pharmaceutical companies, and later that year bought Complete Genomics, based in Mountain View, California. In addition to research offices in all the major cities in China, it also has research collaborations or centers at UC Davies in California, Vancouver, Philadelphia, and Hong Kong, as well as a genetic testing facility in Prague, Czechia. BGI has lowered the price for a complete human genome to under US\$3000, is the world's largest gene sequencer, and is now regarded as one of the most advanced high-tech startups from China.

WuXi PharmaTech is a biopharmaceutical R&D services firm headquartered in Shanghai. Founded in 2000, WuXi established services in synthetic chemistry in 2001, manufacturing process development in 2003, research manufacturing in 2004, bioanalytical services in 2005, service biology in 2006, and toxicology and

formulation in 2007. In addition to opening several Chinese facilities, WuXi acquired the U.S.-based AppTec Laboratory Services in 2008, gaining expertise in medical device and biologics testing and facilities in St. Paul, Philadelphia, and Atlanta. As part of its continued internationalization, it also acquired Abgent, a San Diego-based manufacturer of antibodies for biological research and drug discovery, in 2011. WuXi also has R&D facilities and labs in Cambridge (Mass.), Plainsboro, Munich, Reykjavik, and in Israel and Korea. By end of 2016, WuXi had 14,000 employees in 26 R&D sites that served 2000 corporate clients.

Foreign Pharma in China

Foreign pharmaceutical companies have conducted R&D in China since the late 1990s, although in the earlier years the type of research done was very low key and part of larger studies that were rooted elsewhere. For instance, Roche had an R&D office in Shanghai long before it opened a dedicated R&D center in 2004. It was not until the mid-2000s that global pharma companies discovered China as a harbor for strategic R&D operations, perhaps a decade after global electronics, IT and automotive firms started to invest in R&D in China. There are several reasons for this relative late arrival in China:

- **Uncertain IP protection:** China had reintroduced patent law only as recently as 1985, and neither the general public nor the scientific ecosystem was used to developing, protecting, and honoring intellectual property. The courts, the legal system, and the police had little—if any—experience in dealing with IP cases. Chinese employees had little sensitivity for personal safety or safety as a public good. Tacit knowledge and knowledge that was pre-patent was not easy to secure and appropriate. Of course, these conditions affected also other industries, but in pharma—with its extremely long lead times—such unwanted exposure of technical knowledge is very harmful.
- **Fragmented nature and complexity of China's market:** 3700 domestic companies accounted for 75% of annual sales, of which 95% operated in the low value generics market (Dierks et al. 2013). Most needs are met by local generics, with only between 6% and 7% being patent-protected innovative drugs.
- **Price pressure:** 40% of China's healthcare budget was being spent on medicine compared with 10–12% in Western countries, leading to considerable political pressure to reduce prices (KnowledgeWharton 2013).

On the other hand, there were also several strong China-specific reasons to consider R&D in China:

- **Quick development of a middle-income market demanding medicines for their evolving needs.** These needs stem from rising life expectancy, pollution, and enhanced abilities to detect and diagnose diseases.

- Understanding the uniqueness of the genomics and metabolomics of the Chinese population gives competitive leverage to domestic R&D entrants.
- Access to natural products in China as sources for new chemical entities (NCEs). Newman et al. (2003) calculated that about 60% of nearly 900 NCEs could be traced back to natural products. One famous example is Lipitor, a statin first discovered in natural sources with sales exceeding US\$10 billion annually.
- Access and research on TCM: China-based innovations include Artemisinin, invented in China using sweet wormwood and hailed as a miracle malaria drug, Sobuzoxan, an anti-tumor drug, and Huperzine A (HupA), a novel alkaloid isolated from a Chinese medicinal herb, which improves memory deficiencies in Alzheimer patients.

Testing the waters for captive local R&D operations often begins with R&D collaborations. GlaxoSmithKline (GSK), for instance, invested over US\$10 million in cooperative R&D with Chinese research institutions since the mid-1990s. Novartis started a collaboration with the Shanghai Institute of Materia Medica (SIMM), with the objective of isolating compounds from Chinese medicinal plants for Novartis to further screen and identify lead compounds. After an initial phase and US\$2 million in funding, training and equipment, by 2004 SIMM had isolated more than 1800 compounds from natural herbs covering immunology, oncology, diabetes and the central nervous system.

Other braved the uncertain conditions and started dedicated R&D centers early. In 1997, Novozymes opened an R&D center in the Zhongguancun Science Park in Beijing. Costing 10 million €, the facility focused on the customized development of enzymes and processes for the Chinese market. Roche opened a new R&D center for 40 chemists in Zhangjiang High-Tech Park and established R&D alliances with the state-owned genomics centers in Shanghai and Beijing, to conduct research in the genetic predisposition to diseases such as diabetes and Alzheimer's. Local R&D enabled these foreign pharma companies to enter more credibly into a dialogue with authorities and opinion leaders in the country, which ultimately is good for business in China.

By the mid-2000s, the IP situation in China was better understood, other foreign multinationals had been successful with captive R&D in China, and some of pharma's R&D pioneers seemed to succeed with R&D in China as well. As a result, pharma companies started to invest more strategically in R&D in China, in the expectation to access the natural resource base in China, and to tap into an increasingly large body of medical researchers and pharmaceutical scientists. Also, China is also an attractive base for clinical research, given that there were more than 300,000 hospitals and healthcare facilities. Table 7.3 presents an overview of this early stage of R&D setup in China.

In July 2004, GlaxoSmithKline China set up an OTC (over-the-counter) medicines R&D center at Tianjin Smith Kline & French Laboratories, a joint venture funded by GlaxoSmithKline. Its aim: to excel in creating innovative science-based products to meet consumer needs and support the joint venture's vision of becoming the premier OTC company in China. Pfizer set up an R&D center in Shanghai

Table 7.3 Initial wave of foreign pharmaceutical R&D centers in China

Year	MNC	Location	Investment	Objective
1997	Novozymes	Beijing	10 mn €	Enzymes
1998	Roche	Shanghai	40 scientists	Clinical R&D, factory support, genomics
2001	Servier	Beijing	n/a	Develop potential value for TCM
2002	Novo Nordisk	Beijing	n/a	General biotech research
2003	AstraZeneca	Shanghai	First year: US\$4 mn	Clinical research; Collaboration with Health & Medical Institute in China; Localize therapeutic methods
2003	Eli Lilly	Shanghai	>100 scientists	Combining different kinds of organic substance for new drugs
2004	Roche	Shanghai	50 scientists	Phase I: Chemical drugs; analyzing compound structures Phase II: TCM & genetic engineering
2004	GSK	Tianjin	16 scientists	20 new OTC products over 3 years
2004	Johnson & Johnson	Shanghai	n/a	Develop medications suitable for Chinese and Asians
2005	Pfizer	Shanghai	US\$25 mn	Trial protocol design and assessment
2006	Novartis	Shanghai	US\$100 mn, 400 scientists	Cancer & infectious diseases

Source: SMIE Medicine Information and own research

focusing on developing trial protocol design and assessment of trial results, and Novartis built a US\$100 million drug discovery research center in Shanghai in 2006. The research facility, which expanded to 400 scientists by 2008, focused initially on discovering medicines to treat cancers caused by infections, which make up a considerable proportion of the cancer cases diagnosed in China. Some smaller biotech firms also started local R&D in China, for instance BiColl in Shanghai. While pharma R&D focused initially on Shanghai and Beijing, other industries explored locations in second-tier cities and interior China, a trend that pharma R&D is following only slowly. Even globally, pharma R&D tends to be more concentrated in few hubs, and there is no reason to assume this should be different in China (Fig. 7.3).

In the years after the global financial crisis China benefited from its domestic stimulus program, but as of 2013, China's GDP growth has marked slowed down. This is especially true for the already well developed provinces along the Pacific shoreline, while many of the central provinces continue to enjoy high growth rates, albeit from a lower base level (according to the National Bureau of Statistics in China). Cities in those provinces—e.g., Chengdu, Chongqing, and Wuhan—are expected to become more attractive as hosts for pharma R&D.

At the same time, foreign pharma companies continued to consolidate and expand R&D in their original R&D locations. **Roche**, which has occupied the same location in Shanghai since 1997, poured in RMB 1.8 billion (about US\$300 million) to expand to 19 buildings covering 70,000 square meters and employing 1800 professionals. Shanghai became its third most important strategic R&D site worldwide, with major projects being run from China globally. Construction is under way

Fig. 7.3 Locations of foreign and domestic pharmaceutical R&D centers in China.
Source: GLORAD database (as of 2016)



for the Roche Innovation Campus Shanghai, as is a diagnostic manufacturing facility in Suzhou; these projects cost another US\$450 million. **Novartis**, which started with a 5000-square meter facility in 2006, invested US\$100 million to build a dedicated R&D facility for 400 scientists in 2007. In 2016, it opened a US\$1 billion R&D center in Shanghai, banking on the expectation that the Chinese government's own increased spending on biomedical research and training will deliver talented and highly educated researchers. A drug for liver fibrosis was fully discovered in China and brought into the late clinical stages, with hopes running high that it will be a high-performance global drug soon.

AstraZeneca doubled down on its 2003 start in clinical research in China and in 2007 added a US\$100 million investment in its new AstraZeneca Innovation Center in Shanghai. The center's initial research mandate was "In China, For China," but it has assumed a broader mission as a full-fledged discovery center focusing on diseases more prevalent in Asia. In 2015 it made available US\$150 as an initial investment in a widened collaboration with WuXi Apptec (so renamed after the merger of Wuxi Pharmatech with Apptec Laboratory Services) to produce innovative biological medicines in China, with several hundred million US\$ earmarked for further R&D investments in China across the board.

It is important to note that pharma R&D in China is still very much in its early stages, and it is far from certain that the upfront multibillion-dollar investment will indeed deliver the expected payoffs. Research by Grimes and Miozzo (2015) showed that only 1.78% of the 9543 patents granted by the USPTO between 2004 and 2014 by the top big pharma companies had Chinese citations and only 1.44% had Chinese inventors. Of the latter, Roche accounted for 65% and Novartis for 18%. China's share of biotechnology patents was also at around 1%, which is the same level as its overall USPTO share. While China is often credited with speed and rapid development, many of the problems that kept pharma investment away in the 1990s are perhaps still present, or at least inadequately addressed (see Table 7.4). AstraZeneca's

Table 7.4 12 challenges big pharma faces in China

#	Challenge	Explanation
1	China's size and heterogeneity	There is not one China but 1000 Chinas. A level 3a hospital in a coastal tier 1 city is unrecognizable from a rural polyclinic in Western China
2	Public sector complexity	No 'quick fixes', too many stakeholders involved in public healthcare provision
3	Poor patient-physician relationships	Absence of gatekeepers to control public sector referrals, leading to long waiting times for appointments, high patient dissatisfaction, deterioration in doctor-patient relationships and sub-optimal patient outcomes. Medical practice "a high-risk job"
4	Rationing of high cost drugs; patient self-pay	China's public hospitals treat more patients with less budget. Patients often pay much of the cost of treatment themselves, thus deferring treatment until the condition is very severe
5	Undeveloped private sector	Negative attitudes towards private healthcare, which makes it very difficult for the private sector to attract good doctors, who feel the public hospitals offer them better career progression opportunities
6	Slow drug approvals	CFDA backlog: In 2015, over 18,000 drug applications had yet to be reviewed. Worse for foreign pharma: Phase III trials to be conducted in China regardless of where the product was previously launched
7	Medical tourism and gray market imports	Drugs are expensive in China, and often available much later than abroad. E.g., drugs are the most purchased items by Chinese tourist in Japan
8	Scrutiny on international companies	China's anti-corruption initiatives make pharma companies very tentative when operating in China. Compliance with China specific regulations—including anti-commercial bribing and anti-unfair competition law, is critical
9	Preferential conditions for domestic players	China's domestic pharma are not only less subject to the restrictive compliance regulations but also given preferential access to drug lists—such as the National Essential Drug List (NEDL)
10	Limited access to time-poor physicians	Time for physicians to engage with medical reps or educate themselves on new treatments is extremely limited—especially important in a country that values personal connections ('guanxi')
11	TCM Competition	203 of the 520 compounds on the 2012 edition of the NEDL were TCMS
12	Economic slowdown	For patients, economic slowdown means everything costly becomes even costlier. For foreign pharma, RMB devaluation means China is now a cheaper market to invest in, but also a less attractive one

Source: Marc Yates, eyeforpharma, 16 Nov 2015

former head of R&D in Asia noted that because of China's shortage of experienced toxicologists, pathologists, statisticians and clinicians, it could take several decades before China's pharmaceutical ecosystem was fully developed (McKinsey 2012).

The question is whether economic growth coupled with the shaping of a positive environment will encourage increasing investment into innovative pharmaceutical R&D in China. The global pharma companies are well advised to explore the China option carefully and systematically, given the dangers involved, but certainly they are advised to take this opportunity seriously.

7.3 Reverse Innovation in Healthcare

Reverse innovation is a new paradigm of global innovation describing the reverse flow of innovations from emerging countries to the established industrialized markets of the United States, Europe and Japan (Govindarajan and Ramamurti 2011). It captures not only innovations first introduced in such markets but also those developed there (von Zedtwitz et al. 2015), and it also includes truly indigenous sources of innovation rather than primarily foreign-invested subsidiaries of technology-intensive multinationals in those regions (Corsi and von Zedtwitz 2016). While often associated with low-cost solutions to problems in high-priced markets (Zeschky et al. 2014), reverse innovations are not just cost-efficient products gone global but create value-added benefits specific to targeted market segments in both emerging and mature markets.

Reverse innovations have quickly attracted the attention of healthcare and pharmaceutical experts (Syed et al. 2013), primarily because healthcare costs have been escalating in advanced country markets, and emerging market countries solutions promise a more cost-efficient containment approach to many healthcare-related problems in the West (Crisp 2010). As the largest emerging country, China is the "usual suspect" as a source of such reverse innovations, but other countries and even continents (e.g., Africa) are making substantial contributions as well (see e.g., Harris et al. 2015). India has already developed a reputation for excellent yet affordable healthcare (e.g., the famous Aravind Eye Hospital), adding to its growing expertise in frugal innovation (Weyrauch and Herstatt 2016).

The list of examples illustrating the potential that reverse innovation can have on healthcare in general and the pharmaceutical industry in particular is growing. Among the first instances of reverse innovation mentioned ever are medical devices: GE's Mac400 Electrocardiogram from India, or GE's portable ultrasound devices developed in China. But medicines are also increasingly coming from emerging market countries: Vicks Honey Cough drops were developed by P&G in their Caracas R&D center, initially for their Latin American market, only to see it do well with large populations in the U.S. and Europe as well. Oncovin is a drug that Eli Lilly developed in the U.S. based on active ingredients found—and initial research done—in Madagascar. Most famously perhaps is Artemisin, a key ingredient in Chinese TCM, that was developed further as an anti-malaria drug, and ultimately led

to the 2015 Nobel Prize for Medicine to be awarded to a Chinese researcher, Tu Youyou.

Innovations from emerging markets carry the stigma of being ‘low cost’ or ‘geared towards the needs of under-developed civilizations’ (for a summary of roadblocks against reverse innovation, see Hadengue et al. 2017) and often face steep adoption and acceptance difficulties (DePasse and Lee 2013). Western policymakers and governmental institutions have therefore launched several initiatives at making the reverse transfer of emerging market solutions (from so-called LIC low-income countries) more predictable and more systematic:

- Prize competitions: Snowdon et al. (2015) reported the results of an open competition for healthcare solutions from developing or emerging countries, with the winner to be awarded US\$50,000 for further financing their project. A committee evaluated all 12 submitted projects on the basis of seven weighted criteria. Apart from the winning innovation being supported through the prize money, the competing entries also benefited from project-specific feedback, and through media exposure the public was made aware of the potential of reverse innovation in health care.
- Crossover identifications: DePasse and Lee (2013) described a four-step model to transfer reverse innovations that includes a common problem identification in a LIC, a dissemination analysis in that country, a crossover proposal, and subsequent dissemination in a high-income country (HIC). The trick is not only to execute that crossover effectively, but also to identify suitable reverse innovation candidates and to support dissemination in the home country.
- Scoring assessments: Battacharaya et al. (2017) developed a two-step scoring system with eight assessment criteria, mostly for use by policymakers, public institutions or funding agencies. The purpose of this assessment is to identify potential reverse innovations and qualify them for their suitability to be transferred and applicability to an unmet need in the home country.

In conclusion, the potential of reverse innovation in pharmaceuticals is still difficult to estimate, but the healthcare sector has taken a strong interest in considering any emerging solution from emerging market countries due to the mounting cost pressures in industrialized nations. Pharmaceutical multinational firms that already have R&D centers in those emerging markets are well positioned to leverage their reach into different population groups not only as patient pools but also as sources of innovation, and ultimately may play an important role in acting as conduits of reverse innovation in their home countries.

7.4 Conclusions

R&D in multinational companies has developed from centralized and geographically confined towards distributed and open structures. The pharmaceutical industry is one of the most advanced in terms of R&D internationalization, and one of the most

specific when it comes to regulation and significance of science and technology. Still, maintaining a well-balanced locally responsive and globally efficient R&D network is one of the great challenges of multinational organizations. Rapidly evolving biotech firms and new pharma entrants (whether from emerging economies or in the U.S., Europe or Japan) repeat those growing pains that big pharma companies such as Novartis, Pfizer or Takeda have experienced since the 1980s.

The key lessons learned for managing global R&D in the pharmaceutical industry can be classified as follows:

- Localization of management resources;
- Flat and flexible organizations;
- Introduction of local culture of innovation and know-how;
- Challenging projects coupled with bottom-up creativity;
- Personal interactions more important in decentralized R&D;
- Synchronization of international drug development by means of transnational project management in order to shorten R&D cycles;
- Worldwide integrated R&D data management;
- Acquisition of external ideas and projects as important as internal R&D;
- International teams require new organizations;
- Manage platforms, not individual R&D projects;
- Better inclusion and leverage of local university and national research programs;
- Effective management of local open innovation partners;
- Foster networking and collaboration.

In conclusion, transnational R&D management is a key ingredient to success, and the high stakes of the drug approval and medical safety have made the pharmaceutical innovation pipeline one of the best understood R&D engines (Gassmann and von Zedtwitz 2003b). However, there is still untapped potential to improve this engine with new technologies, new managerial approaches, and new scientific talent drawn from countries around the world.