MITTELSTAND GLOBAL
HEALTH MADE IN GERMANY

GTAI GERMANY TRADE & INVEST

Medical Biotechnology

Profiling China: Markets and Stakeholders

Contents

5 **Executive summary**

6 **Introduction**

6 China – a centrally planned economy
8 Structure of and sources for this publication

9 **Industry support**

9 HEALTH MADE IN GERMANY
9 Further institutions and programs
12 Industry associations

16 **Healthcare in China**

16 China – a “state capitalist” economy
16 Healthcare expenditure and health insurance
16 Healthcare services
17 Medical Market Product Turnover 2015
17 Examples for innovations in the course of “125”
17 Targets for healthcare and medical products in “135”
18 China’s pharmaceutical industry

20 **Infrastructure**

20 General
20 Science, research and higher education
22 Science parks
23 Finance

24 **Clusters for China's medical markets**

24 General introduction
25 The northeastern cluster: capital region
27 The eastern cluster: business and innovation around Shanghai
29 The southern cluster: booming southern metropolis near Hong Kong
30 Rise in the west: Chengdu, Chongqing and the western cluster
31 Concluding remarks

32 **Selected Biopharmaceutical Product Application Areas**

32 Therapeutic monoclonal antibodies
36 Blood products and other therapeutic proteins
41 Human vaccines
44 Anti-infectives
48 In vitro diagnostics (IVD)
50 "Precision medicine"
52 Stem cell technology

56 **Rules to the game**

56 Introduction
56 Registration of drugs
58 GMP certification
59 Intellectual property
60 Technology transfer
62 Contractual issues

63 **Stakeholders**

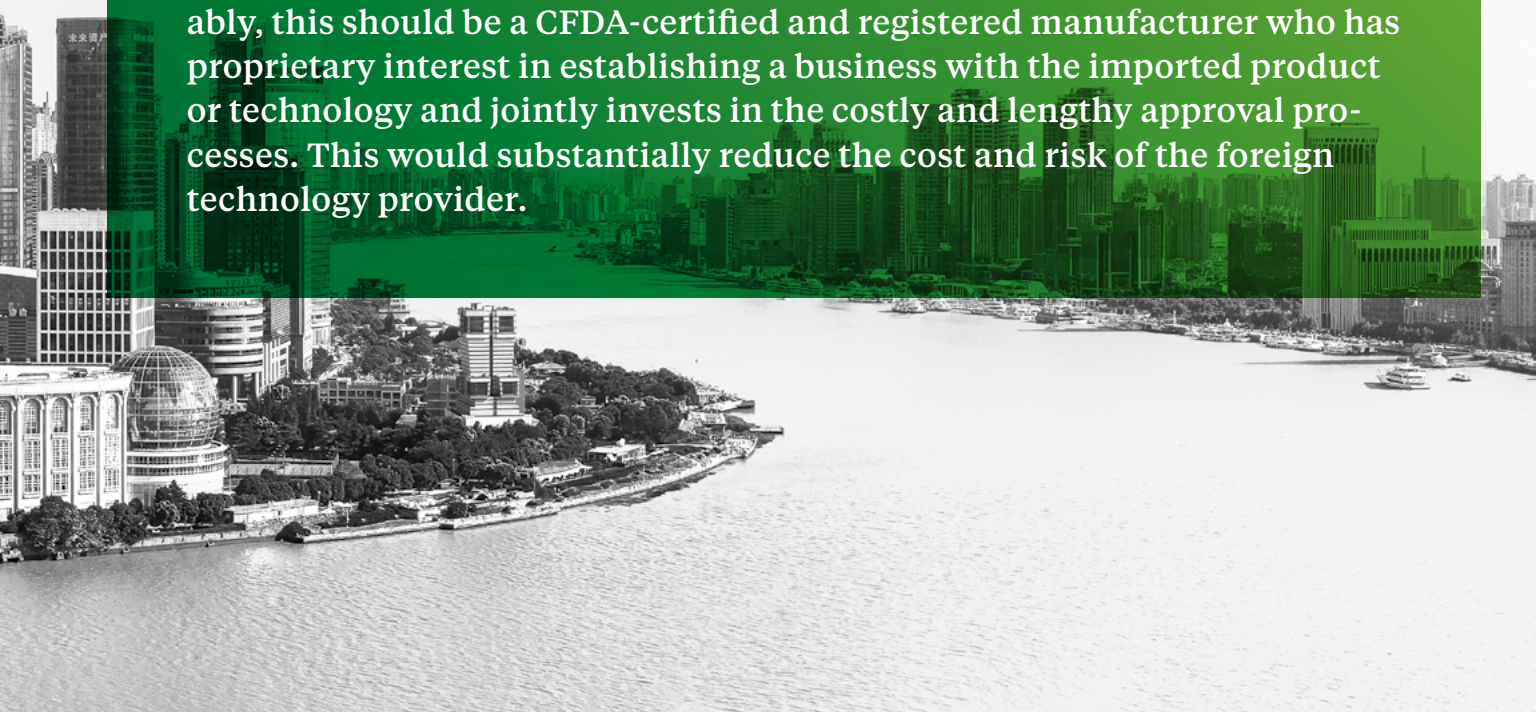
64 APPENDIX

66 IMPRINT

Executive summary

In China's centrally planned economy, improvements in health services are a major national target, which is documented in the "Healthy China 2030" plan. In this framework, the government attempts to create a pharmaceutical industry which is globally competitive and complies in quality and reach-out with the "Made in China 2025" program. To this end, the 13th five-year plan (2016–2020) calls for the formation of four cluster regions (Northeast: Beijing-Tianjin-Hebei-Liaoning. East: Shanghai-Jiangsu-Zhejiang. South: Guangdong. West: Sichuan-Chongqing-Hubei-Shaanxi) which will eventually comprise 80% of China's pharmaceutical research and manufacturing. As of 2016, these four regions already provide some 60% of the pertinent infrastructure in science, manufacturing, health services, and capital supply. Biopharmaceuticals are a minor segment of the Chinese drug market and mostly offered by international and foreign-based companies, whereas phytochemicals ("Traditional Chinese Medicine" – TCM) and telemedicine are indigenous elements of China's future healthcare activities.

While both, the Chinese industry and the government are eager to import foreign technology, access for foreign technology providers is hampered by information barriers (limited disclosures), language barriers and centrally controlled "rules to the game" (e. g., by the Chinese FDA). For SMEs, the easiest approach to China's large and expanding markets is by identifying a suitable mediator, e. g., a Chinese partner company. Preferably, this should be a CFDA-certified and registered manufacturer who has proprietary interest in establishing a business with the imported product or technology and jointly invests in the costly and lengthy approval processes. This would substantially reduce the cost and risk of the foreign technology provider.



Introduction

China – a centrally planned economy

China is the world's most populous nation, with nearly 1.4 billion inhabitants, who live in an area the size of the USA. Until very recently, China's economy has shown a two-digit growth every year, and its GDP has meanwhile surpassed all industrialized nations except the USA.

Economic development throughout China is, however, not well balanced: as shown in Fig. 1.1, 25% of China's population who all live in the coastal region (green) contribute over 50% to China's GDP, whereas the inland provinces with 65% of the population (dark grey) share only 30%. Three large but peripheral states (light grey) contribute 10% to the country's GDP and population.

Fig. 1.1 GDP distribution of China's Provinces[1]
based on: F. Lemoine , S. Poncet & D. Ünal, Panorama du CEPII, N° 2014-A-02 – March 2014

Along the coastal region, three large conurbation zones (Beijing – Tianjin – Hebei, Shanghai – Jiangsu – Zhejiang and Guangzhou – Shenzhen) account for nearly one third (32% in 2014 figures) of China's GDP. This uneven distribution of economic performance translates into political power, capital concentration and technology development: the coastal zones are China's major engines for innovation and growth. This situation also creates rifts; symptoms are 250 million migrant workers and heavy pollution in the coastal areas. China's western provinces tend to depopulate, average age increases, and health services, often based on "migrant doctors", are weak. Among the government's answers to these challenges are attempts to urbanize the country – from 1985 to 2015, China's population living in cities has quadrupled to over 700 million and is expected to reach nearly 1 billion by 2050.[1] Through the "road and belt initiative",[2] this master plan reaches out even further than China's remote provinces.

Untiring efforts to establish science and technology as a foundation for growth are parts of a second master plan ("Made in China 2025").[3] This relates to building an excellent infrastructure for higher education and research as much as launching independent technology such as the BeiDou satellite navigation system,[4] which by 2020 will support IT-related tasks throughout China, e. g. telemedicine support for health services in remote locations. In terms of its national R&D budget (¥ 1.43 T in 2014),[5] China has already surpassed all European nations and Japan.[6] It is now challenging the USA and strives to become the world's technology leader by 2049, the centenary of China's Communist Party's rise to power. Key technologies presently addressed (see box 2.1) also include issues related to healthcare and medical biotechnology, as China's leaders state in their "Healthy China 2030" plan[7] that medical services still need to catch up to Western standards.

Box 2.1

Priority science projects in China's 13th five-year plan (2016–2020)

bold : issues related to medical biotechnology

- Quantum communications and **computation**
- **Brain research**
- National cyberspace security
- Deep space exploration
- Clean, efficient use of coal
- Industrial, **medical** and military **robots**
- **Applications of gene science**
- **Big data applications**
- Deep-sea experimental platform
- New Arctic observatory, Antarctic station

These brief notes may suffice to show that China's leaders plan for future growth. As it will be shown in section 4, healthcare and medical biotechnology are among the focus areas. Consequently, European small and medium-sized enterprises (SMEs) who are looking for growth should include China as an option to expand their businesses. However, access to the Chinese markets meets not a small number of hurdles.

Information retrieval may be on top, as spoken and written Chinese, not English, is the preferred language of communication. Internet access via Google is not possible, and the Chinese search engine Baidu is not only government-controlled but mostly in Chinese language, usually without English mirror sites (however, online-translation through the Youdao system, *fanyi.youdao.com*, is of good quality). Other hurdles for market access consist in the registration of products, rules on company foundations and intellectual property, to name just a few.

It is the objective of this guide to provide the reader with a brief survey of the Chinese landscape and stakeholders in medical biotechnology. In addition, "rules to the game" will be outlined, to be observed before taking a step into this booming and expanding market.

Structure of and sources for this publication

There are several institutions in Europe which offer support for SMEs who prepare for a market entry in China. This will be the topic of section 3.

China's healthcare system and its pharmaceutical industry will be covered in section 4. China's infrastructure for science, technology and capital investments will be the subject of section 5, with special reference to health-related institutions.

In section 6, the four national clusters earmarked as future hubs for China's pharmaceutical industry will be discussed in detail, as will be the structures already in place within and outside these four regions. Seven feature articles in section 7 cover key biological products, in particular those certified by the Chinese FDA (CFDA) as well as manufacturers of such products. As there were about 13,000 drug producers in China by the end of 2015, a selection of the most relevant companies had to be made. The criteria for the selection will be outlined in section 4 "China's health-related industry".

Section 8 sums up the "rules to the game" when entering the Chinese medical markets. This comprises government regulations for product registration including the role of Chinese standards, but also general considerations in regard to intellectual property in China, and contractual issues. Section 9 lists stakeholders involved in China's medical biotechnology such as governmental and non-governmental agencies.

Key Chinese documents used are draft reports for the State Council ("十三五" 战略性新兴产业培育与发展规划咨询研究, "135", Consultation and Research on Strategic Emerging Industry Cultivation and Development Plan)[8] from the Biotechnology committee of the Chinese Academies (2015), covering the period from 2011 to 2015 and containing 10 pages on the successes and failures in medical biotechnology during this period, and the Chinese Government Report on the targets for the 13th Five-Years' Plan ("135", covering 2016 – 2020),[9] "十三五" 生物产业重点发展方向. 100 pages in this report are devoted to the strategies for biomedical technology.

In addition, hundreds of government announcements and press releases published by, e. g., the Chinese Academy of Sciences or the China Bio Organization, which deal with biotechnology in general and precision medicine (personalized medicine), were used, all in Chinese language.

Information about China is affluent, in Chinese language.

Industry support

Germany and China work closely together in the field of life sciences and beyond. To extend and consolidate this cooperation and further ensure prosperous bilateral affairs, several German institutions have initiated instruments and programs for trade promotion, political dialogue and technology exchange.

HEALTH MADE IN GERMANY

HEALTH MADE IN GERMANY is an initiative of Germany's Federal Ministry for Economic Affairs and Energy. Its mission is to promote the German healthcare industry worldwide and connect it with international partners.

HEALTH MADE IN GERMANY supports the export activities of the German health industry with information about health markets worldwide. To improve export conditions for German companies, HEALTH MADE IN GERMANY is initiating a dialogue with political decision-makers in target markets. It is also representing German companies at events abroad.

The initiative informs foreign companies and individuals who are interested in doing business in and with the German healthcare industry. It does this by organizing events in Germany and abroad. Another feature of HEALTH MADE IN GERMANY is its English-language website *www.health-made-in-germany.com*. The website provides news, information and the latest on exhibitions, trade missions, and the German healthcare market in general.

In order to ensure that it is meeting the industry's specific marketing needs, HEALTH MADE IN GERMANY works in close cooperation with the relevant industry associations that represent the specific sectors within the German healthcare industry: pharmaceuticals, medical technology, medical biotechnology and digital health.

HEALTH MADE IN GERMANY is implemented by Germany Trade & Invest, the economic development agency of the Federal Republic of Germany.

Get in touch with us to learn more about what HEALTH MADE IN GERMANY can do for you.

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Further institutions and programs

Germany Trade & Invest
www.gtai.de

Germany Trade & Invest (GTAI) is the economic development agency of the Federal Republic of Germany. With more than 50 offices in Germany and abroad, and its network of partners throughout the world, GTAI supports German companies setting up in foreign markets, promotes Germany as a business location and assists foreign companies setting up in Germany.

GTAI offers you the most important information on the economic climate, industries, business practices, law, customs, tenders and development projects in the People's Republic of China at a glance: *www.gtai.de/china*.

Auslandshandelskammern /
German Chambers of Commerce Abroad
www.china.ahk.de

The network of German Chambers of Commerce Abroad (AHKs), which consists of bilateral chambers of commerce abroad, delegations and representatives of German business, advises, consults and represents German companies worldwide that wish to develop or expand their business activities abroad. The AHKs are institutions of German foreign trade promotion. The Association of German Chambers of Commerce e.V. (DIHK) coordinates and continuously develops the network of German Chambers of Commerce Abroad. They are co-funded by the Federal Ministry for Economic Affairs and Energy (BMWi).

The AHKs represent German business interests in 130 locations in 90 countries. They are membership organizations with approximately 45,000 membership companies worldwide. At the same time, the German Chambers of Commerce Abroad represent links between cultures. They are at home in two mentalities and in numerous languages. They have served as reliable partners for companies in their activities abroad for over 120 years.

AHK Greater China, which is part of the worldwide network of German Chambers of Commerce Abroad (AHK), represents Sino-German bilateral business interests and offers comprehensive services through its business and membership platforms. It has five main offices and eight additional offices in Greater China and Germany.

Asien-Pazifik-Ausschuss der Deutschen Wirtschaft / Asia-Pacific Committee of German Business
www.asien-pazifik-ausschuss.de

The Asia-Pacific Committee of German Business (APA) voices the concerns of German business to policy-makers in Germany and the Asia-Pacific region. It is the most important German forum for the formulation and discussion of Asia-Pacific-related economic and political interests concerning German and Asian business affairs. The objective of the APA is to intensify co-operation with the Asia-Pacific countries and to foster mutual trade and investment. As global economic challenges and the economic importance of Asia-Pacific are increasing, APA's mission is to shape the future in times of change, together with Asia, based on the principles of partnership, equal opportunity and sustainable development.

OAV – German Asia-Pacific Business Association
www.oav.de

OAV offers the ideal platform for exchanging knowledge and experience across different industries, and offers members practical and comprehensive services, regardless of whether the member has experience operating in – or cooperating with – Asia, or has none.

Different event formats, initiatives and publications give its members the excellent opportunity to exchange knowledge on current issues surrounding Asia, to become better informed and to take advantage of the promising business potential of the Asia-Pacific region, a region experiencing dynamic growth. The main office is available to answer any of its members' queries regarding business in Asia, and facilitates business operations in the Asia-Pacific region.

German-Sino-Healthcare Group e.V.
www.gshcg.de

The German-Sino-Healthcare Group e.V. is a group of Chinese and German companies active in the healthcare sector. With their cooperation, its members pursue the goal of exchanging know-how and technologies with regard to an integrated healthcare system. With this intention specific projects are being developed and implemented by joint working groups.

The cooperation is carried out in the following areas:

- Hospital planning
- Hospital management
- Medical and hospital technology
- Medicines
- Research & development
- Education

The driving force for a strengthened cooperation is a joint steering committee, which is formed by representatives from both countries. The steering committee is also responsible for the implementation of the projects.

The German-Sino-Healthcare Group e.V. aims to establish a favorable framework for bilateral cooperation in all areas of healthcare. Its work is based on a framework agreement between the Federal Ministry for Economic Affairs and Energy of the Federal Republic for Germany (BMWi) and the National Development and Reform Commission of the People's Republic of China (NDRC).

Sino-German Life Science Platform
www.sino-german-platform.eu

Germany and China work closely together in the life sciences, from basic research to business cooperation. The aim of the Sino-German Life Science Platform is to support research and development of bilateral cooperation between research institutions and businesses, especially SMEs, and to strengthen this cooperation. The priorities are agreed on between the relevant actors of science, business and politics. The platform aims to provide information on the Life Science Landscape in both countries and to bring together stakeholders from both countries.

EU SME Centre
eusmecentre.org.cn

The EU SME Centre is a European Union initiative that provides a comprehensive range of support services to European small and medium-sized enterprises (SMEs), getting them ready to do business in China. Service offers include market reports, guidelines and case studies. Expert advise is offered as well as training programmes on drafting contracts and other important issues.

Industry associations

BIO Deutschland e. V.

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BIO DEUTSCHLAND
Biotechnologie-Industrie-Organisation Deutschland e. V.

The Biotechnologie-Industrie-Organisation Deutschland (BIO Deutschland) is an independent organization for innovative biotechnology companies in Germany. At its offices in Berlin, the association is developing and supporting an innovative industry based on modern life sciences. Founded in October 2004, BIO Deutschland currently has more than 320 member companies and several supporting members and sector partners. To support its members BIO Deutschland engages in a broad range of activities, including lobbying, public relations, and offering business development opportunities. Using a wide range of political initiatives, BIO Deutschland lobbies for improvements to legal parameters for innovative small and medium-sized enterprises. The association is also very active in a broad range of events with the aim of providing biotechnology with a platform for discussion and interaction. The German Biotechnology Days, a yearly national forum for biotechnology with more than 800 attendees, is organized jointly by BIO Deutschland, the Council of the German Bioregions and regional hosts.

BIO Deutschland is governed by a managing board of CEOs, CFOs and Managing Directors of companies that represent the German biotech sector. This committee comprehensively represents the various fields in the sector.

BIO Deutschland's member companies and their experts are organized in working groups that deal with a variety of subjects relevant to the biotech sector and small and medium sized companies. The groups meet regularly to discuss current developments, to draft position papers, to exchange ideas and to network. A total of twelve working groups and one network for communication and PR are active in the association.

Working groups for the following topics are currently installed:

- Big data and Bio-IT
- Diagnostics
- Finance and Taxation
- German-US Cooperation
- Licenses and Technical Contracts
- Regulatory Affairs
- Entrepreneurship, Innovation and Jobs
- Human Resources
- Industrial Bio-Economy
- Industrial Cell Technology
- Health Policy and Technology Transfer

BIO Deutschland is also partner of several other associations such as BVMW, The German Association for Small and Medium-sized Businesses, Biosingapore, bts – Biotechnology Student Initiative, BVIZ – German Association of Innovation, Technology and Business Incubation Centers, EAPB – European Association of Pharma Biotechnology, EUCOPE – European Confederation of Pharmaceutical Entrepreneurs, German- Sino Healthcare Group, ICLS- International Council for the Life Sciences and VBIO – German Life Sciences Association. Additionally BIO Deutschland administrates the head office of the Council of German Bioregions.

BIO Deutschland is Germany's biotechnology sector representative at the European association, EuropaBio, in Brussels. BIO Deutschland also collaborates closely with other biotech organizations in Europe and the USA in order to lobby for the interests of the sector in an internationally coordinated way. It is a founding member of the International Council of Biotechnology Associations (ICBA) and (affiliated) member of the Biotechnology Innovation Organization (BIO) USA.

Association of German Biotech Companies (VBU)
in DECHEMA e.V.

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VBU Association of German Biotechnology Companies

For a culture of innovation
Innovation is at the bottom of it all. Innovation has not only set the basis for the industrial development in Germany, it has also enabled for Germany to stay at the very top so far in the increasing global competition.

Scientific publications and patent registration are often taken as the indicator of the innovative power of a society. But this is not the whole truth. Innovation requires more than the development of a new industrial design, and it means more than research results and even more than a brilliant idea. Innovation implies that this idea or result is brought to real life, that it finds an expression in new products or services that meet a market demand.

A more positive entrepreneurial culture
Germany has excellent academic research, yet it is not really known as a country with a lively founding scene. A report states that education in schools with regards to founding needs to be improved, societal values and standards need to be adjusted for a more positive entrepreneurial culture, and labor supply needs to be increased for new and growing businesses.

In short: Motivating more people to set out on the big adventure of founding a new business is not so much a question of the financial and institutional framework, it is a question of culture and societal values. While in some other countries the founding of a business is seen as a chance for success, for growth and in any case a valuable experience, in Germany founding is regarded more suspiciously – it contradicts widely accepted values such as security, firm structures, and a potential failure is regarded as a stain in one's CV rather than an interesting feature.

Visibility for founders
The challenges have been identified, though, and countermeasures are being taken. A large number of initiatives are dedicated to technology transfer; universities and other research institutions have established technology transfer agencies that scout academic research groups for marketable technologies. Competitions and funding programs such as the GO Bio Initiative of the German Federal Ministry of Research and Education or the Science4Life competition provide financing, advice and visibility for founders, and their number is increasing. Last year, for example, the ACHEMA Gründerpreis was awarded for the first time to innovative entrepreneurs active in the fields of energy, industrial biotechnology and analytics. The nine finalists had the unique opportunity to present their concepts to industry experts from all over the world. This is an invaluable chance as many founders report that one of the hardest tasks is to identify and approach the right people in large companies in order to position themselves as potential suppliers, customers or development partners.

Our mission: innovation
From its beginning, the VBU Vereinigung Deutscher Biotechnologie-Unternehmen set out to enable technology transfer and facilitate networking between academic research and industry. With a special focus on small and medium sized enterprises, the VBU offers advice and organizes events tailored to give information and support to start-ups during their growth and expansion phase, both nationally and internationally. Being a part of DECHEMA, the large network for chemical process technology and biotechnology, it is the home for people active in research whether in universities, independent research institutions, start-ups or "big businesses". The activities of VBU supplement the approximately 120
topical working groups within DECHEMA, around 20 of them covering biotechnology from Omics and Cell Culture to Bioprocessing and Single-Use Technologies. The mission of VBU is as up-to-date as it was 20 years ago, and as long as there are people with brilliant ideas, it will always be up-to-date.

GERMAN ASSOCIATION OF BIOTECHNOLOGY INDUSTRIES

within the German Chemical Industry Association.

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The German Association of Biotechnology Industries (DIB) and its national, European and global networks are the voice and leading industry representation for the innovative and dynamic biotechnology industry that operates in and from Germany.

DIB is the biotechnology division of the Association of the German Chemical Industry Association (VCI).DIB is supported by 10 member associations and sector groups of the VCI:

- German Crop Protection, Pest Control and Fertilizer Association
- German Diagnostic Manufacturers Association
- German Cosmetics and Detergents Association
- VCI Sector Group Food Additives
- German Association of Research-Based Pharmaceutical
- Companies
- German Association for Food Law and Food Sciences
- German Medical Technology Association
- Association of the German Pharmaceutical Industry
- German Animal Health Association
- Association of the German Chemical Industry Association

Member companies and the above listed industry associations and sector groups are members of DIB. They constitute all in all about 95 % of the biotechnology business operating in and from Germany. This includes many different industry sectors such as polymers, plastics, fine and specialty chemicals, crop protection, plant breeding, enzymes, pharmaceuticals, diagnostics, animal health products, personal care products, detergents, animal feeds, foodstuffs, renewables and derived products. DIB is one of the largest biotechnology industry representations worldwide.

Role of DIB

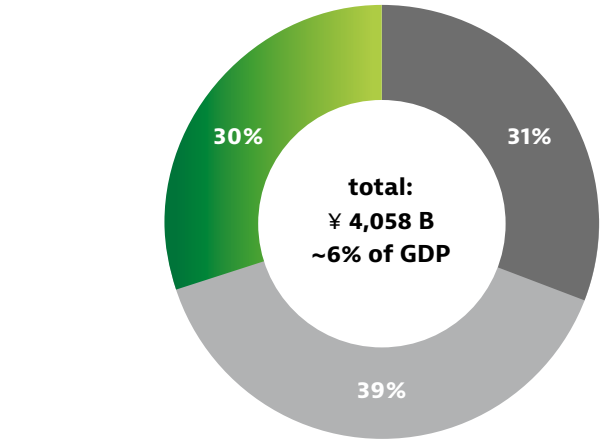
DIB's mission is to advocate national, EU and international policies and legislation that uphold a natural science and risk-based approach, foster innovation, operate in a predictable and proportionate way, enable the industry to perform efficiently, protect intellectual property and reward the introduction of new technologies and practices.

- DIB contributes to the creation of internationally competitive framework conditions for use of biotechnology in research, development, production and products.
- DIB represents the political-economic interests of companies that use biotechnology in order to strengthen sustainable growth and the international competitiveness of biotechnology in Germany.
- DIB represents the interests of their members vis-à-vis high-level representatives of legislative bodies, political decision-makers, regulatory authorities, public administration, media and the general public, both nationally and internationally.
- DIB contributes to further strengthening Germany as an industry location.

DIB is a member of the European biotechnology association EuropaBio, member of the board of EuropaBio and currently chairs the National Association Council of EuropaBio.

Healthcare in China

China's healthcare expenditure 2015



T = trillion
B = billion
M = million

¥ 1 M corresponded to € 0.138 M in December 2016

China – a "state capitalist" economy

China's economy is centrally controlled. Since 1983, there have been repeated cycles of liberalization which allowed private capital, foreign investors and companies into the economy. But in 2015, most of the economy was still controlled by the central or provincial governments. The state sector is concentrated within state-owned enterprises which rule the ‚commanding heights' of the economy, with a growing private sector engaged primarily in commodity production and light industry. Health-related markets are under strict government control. However, the government attempts to enhance productivity and innovation by opening parts of this market to private competition. The directives of the government are documented in Five-Years Plans issued by the National Reform and Development Commission, and since January 2016, the 13th Five-Years Plan has been implemented (throughout this publication abbreviated as "135").

Healthcare expenditure and health insurance[10]

As of 2015, China spent ¥ 4,058 B (~€ 560 B) or 6% of its GDP on healthcare, significantly less than Germany (11.2% of GDP). The expenditure per capita is about ¥ 2,952. According to the Annual Report 2015 of the National Health and Family Planning Commission (NHFPC) (former name: Ministry of Health, MOH), ¥ 1,253 B are spent by the government for hospitals, TCM, healthcare education, public health services etc.. Expenditures by social health systems account for ¥ 1,589 B and include commercial health insurances, non-governmental medical service expenditures, social donations and administrative fees. Private expenditures for healthcare amount to nearly one third of the total (¥ 1,216 B).

Through decades of failure and reforms, there is now a health insurance system which covers some 95% of the Chinese population, though there are still disparities between the urban and the rural areas. The health insurance system distinguishes urban residents (315 million in 2015), urban employees which include migrant workers (277.5 million in 2015) and people insured through "new cooperative health insurance" (670 million in 2015). Urbanization (now at 56%), improvement of personal income, and an aging society continue to raise the demand for medical care and medical products.

Healthcare services

A 2016 government report[11] provides the following data: by the end of 2014, 95% of all Chinese used public healthcare services. Private doctors and hospitals exist only in the big cities. The public hospitals are classified into a 3-tier system that recognizes a hospital's ability to provide medical care, medical education, and to conduct medical research. In 2015, there were 1,236 "tertiary hospitals" (highest rank).

They have high quality physicians, are well equipped and consume the lion's share of healthcare costs. In contrast, hospitals and community health centers in the countryside (over 13,000 in 2015) tend to be underdeveloped, are poorly funded and often not well connected to health education, which is true for most private hospitals as well (14,500 in 2015).[12] In 2015, there were some 3 million registered private doctors in

China, plus over a million "migrant doctors" and healthworkers in remote regions. In 2014, the State Council (China's highest executive organ) released guidelines to reform the hospital system. They will be implemented in the course of "135" and are designed to separate the sales of drugs from hospital operation and medical services, hitherto a major flaw in Chinese hospitals. The guidelines also encourage the establishment of private health clinics.

Medical Market Product Turnover 2015 (end of "125")

China's market for medical products in 2015 amounted to sales of ¥ 2,688,519 M (~€ 371 B) and had grown by 9% from 2014. Table 4.1 shows the share of products and their growth rate in this market.

As can be seen from this table, the drug market in China is dominated by chemically synthesized active pharmaceutical ingredients (APIs) and by products of Traditional Chinese Medicine (TCM) which make up more than two third of the whole market for medical products. Biologics, a major component of medical biotechnology, are yet playing a minor role but are growing at a CAGR of over 10%. The market for biologics is still dominated by foreign companies but the government has announced to take further steps, in the course of "135", to support Chinese companies to conquer this market segment.

Examples for innovations in the course of "125"

According to a report by the Chinese Association of the Pharmaceutical Industry,[14] innovation in pharmaceutical R&D was significantly improved during the "125" period. Within 5 years, 52 priority projects were completed, 74 new drugs were approved, 964 patents were granted and 816 new norms were passed.
As shown in table 4.2 next page, among the Class I (most important) 18 innovative drugs certified by the China Food and Drug Administration (CFDA), 7 were bio-pharmaceutical products.

"125"
12th Five-Year Plan
(2011-2015)

"135"
13th Five-Year Plan
(2016-2020)

Targets for healthcare and the medical industry in "135"

The strategic goal of biomedical technology in the course of "135" is to increase innovation and competitiveness of a national Chinese biomedical industry in order to reduce dependency on the big international players which presently hold about 30% of the Chinese markets (and even much higher market shares in innovative drugs such as biologics). To this end, a group of internationally competitive large conglomerates and innovative SMEs shall be developed which are designed as global leaders with their own unique features and shall make an impact on international biomedical developments. According to "135", Chinese companies shall dominate, in 2020, the domestic biomedical markets, and their global market share should have significantly increased. Box 4.1 provides a list of targets contained in "135".[15]

Table 4.1 **Share of products and growth rates of medicinal products in the Chinese market 2015**

type of product	sales 2015 (¥ M)	share of total (%)	CAGR since 2014
Chemical drugs	461,421	17.2	9.8
Chemical drug formulations	681,604	25.4	9.3
Traditional Chinese Medicines (TCM)	616,739	22.9	5.7
TCM decoction pieces (crude drugs)	169,994	6.3	12.5
Biologics	316,416	11.8	10.3
Consumption material (syringes etc.)	185,894	6.9	10.7
Medical instruments and devices	238,249	8.9	10.3
Other (manufacturing related)	18,202	0.7	8.9
Total	2,688,519	100	

Source: Chinese Ministry of Industry and Information Technology, 2015[13]

Table 4.2 **Class I* innovative biopharmaceuticals during the "125" period**

#	biopharmaceuticals	manufacturer
1	Nimotuzumab, a humanized antibody for cancer treatment (EGFR-binding)	Biotech-Pharmaceutical
2	Meningococcal group A,C bivalent polysaccharide conjugate vaccine, freeze-dried	Walvax Biotechnology
3	Recombinant human pro-urokinase for injection	Tasly Holding Group
4	PEGylated recombinant human granulocyte colonystimulating factor for injection	CSPC Pharmaceutical Group
5	Hepatitis E vaccine	Innovax Xiamen
6	Conbercept ophthalmic injection against wet agerelated macular degeneration	Kanghong Pharmaceutical Co.
7	Oral Heliobacter pylori vaccine	Chongqing Kangwei Biotechnolohy

*Class I pharmaceuticals are defined by CFDA as not being previously approved for marketing as a drug anywhere else in the world

China's pharmaceutical industry

By the end of 2015, 48% of the Chinese drug market was served by foreign companies or foreign-Chinese joint-ventures, with headquarters mostly in Taiwan or Hong Kong. In 2014 ¥ 167.2 B or 7.4% of total revenues of the pharmaceutical industry fell to the top 10 global drug companies (Pfizer, GSK, Sanofi, Bayer and others).[16] The remaining 52% of drug sales were divided among over 460,000 pharmacies and some 13,000 companies, of which more than 70% achieved annual revenues of less than ¥ 500 M (~€ 70 M), over 20% among them being unprofitable.

Most of those thousands of small biotech companies[19] and startups which populate hundreds of science parks in China do not fall into this category and cannot afford GMP certification which now stands at ¥ 40 M per product. One target of the "135" program is thus to concentrate the pharmaceutical industry into larger conglomerates which are able to push back international competition. Using a "carrot-and-stick" procedure to achieve this goal, the government provides incentives for the fusion or M&A of smaller companies and retracts GMP certificates from smaller companies (over 2,000 certificates were withdrawn by CFDA in 2015 alone).

This usually leads to the situation that the larger pharmaceutical companies are conglomerates with highly diverse production units which offer a "hawker's tray" of very different products. Two examples may illustrate this situation.

Jiangsu Heng Rui Medicine Co. Ltd. (short: Heng Rui Medicine) was founded in 1970 and was listed in 2000 on the Shanghai stock exchange. Revenues in 2015 were ¥ 9.32 B. The company is a leader for anti-cancer drugs in China. In 2014, Heng Rui Medicine independently developed a 1.1-Class innovative medicine named Apatinib, the world's first small molecule anti-angiogenesis targeting agent to treat late gastric cancer. Apart from antineoplastic agents, the product portfolio covers contrast media, anaesthetic drugs and standard chemical drugs such as aspirin. As a leading biopharmaceutical company, Heng Rui Medicine has acquired several startups and now also produces several antibiotics, PD-1 monoclonal antibodies and PEGylated recombinant human granulocyte colony stimulating factor.

Shanghai Fosun Pharma Co. Ltd. (short: Fosun Pharma) was established in 1994 and is listed on the Shanghai and Hongkong stock exchanges since August 1998. Revenues were ¥ 12.5 B in 2015. Fosun Pharma has built up a leading position in diagnostic products and medical devices while actively developing its presence in healthcare services. The company is the second largest shareholder of Sinopharm, China's largest pharmaceutical distributor. Through mergers and acquisitions, the portfolio now covers hormone drugs such as insulin, anti-infectives, cardiovascular drugs, anti-cancer drugs, influenza vaccine, diagnostic kits and medical instruments. The company has also a segment for numerous medical devices.

Among thousands of companies producing TCM drugs, 57 were registered on the Chinese stock markets by August 2016. This segment accounts for 30% of all sales, and for 33% of profits, of China's pharmaceutical industry. One of the biggest, Yunnan Dianhong Pharmaceuticals, was taken over by Bayer AG in 2014.
For Western companies they are difficult to contact as 70% of them have no English website, and even many of their Chinese websites often cannot be accessed. However, they should not be ignored as the government has announced a huge development package to modernize TCM in "135" and decided that, by the end of the 2020, at least 33% of all prescribed drugs must fall in the TCM category.

SMEs in China
China's Office of Statistics classifies manufacturing enterprises as follows.

large:
> 1,000 employees or > ¥ 400 M sales
medium:
300 – 1,000 employees or ¥ 20 – 400 M sales
small:
20 – 300 employees or < ¥ 20 M sales
mini:
< 20 employees or < ¥ 3 M sales

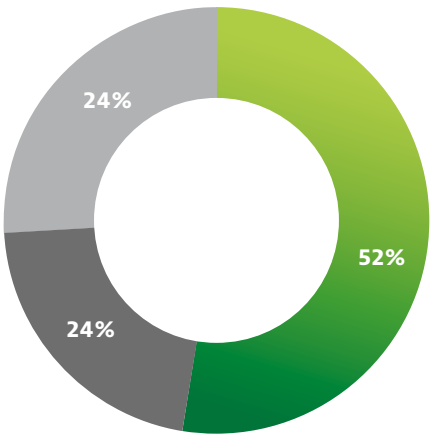
Box 4.1

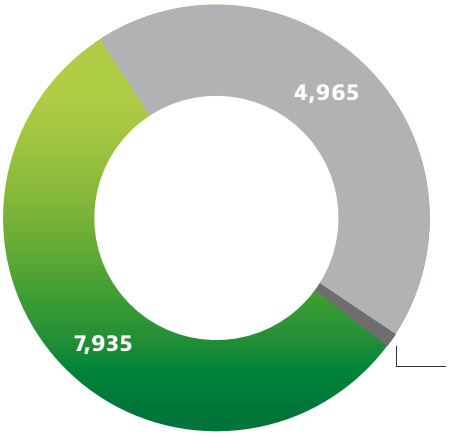
Some "135" targets related to China's healthcare and the pharmaceutical industry

- China's expenditures for healthcare will rise from present 6% of the GDP to 10% by 2020
- most of China's future biomedical industry will be reorganized into four big clusters
- these, by 2020, will comprise more than 200 incubators in 100 bio-industrial parks which host 7,500 life science companies, over 500 universities and research institutes, 2,500 highly ranked researchers, and more than 150,000 bio-scientists with bachelor and higher academic degrees
- the focus of drug development will move from treatment to prevention, leading to a drastic increase of supply of TCM, vaccines and diagnostic products
- by 2020, at least 30% of all drugs prescribed in the clinics will be TCM, and TCM-based healthcare, rehabilitation, etc. will be developed
- approved therapeutic antibodies (biosimilars) shall be manufactured at a large scale (> 100 kg) and, by 2020, achieve a market volume of at least ¥ 2–5 B
- for the manufacturing of key production equipment (standard and single-use bioreactors), 2–3 leading enterprises will be formed with a turnover above ¥ 10 B, leading to GMP-certified product revenues above ¥ 100 B
- by 2020, there will be cell-based regenerative products for diseases of the heart, liver, kidney, etc.
- in-vitro diagnostic reagents (IVD) are considered a particularly promising field as China, with ~20% of the world's population, has yet established only 3% of the global diagnostic markets; in the course of "135", the Chinese market for diagnostic reagents is expected to grow annually by 15–20%
- for a personalized ("precision") medicine, health-related data banks for millions of people will have been established
- artificial intelligence, intelligent hardware, new displays, mobile intelligent terminals, 5G mobile communication, advanced sensors and wearable equipment will all contribute to advances in telemedicine and cloud-based healthcare

Among the Chinese producers, China's Food and Drug Administration (CFDA) had 5,065 companies approved as pharmaceutical manufacturers by the end of 2015.[18] Only such "enterprises above designated size", with sales of ¥ 20 M or more, are registered by China's Statistical Office.

China's pharmaceutical industry





100
top 100: ¥ 613.1 B (23% of all sales)
They own stock market registry numbers, provide a website (if often only in Chinese) and may be contacted using English language.[17]

Infrastructure

General

Central government control also comprises public R&D as China follows a coherent approach to transform the nation and its industry into a global technology leader – consequently government expenditure of R&D is already scheduled to rise from a present 2.1% to 2.5% of the GDP by 2020.

Science, research and higher education

The Chinese Academy of Engineering is China's "think tank" for technology development

China's structures for science, research and higher education comprise national research centers, universities, academy institutes, the institutions under the People's Liberation Army and the National Health and Family Planning Commission.

Universities. Under the so-called "985" program passed in 1986, 39 universities were selected as leaders. Among these, nine form the national flagshipsof research and higher education ("C9 League").[20] Examples are Peking and Tsinghua University in Beijing, and JiaoTong and Fudan University in Shanghai. Another 116 fall into the category of National Key Universities and Colleges selected under the "211-program".[21]

There are 2,000 more universities and colleges for 26.3 million students with access to higher education (2015). Most universities in China are under the supervision of the Ministry of Education (MOE). Many of them have faculties relating to medical biotechnology and participate in local science parks where their spin-offs start business operation. During the "135"-program, the above programs will be closed in favor of a new scheme which resembles the German "excellence initiative".

China has over 26 million students in higher education.

Academy Institutes. A major part of science and research is done at institutes belonging to an academy. The most powerful is the Chinese Academy of Engineering (CAE).[22] It is directly associated to the State Council and its 835 lifelong members serve as the "think tank" of China. In terms of research, the Chinese Academy of Sciences (CAS) is the main organization.[23] It operates 104 research institutes throughout mainland China, and two universities which are highly ranked, further 80% of China's large-scale facilities, e. g., the Synchrotron Radiation Facility in Shanghai (SRFS). CAS has 759 elected academicians and some 56,000 professional researchers. The CAS budget was ¥ 35 B in 2013. CAS is also directly associated to the State Council.

The Chinese Academy of Medical Sciences (CAMS) is synonymous with its headquarter at Peking Union Medical College (PUMC)[24] (see box 5.1 on next page). It is associated to the National Health and Family Planning Commission (NHFPC) under the State Council, since 2012 the successor of the former Ministry of Health (MOH). Affiliated with Tsinghua University, PUMC is considered the best medical school in China; it operates research centers and hospitals throughout China in addition to several WHO Collaborating Research Centers.

The Chinese Academy of Military Medical Sciences (CAMMS) is under the People's Liberation Army. It supervises several high-ranked hospitals in Beijing, Shanghai and elsewhere which are involved in virus research, wound healing techniques, tissue engineering and related topics. Universities, academies and even companies may form joint research facilities on a focused research subject which is additionally funded, e. g., from the Ministry of Science and Technology (MOST).

Box 5.1

Chinese Academy of Medical Sciences and the Peking Union Medical College

The Chinese Academy of Medical Sciences (CAMS), with headquarters in Beijing, operates six research centers in Beijing, Tianjin, Nanjing and Suzhou (Jiangsu), Chengdu (Sichuan) and Kunming (Yunnan).

Six hospitals are directly affiliated (Peking Union Medical College Hospital, Fu Wai Hospital, Cancer Hospital, Plastic Surgery Hospital, Blood Diseases Hospital, Skin Disease Hospital). With one cooperating hospital (Tianjin Taida Cardiovascular Hospital), these clinics offer about 6,000 beds and are considered China's leaders in the diagnosis and treatment of cardiovascular diseases, malignant tumors, blood-related, dermatological, endocrine, autoimmune and hereditary diseases, as well as in organ reconstruction.

The Chinese Academy of Medical Sciences (CAMS) operates 5 State Key Laboratories (SKLs), all in Beijing and in collaboration with other institutions:

- The State Key Laboratory of Cardiovascular Diseases at Fu Wai Hospital in Beijing (co-organized with Ministry of Science and Technology MOST)
- The State Key Laboratory of Molecular Oncology at Peking Union Medical College
- The State Key Laboratory of Medical Molecular Biology at Peking Union Medical College
- The State Key Laboratory of Bioactive Substance and Function of Natural Medicines
- The State Key Laboratory of Experimental Hematology, associated to the Institute of Blood Diseases and Hematology Hospital in Beijing

Depending on the source of funding, these joint facilities are called "State Key Laboratories" or "Provincial Key Laboratories" and provide additional prestige to a research body. In 2015, there were 252 State Key Laboratories (SKL) of which about 38 are related to molecular medicine.

Examples are:

- SKL for Medical Gene Technology at Jiaotong University[25]
- SKL of Pharmaceutical Biotechnology at Nanjing University[26]
- SKL of Biotherapy at Sichuan University[27]
- SKL of Medical Molecular Biology at Peking University[28]
- SKL of Molecular Biology at CAS Shanghai Institute for Biological Sciences
- SKL of Brain and Cognitive Sciences at CAS Institute for Biophysics
- SKL of Virology at Wuhan University
- SKL of Natural and Biomimetic Drugs at Peking University

According to a survey of the Chinese Patent office in July 2016,[29] many patent applications filed by Chinese inventors originated not only from Chinese enterprises, but also from universities and research institutes.

The top 10 institutions for granted patents in the "125" period

- Guangzhou Institute of Biomedicine and Health, CAS (519)
- Nanjing Guangkangxie Biomedicine Co., Ltd. (267)
- Sichuan Jintanghaina Biomedicine Institute (236)
- Suzhou Paiteng Biomedicine Co., Ltd. (225)
- Guangzhou Jinan Biomedical R&D Center (212)
- Abon (Hangzhou) Biopharma Co., Ltd. (205)
- Shanghai Fudan Zhangjiang Biopharmaceutical Co., Ltd. (162)
- Qingdao Kowloon Biological Co., Ltd. (152)
- Yantai Ruizhi Biopharmaceutical Co., Ltd. (148)
- Zhangjiagang Weisheng Biopharmaceutical Co. Ltd. (138)

(number of patents in brackets)

Science parks

As of 2015, China had built 145 national science parks and over 1,000 provincial or municipal technology parks

Since the late 1980s, the Chinese government has promoted the construction of national science and technology parks. The objective was to promote technology-oriented firms, facilitate the commercialization of scientific research, and to revitalize regional economies.[30] By the end of 2015, there were 145 national science parks in China,[31] but at least another 1,000 which operated on the provincial or municipal level.

Usually, the national science parks are more international and offer much better access points to foreign companies and investors. Box 5.2 indicates China's ten most advanced science parks related to pharmaceutical developments.

Those parks with a major focus on medical biotechnology will be discussed in more detail in the framework of the four future clusters for national innovation (section 6).

Science parks in Beijing. Among the science parks in Beijing, there are three which put focus on medical biotechnology. Zhongguangcun Science and Technology Zone[32] hosts most of the high-tech companies in Beijing. Peking University, Tsinghua University and the headquarter of the Chinese Academy of Sciences are located adjacent to this zone. Beijing SL Pharmaceutical Co., Beijing Strong Biotechnologies Inc. are examples for companies located in this science park. In Beijing Economic Technological Development Area (Beijing-ETown, 北京亦庄科技园), over 400 companies are involved in pharmaceutical production including Staidson (Beijing) BioPharmaceuticals Co. mentioned below.

The Zhonggangcuan Science Park in Beijing may serve as an example. The predecessors of this science park date back to the 1980 until it was declared by the State Council as a National Technology Demonstration Zone in 2009. During the past two decades, Zhongguancun has gathered nearly 20,000 high and new-tech enterprises such as Lenovo and Baidu. Its sub-parks feature electronic information, biomedicine, energy and environmental protection, new materials, advanced manufacturing, aerospace, R&D and service.

Top universities like Peking University and Tsinghua University and their own science parks, the headquarter of the Chinese Academy of Sciences and many research centers are located here.

Box 5.1 **Ten national science parks leading in medical biotechnology**

Zhongguancun Life Science Park, Beijing 中关村生命科学园	oldest and most international science park, with headquarters of Genzyme, Syngenta, Novo Nordisk and others
Beijing Economic Technological Development Area (Beijing-ETOWN) 北京亦庄科技	more than 400 enterprises engaged in pharmaceutical production, such as Bayer, GE Healthcare and others
Beijing Daxing Biomedicine Industry Park 北京大兴生物医药产业基地	more than 500 biomedical enterprises, such as Fresenius Kabi, Beijing Minhai Biotechnology etc.
Tianjin Economic – Technological Development Area (TEDA), Tianjin 天津经济技术开发区	some 120 bio-pharmaceutical firms such as Novozymes, Novo Nordisk, GlaxoSmithKline and Jecho Laboratories
Zhang Jiang Innopark, Shanghai 上海张江药谷	more than 300 biotech and pharmaceutical enterprises such as, Boehringer Ingelheim, Roche, GlaxoSmithKline and others
Biobay, Suzhou (Jiangsu) 苏州生物纳米科技园	over 200, but smaller enterprises for drug discovery, medical devices and nanotech, e.g., Alphamab, Brunswick
Taizhou Medical Hi-Tech Zone (China Medical City) (Jiangsu) 泰州医药高新技术产业开发区 (中国医药城)	under development. AstraZeneca, Takeda Pharmaceuticals and others. By 2019, 1,000 pharmaceutical companies should have settled
Guangzhou International Biotech Island (Guangdong) 广州国际生物岛	some 130 pharmaceutical enterprises such as KingMed Diagnostics, Riton Biomaterial
Zhongshan National Health Science and Technology Industrial Base, Guangdong (Guangzhou) 中山国家健康科技产业基地	some 200 enterprises such as Sandoz, Ferring
Chengdu Hi-tech Zone (Sichuan) 成都高新技术产业开发区	some 300 biomedical enterprises such as Maccura, Medtronic
Wuhan Biolake (Hubei) 武汉光谷生物城	over 120 bio-pharmaceutical companies such as Pfizer, Fresenius

Source: Chinese Ministry of Industry and Information Technology, 2015[13]

Zhongguancun's venture capital cases and investments account for about a third of the country's total. The number of listed companies in the zone adds up to 189, comprising 113 domestic and 76 overseas companies. Important sub-parks of Zhongguancun for biomedicine are the Daxing Biomedicine Industry Park and Beijing E-town, forming togther Beijing's National Bio-industrial base.

Science parks in Shanghai. The Zhangjiang Science (ZJ) Park in Shanghai Pudong, built in 1991, belongs also to the earliest hi-tech parks. With a planning space of 80 km², there are some 3,000 operating and some 10,000 registered companies, including top hi-tech enterprises and startups. It is ranked top for China's in-vitro diagnostics (IVD) business, as the Roche Group, DaAn Gene and other leaders in this industry have settled here.

Other science parks will be introduced in section 6.

Beijing-ETown is a major high-tech science park in Beijing.

Finance

In view of the ambitious plans of the Chinese government for national development, financing is of utmost importance. Both governmental and private funds are available in China.

Government guided funds (GGF) are also called „startup guided fund". They come from the government and are issued by local governments, banks and public investment companies as well as from social capital owners such as insurances. GGFs are non-profit funds and invest in entrepreneurial venture capital institutions or venture risk investment funds in the form of equity or debt. These funds are supporting startups for their establishment and development. Currently (Sep. 2016), there are 980 GGFs with a cumulated capital of ¥ 3,000 B (€ 400 B). The GGFs are strongly involved in the development of the four clusters mentioned in section 6.

Investments from government banks. Since 2012, investment from banks are more and more important for industrial companies. An example is how Fosun Pharma, China's largest biopharmaceutical company, is invested: eight of its ten shareholders are banks such as the Construction Bank of China. Of another bio-pharmaceutical company, the Heng Rui Medical Group, seven out of ten shareholders are banks, such as the Bank of China.

Private equity funds (PE). PE play an increasingly important role for financing startups and enterprises. Investors can be business angels or venture funds as well as institutional investors. For example, Shenyang's 3s Biopharmaceutical Co. Ltd (3S Bio), a producer of recombinant human thrombopoietin, received an investment of US-$ 100 M from both the Singapore governmental and Lilly Asia Ventures; these two investors hold 3.5% of shares of 3s Bio. As another example, Shanghai Yunfeng Capital and Shenzhen Cowin Capital jointly invested ¥ 200 M in Shenzhen Huakang Mobile Healthcare for mobile healthcare systems. The Shenzhen Capital Group invested in more than 34 companies for bio- and bio-medical products; investments went to BGI, Zhongshan Akesbio etc.

Venture capital (VC) and other investment institutions. In 2013, Forbes ranked the top 30 investment companies in China.[33] 28 of them had invested in bio-pharmaceutical enterprises. The biggest VC is SCGC in Shenzhen, with a capital of ¥ 13.7 B. SCGC is a major investor in Shenzhen's BGI. Another investor, IDG Capital Partners, has a capital of about US-$ 3 B and is invested, e. g., in Shandong Taibang (CTBB), a company with a focus on blood products. In 2015, Forbes announced again the top 50 investors in China.[34] More than 30 of them had invested in medical products, telemedicine and biomedicine. Sequoia Capital China (top 1) had successfully invested in BGI and Yuwell (diagnostic devices).

As of 2016, the cumulated capital of government guided funds was estimated at €400 B

Clusters for China's medical markets

General introduction

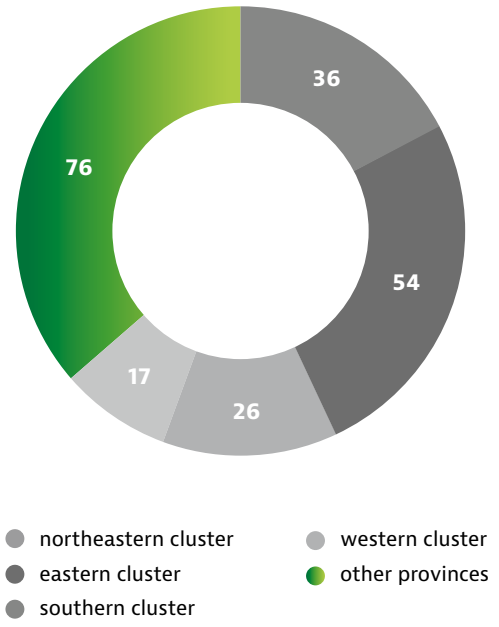
According to an official analysis provided in the "135" master plan,[35] China's medical markets tend to show further unbalanced growth. R&D will further be centralized around Beijing and Shanghai, many production facilities will be located in Jiangsu, Zhejiang and Shandong, and the gap between the mid-western regions and the eastern regions will increase.

This is in contradiction to the growing needs for improved medical services, and many provinces are thus trying to establish a local medical industry, including biomedical clusters; new emerging hotspots for biomedical R&D and production are forming in Shenzhen, Wuhan, Changsha, Taiyuan, Xiamen, Lanzhou and other regions.

In response to these needs, the "135" program contains a plan to form four clusters nationwide which are intended to cover over 80% of all Chinese developments in the biomedical field, within the next five years. These clusters are scheduled to host 7,500 life-science companies, 500 universities and institutes, 2,500 top researchers, over

200 life-science related incubators, more than 100 life science parks and 250,000 industry staff members. In addition to that, they are expected to produce over 150,000 graduates per year. They should also be able to patent more than 3,200 novel drugs per year. This vision is on the grand scale typical for China's central planning and will involve thousands of companies, hundreds of universities and hundreds of thousands of people. To put it in perspective, at present at least one third of China's leading pharmaceutical companies (those registered on the stock market) are still located outside these four cluster regions.

Geographical distribution of all 159 Chinese-owned pharmaceutical companies registered on the Chinese stock market 2016



In the following section, we will analyze how well medical biotechnology is already established in the future four cluster regions. In doing so, we will focus on some of the 5,065 companies registered by CFDA. We will further consider the infrastructure such as academic research, science parks and capital resources.

The northeastern cluster: the capital region

This cluster comprises Beijing and Tianjin as its center, but also the provinces of Liaoning, Hebei and Shandong. By now, Beijing and Tianjin have the most developed medical and pharmaceutical value chain comprising education, research and industry. They are also particularly rich in clinical resources. To some extent, the pharmaceutical industry in these provinces has developed complementary product lines. Thus, Liaoning is a national leader in the production of anti-infectives.

The northeastern cluster

Beijing
Beijing is the seat of government and the center of China's administration. As the nation's capital with 25 million inhabitants, Beijing is also the major center of finance and banking. The National Health and Family Planning Commission (NHFPC), successor of the Ministry of Health (MOH), is located here, as is the China FDA (CFDA) and the Chinese Center for Disease Control and Prevention (CCDCP), home to 12 research institutes.

Other key institutions for research and higher education comprise the headquarters of the Chinese Academy of Sciences with 7 of its 110 institutes, the Chinese Academy of Medical Sciences with 8 subsidiary research institutes and the Ministry of Education (MOE) with two of China's top universities (Peking University and Tsinghua University). Furthermore, another three universities devoted to medicine are involved, namely Beijing University of Chinese Medicine, Capital University of Medical Sciences and Peking Union Medical College. In 2015, Beijing's R&D expenditures were ¥ 137 B, or one tenth of China's total.

Box 6.1

the Beijing Daxing Bio-medicine Industry Park

The China Beijing Bioengineering and Pharmaceutical Industrial Park (CBP) was developed by the Beijing Municipal Government and covers some 28 km^2. It is located close to Beijing International Airport. The CBP counts 73 companies, accounting for a quarter of the total number of bioengineering and pharmaceutical firms in Beijing. Its annual production value was ¥ 2.3 B (US-$ 337 M) (2015) constituting 28% of the pharmaceutical industry in Beijing.

Prominent institutions located in the park include the Chinese Academy of Medical Science, the Chinese Center for Disease Control and Prevention (CDC), the Academy of Military Medical Sciences, the Academy of Traditional Chinese Medicine, Beijing Union Medical College, Beijing University Hospital, Capital Medical Sciences University, the China Food and Drug Administration (CFDA), and the National Institute for the Control of Pharmaceutical and Biological Products. Domestic companies such as Beijing Tri-Prime Genetic Engineering Company and the Union Medical Pharmaceutical Group have also set up their business in this park.

10% of China's R&D expenditures are spent in Beijing

Beijing counts over 4,800 medical institutions including 530 hospitals. Not surprisingly, some of China's most important science parks for bio-medicine are also located in Beijing. Thus, the Zhongguancun Science Park (see section 5) contains, as a sub-park, the Beijing Daxing Bio-Medicine Industry Park where much of the Beijing-based biomedical research and manufacturing is concentrated (see box 6.1). Beijing also accounts for one of the largest shares of China's pharmaceutical companies. Examples for major companies involved in medical biotechnology located in Beijing are Beijing Tiantan Biological Products Co., a national leader in blood products with some 2,600 employees, Beijing Leadman Biochemistry Co. and Beijing Strong Biotechnologies Inc., two of China's leading companies for in-vitro diagnostics. More detailed information on manufacturing companies can be found in the features on individual biomedical products (section 7).

Tianjin

Tianjin[36] is a city with about 15 million inhabitants and one out of four directly controlled municipalities of China. Due to its port and its proximity to Beijing (120 km), the megalopolis is a major hub for industry and trade and boasts China's highest per-capita income. Tianjin is host to important national research centers such as the Tianjin Institute of Industrial Biotechnology (CAS) and the Blood Science Institute (CAMS). Among the 20 universities and colleges in Tianjin, Nankai University ranks first and hosts a State Key Laboratory for Medicinal Chemical Biology.
Most of Tianjin's high-tech industry is located in the Tianjin Economic-Technological Development Area (TEDA) in the Binhai zone. The park comprises 120 bio-pharmaceutical companies, of which 50 are foreign-funded. Novo-Nordisk, Glaxo-Smith-Kline (GSK), Mitsubishi-Tanabe and Otsuka Pharma have their production facilities here. An example for a leading Chinese biomedical company is Zhongyuan Union Cell & Gene Engineering Co., company with 1,700 employees which provides storage of stem-cells and develops products for regenerative medicine.

TEDA is also an important habitat area for the finance sector. SCB, HSBC, CitiBank, Mizuho Corporate Bank etc. have established branch banks in TEDA, and non-banking finance organizations such as Finance Leasing of ICBC, Finance Company of Motorola etc. are located here. With the fast growth of outsourcing service, CSC, ACS, IBM, Wuxi Pharm, Vimicro, SCB operation center, Tencent etc. have chosen TEDA as their location.

Hebei, Jilin and Liaoning

Hebei[37] and Liaoning[38] are two of China's northeastern provinces. Their capitals are Shijiazhuang and Shenyang, with metropolitan populations of 7 to 10 millions. The Chinese market for antibiotics is dominated by companies in Hebei such as North China Pharmaceutical Co. and the CSPC Pharmaceutical Group – two state-owned companies with 12,000 and 20,000 employees, respectively. Neighboring Jilin, not a part of the northeastern cluster, hosts Asia's largest area for vaccine manufacturing in the Changchun-Jilin-Tumenjiang region. An example is Changsheng Bio-technology Co., China's largest producer of vaccines, e. g., for protection against rabies, hepatitis A, varicella and influenza. Hualan Biological Engineering, a state company with some 1,500 employees, is China's major producer of human serum albumin, immunoglobin und prothrombin complexes.

Shandong

Shandong[39] is China's number three province in prosperity (behind Jiangsu and Guangdong) and a top location for manufacturing. The two most important municipalities are Jinan, Shandong's

Beijing counts over 4,800 medical institutions including 530 hospitals.

capital, and Qingdao, one of China's major ports and home to China's Ocean University (under CAS). Shandong is host to one of China's largest manufacturers of antibiotics, Shandong Jincheng Pharmaceutical and Chemical Co., with over 2,000 employees. Half of this company's sales consist of cephalosporin intermediates, sold as API products. Jinan has just established another National R&D Platform for new drugs.[40]

The eastern cluster: business and innovation around Shanghai

The eastern cluster comprises Shanghai and the provinces of Zhejiang and Jiangsu ("Yangtze Delta Region"). Important locations for the biomedical industry are Shanghai as the center, Suzhou, Taizhou, Nanjing in Jiangsu province and Hangzhou in Zhejiang province. Headquarters of some of the largest international biomedical companies are located here. The value chain comprises R&D, industrialization, outsourcing services, international banking and communication.

Shanghai
Shanghai[41] is a global financial and business center and also one of China's centers of science and research. Many headquarters of globally operating companies are based here, as well as some of China's foremost universities and research centers. With a population of 25 million, Shanghai is one out of four municipalities directly controlled by the central government.

Institutes of the CAS, the CAMS and universities involved in medical biotechnology
The Chinese Academy of Sciences (CAS) operates in Shanghai several institutes related to medical biotechnology, such as the Institute of Biochemistry and Cell Biology, the Institute of Neuroscience, the Shanghai Institute of Materia Medica, the Shanghai Pasteur Institute and the National Center for Drug Screening. The Shanghai Institute of Tumor Biology is associated to the Ministry of Education (MOE).

The Ministry of Science and Technology (MOST) and the CAS share in the supervision of the Chinese National Human Genome Center at Shanghai, the Shanghai Synchrotron Radiation Facility and the newly formed National Institute of Protein Science. The Ministry of Defense operates in Shanghai the Second Military University which has become a hub for tissue engineering. Finally, some of China's leading universities have their campuses here, such as JiaoTong University, Fudan University, Tongji University and East China University of Science and Technology.

The eastern cluster

Box 6.2

ZJ Park Biopharmaceutical Incubator

Many of the top international and Chinese companies involved in medical biotechnology are based here. As for the internationals, this is, e. g., the HQ and often the key R&D center of Roche China, Bayer China, Boehringer Ingelheim China, Sanofi, Glaxo-Smith-Kline (GSK) and Pfizer, to name just a few. Among the Chinese giants, Shanghai Fosun Pharmaceutical Co., with nearly 18,000 employees, occupies an own sub-park area where it manifactures blood products, vaccines, anti-infectives, anti-tumor agents and APIs. Shanghai RAAS Blood Products Co., with some 2,400 employees, has a product line based on albumen, immunoglobulins and coagulation factors. Some tenants of the park are national leaders in in-vitro diagnostics, such as Shanghai Kehua Bio-Engineering Co. which provides diagnostic tests and instruments.

The most well-known science park is the Zhangjiang InnoPark which is sometimes dubbed "China's Silicon Valley". Apart from microelectronics and IT, many among the 3,600 Chinese and international companies located here are involved in medical biotechnology. 2004, a subpark was certified as "National High-tech Innovation Service Center (State Specialized Biopharmaceutical Incubator)", box 6.2, by the Ministry of Science and Technology. One of the tenants is Boehringer Ingelheim's China Center.

Zhejiang

Zhejiang[42] province has a particularly rich history, and its capital, Hangzhou, was the capital of China under the Southern Song dynasty (AD 1127–1279). Today, Zhejiang is a manufacturing hub, profiting from its location at the Yangtze river mound and the proximity to Shanghai, from which Hangzhou is just 120 km away. Major cities in Zhejiang, apart from Hangzhou, are Ningbo, Wenzhou and Taizhou (台州). Zhejiang University belongs to the top 10 universities of China and has a faculty of medicine. One of China's leading pharmaceutical companies, Zhejiang Hisun Pharmaceutical Co., is located in Taizhou. Nearly 10,000 employees work here on anti-tumor, anti-infective, cardiovascular and endocrine drugs, but also on veterinary products.

Jiangsu

Jiangsu[43] is the most densely populated Chinese province and boasts China's second highest provincial income, after Guangdong. Jiangsu's capital, Nanjing, 200 km upstream the Yangtze river from Shanghai, was China's capital several times – most recently during the period of the Republic of China (1912 – 1949). In modern China, Jiangsu has become a manufacturing hub like neighboring Zhejiang, but is also striving to become a leader in high-tech areas such as bio-medicine. In respect of medical biotechnology, the four most important cities in Jiangsu are Suzhou, Wuxi, Nantong and another Taizhou (泰州). Jiangsu has more than 300 universities and colleges of which Nanjing University is among the oldest and most renowned ones in China. The Chinese Academy of Sciences has established both its Institute of Medical Bioengineering and the Institute of Nanotechnology and Nanobionics in Suzhou, just 60 km from Shanghai. Among the many science parks in Jiangsu – Nanjing alone counts fifteen – the most important ones for medical biotechnology are Suzhou's Biobay and Taizhou's China Medical City.

Suzhou BioBay[44] 苏州生物纳米科技园 was established in 2006 as a joint-venture with the government of Singapore. It hosts 373 tenants, about half of them involved in drug discovery and medical devices. One example is Innovent Biologics, a US-invested CRO which puts a focus on the manufacturing of generic therapeutic antibodies.[45]

China Medical City (CMC, 中国医药城) in Taizhou is a pharmaceutical technology park of 25 km² planning area. It was founded in 2005 and became a national project under the lead of the central government in 2009. By the end of 2016, the 10-years construction phase has been completed. By now, more than 600 companies have settled in the park, and 400 new drugs have been developed or are under development. Furthermore, thirty-four "1,000-talent" teams have been funded (so called after the "1,000-talent program" of China's central government, recruiting highly successful researchers from abroad as group leaders for R&D projects). CMCs goals for 2019 are to host more than 1,000 pharmaceutical companies and achieve an annual revenue of over ¥ 100 B. One out of hundreds of biopharmaceutical companies and

thousands of startups in Jiangsu is Changzhou Qianhong Biopharma Co., Ltd, a 1,000-employee enzyme producer for pancreatin, elastase, asparaginase as well as heparin.

The southern cluster: booming southern metropolis near Hong Kong

This cluster comprises Guangzhou, Shenzhen (Guangdong province) and Hong Kong ("Pearl river delta region"). It features a mature market environment, a developed economy and a trade system with a tremendous market potential. Medical and pharmaceutical business is already well developed and has good extension potential. Private capital and investment business is very strong here, as is technology trading.

Guangdong

Guangdong is China's most populous province, with over 100 million inhabitants. The capital Guangzhou ("Canton")[46] and Shenzhen[47] (13 and 11 million inhabitants, respectively) are Guangdongs major cities. The province contributes about 12% to China's GDP. Public R&D institutions with outstanding contributions to medical biotechnology are Zhongshan University (also called Sun Yat-Sen University), the First Military Medical University under the People's Liberation Army, the Guangzhou Institutes of Bio-medicine and Health of the CAS, who have a strong focus on stem-cell technology, and the Beijing Genomics Institute (BGI) in Shenzhen, an international leader in genome sequencing and genomic medicine.

The southern cluster

The key science parks in Guangdong are the Guangzhou New & High-tech Industrial Development Zone, and the Shenzhen High-tech Industrial Park. The Guangzhou New & High-tech Industrial Development Zone was established in 1991. In 2016, the State Council nominated the park an entrepreneurial innovation and demonstration base. The Guangzhou International Biotech Island (广州国际生物岛) is part of this high-tech zone and the core area of Guangzhou national biological industry base. It hosts the Military Medical Science Academy of the PLA and 43 other technology transfer/incubator-projects. As of April 2016, "Biotech Island" has supported 140 projects, which incubated successfully 132 enterprises with about ¥ 1.3 B registered capital and attracted more than ¥ 3.7 B investments.

The **Shenzhen High-tech Industrial Park** was established in 1996 on a planning area of 11.5 km². It is one out of six pilot parks from the program „building world-class high-tech parks". In 2011, the high-tech zone accounted for less than 0.6% of Shenzhen's area but achieved sales of ¥ 363 B, with a growth rate above 20%, contributing 18% of the total industrial revenue of Shenzhen; exports were US-$ 17.9 B. DaAn Gene Co., a spin-off of Sun Yat-Sen University with over 2,000 employees, is a major producer of molecular diagnostics in this park, e. g., for cervical cancer assays, immunoassays and blood collection tubes.

China's South is among the most active regions in technology-related capital and investment business

Hong Kong

Hong Kong[48] returned to China in 1997 and since has been one of China's special administrative regions, with a high degree of autonomy (e. g., an independent judiciary system). The metropolis, located in the Pearl River Delta, has some 7 million inhabitants. It is among the world's leading financial centers and has one of the world's highest per-capita incomes. There are eight public and one private universities in Hong Kong, with the University of Hong Kong (HKU, established in 1910–1912) being the oldest. Hong Kong Science & Technology Park (HKSTP)[49] concentrates on stem-cells and regenerative medicine. Founded in 2001, the park hosts 618 enterprises (82% of them domestic), and 12,145 employees are working on healthy-aging issues (stem-cell R&D and regenerative medicine), robotics and smart city projects. The park achieves annual revenues of HK-$ 166 B. At the University of Hong Kong, Beijing's State Key Laboratory for Biopharmaceuticals runs a partner laboratory, supported by the Ministry of Science and Technology (MOST).

More than 20 monoclonal antibody-based immunoassays were already developed here. The City University of Hong Kong, the Center for Biosystems, Neuroscience, and Nanotechnology (CBNN)[50] has a strong research focus on neuro-biotechnology, stem-cell and nanotechnology and implantable biosensors. The Hong Kong University of Science and Technology (HKUST) operates the Shenzhen Research Institute[51] whose State Key Laboratory of Molecular Neuroscience emphasizes diagnostics and new drugs for neuronal diseases.

Rise in the west: Chengdu, Chongqing and the western cluster

This cluster comprises Chongqing, Chengdu (Sichuan province), Xi'an (Shaanxi province) and Wuhan (Hubei province). The Chengdu-Chongqing region is emerging as a major economic zone with high innovation capacity in biomedical engineering. It is also an important zone for technology transfer of biomedical technologies developed in East China. The Changsha-Zhuzhou-Xiangtan region has built a "Changsha High-Tech Zone" and will form a new biomedical industry cluster together with Liuyang Bio-medicine park. Wuhan counts already more than 300 companies which focus on biomedical R&D.

China attempts to industrialize the western provinces with big investments

Sichuan and Chongqing

Sichuan[52] is among the largest and most populous provinces of China. Historically known as "the province of abundance", Sichuan is a key producer of wheat, rice and commercial crops, but also rich in mineral resources and natural gas reserves. Sichuan is also known as the province with the greatest natural diversity, and many TCM products originated here. Sichuan's capital is Chengdu, with some 14 million inhabitants. Chongqing[53] is an economic centre of the upstream Yangtze basin and a major manufacturing centre and transportation hub. It separated from Sichuan in 1997 and became one of the four independent municipalities of China. The population is about 30 million, with an urban residence of some 18 million. In public research related to bio-medicine, the Chinese Academy of Sciences operates the Chengdu Institute of Biology, and the Chinese Academy of Medical Sciences its Institute of Transfusion Medicine. 6 out of 9 universities in Sichuan are located in Chengdu, including the Chengdu University of Traditional Chinese Medicine.

The leading science park is Chengdu High-tech Industrial Development Zone. Established in 1988, the park was opened to APEC countries in 2000 and is – in terms of comprehensive strength – continuously ranked among the top 10 of 153 national high-tech development zones in China. It covers an area of 82.5 km² and consists of a south and a west park. The West Park gives priority to three major industries including bio-medicine. Another key science park in Sichuan is the Chengdu Economic and Technological Development Zone. It was approved as state-level development zone in February 2000. The zone has now a planned area of 26 km². It has attracted investors and developers from over 20 countries, and preferred industries include those related to bio-medicine.

Rise in the west

Wuhan and Xi'an

Wuhan and Xi'an are the capitals of Hubei[54] and Shaanxi,[55] two provinces northwest of Sichuan. Fossil fuel-based and high-tech companies such as aviation and space industries are the major economic drivers. Key R&D institutions in the public sector are the 4th Military Medical University, Xi'an Jiao Tong University and Xi'an Medical University, Wuhan University (State Key Laboratory of Virology) and the CAS Institute for Virology. Wuhan has formed a National High-tech Industry Base ("Optical Valley"). The biological and healthcare industry in Hubei province is being concentrated in a sub-park named "Biolake", with the goal to become a leader in this field and achieve ¥ 300 B revenues by 2020. In Shaanxi province, it is the Baoji High-tech Industrial Development Zone, a national science park, which puts a focus

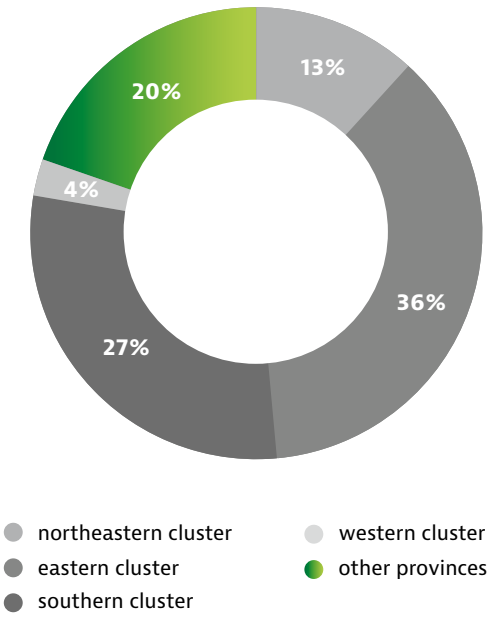
Sichuan exhibits a rich natural diversity, translating into traditional Chinese medicine.

on the pharmaceuticals and bioengineering industries and new materials. In 2009, Chongqing proposed that a West Triangle Economic Zone[56] should combine the economic power of the three largest cities in Western China: Xi'an, Chongqing and Chengdu. This proposition became part of the "125"- Five-Year Plan, as part of China's Western development policy which aims to attract foreign investment through infrastructure construction, ecological protection, education, and retention of talent. During "125", over ¥ 1 T has been spent on the west as a whole.

Concluding remarks

The development of biotechnology, prerequisite for bio-pharmaceuticals, began in China during the 1970s. As of mid-2016, there are 24 biomedical enterprises listed in the Chinese stock market. Whereas 9 of them (38%) are located outside the four cluster regions, those 15 inside the four clusters contributed 80% to annual revenues of ¥ 316.4 B (2015, accumulated for all 24 enterprises). These numbers underpin the government's cluster strategy for the pharmaceutical industry. There are, however, still regional ambiguities: thus, only 63% of 282 approved vaccine formulations[57] are produced by 29 enterprises within the 4 clusters, whereas 37% are fabricated elsewhere in China, suggesting future moves in mergers and acquisitions.

Relative turnover of the 24 biopharmaceutical companies listed on the Chinese stock markets 2015



Selected Biopharmaceutical Product Application Areas

Therapeutic monoclonal antibodies

The Chinese market for therapeutic monoclonal antibodies in 2015 had sales of about ¥ 80 – 100 B. Over 50% of the market share was taken by 10 imported antibodies from seven international companies (Table 7.1).

Ten therapeutic antibodies registered by CFDA originate from Chinese companies (Table 7.2). Major producers in China are Shanghai CP Guojian Pharmaceutical in Shanghai (see box 7.1) and Innovent Biotechnology in Suzhou.

As patent protection of many therapeutic antibodies has already run out or will run out shortly, Chinese manufacturers foresee excellent opportunities for generic antibody production. More than 100 enterprises carry out R&D on this subject, but only a few of them are based on IP generated in China. Most antibodies being studied are "me-too" or "me-better" products acquired through cooperation with universities or by direct purchase from foreign companies.

Box 7.1

Shanghai CP Guojian Pharmaceutical (CPGJ)

Shanghai CP Guojian Pharmaceutical (CPGJ), a state-owned company invested and controlled by the China International Trust and Investment Corporation (CITIC Ltd) hosts the National Engineering Research Center of Antibody Drugs. Since its establishment in 2002, CPGJ has grown into a leading antibody company in China's antibody sector. CPGJ's pipeline comprises some 10 therapeutic antibodies. The company operates several 3,000-to 5,000-liter bioreactors for production, and antibody-manufacturing capacity is among the largest in the industry. CPGJ has participated in the establishment of national antibody drug specifications.

Table 7.1 **Ten imported antibody drugs approved by CFDA**

name	systematic name	indication and target	manufacturer	CFDA approval
OKT3	Muromab	allografts: CD3	Cuba CMIC*	1999
Zenapax	Daclizumab	kidney transplants: CD25	Roche	2000
Rituxan	Rituximab	non-Hodgkin lymphoma: CD20	Roche	2000
Herceptin	Trastuzumab	breast cancer: HER^{2+}	Roche	2003
Simulect	Basiliximab	kidney transplant: CD25	Novartis	2004
Erbitux	Cetuximab	colorectal cancer: EGFR	Merck	2005
Remicade	Infliximab	rheumatoid arthritis: TNFα	Janssen	2007
Humira	Adalimumab	rheumatoid arthritis: TNFα	AbbVie Ltd	2010
Avastin	Bevacizumab	colorectal cancer: VEGF	Roche	2010
Enbrel	Etarnercept	rheumatoid arthritis: TNFα	Pfizer	2010
Lucentis	Ranibizumab	macular degeneration: VEGF	Novartis	2011
Actemra	Tocilizumab	rheumatoid arthritis: IL6	Roche	2013

gray color: imported antibody drugs which are not longer listed by CFDA. * CMIC: Cuba Molecular Immunology Center;

Table 7.2 **Ten therapeutic antibodies approved by CFDA, developed by Chinese companies**

name	indication and target	manufacturer	CFDA approval
anti-CD3 Monoclonal antibody	allografts: CD3	Wuhan institute of Biological Products	1999
anti interleukin – 8 mouse monoclonal AB	psoriasis: IL-8	Dongguan Hongyuanyishi Biological Products	2003
human recombinant type II tumor necrosis factor receptor-antibody fusion protein (injection)	rheumatoid arthritis: TNFα	Shanghai CP Guojian Pharmaceutical	2005
iodine [131] metuximab monoclonal antibody injection	liver cancer: CD147	Chengdu Huasun Group	2006
iodine [131] monoclonal antibody injection for tumor necrosis therapy	lung cancer: tumor cell nucleus	Shanghai Mei'en Biology	2006
Nimotuzumab injection	nasopharyngeal carcinoma: EGFR	Biotech Pharmaceutical	2008
human recombinant TNF receptor-Ig fusion protein for injection	rheumatoid arthritis: TNFα	Shanghai Celgen Pharm	2011
humanized anti-CD25 MAb	kidney transplant: CD25	Shanghai CP Guojian Pharmaceutical	2011
Conbercept	age-related macular degeneration: VEGF	Chengdu Kanghong	2013
human recombinant tumor necrosis factor receptor II -IgG Fc fusion protein	rheumatoid arthritis: TNFαα	Zhejiang Hisun Pharma	2015

Major producers in China are Shanghai CP Guojian Pharmaceutical in Shanghai (see Box 7.1) and Innovent Biotechnology in Suzhou.

In 2015, applications for registration numbered 400 cases.[58] According to a recent summary, Chinese antibody manufacturers still suffer from the following drawbacks[59]:

- lack of independent IP
- production cost is too high
- production capacity is insufficient, e. g., on bioreactor volume and serum-free media
- downstream processing is inadequate
- drug quality testing is immature ("lack of self-inspection")

Cleanroom for bio-pharmaceutical production.

Table 7.3 **Public institutes involved in R&D on therapeutic antibodies**

institution	targets and products	remarks
Academy of Military Medical Sciences (Beijing) *www.bmi.ac.cn/*	tetanus-directed humanized antibodies	state-level therapeutic antibody engineering research institute in China
Institute of Genetics and Developmental Biology, CAS (Beijing) *english.genetics.cas.cn/*	encephalitis B directed monoclonal antibodies	Dongguan Hongyuanyishi Biological Products
Cancer Hospital, CAMS (Beijing) *www.cicams.ac.cn/*	esophagus cancer research and development of humanized antibodies	
Institute of Medical Biotechnology CAMS, and Peking Union Medical College (Beijing) *www.imb.com.cn/en/about.aspx*	R&D on antibody fragments, fusion proteins	leading tumor-related institution
Shanghai Institutes for Biological Sciences, CAS, *english.sibs.cas.cn/*	basic research, proteome platform	
Institute Pasteur of Shanghai, CAS *english.shanghaipasteur.cas.cn/*	tumor immunology and immunotherapy	Shanghai's public R&D platform for the life sciences
Cell Engineering Research Center (CERC), the Fourth Military Medical University (Shaanxi) *xa-cerc.fmmu.edu.cn/* (CN)	phage antibody libraries	national cellengineering platform, large-scale preparation of antibodies
Southern Medical University (former name: First Military Medical University) (Guandong), *www.fimmu.com/english*	tumor-targeted biological treatment, applied gene chip	Guandong's experimental biotechnology base

CAS Chinese Academy of Sciences, CAMS Chinese Academy of Medical Sciences

As shown in Table 7.3, a number of public research institutes are involved in R&D on therapeutic antibodies.

Companies

SOE: state-owned enterprise PE: private enterprise 123456-CN: stock number (searchable in Google) (CN), (E) after URL: website in Chinese or English, respectively. Turnover and number of employees only occasionally available.

Northeastern cluster

Biotech Pharma (PE) 百泰生物药业
Address: Rongjing East Street No. 2, Beijing Economic and Technology Development Area, Beijing 100176, PRC.
en.biotechplc.com/ (E).
Main products: monoclonal antibody nimotuzumab, humanized anti- CD6 monoclonal antibody for injection, recombinant human EGF conjugated vaccine

Eastern cluster

Shanghai CP Guojian Pharmaceutical (SOE) 上海中信国健药业
Address: No.399, Libing Rd., Zhangjiang Hi-Tech Park, Pudong New Area, Shanghai 201203, PRC.
www.cpgj-pharm.com/EN/ (E).
Main products: recombinant human tumor necrosis factor-α receptor II – IgG Fc fusion protein for injection, recombinant humanized anti-CD25 monoclonal antibody for injection

Shanghai Celgen Biopharma (PE) 上海赛金生物
Address: No.300, Chunxiao Road, Pudong Zhangjiang Park, Shanghai, 201203, PRC.
www.celgenpharm.com/ (CN).
Main products: recombinant human TNF receptor-IgG fusion protein for injection

Zhejiang Hisun Pharmaceutical (PE) 浙江海正药业
Address: No.46 Waisha Road, Taizhou, Zhejiang 318000, PRC. 600267-CN.
www.huasungrp.com (CN).
Turnover 2015: ¥ 8,8 B. 9,293 employees.
Main products: Recombinant human tumor necrosis factor-α receptor II: IgG Fc fusion protein for injection

Western cluster

Wuhan Institute of Biological Products (SOE) 武汉生物制品研究所
Address: No.1, Huangjin Industrial Park Road, Zhengdian, Jiangxia District, Wuhan, Hubei 430207, PRC.
www.wibp.com.cn/en/about.asp (E).
Main products: mouse monoclonal antibody against human CD3 antigen of T lymphocyte for injection

Chengdu Huasun Group (PE) 成都华神集团
Address: No.1168 Shuxindadao, Gaoxin District, Chengdu, Sichuan 611731, PRC. 000790-CN.
www.huasungrp.com (CN).
Turnover 2015: ¥ 463 M. 827 employees.
Main products: iodine [131I] metuximab for injection

Companies active in R & D on new therapeutic antibodies, without CFDA-registered products

BeiGen (PE) 百济神州
Address: No.30 Science Park Road, Zhongguancun Life Science Park, Changping District, Beijing 102206, PRC.
www.beigene.com/ (E).

RemeGen biological pharmaceutical (PE) 荣昌生物
Address: No.58, Beijing Road, Yantai Economic and Technological Development Zone, Shandong, PRC.
www.remegen.cn/about/index.html (CN).

Shenyang 3SBio (PE) 沈阳三生制药
Address: Shenyang Economy & Technology Development Zone, Shenyang, Liaoning 110027, PRC.
www.3sbio.com/en/ (E)

Sinocelltech (PE) 神州细胞工程
Adresse: Suite B-211, No.14 Zhonghe Street, BDA, Beijing, 100176.
www.sinocelltech.com/EN/index.html (E)

Innovent Biologics (Suzhou) (PE) 信达生物制药 (苏州)
Adresse: No.168 Dongping Street, Suzhou Industrial Park, Jiangsu 215123, PRC.
www.innoventbio.com/en/ (E).

Jiangsu Hengrui Medicine (PE) 江苏恒瑞医药
Address: No.7 Kunlun Road, Economic and Technological Development Zone, Lianyungang, Jiangsu 222047, PRC. 600276-CN
www.hrs.com.cn/english/ (E).

Shanghai Institute of Biological Products (SOE) 上海生物制品研究所
Address: No.1262 West Yanan Road, Shanghai, 200052, PRC.
www.siobp.com/english/html/enterprise_intro.html (E).

Adagene (PE) 天演药业
Address: 4F, Building C14, No.218 Xinghu Street, Suzhou Industrial Park, Jiangsu, PRC.
www.adagene.com/ (E).

PersonGen Biomedicine (PE)博生吉医药
Address: Room 413, Building B1, BioBAY, No.218 Xinghu Street, Suzhou Industrial Park, Jiangsu, PRC.
www.persongen.com/ (CN)

Zhejiang Medicine (SOE) 浙江医药
Address: F.3, Building A Kechuangyuan, No.398 Mahuan Road, Binhaixincheng, Shaoxing, Zhejiang 312366, PRC. 600216-CN.
www.china-zmc.com.cn/en/ (E).
In 2013, cooperative develop and commercialize a Her2-ADC product with American AMBRX, Inc.

WuXi AppTec (PE) 药明康德
Address: No.88 Fute Zhong Road, Waigaoqiao Free Trade Zone, Shanghai 200131, PRC.
www.wuxiapptec.com/ (E)

Shanghai Fosun Pharmaceutical (PE) 上海复星医药
Address: No.1289 Yishan Road, Building A, Fosun Technology Park, Shanghai 200233, PRC. 600196-CN.
www.fosunpharma.com/en/index.html (E)

Genor Biopharma (PE) 嘉和生物
Address: Building 3, No.1690 Zhangheng Road, Pudong New Area, Shanghai 201203, PRC.
www.genorbio.com/ (CN)

Shanghai Henlius Biotech (PE) 上海复宏汉霖生物
Address: Building C, 1289 Yishan Road, Xuhui District, Shanghai, 200233, PRC.
www.henlius.com/en/index.aspx (E)

Shenzhen Main Luck Pharmaceuticals
(PE) 深圳万乐药业
Address: Main Luck Building, Bagua Road 4, Futian District, Shenzhen, Guangdong 518029, PRC.
www.wanle.com.cn/eng/01intro/ (E)

Wuhan YZY Medical Technology (PE) 武汉友芝友医疗
Address: Building C2-1, Biolake, No.666 Gaoxin-dadao, East Lake Development Zone, Wuhan, Hubei 430075, PRC.
www.yzybio.com/en/index.asp (E)

International

Shanghai Roche Pharmaceuticals 上海罗氏制药
Address: No.1100 Longdong Dadao, Pudong New Area, Shanghai 201203, PRC.
www.roche.com.cn/ (CN).
Main products: tocilizumab injection, trastuzumab injection, rituximab injection

Novartis pharma 诺华制药
Address: No.4218 Jinke Road, Zhangjiang High-Tech Park, Pudong New Area, Shanghai 201203, PRC.
www.novartis.com.cn/ (CN).
Main products: ranibizumab injection, basiliximab injection

Xi'an Janssen Pharmaceutical 西安杨森
Address: No.34, North Wanshou Road, Shanxi 710043, PRC.
www.xian-janssen.com.cn/en (E).
Main products: infliximab for injection

All therapeutic antibodies from international companies are imported products.

Blood products and other therapeutic proteins

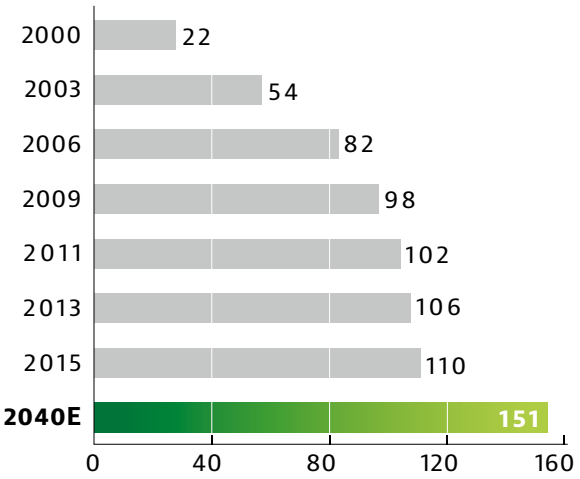
China has established the fabrication of blood products as early as 1960, and initially those were offered by over 70 blood banks. Since 1996, regulations issued by the NHFPC and revised in 2016 have reduced these companies to 25 which all have GMP certificates. Three types of products are officially approved: (1) human serum albumin (2) human immunoglobulins (Ig) such as hepatitis B-directed Ig, rabies Ig, or tetanus Ig, and (3) clotting factors such as factor VIII, prothrombin complex and human fibrinogen. Major players are Sinopharm, Hualan Bio and the China National Biotech Group Beijing which operates 18 blood banks. Shanghai Raas is specialized in the detection of virus contamination in blood and blood products.

Recombinant biologics such as insulin, erythropoietin (EPO) and therapeutic antibodies (see special feature) arrived in China around 1990. Though their share in the Chinese pharmaceutical market is only around 10%, this is a growing market which is dominated by foreign-based companies. Biosimilar products are said to contribute 96% (including antibodies) of sales to this market.[60] In China, biosimilars are classified as new bioproducts and evaluated according to the general rules for class I innovative drugs, based on case-specific data-sets.

Insulin

With an estimated 110 million, China is the country with the largest number of people suffering from diabetes.[61] China's annual health expenditures for diabetes treatment are assumed at ¥ 173.4 B, 13% of total medical expenditures. Only 15% of those diagnosed are receiving comprehensive treatment.

Number of Chinese people with diabetes



Source: data from international Diabetes Federation Atlas, Novo Nordisk

The recombinant insulin market is dominated by Novo Nordisk, Eli Lilly and Sanofi. They control about 90% of the market of which Novo Nordisk holds the lion's share.[62] In the CFDA database, 80 CFDA-approved insulin formulations and 30 registered Chinese manufacturers can be found. With 16 and 15 approved formulations, respectively, Jiangsu Wangbang Medical and Jilin Tongbao Medical are in possession of the most certified

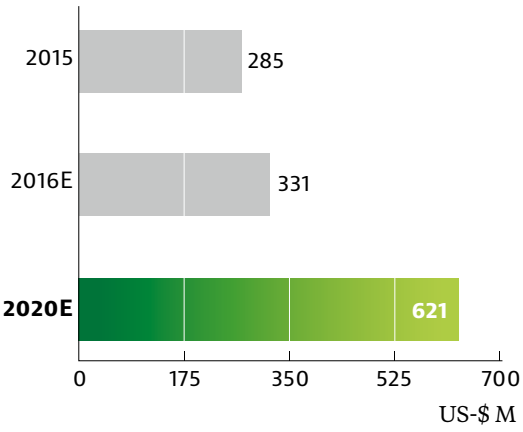
formulations. In 2016, Genovate Biotechnology of Taiwan has started the construction of an insulin-manufacturing facility in Changzhou.[63] Recently, the government has insisted that Chinese CMOs should obtain better access to the manufacture and marketing of insulin.

In 2014, Sanofi has already set up a joint venture with Zhejiang Hisun Pharmaceutical to develop insulin and other diabetes-related drugs. CFDA has approved eight different types of insulins and insulin formulations: recombinant human (rh) insulin, insulin glargine, aspart insulin, insulin lispro, adenosine disodium triphosphate coenzyme A rh insulin, protamine rh insulin, protamine Zn rh insulin, and protamine Zn lispro rh insulin.

Erythropoietin (EPO)

A recent market study sees the recombinant human EPO market in China at US-$ 285 M in 2015, with a projected growth rate of 17%.[64] Major application areas of EPO are chronic kidney diseases (CDK) and the treatment of anemia during cancer therapy. Due to China's aging population, there are some 110 million registered patients with CDK, and the country accounts for 22% of global cancer cases.

Sales of rh EPO in China



The top five EPO manufacturers in China are 3S Bio in Shenyang (Liaoning), Shanghai Chemo Wanbang Biopharma, the Chengdu Di'ao Group, NCPC Genetech Biotechnology in Shijiazhuang (Hebei), and Kyowa Hakko Kirin China Pharmaceutical in Shanghai Pudong.

Interferons[65]

A major interferon applied in China is interferon-ß, for the treatment of hepatitis B and C. The number of people infected with hepatitis B or C in China is estimated at 100 million. As a result, interferon-ß has great potential on the Chinese market, of which more than 60% are occupied by Roche and Merck, Sharp and Dohme (MSD) with their long-acting PEGylated interferons. The CFDA has approved 93 formulations from 20 manufacturers, among which recombinant human (rh) interferon α2a, rh interferon α2b, α1b are dominant. Apart from Roche and Schering-Plough, Beijing's Tri-Prime Gene and Anhui Anke Biotechnology hold approvals for 22 and 11 formulations, respectively. Other domestic manufacturers are Shanghai Huaxing and Shenzhen Kexing Biotech.

Thrombolytics

Strokes are a major cause of death and adult disability in China – fivefold higher than myocardial infarction.[66] Apart from traditional methods, treatment for both diseases is by streptokinase, urokinase and recombinant thrombolytics. CFDA has approved only two recombinant tPA products, namely Alteplase produced by Boehringer Ingelheim China (Shanghai) and Reteplase by Aide Pharmaceutical (Beijing), a subsidiary of the Canadian IND group.

Urokinase, a plasminogen activator, is a thrombolytic agent which is isolated from human urine. The CFDA has approved 131 formulations from 34 manufacturers. Among them Nanjing Nanda Pharm has obtained nine, whereas each of Chengdu Tongde Pharm, Jilin Aodong and Jilin Huinan Changlong have received eight approvals.
Streptokinase is a microbial plasminogen activator which is produced by fermentation. CFDA has approved two streptokinase thrombolytics made by Qingdao Guoda, and three prepared by Shanghai Chemo Wanbang.

Clotting factors

By the end of 2015, about 100,000 patients in China were registered as hemophiliacs. Due to improved diagnostic services, this figure has nearly doubled in the last five years. Less than 10% of hemophiliacs seem to receive proper treatment, as its estimated annual cost per patient for appropriate treatment is ¥ 800,000.[67] CFDA has approved 22 clotting factors from which 21 are based on recombinant human factor VIII. Among the eight com-

panies which have been certified, seven approvals were provided to Shanghai RAAS Blood Products, and five to Hualan Biological Engineering.

Companies

SOE: state-owned enterprise; PE: private enterprise; 123456-CN: stock number (searchable in Google); (CN), (E) after URL: website in Chinese or English, respectively; turnover and number of employees are not always available.

Northeastern cluster

Beijing Tiantan
Biological Products (SOE) 北京天坛生物制品
Address: No.6 Boxing 2 Road, Daxingyizhuang Development Zone, Beijing 100176, PRC. 600161-CN.
www.tiantanbio.com/ (CN).
Turnover 2015: ¥ 1,6 B. 2,680 employees.
Main products: blood products (62%) such as human albumin, human immunoglobulin; vaccines

Shandong Kexing Bioproducts (PE) 山东科兴生物制品
Address: Mingshui Development Zone, Zhangqiu, Shandong 250200, PRC.
www.sdkexing.com/ (E).
Main products: recombinant human erythropoietin injection (EPO), recombinant human granulocyte colony-stimulating factor injection (rh-G-CSF)

Shenyang 3SBio (PE) 沈阳三生制药
Address: No.3 A1, Road 10, Economy & Technology Development Zone, Shenyang, Liaoning 110027, PRC.
www.3sbio.com/en/ (E).
Main products: recombinant human thrombopoietin, recombinant human erythropoietin, recombinant human interferon alpha -2a

Beijing Kawin Technology (PE) 北京凯因科技
Address: No.6 Eastern Rongjing Road, Economy-Technology Development Area, Beijing 100176, PRC.
www.kawin.com.cn/en/ (E).
Main products: recombinant human interferon alfa 2b for injection

Beijing Gan & Lee Biotechnology (PE) 北京甘李生物
Address: No. 8 Jingsheng North 3rd Street, Golden Bridge Science Industrial Base, Zhongguancun Science Park, Tongzhou District, Beijing 101102, PRC.
www.ganlee.com/en/ (E).
Main products: insulin glargine injection, insulin lispro injection

North China Pharmaceutical
Jintan Biotechnology (PE) 华北制药金坦生物
Address: No.106, Tianshan Avenue, New & High-Tech Development Zone, Shijiazhuang, Hebei 050035, PRC.
www.ncpcgt.com.cn/ (CN).
Main products: recombinant hepatitis b vaccine (CHO cells), recombinant human granulocyte macrophage colony stimulating factor rhGM – CSF, recombinant human granulocyte colony stimulating factor, rhG CSF, recombinant human erythropoietin rhEPO

Beijing Tri-Prime Gene (PE) 三元基因
Address: No.1, Jinyuan Road, Daxing Economic Development Zone, Beijing 102600, PRC.
www.triprime.com/en/ (E).
Main products: recombinant human interferon α1b for injection

Qingdao Guoda
Bio-Pharmaceutical (PE) 青岛国大生物制药
Address: No.216, Qianwangang Road, Economic and Technology Development Zone, Qingdao, Shandong 266510, PRC.
www.guodabio.com/ (CN).
Main products: recombinant streptokinase for injection

Eastern cluster

Shanghai Raas Blood Products (PE) 上海莱士血液制品
Address: No.2009, Wangyuan Road, Fengxian District, Shanghai 201401, PRC. 002252-CN
www.raas-corp.com/page.aspx?node=95&f=en (E).
Turnover 2015: ¥ 2,0 B. 2,471 employees.
Main products: albumin, immunoglobulin, coagulation factor

Shanghai Chemo
Wanbang Biopharma (PE) 上海凯茂生物医药
Address: No.518 Nanyangjing Road, Pudong New +Area, Shanghai, PRC.
www.chemowanbang.cn/index.asp (E).
Main products: recombinant human erythropoietin for injection, recombinant streptokinase for injection, recombinant human interferon gamma for injection

Shanghai Xinxing Medicine (SOE) 上海新兴医药
Address: No.518 Nanyangjing Road, Pudong New Area, Shanghai, PRC.
www.medicine-sxx.com.cn/ (CN).
Main products: human albumin, human immunoglobulin, human prothrombin complex, human fibrinogen

Shanghai Institute of
Biological Products (SOE) 上海生物制品研究所
Address: No.1262 West Yanan Road, Shanghai 200052, PRC.
www.siobp.com/english/html/product_center.html (E).
Main products: vaccine; blood products such as Human albumin, human immunoglobulin; recombinant human interferon 1b for injection

Wanbang Biopharmaceuticals (PE) 江苏万邦生化医药
Address: No.6 Yangshan Road, Jinshanqiao Economic Zone, Xuzhou, 221004, Jiangsu, PRC.
en.chinawanbang.com/ (E).
Main products: recombinant human interferon Y for injection, recombinant human erythropoietin (CHO) for injection

Shanghai Hua Xin
High Biotechnology (PE) 上海华新生物高技术
Address: No.1150 Guiqiao Road,
Pudong, Shanghai 201206, PRC.
www.huaxin-bio.com/index.html (CN).
Main products: human recombinant interleukin – 2 injection and human recombinant interferon alpha 2 b injection

Southern cluster

Guangdong Shuang Lin
Bio-Pharmacy (PE) 广东双林生物制药
Address: No.1 East Xinfeng Road, East Island, Zhanjiang, Guangdong 524009, PRC.
www.zjslbio.com/ (CN).
Main products: human albumin, human immunoglobulin for intravenous injection (pH4)

Shenzhen Kexing Biotech (SOE) 深圳科兴生物工程
Address: F.18, Kexing Science Park Building B,
No.15 Keyuan Road, Nanshan District, Shenzhen, Guangdong 518057, PRC.
www.kexing.com.cn/ (CN).
Main products: recombinant human interferon 1b for injection

United Laboratories (PE Hongkong) 联邦制药
Address: 6 Fuk Wang Street, Yuen Long Industrial Estate, Yuen Long, New Territories, Hongkong
www.tul.com.cn/en/ (E).
Main products: mixed protamine recombinant human insulin injection, isophane protamine recombinant human insulin injection, recombinant human insulin injection

Uni-Bio Science (PE Hongkong) 联康集团
Address: Room 3006, the Centrium,
60 Wyndham Street, Centrl, Hongkong.
www.uni-bioscience.com/ (E).
Main products: recombinant human epidermal growth factor

Western cluster

Chengdu Diao Group (PE) 成都地奥集团
Address: No.26 Chuangye Road, Gaoxindadao,
High-Tech Zone, Chengdu, Sichuan, PRC.
www.diao.com/index.aspx (CN).
Main products: recombinant human erythropoietin for injection

Chengdu Rongsheng Pharmaceuticals (PE) 成都蓉生药业
Address: No. 7 Keyuan South Road,
High-Tech Zone, Chengdu, Sichuan 610041, PRC.
www.ronsen.com/eng/index.asp (E).
Main products: human immunoglobulin for intravenous injection, human coagulation factor VIII

Humanwell Healthcare (PE) 人福医药
Address: No.666 Gaoxin Road,
East Lake High-Tech Development Zone,
Wuhan, Hubei 430075, PRC. 600079-CN
en.humanwell.com.cn/ (E).
Turnover 2015: ¥ 10 B. 12,344 employees.
Main products: biological products (4%) such as recombinant human erythropoietin, recombinant human granulocyte colony stimulating factor

Sichuan Yuanda Shuyang
Pharmaceutical (PE) 四川远大蜀阳药业
Address: Jie'eryan, Zhonghe Town,
High-Tech Zone, Chengdu, Sichuan 610214, PRC.
www.shuyang.com/en (E).
Main products: human albumin, human immunoglobulin for intravenous injection (PH4)

Chengdu Tongde Pharmaceutical (SOE) 成都通德药业
Address: No.222 Liutaidadao B, Strait science and Technology Industry Development Park, Wenjiang District, Chengdu 611130, PRC.
www.cd-tdyy.com/ (CN).
Main products: urokinase for injection

Locations outside the four clusters

Hualan Biological Engineering (PE) 华兰生物工程
Address: Jia No.1, Hualan Avenue, Xinxiang, Henan 453003, PRC. 002007-CN
english.hualanbio.com/index.html (E).
Turnover 2015: ¥ 1,5 B. 1,515 employees.
Main products: blood products (92%) such as human albumin, human immunoglobulin, human prothrombin complex; vaccines (7%)

Changchun Institute of Biological Products (SOE) 长春生物制品研究所
Address: No.1616 Chuangxin Road, Changchun, Jilin 130012.
www.ccbio.net/ (CN).
Main products: recombinant human interferonα2a for injection, recombinant human interleukin-2 for injection, vaccines

Chang Chun High & New Technology Industries (PE) 长春高新技术产业
Address: F.5 Building Huoju, No. 2400 Tongzhi Street, Changchun, Jilin 130021, PRC. 000661-CN.
www.cchn.com.cn/ (CN).
Turnover 2015: ¥ 2,4 B. 3,861 employees
Main products: polyethylene glycol recombinant human growth hormone injection, recombinant human growth hormone, human recombinant follicle stimulating hormone

Tonghua Dongbao Pharmaceutical (PE) 通化东宝药业
Address: Dongbao Xincun, Tonghua, Jilin 134123, PRC. 600867-CN
www.thdb.com/ (CN).
Turnover 2015: ¥ 1,7 B. 1,970 employees
Main products: recombinant human insulin injection

Jilin Huinan Changlong pharmaceutical (PE) 辉南长龙生化药业
Address: Pharmaceutical Industrial Park, Economic Development Zone, Chaoyang Town, Huinan Country, Tonghua, Jilin 135100, PRC.
www.jlchanglong.com/ (CN).
Main products: urokinase for Injection

Jiangxi Boya Bio-pharmaceutical (PE) 江西博雅生物制药
Address: No.333 Huiquan Road, High-Tech Park, Fuzhou, Jiangxi 344000, PRC. 300294-CN.
www.china-boya.com/Index.aspx (CN).
Turnover 2015: ¥ 543 M. 1,295 employees
Main products: human fibrinogen, human immunoglobulin, human albumin

Shanxi Kangbao of Biological Product (PE) 山西康宝生物制品
Address: Beihuan West Street, Changzhi, Shanxi, PRC.
www.kbzy.cn/index.html (CN).
Main products: human albumin, human tetanus immunoglobulin, human rabies immunoglobulin

Anhui Anke Biotechnology (PE) 安徽安科生物工程
Address: AnkeBio Building, No.669 Changjiang Road, West, Hefei, Anhui 230088, PRC. 300009-CN.
www.ankebio.com/english/ (E).
Turnover 2015: ¥ 636 M. 1,228 employees
Main products: recombinant human interferon alpha 2b, recombinant human growth hormone

International

Novo Nordisk 诺和诺德 (中国) 制药
Address: F.18 global financial center east building, East Third Ring middle Road, Chaoyang District, Beijing, 100020, PRC.
www.novonordisk.com.cn/ (CN).
Main products: insulin, recombinant human coagulation factor VIIa for injection

Eli Lilly (Suzhou) 礼来苏州制药
Address: No. 6 Bai Yu Rd., Suzhou Industrial Park, Jiangsu 215021, PRC.
www.lillychina.com/ (CN).
Main products: insulin

Sanofi China赛诺菲中国
Address: F. 19, the office building of Jinganjiali Center 3, No. 1228 middle Yanan Road, Jingan District, Shanghai 200040, PRC.
www.sanofi.cn/l/cn/zh/index.jsp (CN).
Main products: insulin glulisine injection, insulin glargine injection, vaccine

Shanghai United Cell Biotechnology 上海联合赛尔生物
Address: No.1150 Guiqiao Road, Jinqiao, Pudong, Shanghai 201206, PRC.
english.unitedbiotech.com.cn/en/Index.asp (E).
Main products: recombinant human growth hormone for injection, recombinant B-subunit/whole cell cholera vaccine (Enteric-coated capsule)

Green Cross (China)
Biological Products 绿十字（中国）生物
Address: Huainan Economic and Technology Development Zone, Anhui 232008, PRC.
www.greencrosschina.com/index.asp (CN).
Main products: human albumin, human immumoglobulin (pH4) for intravenous injection, human coagulation factor VIII, human fibrinogen

Kyowa Hakko Kirin China
Pharmaceutical 协和发酵麒麟（中国）制药
Address: No.970 Longdong Road, Pudong New Area, Shanghai 201203, PRC.
www.kyowa-kirin.com.cn/en/index.html (CN).
Main products: recombinant human granulocyte colony stimulating factor, recombinant human erythropoietin

Boehringer Ingelheim Pharma China 勃林格殷格翰中国
Address: No.138 Pudong Road, Pudong New Area, Shanghai 200120, PRC.
www.boehringer-ingelheim.com.cn/ (CN).
Main products: biological products such as alteplase for injection

Human vaccines

China is the world's largest producer of vaccines. 95% of all vaccines used in China have been nationally produced – predominantly by state-owned Chinese companies. In addition, international companies operate vaccine-manufacturing plants. The vaccine market of China was estimated at sales of ¥ 20 B in 2014,[68] with an annual growth rate of 15%. ¥ 14 B or 70% of this market relate to animal vaccines.[69]

As of October 2016, some 280 vaccines and vaccine formulations have been certified by the CFDA and have been produced by 41 producers. For human vaccination, free EPI („extended program on immunization") vaccines prevail with a share of about 80%. 37% of all approved vaccines are manufactured by companies in Jilin or Henan province, and 71% by companies located in the 4 future cluster regions, with the Northeastern Region coming out on top.
In 2014, the lot-release-volume of EPI vaccines of Chinese state-owned enterprises accounted for 72%, but decreases constantly because the government gradually relaxes control over the vaccine market. As a consequence, the market share of private companies and foreign players in market segments of new EPI vaccines are increasing. Private and foreign brands already hold a dominant position in the markets of Haemophilus influenza B (Hib), human rabies vaccine, varicella vaccine, and influenza vaccine.

The market is dominated
by state-owned enterprises including:

- Beijing Tiantan Biological Products
- Chengdu Institute of Biological Products Co.
- Shanghai Institute of Biological Products Co.
- Lanzhou Institute of Biological Products Co.
- Wuhan Institute of Biological Products Co.
- Changchun Institute of Biological Products Co.
- Institute of Medical Biology (CAMS)

Box 7.2

Problems with vaccination

In 2014, 17 children died after receiving a compulsory hepatitis B vaccination. Following government inspection, companies such as Shenzhen Kangtai, Tiantan Biological and Dalian Hissen halted production because they failed to pass the new GMP certification. As a consequence, China's human vaccine lot-release-volume declined by 2.4% in 2014.

A recent scandal involved more than 20,000 expired and improperly stored vaccines that were sold on the black market for the equivalent of approximately US-$ 90 M since 2010. Some 25 different vaccines for both children and adults are believed to have been sold, including vaccines for polio, rabies, hepatitis B, and influenza. The Chinese government has detained 130 individuals from 29 companies and 16 vaccination centers. A state-run company called Hebei Weifang Biological Products Supply Center linked to the provincial Hebei Center for Disease Control and Prevention (CDC) has reportedly been found to be a part of the illegal distribution network.

Human vaccines approved by CFDA (October 2016)

- Anthrax vaccine (live)
- Brucellosis vaccine (live), cell free DPT vaccine
- Diphtheria Vaccine. adsorbed DPT vaccine
- Enterovirus type 71 inactivated vaccine
- Enterovirus type 71 Vaccine (Vero cells)
- Furunculosis vaccine
- Group A and C Meningococcal polysaccharide vaccine
- Group A Meningococcal polysaccharide vaccine
- H1N1 influenza vaccine
- Haemophilus influenzae type b conjugate vaccine
- Haemophilus influenzae type b vaccine
- Haemorrhagic fever with renal syndrome, bivalent purified vaccine (Vero cells)
- Hepatitis A vaccine (live)
- Combined hepatitis A+B vaccine
- Hepatitis B vaccine (Hansenula)
- Hepatitis E vaccineŒ. coliα
- Inactivated ACYW135 group Meningococci
- Polysaccharide vaccine
- Influenza vaccine, Inactivated
- Japanese encephalitis purified vaccine (PHK cells)
- Leptospira vaccine
- Measles vaccine (live)
- Measles, mumps and Rubella combined vaccine (live)
- Mumps vaccine (live) attenuated DPT vaccine
- Mumps vaccine (live)
- Oral bivalent live vaccine for S.flexneriza-S.sonnei
- Oral rotavirus vaccine
- Pertussis vaccine
- Plague vaccine (live)
- Poliomyelitis vaccine (human diploid cells)
- Rabies vaccine (human diploid cells)
- Rabies vaccine (rat kidney cells)
- Rabies vaccine (Vero cells)
- Rubella vaccine (live) (rabbit kidney cells)
- Trachitis vaccine
- Typhoid and para-typhoid A + B combined vaccine
- Typhoid VI polysaccharide vaccine
- Varicella vaccine (live)
- Yellow fever (live), attenuated

Companies

SOE: state-owned enterprise PE: private enterprise 123456-CN: stock number (searchable in Google) (CN), (E) after URL: website in Chinese or English, respectively. Turnover and number of employees only occasionally available.

Northeastern cluster

Beijing Tiantan of Biological Products (SOE)
北京天坛生物制品
Address: No.6 Boxing 2 Road, Daxingyizhuang Development Zone, Beijing 100176, PRC. 600161-CN.
www.tiantanbio.com/ (CN).
Turnover 2015: ¥ 1,6 B. 2,680 employees.
Main products: blood products (62%) such as human albumin, human immunoglobulin; vaccines such as yellow fever vaccine, live

Sinovac Biotech (PE) 科兴控股生物技术有限公司
Address: No. 39 Shangdi Xi Road, Haidian District, Beijing, 100085, PRC.
www.sinovac.com/ (E).
Main products: vaccines such as enterovirus type 71 vaccine (vero cell) inactivated, hepatitis A vaccine (human diploid cell), inactivated

Dalian Hissen Bio-Pharmaceutical (PE)
大连汉信生物制药
Address: No.35 Wanda Road, Economic and Technological Development Zone, Dalian, Liaoning 116100, PRC.
www.hissen.com/englishweb/ (E).
Main products: recombinant hepatitis B vaccine (hansenula polymorpha), influenza vaccine (split virion), inactivated

Liaoning Cheng Da Biotechnology (PE) 辽宁成大生物
Address: No.1 Xinfang Street, Hunnan New District, Shenyang, Liaoning, PRC.
www.cdbio.cn/default.aspx (CN).
Main products: Rabies Vaccine, encephalitis inactivated vaccines

Beijing Luzhu Biotechnology (PE) 北京绿竹生物
Address: No.3 Guangtong Street, Tongzhou Industrial Development Zone, Beijing.
www.luzhubiotech.com/about.html (CN).
Main products: typhoid VI polysaccharide vaccine, group A and C meningococcal polysaccharide vaccine

Eastern cluster

Shanghai Institute of Biological Products (SOE) 上海生物制品研究所
Address: No.1262 West Yanan Road, Shanghai, 200052, PRC.
www.siobp.com/english/html/enterprise_intro.html (E), see *www.baidu.com*
Main products: varicella vaccine, live; measles, mumps and rubella combined vaccine, live

Royal (Wuxi) Bio-Pharmaceutical (PE) 罗益（无锡）生物制药有限公司
Address: No.32 Changjiang South Road, National High-Tech Industrial Development Zone, Wuxi, Jiangsu 214028, PRC.
www.chinaroyal.cn/aboutus.asp (CN).
Main products: haemorrhagic fever with renal syndrome bivalent vaccine (vero cell), inactivated; group A and group C meningococcal conjugate vaccine

Southern cluster

Shenzhen Kangtai of Biological Products (PE) 深圳康泰生物制品
Address: No.6 Kefa Road, science and Technology Park, Nanshan District, Shenzhen, Guangdong, PRC.
www.biokangtai.com/docc/default.html (CN).
Main products: Recombinant Hepatitis B Vaccine (Saccharomyces cerevisiae)

Western cluster

Wuhan Institute of Biological Products (SOE) 武汉生物制品研究所
Address: No.1, Huangjin Industrial Park Road, Zhengdian, Jiangxia District, Wuhan, Hubei 430207, PRC.
www.wibp.com.cn/en/about.asp (E).
Main products: measles and mumps combined Vaccine, live; measles vaccine, live

Locations outside the four clusters

Hualan Biological Engineering (PE) 华兰生物
Address: Jia No.1, Hualan Avenue, Xinxiang, Henan 453003, PRC. 002007-CN
english.hualanbio.com/index.html (E).
Turnover 2015: ¥ 1,5 B. 1,515 employees.
Main products: blood products (92%) such as human albumin, human immunoglobulin, human prothrombin complex; vaccines (7%) such as recombinant hepatitis B vaccine (hansenula polymorpha)

Changchun Changsheng Bio-technology (PE) 长春长生生物
Address: No.1615 Yueda Road, Changchun, Jilin 130103, PRC. 002680-CN
www.cs-vaccine.com/en/index.asp (E).
Turnover 2015: ¥ 796 M. 1,105 employees.
Main products: rabies vaccine (vero cell) for human use, freeze-dried; hepatitis A (live) vaccine, freeze-dried; influenza vaccine split; varicella vaccine (live)

Changchun Institute of Biological Products (SOE) 长春生物制品研究所
Address: No.1616 Chuangxin Road, Changchun, Jilin 130012, PRC.
www.ccbio.net/ (CN).
Main products: DPT vaccine, rabies vaccine, typhoid VI polysaccharide vaccine

Lanzhou Institute of Biological Products (SOE) 兰州生物制品研究所
Address: No.888 Yanchang Road, Lanzhou, Gansu 730046, PRC.
www.vacmic.com/htm/list/45_1.html (E).
Main products: measles vaccine, live; rubella vaccine (rabbit kidney cell), live

Walvax Biotechnology 云南沃森生物技术股份有限公司
Address: 19/F Building 9A, Dingyi Tiancheng Residential Quarter, Keyuan Road No. 99, High & New Tech Development Zone, Kunming, Yunnan 650106, PRC. 300142-CN.
www.walvax.com/wosen/27.aspx (E).
Main products: group A and C meningococcal polysaccharide vaccine, inactivated ACYW135 group meningococci polysaccharide vaccine

Institute of Medical Biology Chinese Academy of Medical Sciences (SOE) 中国医学科学院医学生物学研究所
Address: No.935 Jiaoling Road, Wuhua District, Kunming, Yunnan 650031, PRC.
www.imbcams.ac.cn/Category_2142/Index.aspx (E).
Main products: vaccines, immunological and genetic engineering products

Xiamen Innovax Biotech (PE) 厦门万泰沧海生物
Address: No.130 Xinyuan Road, Haicang District, Xiamen, Fujian 361022, PRC.
www.innovax.cn/en/index.aspx (E).
Main products: hepatitis E vaccine (E.coli)

International

GlaxoSmithKline Biologicals 葛兰素史克
www.gsk-china.com/
Main products: inactivated split Influenza vaccine, recombinant hepatitis B vaccine (saccharomyces cerevisiae)

Sanofi Pasteur 赛诺菲巴斯德
Address: F.6, No.112 Jianguo Road, Chaoyang District, Beijing 100022, PRC.
www.sanofipasteur.cn/ (CN).
Main products: inactivated hepatitis A vaccine, adsorbed; poliomyelitis vaccine, inactivated

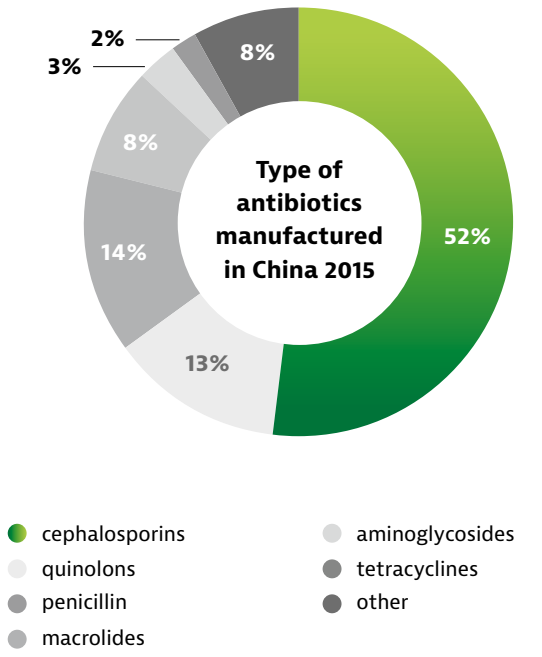
Adimmune Corporation (PE Taiwan) 国光生物科技
Address: No.3, Section 1, Tanxing Road, Tanzi District, Taichung 42743, Taiwan.
www.adimmune.com.tw/eng/index.php (E).
Main products: influenza vaccine (split virion), inactivated

Anti-infectives

With 210,000 t of antibiotics (2015), of which 30,000 t are exported, China is the global leader in this production sector. In China many antibiotics are on sale over the counter, and the annual per-capita consumption is 138 g[70] – tenfold the amount of the USA. The value of clinical antibiotics prescribed in the hospitals of China's major clinics in 2014[71] was about ¥ 14 B, about 10% more than in the preceding year.

β-Lactam antibiotics accounted for more than 80% of these drugs, including penicillin and its derivatives, cephalosporins, monoamide rings, carbapenems and penem enzyme inhibitors. Most of the remaining 20% were macrolide and glycoside antibiotics. China holds a monopoly on the production of lincomycin, a reserve antibiotic for patients who do not tolerate penicillin.

Anti-infectives



According to a recent study by Zhejiang University, School of Public Health, 90% out of 12,000 college students in 6 provinces are buying antibiotics without consulting a doctor. 58% of urine samples taken from 1,064 eight-to-eleven-year-old school children in Shanghai, Jiangsu and Zhejiang contained antibiotic metabolites, sometimes even from antibiotics restricted to animal use[72]. Due to the wide and indiscriminate use of antibiotics on humans, and their often uneducated use in agriculture, antibiotic resistance is a growing problem in China as well. A 2015 "antibiotic-pollution-map" of Chinese rivers[73] found relatively high concentrations of amoxicillin and quinolones in practically all rivers at the east coast of China.

There are over 10 major producers of antibiotics, distributed throughout China. These are

1. North China Pharmaceutical (NCPC) and CSPC Pharma, both in in Shijiangzhuang (Hebei), (penicillins, amoxicillin, chlorotetracycline and others),
2. United Laboratories (Hong Kong) (penicillins, erythromycin),
3. Shandong Lukang Pharmaceutical in Jilin (penicillins),
4. Guangzhou Baiyunshan Pharmaceutical (Guangdong) (cephalexin),
5. Qilu Pharmaceutical in Jinan (Shandong) (cephalexin and levofloxacin),
6. Sinopharm Weiqida Pharmaceutical in Datong (Shanxi) (cephalexin),
7. Merro Pharmaceutical in Dalian (Liaoning) (Erythromycin and Gentamycin),
8. Zhejiang Medicine Co., Ltd. Xinchang Pharmaceutical Factory in Xinchang (Zhejiang) (levofloxacin),
9. Yidu HEC Pharmaceutical in Yicheng (Hubei) (erythromycin and gentamicin),
10. Henan Kaifeng Pharmaceutical (Group) Co. Ltd. in Kaifeng (Henan) and Henan Renhua Biotech in Ruzhou (both gentamicin).

Major academic institutions involved in the development of new antibiotics are

1. Sichuan Industrial Institute of Antibiotics (SIIA)
2. Institute of Medical Biotechnology Chinese Academy of Medical Sciences, Beijing
3. The Shanghai Institutes of Biological Sciences, CAS
4. The Institute of Microbiology, CAS, Beijing

Box 7.3

Infectious diseases in China, 2015

According to a 2015 report, there have been about 3 million registered cases of class-a (enforced management) and class-b (strict management) infectious diseases, which have caused 16,584 deaths. AIDS, tuberculosis (TB) and rabies are accountable for the highest death tolls, but hepatitis B accounts for the largest number of patients, even though their number has fallen by about 10% over the past 5 years.

Table 7.4 **Infectious diseases in China 2015**

infectuous disease	registered cases	mortality	estimated number of patients
total new case	3,046,447	16,584	
hepatitis B	1,218,946	474	90 million
tuberculosis	864,015	2,280	4.5 million
syphilis	433,974	58	
AIDS	50,330	12,755	575,000
measles	42,361	32	
epidemic hemorrhagic fever	10,314	62	
malaria	3,116	20	
rabies	801	744	
epidemic encephalitis B	624	19	
H7N9 avian flu	196	92	
epidemic cerebrospinal meningitis	106	13	
anthrax	288	1	

2015 Stastistical Bulletin on the Development of China's Health and Family Planning Program

Companies

SOE: state-owned enterprise PE: private enterprise 123456-CN: stock number (searchable in Google) (CN), (E) after URL: website in Chinese or English, respectively. Turnover and number of employees only occasionally available.

Northeastern cluster

Qilu Pharmaceutical (PE) 齐鲁制药
Address: No.243, Gong Ye Bei Road, Jinan, Shandong 250101, PRC.
en.qilu-pharma.com/ (E).
9000+ employees
Main products: cephalexin and levofloxacin

Shandong Lukang Pharmaceutical (SOE) 山东鲁抗医药
Address: No.173 West Taibailou Road, Jining, Shandong, 272021, PRC. 600789-CN.
www.lkpc.com/ (CN).
Turnover 2015: ¥ 2,4 B. 5,940 employees
Main products: penicillins

Northeast Pharmaceutical (SOE) 东北制药
Address: No.8 Kunminghu Street, Economic and Technological Development Zone, Shenyang, Liaoling 110027, PRC. 000597-CN.
www.nepharm.com.cn/ (CN).
Turnover 2015: ¥ 3,8 B. 8,580 employees
Main products: gentamycin

Shandong Luoxin Biotechnology (PE) 山东罗欣药业
Address: Luoqi Road, national high tech Industrial Development Zone, Linyi, Shandong 276017, PRC.
www.luoxin.cn/INDEX.ASP (CN).
Main products: azithromycin, cephalosporin

North China Pharmaceutical (SOE) 华北制药
Address: No. 388 East Heping Road, Shijiazhuang, Hebei 050015, PRC. 600812-CN.
www.ncpc.cn/ (CN).
Turnover 2015: ¥ 7,9 B. 11,871 employees
Main products: penicillin, amoxicillin, chlortetracycline

China Shijiazhuang Pharmaceutical Group (SOE) 石药控股集团
Address: No.226 Huanghedadao Rd., Shijiazhuang, Hebei 050035, PRC.
www.e-cspc.com/english/index.aspx (E).
Main products: penicillin, amoxicillin

Merro Pharmaceutical 美罗药业
Address: No.9 Yingsheng Road, Yingchengzi Industrial Zone, Ganjingzi District, Dalian, Liaoning 116036, PRC.
www.merropharm.com/ (E).
Main products: erythromycin and gentamycin

Eastern cluster

Shanghai Shyndec Pharmaceutical (SOE) 上海现代制药
Address: No. 1320 West Beijing Road, Shanghai 200040, PRC. 600420-CN
www.shyndec.com/index.php?lang=en (E).
Turnover 2015: ¥ 2,7 B. 5,695 employees
Main products: roxithromycin, azithromycin, cephalosporin

Zhejiang Jingxin Pharmaceutical (PE) 浙江京新药业
Address: No.800 Xinchang East Road, Yulin subdistrict, Xinchang County, Zhejiang 312500, PRC. 002020-CN
www.jingxinpharm.com/en/ (E).
Main products: azithromycin, norfloxacin

Yangtze River Pharmaceutical Group (SOE) 扬子江药业集团
Address: No.1 Yangtze River South Road, Gaogang District, Taizhou, Jiangsu 225321, PRC.
www.yangzijiang.com/en/index.aspx (E).
Main products: roxithromycin, levofloxacin

Zhejiang Medicine Xinchang Pharmaceutical Factory (SOE) 浙江医药新昌制药厂
Address: No.59 xinchangxian ring east road, Zhejiang Prov., 312500
www.xcpharma.com/1-qygk.html (CN).
Main products: Levofloxacin

Southern cluster

Sinopharm Shantou Jinshi Pharmaceutical (SOE) 国药集团汕头金石制药
Address: No.36 Taishan Road, Shantou, Guangdong 515041, PRC.
Main products: Cephalosporin

Guangzhou Baiyunshan Pharmaceutical general Factory (SOE) 广州白云山制药总厂
Address: No.88 Yunxiang Road, Tonghe Street, Baiyun District, Guangzhou, Guangdong 510515, PRC.
www.byszc.com/EN/index.aspx (E).
Main products: cephalexin

United Laboratories (PE Hongkong) 联邦制药
Address: 6 Fuk Wang Street, Yuen Long Industrial Estate, Yuen Long, New Territories, Hongkong.
www.tul.com.cn/en/ (E).
Main products: penicillins, erythromycin

Western cluster

Sichuan Hexin Pharmaceutical (PE)
四川合信药业有限责任公司
Address: No.12 Kedong three Road,
Wuhou district, Chengdu, Sichuan, PRC.
www.hexinpharma.com/ (CN).
Main products: cephalosporin

Locations outside the four clusters

Sinopharm Weiqida Pharmaceutical
(SOE) 国药集团威奇达药业
Address: No. 1 Medical Park, Shanxi Datong Economic Development Zone, Shanxi 037300, PRC.
www.weiqida.com/EN/ (E).
Main products: cephalexin

Henan Kaifeng Pharmaceutical (SOE) 河南开封制药
Address: 4/F, Block B, Building 8, Lane 1305,
Huajing Road, Xuhui District, Shanghai, PRC.
www.rhpharm.com/about_en.html (E).
Main products: gentamicin

Henan Ren Hua Biotech (PE) 河南仁华生物
Address: No.2 Xingfudadao, Ru'nan industry gathering area, Ruzhou, Henan Prov.
www.hnrhswkj.com/index.html (CN).
Main products: gentamicin

Harbin Pharmaceutical Group (SOE) 哈药集团
Address: NO.7 Qunlidadao, Daoli District,
Harbin, Heilongjiang 150070, PRC. 600664-CN.
en.hayao.com/ (E).
Main products: cephalosporin

International

Shanghai Roche Pharmaceuticals 上海罗氏制药
Address: No.1100 Longdong Dadao,
Pudong New Area, Shanghai 201203, PRC.
www.roche.com.cn/ (CN).
Main products: Anti-tumor, anti-virus, transplantation, anti-infective

Bayer HealthCare AG 拜耳医药保健
Address: No. 33, Huayuan Shiqiao Road,
Pudong 18-19/F, 23-26/F, Citigroup Tower,
Shanghai 200120, PRC.
www.bayer.com.cn/ (CN).
Main products: Cardiology, oncology, gynecology, hematology

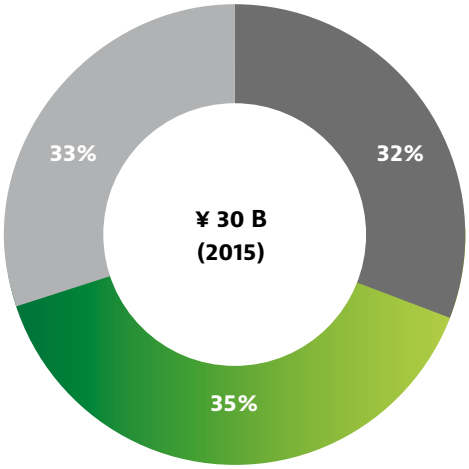
Beijing Novartis Pharma 北京诺华制药有限公司
Address: No.4218 Jinke Rd., Zhangjiang High-Tech Park, Pudong New Area, Shanghai 201203, PRC.
www.novartis.com.cn/ (CN).
Main products: Cardiovascular, endocrine, anti-infection, tumor, transplantation immunity, rheumatic pain, bone metabolism, eye, central nervous system, Vaccines and diagnostic products

Tele-medicine is among China's major targets.

In vitro diagnostics (IVD)

The Chinese sales for in vitro diagnostics in 2015 was ¥ 30 B or ¥ 13 per capita, which is still little in view of the country's large population (EU-15: € 22.5/capita in 2014).[74] Test kits accounted for 80% of this market, instruments represented about 20%. Multinational companies such as Roche, Abbott and others are said to control about 60% of the Chinese IVD market. Two factors suggest that the Chinese diagnostic market might have doubled to ¥ 64 B by 2020, including ¥ 13 B for instruments:[75] there is an increase of disposable income and insurance coverage, and the aging of the population accelerates, stimulating market demand.

Segments of the Chinese IVD market



Second-generation sequencing, precision medicine, and improved health management will support the development of this market on the technical side. The majority of IVD-test results can be expressed in numerical data and thus be directly quantified. Blood-glucose monitoring and other point-of-care products thus provide a good foundation for innovative medical services based on telecommunication, "big-data" management and the internet. China is already investing huge to create its own "internet of things" based on the Beidou ("North Star") satellite system, which already connects 450 million out of China's some 1.6 billion mobile phones. It is supposed to involve 30 satellites and will be completed by 2020.
The management of this kind of "big data" will allow an efficient development of telemedicine for the remote regions of the country and further on following the "belt-and-road" initiative.

Companies

SOE: state-owned enterprise PE: private enterprise 123456-CN: stock number (searchable in Google) (CN), (E) after URL: website in Chinese or English, respectively. Turnover and number of employees only occasionally available.

Northeastern cluster

Beijing Leadman Biochemistry (PE)
北京利德曼生化股份有限公司
Address: No.5 Xinghai Road, BDA,
Beijing 100176, PRC. 300289-CN.
www.leadmanbio.com/html/en/ (E).
Turnover 2015: ¥ 682 M. 621 employees
Main products: 84% in-vitro diagnostic reagents, e. g., for liver function, lipid profile

BioSino Bio-Technology & Science
(SOE) 中生北控生物科技
Address: No.27 Chaoqian Road,
Changping District, Beijing 102200, PRC.
www.sinobio.com.cn/ (E).
Main products: diagnostic products for immunology, hematology, molecular diagnostics

Beijing Strong Biotechnologies
(PE) 北京九强生物技术股份有限公司
Address: F.5 Kuang Yi Building,
No.15 Hua Yuan Dong Road, Haidian District,
Beijing 100191, PRC. 300406-CN.
www.bsbe.com.cn/en/ (E).
Turnover 2015: ¥ 566 M. 248 employees
Main products: 91% in-vitro diagnostic reagents

Beijing WANTAI Biological
Pharmacy Enterprise (PE) 万泰生物药业
Address: No.31 Kexueyuan Road,
Changping District, Beijing, 102206.
www.ystwt.cn/ (CN).
Main products: biological diagnostic reagents, vaccine development and production

Eastern cluster

Shanghai Kehua Bio-Engineering (PE) 上海科华生物工程
Address: No.1189 North Qinzhou Road,
Shanghai 200233, PRC. 002022-CN.
www.skhb.com/en/ (E).
Turnover 2015: ¥ 1,2 B. 1,039 employees
Main products: 44% diagnostic reagents, 55% lab instruments

Shanghai Fosun Pharmaceutical (PE) 上海复星医药
Address No.1289 Yishan Road Building A, Fosun Technology Park, Shanghai 200233, PRC. 600196-CN.
www.fosunpharma.com/en/index.html (E).
Turnover 2015: ¥ 12,6 B. 17,842 employees
Main products: 71% pharmaceuticals, 18% medical diagnostics products and medical devices

Zhejiang Di'an Diagnostics (PE) 浙江迪安诊断技术
Address: F.5-6, Building Zanyu, No.702 Gudun Road, Xihu District, Hangzhou,
Zhejiang 310030, PRC. 300244-CN.
www.dazd.cn (E).
Turnover 2015: ¥ 1,9 B. 3,970 employees
Main products: diagnostic services, diagnostic products

Shanghai Rongsheng Biotech (PE) 上海荣盛生物
Address: No.888 Xiangyang Road,
Shanghai 201108, PRC.
en.rsbio.com/ (E).
Main products: in vitro diagnostic reagents

Ningbo Medicalsystem Biotechnology (PE) 美康生物
Address: No.299 Qiming South Road, Yinzhou District, Ningbo City, Zhejiang 315104, PRC. 300439-CN.
www.nb-medicalsystem.com/index.php?lang=en (E).
Turnover 2015: ¥ 683 M. 958 employees
Main products: 78% in-vitro diagnostic reagents, 11% medical instruments

Southern cluster

Livzon Pharmaceutical Group (PE) 丽珠医药集团
Address: No.132 Guihua Road North, Gongbei, Zhuhai, Guangdong 519020, PRC. 000513-CN.
www.livzon.com.cn/English/ (E).
Turnover 2015: ¥ 6,6 B. 5,913 employees
Main products: 7% diagnostic reagents and equipment

Da An Gene of Sun Yat-Sen Unversity
(PE) 中山大学达安基因股份有限公司
Address: No. 19, Xiangshan Rd., Science Park,
High & New Technol. Development District,
Guangzhou, Guangdong 510665, PRC. 002030-CN.
daan.joomcn.com/ (E).
Turnover 2015: ¥ 1,5 B. 2,156 employees
Main products: molecular diagnostic and immunoassay products, cervical cancer screening

Shenzhen Mindray Bio Medical Electronic (PE) 深圳迈瑞生物医疗电子
Address: Mindry Building, South twelve Road, High-Tech Industrial Park, Nanshan District, Shenzhen, Guangdong 518057, PRC.
www.mindray.com/en/about.html (E).
Main products: point-of-care systems, in vitro diagnostics, medical imaging system

Shenzhen New Industries Biomedical Engineering (PE) 深圳市新产业生物医学工程
Address: F.21, Block A, Building 1, Shenzhen Software Industry Base, No.1008, Keyuan Road, Nanshan District, Shenzhen 518000, PRC.
www.snibe.com/en/ (E).
Turnover 2015: ¥ 732 M. 1,032 employees
Main products: clinical laboratory instruments and in vitro diagnostic reagents

Western cluster

Sichuan Maccura Biotechnology (PE) 四川迈克生物
Address: No.16, Baichuan Road, Hi-Tech Industrial Development Zone, Chengdu, Sichuan 611731, PRC. 300463-CN.
www.maccura.com/en/main/ (E).
Turnover 2015: ¥ 1,1 B. 1,166 employees
Main products: 84% diagnostic reagents, 15% medical instruments

Locations outside the four clusters

Dirui Industrial (PE) 长春迪瑞医疗
Address: No.3333 Yiju Street, New & High Technological Development Zone, Changchun, Jilin 130103, PRC. 300396-CN.
www.dirui.com.cn/ (CN).
Turnover 2015: ¥ 567 M. 1,592 employees
Main products: laboratory equipment and reagents for clinical diagnostics

Autobio Diagnostics (PE) 安图生物
Address: No.87 Jingbei Yi Road, National Economic & Technological Development Area, Zhengzhou, Henan 450016, PRC.
www.autobio.com.cn/en/index.php (E).
Main products: clinical diagnostic products

Boson Biotech (PE) 波生生物技术有限公司
Address: No.90-94 Tianfeng Road, Jimei North Industrial Park, Xiamen, Fujian 361021, PRC.
www.bosonbio.com/ (E).
Main products: in-vitro diagnostic kits

International

Roche Diagnostics罗氏诊断产品（上海）
Address: Building 2, Hongqiaotiandi, No.900 Shenchang Road, Shanghai 200335, PRC.
www.roche-diagnostics.cn/Pages/default.html (CN).
Main products: diagnostics products

Abbott Trading (Shanghai) 雅培贸易 (上海)
Address: F.23 Xianlesi square, No.388 Nanjing West Road, Shanghai 200003, PRC.
www.abbott.com.cn/about-abbott/abbott-china.html (CN).
Main products: nutrition products, diagnostic products, cardiovascular products

Beijing Novartis Pharma 北京诺华制药有限公司
Address: No.4218 Jinke Road, Zhangjiang High-Tech Park, Pudong New Area, Shanghai 201203, PRC.
www.novartis.com.cn/ (CN).
Main products: cardiovascular, endocrine, anti-infection, tumor, transplantation, immune-system related and diagnostic products

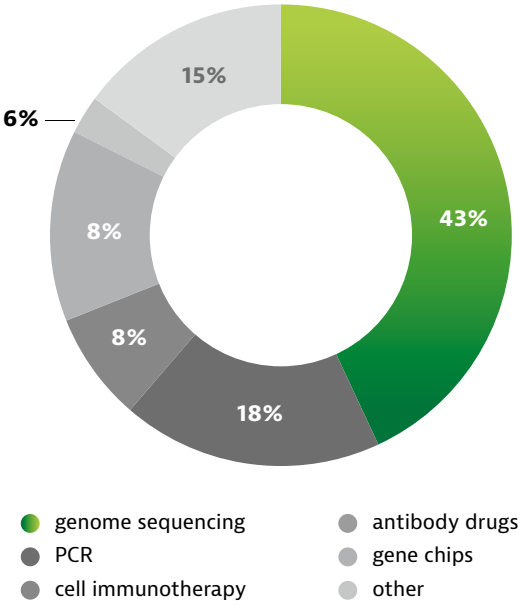
InTec Products, Inc. (Xiamen) 英科新创（厦门）
Address: No.332 Xinguang Road, Xinyang IND Area, Haicang, Xiamen, Fujian 361022, PRC.
www.asintec.com/Home/EIndex (E).
Main products: products for rapid diagnostic tests, enzyme Immunoassays, fluorecscence-based PCR tests, clinical chemistry reagents and glucose monitoring systems

"Precision medicine"

Personalized medicine, often called "precision medicine", is an active field of research and investment in China. Whereas the majority of these activities are concerned with precise individual-diagnostic analysis, comprising gene sequencing, PCR, gene chips and liquid biopsy, other directions comprise cellular immunotherapy and the development of antibody drugs as well as of global tumor maps based on big data.

A review from October 2016 counts 276 Chinese stakeholders in this field, including 76 companies,[76] mostly located in Beijing, Shanghai, Zhejiang and Guangdong. The majority of these companies is rather small. An important player in this field, however, is BGI (Beijing Genomics Institute),[77] China's largest genome sequencing facility located in Shenzhen.

Segments of China's market for "precision medicine"



Most companies are associated with four big consortia, namely Legend Capital and Legend Star Holdings in Beijing, Qiming Venture Partners in Shanghai and Shenzhen Capital in Shenzhen.

Consortium under Legend Capital, Beijing

- gene sequencing: Genetron Health, Berry Genomics, New Horizon Health, Ribobio
- PCR: U-Star Biotechnologies
- cellular immunotherapy: Shanghai Cell Engineering Technology Research Center
- antibody drugs: Innovent Biologics, Shenogen Pharma Group
- other: Zai Lab, Sangon Biotech

Consortium under Legend Star Holdings, Beijing

- gene sequencing: iGene Tech, Coyote Bioscience, Burning Rock
- antibody drugs: Kintor Pharmaceutical Inc., BiotechSino
- other: Percans Oncology, Suzhou Ribo

Consortium under Qiming Venture Partners, Shanghai

- genome sequencing: Berry Genomics,
- PCR: Rendu Biotechnology, JFK Biotech, Amoy Diagnostics, Tellgen Corporation
- antibody drugs: Shenogen Pharma Group
- other: Zai Lab, Sangon Biotech

Consortium under Shenzhen Capital, Shenzhen

- genome sequencing: Akeso Biopharma, BGI, Fenghua Bioengineering
- cellular immunotherapy: Hornetcorn Biotechnology
- antibody drugs: Shenogen Pharma Group
- other: Celgen Biopharma, Beike Biotechnolog

Other bioventure companies involved in "precision medicine" R&D

- genome sequencing: KL Biotech, Creative Biosciences
- cellular immunotherapy: Ascentage Pharma
- antibody drugs: Xingkanghe, Kechow Pharma, IMPACT Therapeutics, Kontor Pharmaceuticals
- other: Obio

Box 7.4

Beijing Genomics Institute (BGI)

Founded in 1999, the company has grown to a world-wide CRO supplying genome sequencing and more. In China, the company is market leader for prenatal sequencing of genetic diseases, an important issue in a nation conducting birthrate control (abortion is not legally prosecuted in China).

BGI claims that as of March 2016 its NIFTY test for non-invasive prenatal genetic screening of Down, Edwards and Pätau syndrome was done 1 million times world-wide; it is also available in Germany. BGI's sequencing facilities and computing power are so advanced that in April 2016, BGI Online could complete a whole exome analysis on 1,000 human samples within 22 hours.

In September 2016, the first Chinese Gene Bank was opened in Shenzhen. Nearly half of the investment of ¥ 780 M came from BGI. The gene bank will not only provide a wide range of databases throughout China, but will also store 10 million biological specimens on 47,500m^2. Additional gene banks following the same concept have already been announced to open in Qingdao and Henan (marine and agricultural specimen, respectively).

In November 2016, BGI, Alibaba and Intel China signed a strategic-cooperation memorandum on the combination of cloud computing, big data and artificial intelligence within the „Healthy China 2030"-program.[78]

Selected companies

SOE: state-owned enterprise PE: private enterprise; (CN), (E) after URL: website in Chinese or English, respectively. Most companies are startups or newly founded (later than 2013) therefore, the information about size of the company and turnovers are limited.

Genetron Health (PE) 泛生子
Address: Building 11, No.8 Shengmingyuan Road, Zhongguancun Life Science Park, Changping District, Beijing, PRC.
www.genetronhealth.com/html/HOME/index.html (E).

Suzhou Ribo (PE) 苏州瑞博生物
Address: No.168 Yuanfeng Road, Yushan Town, Kunshan, Jiangsu 215300, PRC.
www.ribolia.com/en/default/index.aspx?HeadID=1 (E).

U-Star Biotechnologies (PE) 杭州优思达
Address: 8/F, New Century Tower, No.3766 Nanhuan Road, Binjiang District, Hangzhou, Zhejiang 310053, PRC.
www.bioustar.com/en/ (E).

Shanghai Cell Engineering Technology Research Center (SOE) 上海细胞治疗工程技术研究中心
Address: Building A, No.75 Qianyang Road, Jiading District, Shanghai 201805, PRC.
www.shcell.com/ (CN).

Shenogen Pharma Group (PE) 北京珅奥基医药科技
Address: Suite 101, Building B, No. 29 Life Science Park Road, Changping District, Beijing 102206, PRC.
www.shenogen.com.cn/ (E).

Zai Lab (PE) 上海再鼎医药
Address: No.1043 Halei Road, Building 8, Suite 502 Zhangjiang High-Tech Park, Pudong, Shanghai 201203, PRC.
www.zailaboratory.com/ (E).

Coyote Bioscience (PE) 卡尤迪生物
Address: 2th Floor Zhongguancun Development Building, No.12 Shangdixinxi Road, Haidian District, Beijing, PRC.
www.coyotebio.com/en/ (E).

BiotechSino (PE) 博泰神州
Address: Room104, North Block, A1 Building, No. 218 Xinghu Street, Suzhou Industrial Park, Jiangsu, PRC.
www.biotechsino.com/Earticle/list-20.html (E).

Stem cell technology

According to a recent survey,[79] China's stem cell industry has formed a complete industrial chain from upstream storage to downstream clinical applications. Various types of cell banks, in particular a national cord blood bank have been established, and clinics have started to use stem cells in plastic surgery and health services.

Among them, the Chinese Cord Blood Cooperation (CCBC) is the first cord blood banking operator approved by the National Health and Family Planning Commission (NHFPC). It is China's largest CB bank and has subsidiaries in Beijing, Guangdong and Zhejiang. A leading private company in this field is Beike Biotechnology (see box 7.7).
The income of stem-cell-related industries is currently estimated at ¥ 2 B annually. It is expected to grow annually by 170%, reaching ¥ 30 B in 2020, at the end of "135".

Regulations
Prior to 2009 stem cell therapy was not clearly regulated, and many hospitals offered such treatment. After 2009, regulations became stricter, and stem cell therapy partially "went underground". However, in view of its great health and market potential, MOST eased regulations in 2015[80] and initiated the establishment of controlled cell banks in 16 major cities.[81] Referring to Good Manufacturing Practice (GMP) and guidelines for clinical

Table 7.5 **Hospitals involved in clinical research on stem cells**

Peking Union Medical College Hospital 中国医学科学院北京协和医院	Beijing
China-Japan Friendship Hospital 中日友好医院	Beijing
Fu Wai Hospital 中国医学科学院阜外心血管医院	Beijing
Peking University People's Hospital 北京大学人民医院	Beijing
Peking University Third Hospital 北京大学第三医院	Beijing
Peking University School of Stomatology 北京大学口腔医院	Beijing
Blood Diseases Hospital, CAMS 中国医学科学院血液病医院	Tianjin
Tianjin Medical University General Hospital 天津医科大学总医院	Tianjin
Tianjin Huanhu Hospital Tianjin	Tianjin
The First Hospital of Hebei Medical University 河北医科大学附属第一医院	Hebei
The First Affiliated Hospital of Dalian Medical University大连医科大学附属第一医院	Liaoning
China Japan Union Hospital of Jilin University 吉林大学中日联谊医院	Jilin
Fudan University Affiliated Huashan Hospital 复旦大学附属华山医院	Shanghai
Shanghai Eastern Hospital 上海市东方医院	Shanghai
Shanghai Jiaotong University School of Medicine Affiliated Ninth People's Hospital 上海交通大学医学院附属第九人民医院	Shanghai
Shanghai Jiaotong University School of Medicine Affiliated Renji Hospital 上海交通大学医学院附属仁济医院	Shanghai
Nanjing Drum Tower Hospital 南京大学医学院附属鼓楼医院	Jiangsu
Affiliated Hospital of Nantong University 南通大學附属医院	Jiangsu
The Second Affiliated Hospital of Zhejiang University School of Medicine 浙江大学医学院附属第二医院	Zhejiang
The First Affiliated Hospital of Nanchang University南昌大学第一附属医院	Jiangxi
Liaocheng City People's Hospital聊城市人民医院	Shandong
The First Affiliated Hospital of Zhengzhou University郑州大学第一附属医院	Henan
Renmin Hospital of Wuhan University武汉大学人民医院	Hubei
Xiangya Hospital Central South University中南大学湘雅医院	Hunan
The Third Affiliated Hospital of Sun Yat-Sen University中山大学附属第三医院	Guangdong
Zhongshan Ophthalmic Center of Sun Yat-Sen University中山大学中山眼科中心	Guangdong
Guangdong Hospital of Traditional Chinese Medicine广东省中医院	Guangdong
West China Hospital of Sichuan University四川大学华西医院	Sichuan
Guizhou Medical University Affiliated Hospital贵州医科大学附属医院	Guizhou
Zunyi Medical College Affiliated Hospital遵义医学院附属医院	Guizhou

CAS Chinese Academy of Sciences, CAMS Chinese Academy of Medical Sciences

trials, the China Pharmaceutical Biotechnology Association recently issued self-regulatory „stem-cell preparation quality management norms.[82]" Apart from various aspects of quality control, these guidelines also insist that therapies with stem cell preparations should be limited to treat diseases or improve the health status, displaying clear biological effects.

Public and translational R&D

Based on grants obtained during "125", stem-cell-related therapies are investigated in hospitals and academic institutions throughout China, as it can be seen in table 7.5 and box 7.5. Until 2015, cell-based therapies were regulated by the National Health and Family Planning Commission (NHFPC) as class-III medical interventions, limited to clinical research. Due to irregularities, this procedure is officially prohibited since May 2016, but still practiced in some hospitals.

Box 7.5

Ongoing stem-cell-related projects in the public domain (topic, institution, principal investigator)

- Regulatory mechanism of self-renewal and maintenance of pluripotent stem cells, Shanghai Jiaotong University, JIN Ying
- Establishment of naive pluripotent stem cell line and analysis of pluripotent regulatory mechanism, Northeast Agricultural University, LIU Zhonghua
- Mechanisms of metabolism, autophagy and DNA damage repair in maintenance of dryness and chromosome stability of multipotent stem cells, Guangzhou Institute of Biomedicine and Health, CAS*, QIN Baoming
- Interrelation and dynamic mechanism of histone and DNA modification in cell programming and reprogramming, Tongji University, GAO Shaorong
- Cell cycle regulation of pluripotent stem cell self-renewal and directional differentiation, Beijing University, ZHANG Chuanmao
- Regulatory mechanism of development, maintenance and regeneration of hematopoietic stem cells, Hematology Hospital, Institute of Hematology, CAMS*, CHENG Tao
- Regulation of non-coding RNA-mediated dynamic changes in chromosome high-level structures on cell fate and molecular mechanisms, Institute of Basic Medical Sciences, CAMS*, ZHU Dahai
- Mechanisms and transformation of spinal cord injury based on mobilization of endogenous neural stem cells, Tongji University, CHENG Liming
- Molecular imaging study on in vivo tracing and functional analysis of stem cells after transplantation, Zhejiang University, ZHANG Hong
- New strategies and applications of molecular immunoregulation of stem cell transplantation and key techniques in clinical treatment of immune-related diseases, Institute of Basic Medical Sciences, CAMS*, ZHAO Chunhua
- Construction of autologous stem cell heart valve, Huazhong University of Science and Technology, DONG Nian-guo
- Normal stem cell development, variations and tumor stem cell formation mechanism, Third Military Medical University, PLA*, BIAN Xiuwu
- Nervous system and heart-related diseases of major stem cells and pathological tissue bank, Tongji University, HONG Jiuhong
- Targeted gene editing in the establishment of neurological diseases in monkey models and stem cell therapy, Kunming University of Science and Technology, Niu Yuyu
- Clinical grade stem cell standardization assessment system, National Institute for Food and Drug Control, YUAN Baozhu

*CAS Chinese Academy of Sciences, CAMS Chinese Academy of Medical Sciences, PLA People's Liberation Army

Box 7.6

Beike Biotechnology

Beike Biotechnology Co., Ltd.
(Beike Biotech, *www.beikebiotech.com*) is a private company based in Shenzhen that specializes in research, clinical translation, and technology support services related to adult stem cells. Founded in 2005 with investments from Peking University, Hong Kong University of Science and Technology and Shenzhen City, the company has some 700 employees, and subsidiaries in seven Chinese provinces. It has partnered with medical professionals, medical-tourism professionals and a significant number of hospitals to offer patients premier adult stem cells treatment protocols. Beike Biotechnology cooperates in research alliances with numerous Chinese universities, e. g., the PLA Navy General Hospital.

Beike Biotech provides stem cells from two sources. **Umbilical Cord Blood-Derived Stem Cells (UCBSC)** are used for the treatment of ailments such as spinal muscular atrophy, ataxia, and optic nerve conditions. UCB-stem-cell injections consist of three subsets of stem cells: hematopoietic stem cells, endothelial progenitor stem cells, and mesenchymal stem cells. Hematopoietic stem cells and endothelial progenitor stem cells are likely to form tissues in the body, whereas mesenchymal stem cells can assist in the growth of chondrocytes, liver cells, kidney cells and neurons. They can also conduct repairs in relation to vascular disorders within the brain, the eyes, and throughout the body including heart, kidney, and pancreas. At this stage of stem cell research, it is believed that the benefits, patients report, have come from the cell-growth factors that are released by the stem cells after their administration.

Umbilical Cord-Derived Mesenchymal Stem Cells (UCMSC) closely resemble the makeup of the injections cultured from patients' own bone marrow. They are used for therapies on multiple sclerosis (MS) and spinal cord injury (SCI) but can also regulate the immune system, reducing inflammation, scarring, and cell apoptosis.

Two companies involved in stem cell development

Beike Biotechnology (PE) 深圳市北科生物科技
Address: 16F Beike Building, 18 Keyuan Road, South Area, High-Tech Industrial Park, Nanshan, Shenzhen 518057, PRC.
www.beikebiotech.com/ (E).
Main activities: stem cell basic research, research on clinical applications, stem cell technology service

Zhongyuan Union Cell & Gene engineering
(PE) 中源协和细胞基因工程
Address: No.45, Dongjiudao, Konggang Economic Zone, Tianjin 300304, PRC. 600645-CN.
www.vcanbio.com/about.html (E).
Turnover 2015: ¥ 709 M. 1,700 employees
Main activities: preparation and storage of cells, genetic assays

Cell technology is studied in many clinics and research centers.

Rules to the game

Introduction

This section will introduce general aspects for the registration of medical products, bio-medical drugs and diagnostic products in China. The IP situation in China will also be briefly discussed, as will be issues on technology transfer.
As there is abundant information on both subjects available in the public domain, discussion will be limited to essentials.

Registration of drugs

Registration of drugs in China is under the responsibility of the China Food and Drug Administration (CFDA).[83] The headquarter of CFDA is in Beijing, but there are 31 CFDA Provincial Bureaus.

Registration of novel drugs in China is a lengthy process and may lead to years of delay. The critical step is the approval for clinical trial registration which needs to be done by the Chinese Center for Drug Evaluation (CFDE).
According to a recent review,[84] it takes at least 1 to 2 years to get the approval, even for generic drugs, because the agency, with a staff number of only 120, receives nearly 9,000 applications every year (the submission of an application is free of cost); in comparison, for chemical drugs alone there are 5,000 staff members in the U.S. FDA's Center for Drug Evaluation and Research. Once a clinical trial is registered, the biggest hurdle for generic drugs is taken, and they often obtain approval.

The CFDA does not have a mechanism for prioritization yet, regardless of the nature of the drug concerned. At the end of 2014, the total number of drug-registration applications awaiting approval exceeded 18,000. To correct this deficiency, the CFDA plans to hire third-party experts to participate in the CFDE clinical trial reviews. Also, a "4-color strategy" was proposed, where "green-light" applications would designate innovative drugs aimed at the prevention and cure of children's diseases and severe diseases, such as AIDS, cancer, major infectious diseases, and rare diseases. These agents would then receive priority approvals.

Table 8.1 shows the catalogue for bio-products in CFDA's "Drug registration administration guidance" from 2007,[85] annex 3. It is stipulated that each formulation of any drug needs to be approved separately, and that additional

Fig. 8.1 **Scheme of drug registration by CFDA**

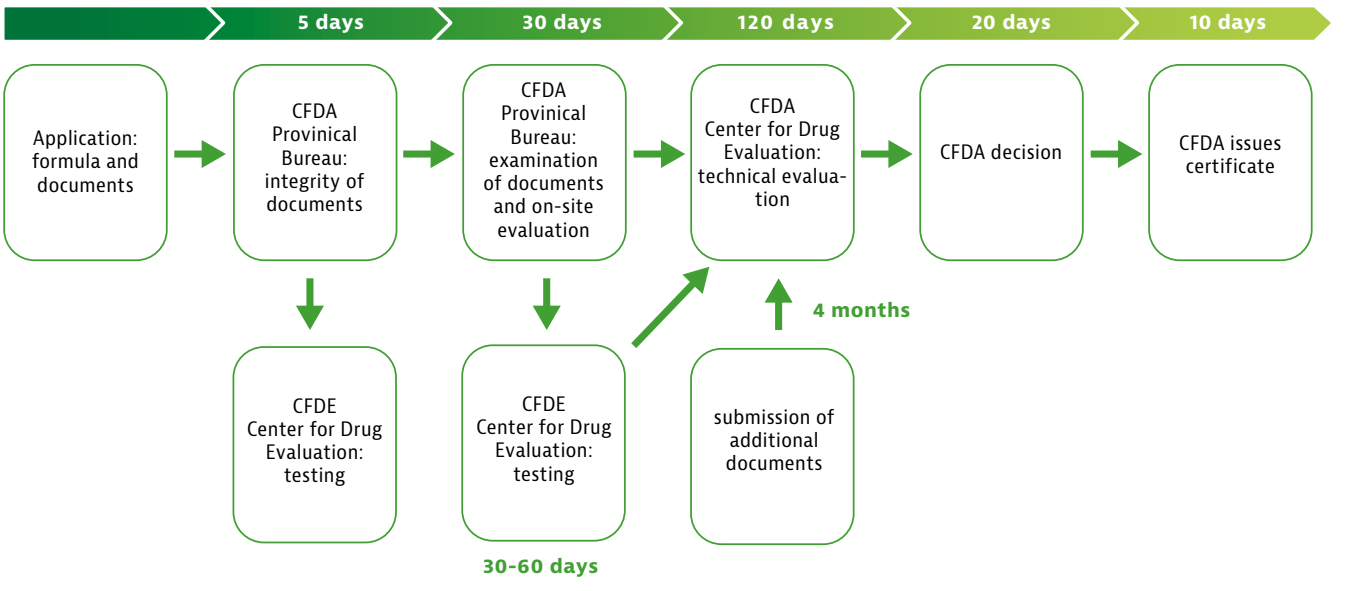


Table 8.1 **Classification of bio-products and IVD reagents**

class	definition	sub-class	fees
I	new products, nowhere approved	I.1 bio-products never marketed before	provincial preapproval: ¥ 4,300 CFDA approval: ¥ 25,000
II	approved abroad, not included in pharmacopeial or official recommendation, not approved in China	II.2. monoclonal antibody for therapy or IVD II.3 gene-, cell- therapy product II.4 allergen II.5 human/animal tissues or body fluids, bioactive products from fermentations II.7 already marketed abroad II.11 production process changed to rDNA technology	provincial preapproval: ¥ 4,300 CFDA approval: ¥ 25,000
III	A new formulation, effects based on bioproduct B production process/ technology with significant changes	III.6 new formulation of bioproducts already marketed III.8 microbiological products using non-approved strain III.9 products with differences to marketed products (e. g., caused by mutation, deletions, etc.) III.10 production process differs from marketed product (e. g., different expression system is used)	provincial preapproval: ¥ 3,500 CFDA approval: ¥ 20,000
IV	A included in foreign pharmacopeial or official recommendation B approved for import and registration C changes of formulation or administration	IV.7 not marketed in China: see II.7. IV.15 already marketed in China see IV.15. IV.12 not marketed in China, and changes from ingested to injected, or from IV.13 marketed in China, change of formulation without change in administration IV.14 change in administration for products already marketed in China	provincial preapproval: ¥ 3,500 CFDA approval: ¥ 20,000
V	new indications	approval as new medicine	provincial preapproval: ¥ 3,500 CFDA approval: ¥ 10,000

formulations cost an additional 20% each. In-vitro diagnostic (IVD) reagents are approved as Class 4 and 5 bio-products. In March 2016, CFDA has announced[86] that a modified guidance containing further regulations for bio-product will shortly be released by the State Council.

As mentioned above, the process by CFDA is very strict and time-consuming. To put this in perspective: in 2015, CFDA approved 24 new drug applications, and 37 manufacturing applications. For generic drugs, 404 approvals and 143 manufacturing permissions were issued. In case of foreign imported drugs, 348 applications for clinical investigation were approved, and 36 certificates were issued. Only one single bio-product was approved in 2015, and 19 clinical studies were permitted.

GMP certification

GMP certification for manufacturing processes is still under development in China. A GMP certificate for a pharmaceutical manufacturer is valid for 5 years. Six months prior to expiration, an application for renewal must be filed. If the pharmaceutical company is newly established, the first GMP certificate is valid for just one year, and application for renewal must be filed after nine months; if accepted by CFDA, the new certificate is valid for 5 years. A "Temporary GMP Unannounced Inspection Act" was released in 2006 and enacted as the "Unannounced Inspection for Drugs and Medical Devices"[87] in 2015.

It pertains that CFDA shall inspect each company at least once every 5 years, and inspection should take 3 to 5 days. After this act came into effect in September 2015, more than 600 bio-products lost their certificates, of which 372 were vaccines. While 1,889 bio-products were approved by CFDA[88] in January 2015, this number had fallen to 1,672 by November 2016, and only 41 enterprises were issued with certificates according to the new GMP guidance.
Regarding the Chinese pharmaceutical industry as a whole, 1,795 out of 7,179 enterprises were not certified according to the new GMP rules by the end of 2015 and therefore lost their manufacturing permission.

From September to November 2016, over 140 certificates were retracted after unannounced inspections, and another 68 in the first six months of 2016.[89] 80% of these actions concerned TCM manufacturers. Apart from a crackdown on manufacturers with inadequate quality and management, this move of CFDA can also be seen as a strategy to induce the formation of larger pharmaceutical conglomerates: both, the "135"- and the "Made-in-China 2025"- plan encourage M&A in order to form larger and more powerful

Box 8.1

CFDA definition of therapeutical and preventive bio-products

Therapeutical bio-products are monoclonal antibodies, gene therapeutics as well as human-cell-based therapies and its products; moreover they include bioactive components and products isolated from human/animal tissues or body fluids or such produced through fermentation via microorganisms. To this category belong also new products combined with approved bio-products from abroad, products from non-approved microorganisms or not-equal to approved products (e.g., proteins with mutated amino acids), products manufactured with host-strain different from those of approved products, products produced via recombinant DNA technology, change of administration methods (injection to oral or others), new formulations.

Preventive bio-products are vaccines, DNA vaccines, approved vaccine with modified adjuvant/carrier, products which have undergone changes from non-purified vaccines/whole cell vaccines (bacteria/virus) to purified vaccines, vaccines produced by strains which are not-CFDA approved, approved vaccines from abroad, combined multiple vaccines using approved products and recombinant vaccines with antigens different to approved products. Moreover they include lines with modified production processes (e.g., change of the host strain) with different methods used for inactivation/attenuation, manufactures with a change of administration (muscle injection to oral) or with another formulation without change of administration, products with a change of dosage or alterations concerning applicable age/population as well as vaccines with approved drug standards.

pharmaceutical groups. Thus, more than 70% of the small- and middle-size pharmaceutical companies might eventually disappear, not least because the cost to comply with GMP requirements is estimated at ¥ 40 M per certificate, whereas most pharmaceutical companies have annual turnovers below ¥ 5 M.

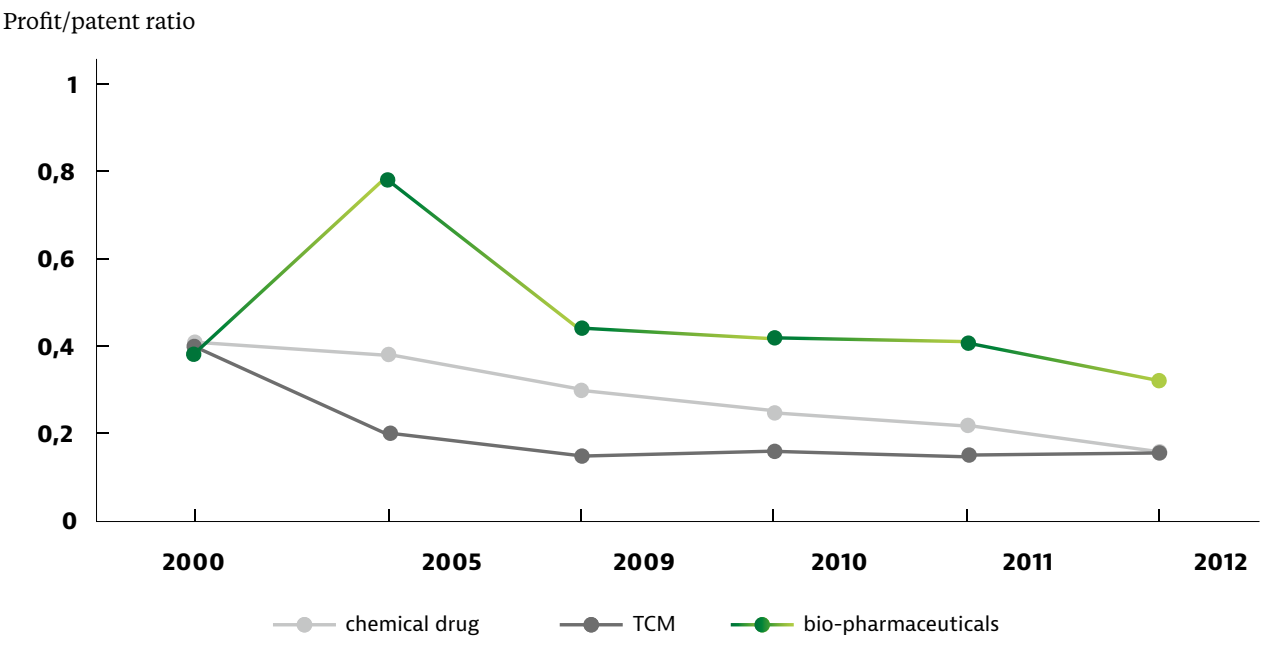
Intellectual property

IP protection is among the key issues in technology-related cooperations with China. The EU has, in cooperation with the European Patent Office (EPO), established an agency, IP Key[90] with affiliations in Alicante and Beijing which is specialized on such issues.

§ 35 of the CFDA **Regulations for Implementation of the Drug Administration Law of the People's Republic of China**[91] – issued in 2002 – clarify the protection of IP rights for new pharmaceutical substances which have been approved for marketing in China. According to CFDA's **Provisions for Drug Registration** released in 2002, protection of IP is limited to 6 years starting on the day of approval. They also stipulate that applications will be rejected if the applicant cannot submit proprietary original data. Applicants must further submit a patent search summary which documents that the applicant's product or process is based on own IP and will not infringe patent rights from third parties.
As to the registration of generics, applicants are allowed to submit their request 2 years prior to the date when protection of existing products expire. However, approval for a generic will be issued only once IP protection for the existing product has ended.

China has become a leader for new patent applications. In 2015, the Chinese Patent Office (state intellectual property office, SIPO) has received a total of 1,101,864 patent applications from domestic and international inventors, which is about one third of the global number.
Although it can be seen from patent applications that R&D is very active, innovation of China's pharmaceutical industry is still hampered by CFDA's lengthy approval process and the slow recognition of new drugs by the medical insurance directory. Thus, the ratio of company profits vs. patent applications has continuously fallen during the period between 2000 and 2012, as documented by SIPO.[92]
Where as the universities and the CAS file many patent applications and generate much technology, technology transfer and collaboration with industry is still a weak point in China's R&D system. This is aggravated by the fact that traditional Chinese industries invest little in their R&D capacities and thus lack know-how and qualified staff for technology transfer.

Fig. 8.2 **Profit/patent ratio 2000 – 2012**



Technology transfer

In view of the acknowledged difficulties regarding the translation of public R&D to the industry, several technology transfer platforms have been established in China.

The state intellectual property office (SIPO) has installed 41 national technology exhibition and exchange centers (at least one in each province and municipal city)[93] (see table 8.2).

Table 8.2 **National Patent Technology Exhibition and Exchange Centers (as of June, 2016)**

class	province or municipality	city	name
1	Beijing	Beijing	China Technology Exchange
2	Tianjin	Tianjin	Tianjin Intellectual Property Service Center
3	Shanghai	Shanghai	Shanghai Intellectual Property Service Center
4	Chongqing	Chongqing	Chongqing Intellectual Property Office
5	Anhui	Bengbu	Bengbu Science and Technology Intelligence Institute
6	Anhui	Huaibei	Huaibei High-Tech Innovation Center
7	Anhui	Hefei	Hefei Science & Technology Innovation Public Service Center
8	Fujian	Fuzhou	Fuzhou Technology Market
9	Gansu	Lanzhou	Lanzhou Jinqiao National Patent Technology Exhibition and Exchange Center
10	Guangdong	Foshan	Foshan Productivity Centre
11	Guangdong	Dongguan	Dongguan Technology and Intellectual Property Service Center
12	Guangdong	Guangzhou	Guangzhou Intellectual Property Information Center
13	Guangdong	Shenzhen	Shenzhen Lianchuang Intellectual Property Service Center
14	Guizhou	Guiyang	Guizhou Sun Property Rights Exchange Co., Ltd.
15	Hainan	Hainan	Hainan Property Rights Exchange Center
16	Henan	Henan	Henan Patent Incubator Transfer Center Co., Ltd.
17	Henan	Xinxiang	Xinxiang Productivity Centre
18	Hubei	Wuhan	"Wuhan · Optical Valley of China" Intellectual Property Information Center
19	Hubei	Yichang	National Patent Technology Exhibition and Exchange Center of Yichang
20	Hubei	Xiangfan	Xiangfan Patent Service Development Center
21	Hunan	Changsha	Changsha Technology Property Right Exchange Co., Ltd
22	Jilin	Changchun	Changchun High-Tech Intellectual Property Service Center
23	Tianjin	Suzhou	Suzhou Industrial Park, Intellectual Property Service Center
24	Jiangsu	Changzhou	Changzhou Technology Property Trading Center
25	Jiangsu	Wuxi	Wuxi High-Tech Property Right Trading Market Co., Ltd.
26	Jiangsu	Nanjing	Nanjing Transform & Service Platform for the Fruits of Science and Technology
27	Jiangxi	Nanchang	Jiangxi Enterprise Technology Innovation Service Co., Ltd.
28	Liaoning	Shenyang	Shenyang Technology Exchange
29	Liaoning	Anshan	Anshan High-Tech Trading Center
30	Inner Mongolia	Hohhot	Hohhot Intellectual Property Service Center
31	Ningxia	Yinchuan	The Ningxia Hui Autonomous Region Intellectual Property Office
32	Shandong	Jinan	Jinan Intellectual Property Information Center
33	Shandong	Qingdao	Qingdao Technology Transfer Center

Table 8.2 **National Patent Technology Exhibition and Exchange Centers (as of June, 2016)**

class	province or municipality	city	name
34	Shandong	Yantai	China's Patent Market (Yantai)
35	Shanxi	Taiyuan	Shanxi Technology Property Rights Exchange
36	Shanxi	Xi'an	China Yangling Agricultural Intellectual Property Information Center
37	Sichuan	Chengdu	Sichuan Intellectual Property Service Center
38	Xinjiang	Urumqi	Xinjiang Development of Science and Technology Exchange Center
39	Yunnan	Kunming	Kunming Productivity Center
40	Tianjin	Ningbo	Tianjin Intellectual Property Service Center
41	Zhejiang	Shanghai	Shanghai Intellectual Property Service Center
42	Chongqing	Chongqing	Chongqing Intellectual Property Office

Most of these centers have a website in Chinese language. However, no further information is provided, e. g., on how a patent can be transferred or offered, who can be contacted for consultancy etc. Different from the governmental centers, internet-based technology exchange portals become more and more active. Among them, the biggest exchange service portal is the Chinese Technology Exchange Web *www.ctex.cn*. It is owned by the Chinese Institute of Technology Trading, which has a registered capital of ¥ 224 M and was co-founded by Beijing Equity Exchange, Beijing High-Tech Start-up Service Center and Beijing Zhonghai Investment. All three shareholders are SOEs, and the website is promoted by the Beijing government.

The CTEX portal presents technology offers and bids in real time. A minimal price request can be indicated, and the bidder can negotiate online with the technology provider. Companies or technology providers can also look for venture capital, private equity and other investments on this website. CTEX contains various sub-portals, including one for bio-medical products. Since the foundation of CTEX in 2009, 78,000 technology consultancies and transfers have been processed, with a total volume of ¥ 147.6 B.

Other examples for technology transfer portals are:

- Technology Exchange 1633 in Xiamen, 科易网, which has achieved about ¥ 800 M worth of contracts since its foundation in 2007,[94]
- China International Technology Transfer Center , 全国技术转移公共服务平台[95]
- UPEX Technology Transfer Center 联交所技术转移平台[96]
- Technology Transfer Service Platform[97] in Beijing. This service portal is managed by Tech Heng guan Beijing and offers consultancy to the whole of China and also to international companies. Tech HG has a data base with information on 110 M patents from 102 countries and holds a cooperation contract with Steinbeis Asia-Tech Consulting, *www.asia-tech.eu*.

Box 8.2

A typical technology offer on CTEX

Jinan Kanghe Medical Technology Co. Ltd., a small bio-medical technology company in Jinan which was founded in 2011 with a capital of ¥ 10 M, has developed a generic bio-product – Teriparatide for injection. This product was initially developed by Eli Lilly and obtained US-FDA approval in 2002. CFDA approval for the Eli Lilly product in China was issued in 2011 and renewed in 2015. The Chinese company now offers manufacturing technology for this product, as the company is only engaged in R&D and has not enough capital to obtain CFDA approval and place the product into market.

They all have been initiated by the government. However, Chinese pharmaceutical companies are increasingly active on their own concerning international technology transfer. According to a recent review[98] on transfers in 2016, the rights on 14 new drug candidates (7 among them bio-products for diabetes or cancer therapy), which are now under pre-clinical or clinical study in the EU or the USA, have been acquired by Chinese pharma makers. 11 drugs and devices approved by CFDA have been transferred from international to Chinese companies, e. g., an influenza drug from Bayer AG to Shanghai Pharmaceuticals Holdings. Moreover, 29 major capital investment deals on new drugs have been closed, several of them above US-$ 100 M: 18 of these cases related to bio-products.

Contractual issues

There is ample literature on technology transfer contracts with China, and help desks are available at the European[99] and national level.[100,101] SMEs who have interest to market their products or services in China are advised to identify a Chinese mediator who can assist the further process in the field (Box 8.3). Ideally, such mediator is located in the home country of the SME and has valid contacts to China. He or she is able to identify a proper partner in China who has proprietary interest in CFDA's approval of the SME's products or services.

In an ideal situation, such partner is a CFDA-certified manufacturer or a registered medical technology company. In other words, the Chinese partner, identified by the mediator, should not be a regulatory affair agency or a trading company, as their interest may end after charging a consultancy or agent fee. A CFDA-certified partner, on the other hand, has own interest to generate a profitable business via marketing or even joint-investment in the approval process, which can reduce the cost and risk of CFDA certification dramatically.

Box 8.3

The interaction with a mediator and Chinese partner is attractive for the following reasons:

- Most information about China is not available in English language. Moreover, English is usually not spoken by Chinese managers and only occasionally by Chinese scientists.
- Whereas a foreign SME may register in China and approach CFDA for approval of products or medical services directly, a lack of experience how to deal with the Chinese trading system, its legal foundations, or the Chinese healthcare system may hamper success.
- Key stakeholders with interest in innovative products are ministries and central governmental departments which are involved in drafting laws and regulations and oversee the healthcare industry and associated markets. It will be quite impossible for a foreign SME to get into direct contact with these central regulatory offices. A well-chosen Chinese partner, on the other hand, has experience to channel the regulatory approval and to get the necessary licenses and certificates from different administrative offices.
- In this context, support from provincial governments should not be underestimated. If a local government considers a product or service as suitable to the provincial strategy (in the framework of this study: if the northeastern cluster would put emphasis on innovative antibody-based therapeutics, and the foreign SME offers such technology), it may offer support and guidance to access the local industry and relevant governmental offices.
- Government guidance also implies a better overview of the market situation, which is important in scenarios such as the following: Even if the SME product or service is technically perfect, the expected price may be absolutely unacceptable for a bidding and tendering process because a big global company may be already producing a competitive product within China, resulting in a lower price. As each province organizes biddings for a variety of products at different times and intervals, such information, and how the bidding price should be defined, are key issues for the successful marketing of a new product or service – information which cannot be collected easily by a foreign SME.
- Once political support from the central or a local government has been ensured by help of a Chinese partner organization, the rights of the foreign SME, including IP rights, are much better protected.

Stakeholders

State Council
Central Government of China
www. gov.cn/

National Health and Family Planning Commission
Address: No 1 Xizhimen Outer South Road, Xicheng District, Beijing
www.nhfpc.gov.cn/
Issues regulations, standards and policies about healthcare. Develops Traditional-Chinese-Medicine formulates and carries out administrative measures for medical institutions and the medical services industry; draws up and implements regulations and standards for medical techniques, healthcare quality, medical safety and services of medical institutions, as well as management measures for blood collection and supply agencies.

China Food and Drug Administration (CFDA) Address: 26 Xuanwumen Xidajie, Beijing, 100053, PRC
www.sfda.gov.cn/WS01/CL0001/
Responsible for regulatory affairs concerning food, drug, medical devices and cosmetics.

National Development and Reform Commission Address: No. 38 Yuetan Street, Beijing 100824, PRC
www.ndrc.gov.cn/ (CN).
Formulates and implements strategies concerning the national economic and social development. Formulates annual, medium and long-term development plans. Monitors macroeconomic and social development trends and provides forecasts, warning and information guidance. Plans the layout of key construction projects and productivity. Formulates regulatory targets, policies and measures concerning the total size and structure of fixed asset investments in the whole society.

Ministry of Industry and Information Technology
Address: No. 13 Xichang'an Road, Beijing 100084, PRC.
www.miit.gov.cn/ (CN).
Drafts and formulates the strategy for high-tech developments relevant for biomedicine, new materials etc.

State Intellectual Property Office (SIPO)
Address: No. 6, Xitucheng Road, Jimenqiao Haidian District, Beijing 100088, PRC.
english.sipo.gov.cn/lxfs/ (E).

Ministry of Science and Technology (MOST)
Address: 15B, Fuxing Road, Beijing 100862, PRC.
www.most.gov.cn/eng/ (E)

China National Center for Biotechnology Development (CNCBD)
Address: No. 16 Xisihuan, Beijing 100039, PRC.
www.cncbd.org.cn/English/ (E).

Ministry of Human Resources and Social Security (MHRSS)
Address: No. 3 Hepingdongjie, Beijing 100013, PRC.
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Appendix

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