CHINA REGULATORY AND MARKET ACCESS PHARMACEUTICAL REPORT

2014

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CHINA REGULATORY AND MARKET ACCESS PHARMACEUTICAL REPORT (2013)

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I. CHINA PHARMACEUTICAL MARKET OVERVIEW

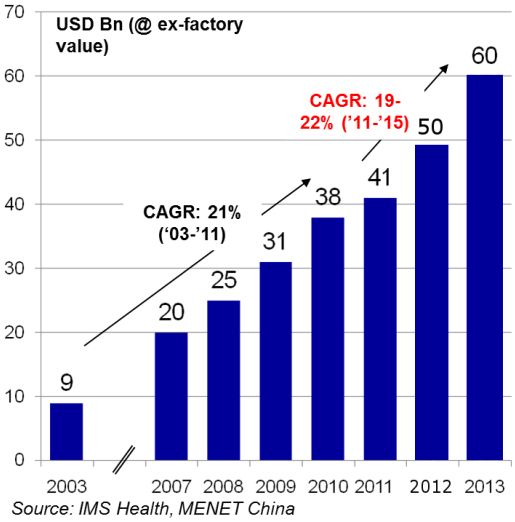
A. Overview

China is one of the largest and fastest growing economies in the world today. GDP between 2008 and 2010 grew by an average of 9.7% annually. In 2012, China's GDP growth rate was 7.8%. This was the slowest growth rate since 1999. But it was still significantly stronger than OECD countries' average of 3.0%. China's GDP growth is estimated to remain strong at 8.4% in 2013.

China has over 1.3 billion people. This comprises 20% of the world's population. The enormous consumer potential in China draws many foreign companies. China has become more economically open and affluent. There is a direct correlation between China's increasing affluence and the people's increasing healthcare standards. Many Chinese citizens are cultivating greater healthcare awareness and demanding better healthcare. As a result, China's pharmaceutical market is booming. The pharmaceutical market has experienced an average annual growth rate of between 15% and 17% over the past decade. According to a variety of sources, China's pharmaceutical market in 2012 was worth approximately $60 billion. The pharmaceutical market will continue to grow at an annual growth rate of 12% from 2013 to 2020. About half of all sales go to Western drugs, a third to Traditional Chinese Medicines (TCM), while the rest goes to nutraceuticals and biologics. China became the world's third largest drug market in 2011, bigger than the UK, Italy, Canada, Spain, or Brazil.

China has become the 3rd largest pharma market globally since 2011

China pharmaceutical market size



Source: IMS Health, MENET China

Top 4 pharmaceutical markets

1. US	$310 billion
2. Japan	$102 billion
3. China	$60 billion
4. Germany	$40 billion

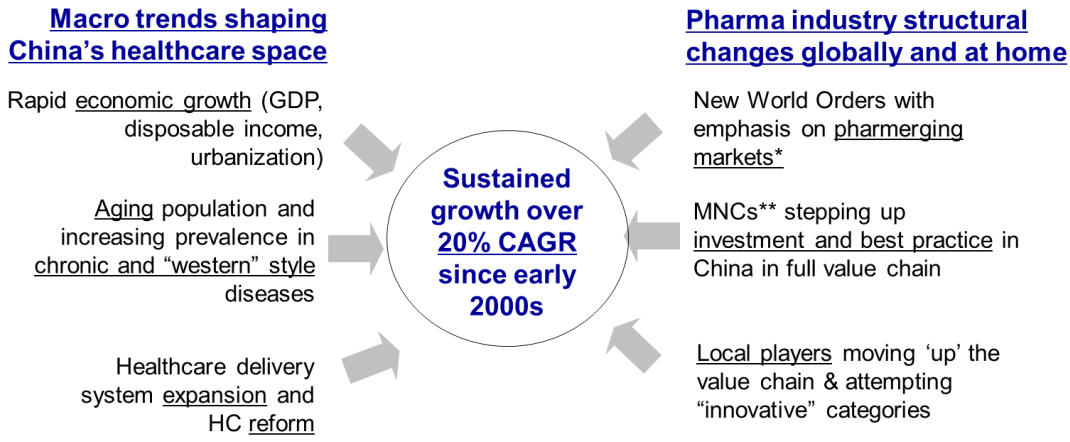
Note: IMS data tends to under-estimate China's market

As China becomes more developed, its epidemiological profile is changing. Chinese people are eating more unhealthy Western foods, smoking more, and exercising less. Chronic diseases are on the rise in China. These diseases now account for over 75% of deaths. According to the "2011 Health Statistics Yearbook" announced by China's Ministry of Health (MOH) on January 16, 2013, the leading causes of death are cancer (26%) and cardiovascular diseases (21%). These two diseases combined account for 47% of deaths in China. This is followed by cerebrovascular disease (20%) and respiratory illnesses (11%). Doctors are seeing more patients in their 20's, 30's and 40's falling victim to cardiovascular disease. Thus, cardiovascular drugs are in very high demand. Drugs in other therapeutic categories, including respiratory, anti-inflammatory, anti-ulcer and neurological drugs are also in high demand. Chinese people are living longer, and are consuming more healthcare products to maintain healthy lifestyles. The average life expectancy in China is now 71.4, higher than the global average of 68.

Despite growth in China's urban coastal regions, the Chinese rural interior is still developing very slowly. Urban residents have much higher standards of living than rural residents. Development in China has been criticized for being too concentrated in the bigger cities. Residents of Shanghai, Guangzhou, Shenzhen, Hangzhou, Tianjin, and Beijing have much higher standards of living than citizens from smaller cities or in the rural interior. The lower standard of living in the rural areas has driven scores of rural Chinese to the urban areas since the early 1980s. An estimated 200 million people from rural areas have migrated to the cities for better work opportunities, driving urban growth.

China's distribution of healthcare resources is also extremely unequal. Although over 60% of the population lives in rural areas, only 20% of China's healthcare resources reach the rural interior. The health care system in China is expected to change and expand over the next five years as a result of the new health care reform plan that was implemented in 2009. All levels of government invested a total of RMB 850 billion (approximately US $125 billion) between 2009 and 2011 for this reform. China aims to cover all 1.3 billion urban and rural residents with some type of basic medical insurance, improve access and standards for basic medical care, and reduce unaffordable healthcare for all citizens. This is a challenging goal for China. Three years after the execution of this reform plan, it looks as though the government has achieved this goal. Health insurance coverage has improved dramatically. In 2012, it had already covered more than 95% of the population. Even for people living in rural areas, coverage had reached 96% by the end of 2010. This coverage, although widespread now, only provides the basic benefits and still requires most Chinese to pay high co-pays.

The impetus for growth is a timely combination of macro-environmental and industry-driven factors



**: Pharmerging markets – Brazil, China, India, S. Korea, Mexico, Russia, Turkey*
***: MNC - multi-national company*

Navigating the market in China is no easy task, as the value chain involves a complex set of stakeholders

Illustration of the business of Rx commercialization in China

Key constituents -

- Drug manufacturers
- Distributors
- Central government: various agencies
- Provincial governments: various agencies
- Hospitals: various classes and levels
- KOLs and physicians

**: RDL – Reimbursed Drug List*

B. China Pharmaceutical Market Trends

With economic expansion and increased affluence, the pharmaceutical market in China will continue to experience enormous growth. Strong growth is expected in both the prescription and over-the-counter (OTC) drug markets. China's OTC market is expected

to become the world's largest within only ten years. OTC sales almost doubled from 2003 to 2009 to approximately $12 billion. Prescription sales grew at around 20% annually over the same period. Although Traditional Chinese Medicines (TCM) play an important role in Chinese healthcare, Western medicines for infectious disease, acute symptoms, illnesses, and surgical procedures are often considered more effective and are higher in demand. Due to the demand for pharmaceuticals, many foreign drug companies have made significant progress in developing their own manufacturing and distribution networks in China.

While there are many domestic Chinese pharmaceutical companies, foreign companies remain the dominant players in the Chinese drug market. Currently, the majority of domestic pharmaceutical companies in China are often too small to compete with foreign companies. Therefore, almost all Chinese domestic pharmaceutical manufacturers are focused on producing generic drugs. Compared with foreign companies, local companies have made little investment in research and development. As a result, over the past decade, many local Chinese firms decided to partner with foreign firms in Sino-foreign joint ventures (JVs) to become more competitive in the Chinese pharmaceutical market. However, over the last decade, foreign drug companies have increasingly set up their own wholly foreign-owned enterprises (WFOEs) *without* Chinese partners.

Recently, due to their lowered profits from intense competition and government price cuts, some domestic Chinese pharmaceutical companies are trying to develop and market innovative Western-style products. However, it will take time before these initiatives are successful and new compounds are developed by local Chinese firms.

As part of China's new healthcare reform plan, the government released an Essential Drug List (EDL) in March 2009 and an updated version in March 2013. The latest EDL has 520 drugs which are to be sold at government-controlled prices. The government also released a new National Reimbursement Drug List (NRDL) in November 2009.

Under the reform plan, China aims to establish a national essential drug system, i.e., a systematic way to determine what drugs should be on the national essential drug list. Most small public clinics and healthcare centers are required to purchase essential drugs, and larger hospitals must operate with a set ratio of essential to nonessential drugs. All essential drugs will also be added to the national drug reimbursement list for basic medical insurance programs.

To ensure drug quality control, safety and drug efficacy, the 2005 Chinese Pharmacopoeia was also revised. Completed in 2009, the revised 2010 Chinese Pharmacopoeia came into effect on October 1, 2010. Manufacturers in each Chinese province are now expected to adhere to its contents. All drug manufacturers were required to make all necessary changes by October 1, 2010 to adhere to the Pharmacopoeia's guidelines for specifications and labeling. This included filing supplemental applications to the provincial FDA, where necessary.

The 2010 Chinese Pharmacopoeia also includes standards for national drug development, manufacturing, operations, use, and management. Drawing from foreign drug standards, the book includes recent innovations, developments, and evidence-based foundations.

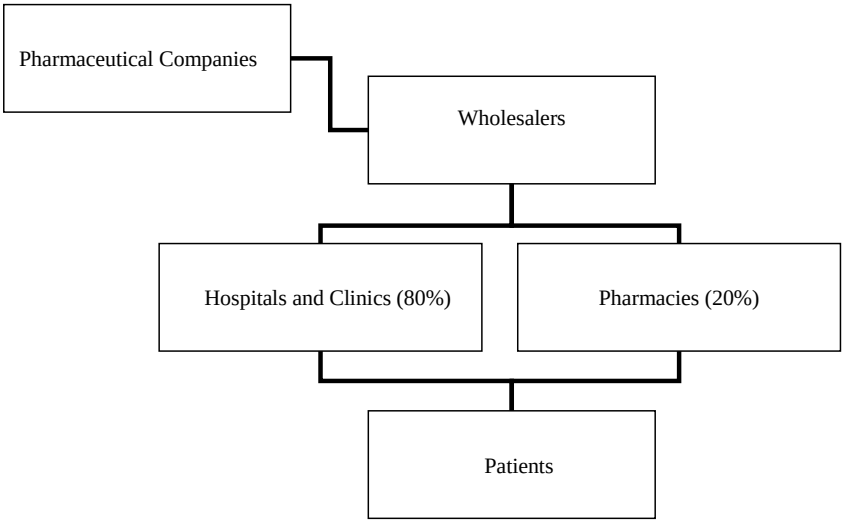
Published by the China Medical Science and Technology Press, the 2010 Chinese Pharmacopoeia is split into three volumes. These volumes cover Traditional Chinese Medicine (TCM), chemical drugs, and biological products. In total, there are 4,600 varieties of drugs covered – 1,300 of which are new. The drugs in the 2009 National Essential Drug List and the National Medical Insurance Drug List have also been incorporated into the 2010 Chinese Pharmacopoeia. Updates and new information focus on increased safety inspection requirements and standards for high risk drugs, TCM, as well as drugs with heavy metal or other harmful elements.

The first revision of the 2010 Chinese Pharmacopoeia was published in July 2012. There are 139 new drug standards, along with 504 drug standard revisions. The information in this supplement has been in effect since October 1, 2012.

In China's drug market, hospitals are the main channel for dispensing drugs. The pharmacy market represents 75% of market share, but the OTC market is growing at a more rapid pace. Generics dominate the market by volume with lower prices. In China, one product can have dozens of manufacturers. For example, 35 companies make the drug Erythropoietin. Also, unlike in the West, a typical Chinese blockbuster is worth about $125 million in sales.

The pharmaceutical market in China is mostly concentrated in coastal areas, but it is spreading out quickly. In addition, there is an increasing concentration of drug distributors. Before, many small players dominated local markets. Now, they are often being bought up by bigger companies through mergers and acquisitions. However, the top ten distributors in China still represent only about 35% of the market.

C. China's Pharmaceutical Distribution System



Currently, China has a three tiered distribution system through which most major or multinational pharmaceutical manufacturing companies distribute their drugs via national and provincial wholesalers. Those national and provincial wholesalers then sell the drugs to hospitals, clinics and pharmacies, which in turn "sell" the drugs to patients. The majority, approximately 80% of all Western-style drugs, are distributed at pharmacies at *hospitals* and *clinics*.

Due to a lack of infrastructure and logistical expertise in the rural areas, it has been difficult to establish secure and efficient delivery of drugs to China's rural population. These conditions and a pharmaceutical distribution system that is made up of mainly small, local distributors have made it difficult for regulators to monitor drugs. It is also difficult for manufacturers to track their sales in rural areas of China. Another consequence of this distribution system, where nearly 80% of distributors are considered small, is that manufacturers eager to distribute their products on a national level need to utilize multiple distributors. A further challenge is that until recently, there was no comprehensive product tracking system set up between manufacturers, and distributors, which makes product tracking or product recalls more difficult.

However, to improve traceability and tracking, China plans to implement a national drug barcode system under the *Administrative Provisions for Drug Registration*. There will be three different kinds of codes: a basic code given after the product is registered, an inspection code used for a drug monitoring tracking system, and an identification code used for medical insurance/supply, classification, and research purposes. Drug codes will be revised accordingly as drug registration information changes.

In addition, the Chinese government's compliance mandates to meet Good Supply Practices ("GSP"). It has started to remove companies that engage in questionable distributor practices throughout the pharmaceutical system. The Chinese government has been encouraging the development of more "professional" distributors in order to strengthen the distribution system. Examples include both the first modern pharmaceutical logistics center built in 2004 and the first cold chain logistics network launched in 2007 to provide 36 cities with access to temperature-controlled products. Analysts predict that there will be additional improvement with the emergence of more foreign distributors in China.

D. Brief Overview of China's Pharmaceutical Regulations

The Drug Administration Law of the People's Republic of China, the country's first comprehensive legislation regulating the research, production and distribution of drugs was adopted in 1984. This law was revised "to strengthen drug regulation and to ensure drug quality and safety", according to the government, at the 20th Session of the Standing Committee of the 9th National People's Congress on February 28, 2001, and became effective on December 1, 2001.

The *Regulation for the Implementation of the Drug Administration Law of the People's Republic of China* was approved by the State Council and effective September 15, 2002.

The basic regulations for the administration of the pharmaceutical industry in China are outlined in these two laws. These laws regulate all pharmaceutical areas, including drug manufacturers, drug distributors, and medical institutions' use of drugs, new drug registration, drug packaging, pricing, advertising, and post-marketing surveillance.

E. China Food and Drug Administration (CFDA)

Starting in 1998, the State Drug Administration (SDA) was in charge of regulating the pharmaceutical industry in China. However, in 2003, the State Food and Drug Administration (SFDA) was established, replacing the SDA. In March 2013, it was reorganized and re-named the China Food and Drug Administration (CFDA). The CFDA, modeled after the US FDA, works under the control of the State Council. The CFDA is the governing body that regulates all drugs, medical devices, food, and cosmetics. It also controls all registration, inspection, sale, research, and advertising for these products.

On September 1, 2008, the CFDA officially came under the direct management of the Ministry of Health (MOH), ending the CFDA's five-year administrative independence. This was in response to the CFDA's failure to prevent multiple food and drug safety scandals in 2006 and 2007. The CFDA is in the process of further reorganization, with the MOH gaining more responsibility. Such changes currently seem unlikely to significantly affect the drug regulatory regime in China. However, there is some concern that the MOH could use its authority to interfere with drug regulation for political or other reasons.

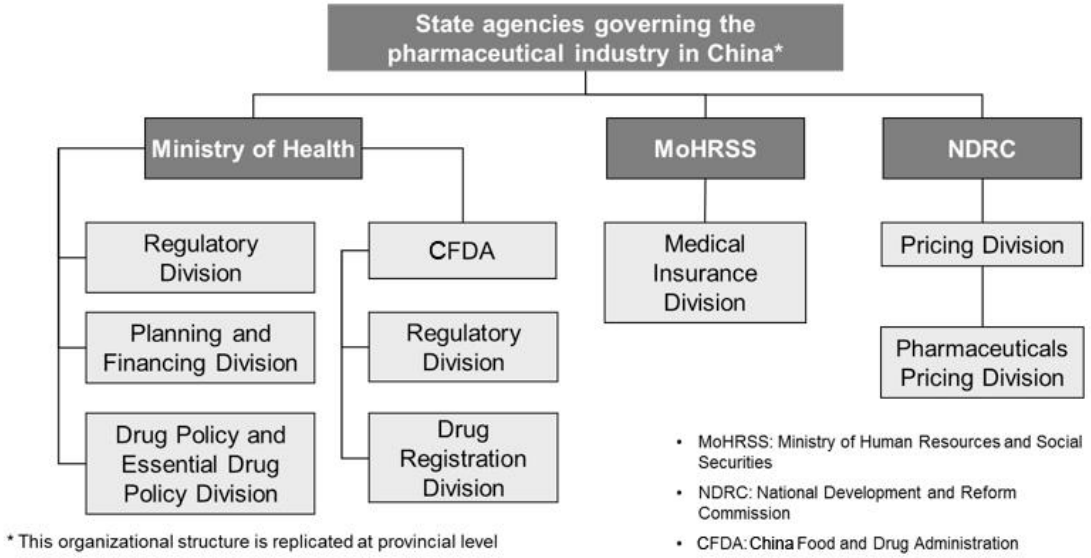
The CFDA, under the MOH, is in charge of all new drug registration approvals. Drug registration in China is complex and takes one to two years for new drugs. Even if a product is approved elsewhere, the CFDA will most likely still require the foreign manufacturer to conduct at least some clinical testing in China before the drug is approved in China.

Contact Information for Regulatory Departments:

China Food and Drug Administration (CFDA)
A38, Beilishi Road, Beijing 100810, P.R. China
Phone: +86 10 6831 3344
Fax: +86 10 6831 0909
Email: inquires@sfda.gov.cn
Website: http://eng.sfda.gov.cn/WS03/CL0755/

Center for Drug Evaluation, China Food and Drug Administration
Floor 14, Building A, Zhonghuan Plaza
No. 70, Zaolinqian Street, Xuanwu District, Beijing 100053, China
Phone: +86 10 8397 9589

Multiple government agencies are responsible for policy-making and for monitoring the industry



Various agencies and their responsibilities

	MOH (Central) & Provincial Health Bureaus	CFDA	NDRC	MOHRSS (Central & Provincial)
Drug registration	◔	●		
GMP monitoring		●		
Pricing & price review	◔		●	●
Reimbursement/NRDL	◔	◔	◔	●
Essential drug list	●		◔	
Tendering	●			
Clinical trial		●		
Post-market surveillance		●		

Level of Influence: Low ○ → ● High

II. THE CHINA HEALTHCARE SYSTEM

A. History of China's Healthcare System

In the past, China had a state-run healthcare system. Virtually all medical costs were paid for by the government or by employers. When the People's Republic of China was established in 1949, the Chinese Communist Party extended healthcare services to rural areas. Healthcare was usually offered by town or village governments. Life expectancy in China's rural areas increased dramatically from 1949 to 1975. However, healthcare services were not very advanced. During the Cultural Revolution from 1965-1975, the Chinese government punished intellectuals and replaced skilled physicians with "barefoot doctors" who had only basic training. As Mao Zedong lashed out against all "intellectuals," most trained physicians were sent to the countryside to be re-educated. However, throughout this time, almost all Chinese citizens received equal, though minimal, healthcare coverage.

B. Struggling Healthcare Services Sector

Currently, China's medical services sector is in need of reform. It is increasingly difficult for people to afford healthcare services. Based on the nationwide health services survey taken in 2008, nearly 40% of people who should seek external medical care self-medicate. Also, only 25% will visit a medical facility when they need prescription drugs for chronic diseases while only 20% will go for a yearly checkup or treatment of a serious disease.

These health services problems are due to the high cost of medical treatment in China. Medical service costs have increased dramatically. Now, the medical insurance coverage has improved dramatically since the implementation of the 2009 healthcare reform plan. In 2012, it already covered more than 95% of the population. But the spending covered by medical insurance is still very low. For the treatment of serious diseases or chronic diseases, the majority of medical expenses are still covered by out-of-pocket spending.

C. 2009 Healthcare Reform

China's State Council took measures towards health care reform in 2009. On January 21, China's State Council approved the implementation of China's long-awaited healthcare reform plan. All levels of government were allocated RMB 850 billion (approximately US $125 billion) between 2009 and 2011 to implement the reform.

Major issues to tackle in the healthcare reform include:

- Imbalanced healthcare development between rural and urban areas
- Operational weaknesses in public health sector
- Lack of government investment in healthcare
- Increasing medical expenses by Chinese households and individuals

In broad terms, the reform aims to improve the following:

- Strengthening China's public healthcare service system, especially in rural areas
- Improving management and supervision of public medical institutions
- Increasing basic medical insurance coverage of the people
- Allowing more affordable pharmaceutical drugs on the market

D. Hospitals and Medical Resources

1. Hospitals in China

There were 20,918 hospitals in China according to the Health Statistics Yearbook 2011, issued by the MOH in January 2013. Most general hospitals are state-run and divided into three tiers. Tier 3 hospitals are the largest and most sophisticated hospitals. Tier 2 hospitals are medium-sized and provide general medical services. Tier 1 hospitals are clinics that provide basic medical care but not advanced medical services. There are also many small community healthcare service centers which are classified as hospitals but not included in the tier system.

HOSPITALS IN CHINA: SCALE

	2009	**2010**
TIER 3: LARGE GENERAL HOSPITALS	1233	1284 (+4%)
TIER 2: MEDIUM-SIZED GENERAL HOSPITALS	6523	6472 (-1%)
TIER 1: POLYCLINICS	5110	5271 (+3%)
NONTEIRED HEATHCARE SERVICE CENTERS	7425	7891 (+6%)

HOSPITALS IN CHINA BY CAPACITY (BEDS)

# Beds	**<100**	**100-199**	**200-499**	**500-799**	**>800**
2007	12,075 (61%)	3,700 (19%)	2,869 (14%)	814 (4%)	394 (2%)
2008	11,725 (59%)	3,572 (18%)	3,020 (15%)	907 (4.6%)	488 (2.5%)
2010	12,394 (59%)	3,496 (17%)	3,241 (15.5%)	1,069 (5%)	718 (3.4%)

**Ministry of Health Statistics Yearbook, 2012*

2. Current Problems in the Hospital Sector

Because the majority of hospitals in China are state-run, the costs for general medical supplies and services are controlled by the government. However, these state-run hospitals do not receive enough funding from the government to maintain their operations. Due to this situation, many state-run hospitals behave like for-profit institutions to maintain their operations. In order to generate profits for the hospital, many physicians prescribe more drugs and/or more expensive drugs than necessary. They also routinely encourage patients to undergo unnecessary expensive medical procedures.

3. Private Investment in the Hospital Sector

Chinese citizens of low socioeconomic status are often unable to pay for their medical services and end up indebted to hospitals. These citizens commonly cite high cost as the primary reason for avoiding hospital care. The inability of the poorer Chinese to pay for healthcare has led the Chinese government to implement new reforms in the hospital sector.

In the fall of 2004, in an attempt to improve hospital services, the Chinese government started to allow private investment in public hospitals. The government had hoped that external investment would give public hospitals a financial boost and encourage competition. This was intended to make medical care more accessible to Chinese citizens.

At the end of 2009, 15% of Chinese hospitals were for-profit. The absolute number of for-profit hospitals increased by over 1,000 from 2005 to 2008, with approximately 6,000 currently in operation. However, the actual *percentage* of for-profit hospitals out of all hospitals is not increasing significantly, because the government is also building many new nonprofit state-owned medical institutions.

Although privatization in many other sectors within China has proven successful, current planned healthcare reforms focus on "restoring the nonprofit character" of medical institutions, rather than encouraging privatization further. This is because the government believes that although private investment helps urban hospitals grow and develop, it does not improve access for low-income Chinese in cities or the countryside.

While state-run hospitals are still the main medical service providers, business opportunities are improving for private hospitals.

In December 2010, China stepped up plans to promote private investment in healthcare services. New policies were established for the private sector to participate in the restructuring and management of Chinese state-owned hospitals. This aims to reduce the number of state-owned hospitals by gradually converting some public health institutions into private ones.

Foreign investors will also be able to participate either in joint ventures (JVs) or as wholly-owned foreign enterprises (WOFEs). This is a big step from the previous restriction where wholly foreign-owned hospitals and clinics were not allowed in China. Currently on a pilot basis, priority for WOFEs establishment is given to investments from Hong Kong, Taiwan and Macau. With regards to hospital JVs, the previous limit of 70% in foreign shareholding is expected to be gradually lifted.

China intends to simplify the business processes for foreign participation. Application procedures and requirements will be streamlined by central and local government authorities. Wholly foreign-owned hospitals will be approved by the Ministry of Health and the Ministry of Commerce. In the meantime, approval for joint-ventures in medical institutions will still be given by the provincial authorities.

Aside from greater ease of equity participation, China is giving private medical institutions the same preferential tax as its state-owned hospitals. China will also exempt non-profit private hospitals and clinics from the medical service income tax, the medicine value-added tax as well as housing, land, vehicle and vessel usage taxes. Profit-oriented hospitals and clinics will be exempted from business tax. They will also have a three-year tax break on other items such as real estate, property and medicines.

These policies combined provide a fairer competition platform for all hospitals. Previously, high tax obligations were a barrier for the development of private hospitals. Although these hospitals provided similar products and services as their state-owned counterparts, higher taxes capped their profits.

There are at least 1,000 medical partnerships established between Chinese medical institutions and foreign investors. The main investors are from the US, with a 32% share of the total medical partnership investments. This is followed by Hong Kong, with a 30% share. Other investors originate from Japan, South Korea and Australia.

Foreign investment in private hospitals has increased, as shown by the following:

- The Parkway Group is a Singapore healthcare company which has been in China since 2005. It currently has 8 medical centers in Shanghai. One of these opened in mid-2008 in the prestigious Hongqiao district, catering specifically to Japanese in the area. It also established 1 state-of-the-art international clinic in Chengdu. It is expanding aggressively, having purchased the rival health network Worldlink. The company is moving to second-tier Chinese cities like Hangzhou, Ningbo, and Xi'an.

- United Family Hospitals is a network operated by the American company Chindex International. It currently has hospitals and clinics in Beijing, Shanghai, Guangzhou, and Wuxi, and is working to expand from its traditional expatriate client network to wealthier Chinese. It is also changing its membership system, which currently focuses on individual memberships, to also allow corporations to enroll their employees.

- There are also a number of Taiwanese-invested hospitals in China. The Formosa Plastics Group, for example, founded its first hospital on the mainland in 1976, and in 2008 it opened a new 500-bed hospital in Xiamen (to expand to 2,000 beds). Unlike hospitals intended for Western expatriates, this hospital's fees are within reach of middle-class Chinese. Another Taiwanese company, BenQ, opened a full-service 3,000-bed hospital in Nanjing in 2008.

4. Hospital Reform

An aspect of the 2009 healthcare reform focuses on hospitals' revenue-generating methods. The government aims to end hospitals' financial reliance on drug sales or unnecessary procedures. However, due to a lack of government funding, public hospitals

have traditionally operated mainly via medical service fees and drug sales. This resulted in heavy burdens on patients and waste of medical resources due to overtreatment. The government hopes that the healthcare reforms would remedy this issue by eliminating the permitted 15% markup that hospitals typically charge on drugs. By separating drug sales from hospital services, the hope is that there would be a significant lowering of drug prices, medical supply prices, and medical service fees for patients. The resulting shortfalls in hospital income would be met by government subsidies and a "reasonable" rise in patients' medical service fees. The healthcare reform also includes plans to set up hospital-monitoring institutions to ensure transparency in the management and quality of medical services.

Another important aspect of the healthcare reform is the new government subsidies to help build public hospital infrastructure, purchase new medical equipment, support academic research, train healthcare professionals, and cover medical costs for retirees. The Chinese government is expected to fund the construction of 2,000 county-level hospitals and an additional 5,000 clinics by 2011. Larger urban hospitals are also expected to provide greater support to small, local hospitals in terms of personnel, expertise and equipment. The Chinese government also intends to provide additional training to general practitioners in healthcare institutions below the Tier 3, 2 and 1 hospitals.

The government will give special subsidies to hospitals providing public health services such as disease prevention, inoculation, and health education. The plan will also likely give more funding to hospitals if they specialize in epidemic diseases, occupational diseases, psychiatry, maternity, and pediatrics.

To correct the imbalance in allocation of medical resources, which are skewed towards major urban hospitals, the government is planning to relocate or merge some state-run hospitals.

From the Health Statistics Yearbook 2011, it is obvious that the number of private hospitals has increased dramatically in the past three years. Of a total 20,918 hospitals in 2010, almost one-third (7,068) are privately invested.

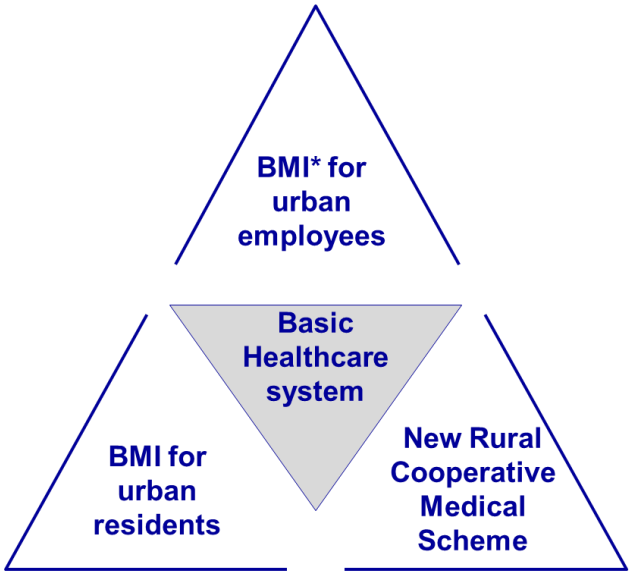
E. Health Insurance in China

The closing or privatization of many state-owned enterprises in the late 1990s, which provided healthcare for employees, left about 50% of urban workers without healthcare insurance. Since then, China's central, municipal and local authorities have worked to set up new public funding mechanisms.

The government established the Basic Medical Insurance (BMI) system to give most urban residents basic medical coverage. At the end of 2007, BMI covered 221 million out of China's 580 million urban residents, and enrollment was increasing rapidly. The aim of the BMI was to make it easier for lower and middle-class Chinese to receive healthcare and medications regularly. BMI continued to expand over 2008. In November

2008, the government put forward a plan to extend coverage to over 20 million college students. Today, almost all urban dwellers have BMI.

The government funding comprises BMI for urban employees, BMI for urban residents, and NRCMS



*: BMI: Basic Medical Insurance; funded by the government

Provinces and large cities design and specify their own policies

	Insured	Funding	Coverage
BMI for urban employees	Urban employees	• Both employee and employer contribute • Premium is based on individual salary and payroll of employer	• Annual max: >US$47,000 in 2011 among the coastal developed areas
BMI for urban residents	Urban residents	• Central government • local government • individual	• Annual max: >US$24,000 in 2011 among the coastal developed areas

In the countryside, access to healthcare is extremely low compared to in cities. The former cooperative medical systems in rural areas withered due to lack of funding, leaving most of the rural population without any public healthcare access. More recently, the government has been building the "New Rural Cooperative Medical System," to be administered at the county level rather than the municipal level. In the past, this system

took personal contributions of RMB 10 (about $1.40) per year, plus total central and local government contributions of RMB 40 (about $5.80) per year. At present, the system takes personal contributions of RMB 20 (about $2.90), plus government contributions of RMB 80 (about $11.70).

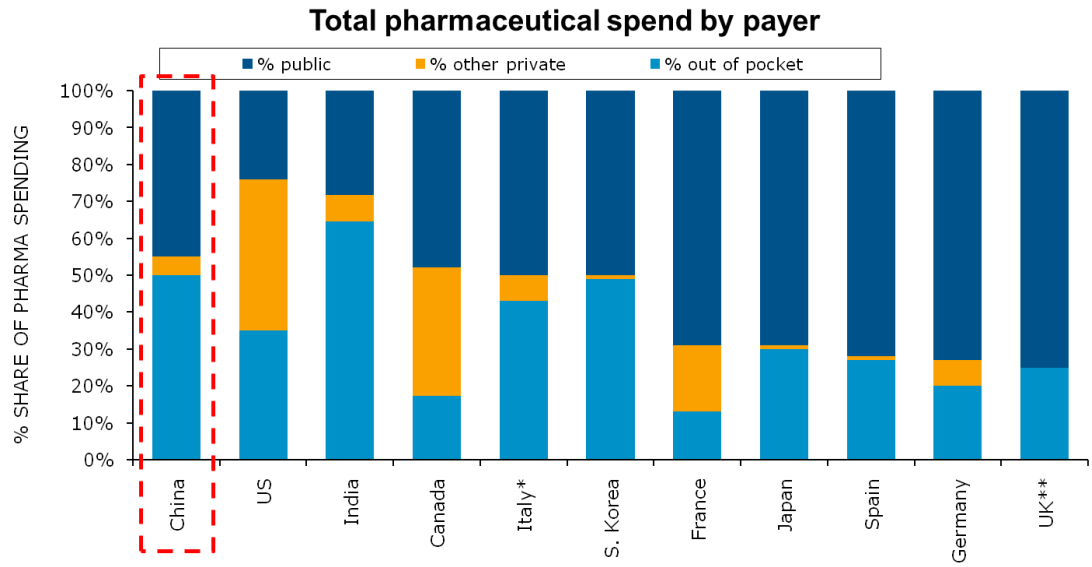
After implementing the BMI system in many urban areas of China, the government focused on extending it to the entire rural population. Under the recent 2009 healthcare reform, China has targeted having 90% of the population covered by medical insurance by the end of 2012. By 2020, China aims to have its *entire* population covered by medical insurance. This will be a challenging task. At the end of 2009, over 800 million people were covered in this system. However, many farmers remain so poor that they are reluctant to pay even these small premiums. In addition, the system requires large co-pays for many types of treatment. Even though the government optimistically plans to make huge infrastructure investments in the rural healthcare system, at best it will only give farmers very basic coverage.

China announced plans to expand medical insurance coverage for all urban employees and residents. Higher reimbursement rates have been targeted for both urban and rural residents under their respective insurance programs for inpatient expenses. The government is also pushing to reimburse patients at the time of discharge, as opposed to making delayed reimbursements.

The government will also increase subsidies for two separate health insurance programs to RMB 200 ($30) per head from RMB 120 ($18). These are health insurances for urban workers and the rural cooperatives.

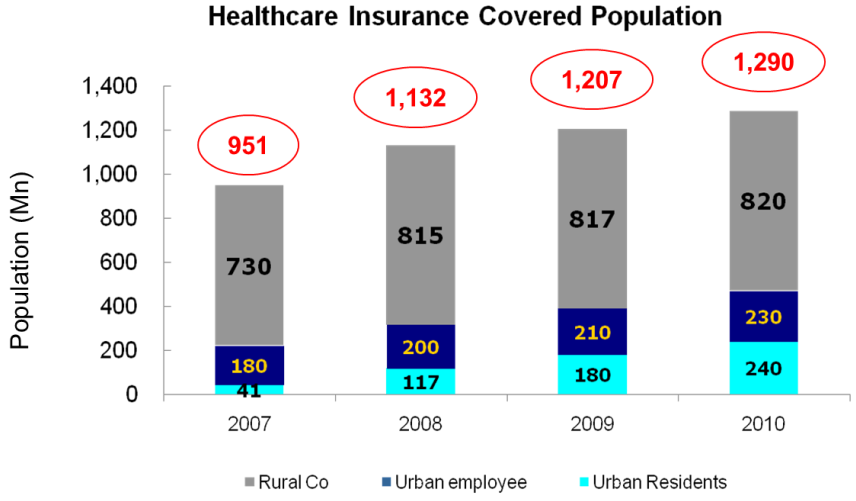
Nevertheless, rural access to healthcare remains so low that it is barely comparable to the situation in urban areas. For some time to come, foreign pharmaceutical companies are expected to conduct more business in the urban, rather than rural areas.

Healthcare in China is paid for by a combination of government funding and self-pay



Sources: WHO Model List of Essential Medicines, 2010, OECD, China MOH, etc.

The government's goal was to provide basic insurance to essentially everyone by 2011



Sources: MOH, National and Local Health Statistics

III. DRUG REGISTRATION REGULATIONS

A. Drug Registration Policy

The latest *Administrative Provisions for Drug Registration* was promulgated on June 18, 2007 by the CFDA (Order No. 28) and became effective on October 1, 2007. These Provisions replaced the previous version of the regulation, Order No. 17.

A series of provisions and guidelines regulate drug development and approval in China. They cover clinical trials (IND), new drug manufacturing, marketing licenses (NDA), registration supplements and license renewal. The three major divisions of drugs covered by these guidelines include new drugs, generic drugs and imported drugs.

B. Classification of Drugs

In China, drugs are classified as 3 types: Chemical Drugs, Biological Drugs, or Traditional Chinese Medicine/Natural Drugs.

For chemical drug registrations, there are 6 different classes:

1. A new drug which has never been marketed in any country.

2. A new drug preparation which changes the administration route[1] of the marketed drug, and has not been marketed anywhere in the world in this form.

3. A new drug which is already marketed outside of China, but has not been marketed in China.

4. A new drug which changes the acid or alkali (or metal) radical of a product marketed in China, but does not change the pharmacological effect.

5. A new drug preparation which has a different dosage form from drugs already marketed in China, but does not change the administration route.

6. Drugs that have already established national specifications in China (generics).

For therapeutic biological product registration, there are 15 different classes:

1. A new biological product which not been marketed before in any country.

2. Monoclonal antibody.

3. Gene therapy, somatic cell therapy, and their preparations.

[1] Administration route means how the drug is taken such as orally, topically, or through injection.

4. Allergen preparation.

5. Multi-component bioactive products extracted from human and/or animal tissues and/or body fluid, or by fermentation.

6. A combination drug preparation which consists of biological products that are already marketed in China.

7. A drug currently marketed outside of China, but has not been marketed in China.

8. Microbial drug preparations which are produced from cell strains that are not yet approved.

9. A drug preparation with a changed structure from an already-marketed product, where this changed new preparation has not been marketed anywhere around the world (changes include chemical modification, amino acid locus mutation or absence, different expression system, etc.)

10. Drug preparation with different manufacturing processes from an already marketed product (different host cells, expression system, etc.)

11. A drug preparation made for the first time with DNA recombination technology.

12. A new drug preparation with a changed administration route from a marketed product, such as non-injection vs. injection or topical vs. systemic administration, where the new preparation is not marketed anywhere in the world.

13. A new drug preparation which has a different dosage form from a drug already marketed in China, but the same administration route.

14. A new preparation with changes in the administration route from a marketed product, but not including cases falling into class 12.

15. Drugs that have already established national specification in China (generics).

<u>For preventive biological product registration (vaccines), there are 15 different classes:</u>

1. A vaccine not currently marketed domestically or overseas.

2. A DNA vaccine.

3. A currently marketed vaccine with a new drug-enhancing agent (adjuvant) or a changed carrier for a combined vaccine.

4. An unpurified vaccine or full cell vaccine (bacteria, virus) changed into a purified vaccine, or combined vaccine.

5. A vaccine with strains not yet approved in China (except for vaccines for influenza, leptospirosis, etc.).

6. A vaccine already marketed overseas but not yet marketed in China.

7. A conjugate or combined vaccine prepared from a vaccine that is already marketed in China.

8. A recombination vaccine with a protective antigen spectrum different from the one currently marketed in China.

9. A vaccine manufactured with a change of the approved expression or cellular stroma. The vaccine using a new process should have been proven to have higher safety and efficacy based on laboratory data.

10. A vaccine with a change in the de-activator (method of deactivation) or the method of de-toxicity.

11. A vaccine with a change in the administration route.

12. A vaccine marketed in China with a change in the dosage form but no change in the administration route.

13. A vaccine with a dosage of immunity or immunity procedure.

14. A vaccine for an enlarged group of people (enlarged age range).

15. A vaccine admitted with National Standards[2] (generics)

<u>For traditional Chinese medicine (TCM) and natural drug registration, there are 9 different classes:</u>

1. A new active ingredient and its preparations extracted from a plant, animal, or mineral source, and which has not been marketed before in China (active ingredient must be at least 90%).

2. A newly-discovered drug material and its preparations.

3. A new replacement product for a currently-used traditional Chinese medicine.

4. A new ingredient of an existing drug material to be used as a drug.

[2] National Standards are the technical requirements for quality and production for drugs. These standards were established by the Chinese government to ensure quality. These standards have been approved by the CFDA for specific drugs and all pharmaceutical companies must comply with these standards in China.

5. A new active ingredient and its preparations extracted from a plant, animal, or mineral source, and which has not been marketed before in China (active ingredient must be at least 50%).

6. A new combination product of traditional Chinese medicines, natural drugs, and/or chemical drugs, which has not been marketed in China.

7. A new preparation which has a changed administration route from a currently marketed traditional Chinese medicine or natural drug.

8. A new drug preparation which has a changed dosage form from a currently marketed traditional Chinese medicine or natural drug.

9. Generic drugs.

C. Drug Registration Applications

There are four types of drug applications in China:

1. New drug application
2. Generic drug application
3. Imported drug application (includes foreign new drugs)
4. Supplemental application
5. License renewal

New drug applications:

1. Class 1 to 5 new chemical drugs
2. Class 1 to 14 new therapeutic biological drugs
3. Class 1 to 14 new preventative biological drugs
4. Class 1 to 8 new traditional Chinese medicines and natural drugs

Generic applications:

Generic applications can be used for drugs that already have National Standards in China or are listed in the Chinese Pharmacopoeia. Specifically, Class 6 of chemical drugs, Class 15 of preventative biological products, Class 15 of therapeutic biological drugs, and Class 9 of traditional Chinese medicine and natural drugs fall into this category.

Imported drug applications:

All drugs manufactured outside China must be registered via the imported drug application, even if they are new drugs.

Registration supplements:

Registration supplements are for changes to already-approved drugs. There are a total of 33 kinds of supplements. 17 of these require the CFDA's approval; another 10 situations require approval from the provincial drug authority (PDA), or alternatively can just be filed for record (without approval) with the CFDA. The final 6 situations can be filed for record with the PDA.

A supplemental application needs to be approved by the CFDA in the following situations:

1. Application for Drug Approval Number of a new drug by the New Drug Certificate holder of the drug.
2. Application for use of a drug trade name.
3. Additional indications or functions of TCM or natural drugs, or the indications approved in China for chemical drugs or biological products.
4. Change in the usage or dosage of a drug, or the group of patients to use the drug, but without change in route of administration.
5. Change of strength of drug.
6. Change to supplementary (inactive) ingredients in the formula of the drugs, where there is a medical requirement for it.
7. A change in drug manufacturing technology and process that affects drug quality.
8. Amendment of drug registration standards.
9. Substitution or removal of drug material listed in National Standards as toxic or endangered.
10. Change of immediate packaging material or container of import drugs, domestic injections, ophthalmological drugs, sprays, powder aerosols, or inhalers. Use of new immediate packaging material or container.
11. Application for combined packing of drug.
12. Transfer of new drug technology.
13. Addition or amendment of items in insert sheet of TCM or natural drug, such as pharmacology, toxicology, clinical trials, or pharmacokinetics.
14. Change in items within the import drug registration certificate, such as drug name, drug enterprise name, registered location, packing specification.
15. Change of location where imported drug is manufactured.
16. Change of location where imported drug is packed overseas.
17. Repacking of import drugs in China.

A supplemental application can be approved by the PDA or filed for record with the CFDA in the following situations:

1. Change of name of domestic drug manufacturer.
2. Internal change to manufacturing facility of domestic drug manufacturer.
3. Change to immediate packaging material or container (if not included in item 10 above).
4. Change to validity period of domestic drug.
5. Change of manufacturing location where raw material for imported preparation is manufactured.
6. Change of appearance of drug without change in drug standards.
7. Amendment of drug insert sheet according to national drug standards or as required by CFDA.
8. Supplementing and improving drug safety section of insert sheet.
9. Modification of design of drug packaging and labeling according to regulations.
10. Change of agent for imported drug registration.

A supplemental application can be filed for record with the PDA in the following situations:

1. Amendment to insert sheet of domestic drug according to national drug standards or as required by CFDA.
2. Supplementing and improving the drug safety part of the domestic drug insert sheet.
3. Modification of design of domestic drug packaging and labeling according to regulations.
4. Change to packing specification of domestic drug.
5. Change of manufacturing location of domestic drug.
6. Change of appearance of domestic drug without change to drug standards.

<u>License renewal:</u>

Import Licenses or Drug Product Certificates are valid for 5 years. Renewal applications should be submitted 6 months prior to the product license expiration date. Post-marketing surveillance reports must be submitted with the renewal application.

<u>Fast-track Review:</u>

A fast-track application process is also available for designated drugs, such as:

1. Formulations made from plants, animals or minerals that have never been marketed in China or elsewhere. Newly discovered herbs and their preparations.

2. New chemical entities or biological products that have never been launched in any country.

3. New drugs to treat HIV, cancer and rare diseases (orphan drugs).

4. New drugs to treat diseases which still do not have effective therapeutic methods.

5. Requisite drugs to treat emergency healthcare events.

D. Application Documents for New Drug Registration

The new drug registration application consists of 4 sections:

1. Summary materials

2. Pharmaceutical research materials

3. Pharmacological and toxicological research materials

4. Clinical research materials

For each section, the CFDA has issued a detailed documentation list for chemical drugs, biological products, and traditional Chinese medicine. The CFDA also gives explanations in the appendices of the *Administrative Provisions for Drug Registration* for each document section. In addition, the CFDA has issued technical guidance for some document sections. Usually for imported products, if the documents are prepared in accordance with ICH guidelines, the drugs will be accepted by the CFDA, even without referring to the CFDA's technical guidance.

Overall, during the registration process, pharmaceutical companies should not encounter problems with different data requirements in China and foreign countries. Since Chinese registration document requirements follow ICH guidelines, requirements are fairly similar for China versus the United States and the European Union. Problems often arise when a drug company does not wish to submit sensitive, confidential data for drug registration in China. These companies are often reluctant to divulge information about the manufacturing process or quality control of raw materials. Drug companies registering a drug must discuss the case informally with experts from the Center for Drug Evaluation to ascertain the minimum requirements for their therapeutic area. **For Chemical drugs, the full list of application documents includes the following 32 items:**

Summary Materials:

1. Drug name.

2. Certified Documents (Drug Manufacturing License, GMP Certificate, patent status, business licenses, etc.).

3. Drug discovery and current status of the drug, including R&D and summary of the use and production of the drug both domestically and overseas.

4. Summary and evaluation of main research results including a comprehensive analysis of the safety, efficacy, and quality controllability of the drug.

5. Product insert, drafting notes[3], and latest literature[4].

6. Package and label design.

Pharmaceutical Research Materials:

7. Pharmaceutical research material summary (i.e. summary of experimental literature about the study, synthesis process, and dosage selection).

8. Manufacturing process.

9. Experimental data for confirming chemical structure and components (i.e., physical-chemical properties and purity validation).

10. Experimental data for quality validation.

11. Product specification and notes, including product reference standard.

12. Sample testing report.

13. Source, specification, and testing report for active ingredients and excipients.

14. Drug stability research data.

15. Specification of immediate packaging material and container.

Pharmacological and toxicological research materials:

16. Summary of pharmacology and toxicology research materials.

[3] The drafting notes are a brief explanation of how the draft is made, with methodology and justifications.
[4] The latest literature refers to reference articles or literature used or related to the research work. These articles must be up to date and accurate.

17. Primary pharmacodynamics research data.

18. General pharmacology research data.

19. Acute/single-dose toxicology research data.

20. Long-term toxicology research data.

21. Special safety research data and references on irritability (topical, systemic, phototoxicity), hemolysis and local irritation (blood vessels, skin, mucous membranes, muscle, etc.), and other special safety experiments as appropriate.

22. Research data on interactions of combination drug in terms of pharmacodynamics, toxicology, and pharmacokinetics.

23. Mutagenicity research data.

24. Reproductive toxicity research data.

25. Carcinogenicity research data.

26. Drug dependence research data.

27. Pre-clinical pharmacokinetics research data.

Clinical research materials:

28. Summary of global clinical research.

29. Clinical research protocol to be conducted in China.

30. Investigator's Brochure for clinical research to be conducted in China.

31. Draft of Informed Consent Form and Institutional Review Board (IRB) approval document.

32. Clinical research report.

Different classes of drugs have different requirements for the above documents. For example, drug dependence research data is only required for Class 1 new drugs, and even then only when the drug acts on the central nervous system or otherwise may be liable to cause dependence. In generic applications for Class 6 chemical drugs (generics), a number of the above documents (especially in the pharmacology and toxicology section) can be waived or replaced with summary reports.

For Therapeutic Biological drugs, the full list of application documents includes the following 38 items:

Summary Materials:

1. Drug name.

2. Certified Documents (Drug Manufacturing License, GMP Certificate, patent status, business licenses, etc.).

3. Drug discovery and current status of the drug, including R&D and summary of the use and production of the drug both domestically and overseas.

4. Summary and evaluation of main research results, including a comprehensive analysis of the safety, efficacy, and quality controllability of the drug

5. Insert sheet, notes, and latest literature.

6. Design for packaging and label.

Pharmaceutical Research Materials:

7. Summary of pharmaceutical study information.

8. Research information about the raw materials used for production.
    a. Research information about the sourcing, collection, and quality control of the animal or plant tissues or cells, or unprocessed blood plasma.
    b. Research information about the sourcing, collection (or selection) process and determination of cells used for production.
    c. Information about the establishment, determination, and storage of the strain banks, as well as the stability of culture transfer.
    d. Research information about the sourcing and quality control of other raw materials used for production.

9. Research information about the production process for the raw materials or unprocessed fluids.

10. Research information about the formula and process for the preparations, sourcing and quality standards of supplements, and relevant literature.

11. Experimental information and literature about product quality, including the preparation and standardization of the standard material or controls, as well as comparisons with similar products that have already been marketed domestically or overseas.

12. A record of manufacturing and testing of the sample products to be used for clinical study applications.

13. A draft of the manufacturing and testing standards, with notes about the drafting and verification of testing methods.

14. Preliminary research information about the stability of the drug.

15. Explanation of the basis for selection and quality standards of immediate packing material and container.

Pharmacology and Toxicology Research Materials:

16. Summary of the pharmacology and toxicology study information.

17. Pharmacodynamics research data and literature.

18. Regular pharmacology research data and literature.

19. Acute toxicity research data and literature.

20. Long-term toxicity research data and literature.

21. Animal pharmacokinetics research data and literature.

22. Mutagenicity research data and literature.

23. Reproductive toxicity research data and literature.

24. Carcinogenicity research data and literature.

25. Immunotoxicity and/or immunogenicity research data and literature.

26. Hemolysis and local irritation research data and literature.

27. Experimental information and literature on the efficacy, toxicity and pharmacokinetics of the interactions between multiple components in the combination products.

28. Experimental information and literature on drug dependence.

Clinical Research Materials:

29. Summary of domestic and international clinical studies.

30. Clinical study plan and protocol.

31. Investigator's Brochure.

32. Sample draft of Informed Consent Form; IRB approval documents.

33. A summary report from the clinical study.

Other Research Materials:

34. Brief summary of pre-clinical research.

35. Experiment and study information and summary of the production process improvement, quality assurance, the pharmacology and toxicology study and other work conducted during the clinical study.

36. Amendments and explanation of amendments to the approved manufacturing and testing standards.

37. Drug stability test research data.

38. Manufacturing and testing records for three consecutive batches of trial products.

For Preventive Biological drugs, the full list of application documents includes the following 18 items:

1. Formula and manufacturing process including:

    a. Name of the new products.
    b. Certified Documents (Drug Manufacturing License, GMP Certification, business license, etc.).
    c. Objectives and basis for application (including relevant research and literature).
    d. Insert sheet, notes, and literature.
    e. Sample design of packaging and labeling.

2. Research information summary and evaluation

3. Research information about on bacterial production and toxicity strains.

    a. Source and characteristics: including source of the bacterial production and toxicity strains, research information or certified documents to show the bacterial and toxicity strains can be used for production, history including history of separation, determination and de-toxicity characteristics, research information on the adaptability to cellular stroma, infective titer, antigenicity, and toxicity.

b. Batches of the strains: relevant information on initial batch of the production bacterial and toxicity strains, primary generation batch, information on the establishment of production batch bank (including generation numbers), the preparation, storage of sub-batch of production strains, test report of each batch of production bacterial and toxicity strains, items to be tested including exogenesis factors, determination test, infective titer, antigenicity, and for strains of primary generation, gene sequence should be determined.
c. Stability during transfer of culture: determining the limitation of the last generation number to be used. For items to be tested, refer to the test items of batches of strains.
d. Test report on batches of bacterial and toxicity strains used for production from the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP).

4. Research information on the cellular stroma for production.

    a. Characteristics and sources: source of cellular stroma used for production, certified documents and research information to show that the cellular stroma can be used for production, history (including the history of the cells system, and the history of the culture transfer), biological characteristics, exogenesis factor test, karyotype analysis, tumorigenesis test, and other studies.
    b. Cell bank: including information on the establishment of production cellular stroma initial cell bank, primary cell bank, production cell bank, including the generation number, preparation, storage, and administration of the various production cell banks, and comprehensive tests of cell banks. Items to be tested include biological characteristics, karyotype analysis and exogenesis factor inspection.
    c. Stability during transfer of culture: determining the limitation of last generation number to be used. For items to be tested, refer to items to be tested from the cell bank, with the addition of tumorigenesis.
    d. NICPBP test report of the production cell bank for cellular stroma used for manufacturing the drug.
    e. Source and quality standards for culture fluid and additives; in the event that material sourced from cows is used, relevant information should be provided in accordance with CFDA requirements.

5. Research information regarding the production process and technology.

    a. Research regarding the production process of the original fluid from the vaccine: the main technical parameters to optimize the production process, including inoculation, quantity of bacteria (or virus), culture conditions, fermentation conditions, activity and crack process conditions, extraction and purifying of the bioactive material, removal of potentially toxic material, activation, coupling and combination technology for the

antigen and carrier for the combined vaccine, research information for the percentage of various bioactive components, and compatibility of antigen. Summary of the materials input, output of various intermediary products, and the quality during the production process. The output and quality for the finished product should also be provided.

b. Formula and production process for the preparations and the basis for determination shall be provided. Source and quality standards for supplements should also be provided.

6. Research information regarding the product quality: after the determination of the production process, the following information should be determined using statistical methods, based on test results from several batches of the pilot product:

    a. Quality standards and test results of the products, including quality standards and test results of each single component of the combined vaccine.
    b. Research and verification information for the method of testing.
    c. Analysis of product antigenicity, immunogenicity, and animal testing protection.
    d. For any potentially toxic material introduced during the production process, research regarding effects of the removal process should be provided. The standard to control the material within the limit should be established, and basis for the standards should be provided.
    e. Research regarding the animal hypersensitivity test.
    f. Comparative information with similar products.
    g. Measuring of antigen components, contents, molecular weight, purity; specificity determination, and measuring and testing of the content (or residual) of the non-effective component.
    h. Information regarding the animal safety evaluation of the product.
    i. For vaccines manufactured with the use of DNA recombination technology, requirements for therapeutic biological products shall apply.

7. Draft manufacturing and testing standards drafted in accordance with relevant regulations, with notes and relevant literature.

8. A record of the manufacturing and testing for sample products to be used for the application for clinical study.

9. Preliminary stability test information.

10. Quality certificate of animal used for production, research, and testing.

11. Clinical study plan and protocol.

12. A summary of pre-clinical research.

13. Summary information from the relevant domestic and international clinical studies.

14. A summary of the clinical study report, including a sample Informed Consent Form and IRB approval documents.

15. Summary of work, experiments, and study information on the improvement of production technology and the perfection of quality standards during clinical study.

16. Stability research information to determine the storage and validity period of the vaccine.

17. Amendments and reasons for amending the approved manufacturing and testing standards.

18. A record of production and testing for the 3 consecutive batches.

For <u>Traditional Chinese Medicine</u>, the full list of application documents includes the following 32 items:

<u>Summary Materials:</u>

1. Drug Name.

2. Certified Documents (i.e. Drug Manufacturing License, GMP Certificate, and patent status).

3. Objectives and basis for application, including discovery, R&D status, traditional Chinese medical texts if relevant, and summary of the use and production of the drug both domestically and overseas.

4. Summary and evaluation of main research results, including a comprehensive analysis of the safety, efficacy, and quality controllability of the drug.

5. Draft product insert sheet, notes to insert sheet, and the latest literature.

6. Sample package and label design.

<u>Pharmaceutical research materials:</u>

7. Pharmaceutical research material summary (i.e. summary of experimental literature about the study, synthesis process, and dosage selection).

8. Source and identification of raw drug materials.

9. Environmental information, identity, growing characteristics, cultivation method, and processing steps for raw drug materials.

10. Draft specifications for raw drug materials, including drug standard material.

11. Sample of the plant and mineral. For a plant, provide the flower, seeds, and fruit as appropriate.

12. Research material regarding the manufacturing process, including verification information and excipient standards.

13. Experimental data for confirming the chemical structure.

14. Experimental data for quality validation.

15. Finished product draft specifications, including drug standard material.

16. Sample testing report.

17. Drug stability research data.

18. Specification of packaging and container as well as basis for selection.

Pharmacological and toxicological research materials:

19. Summary of pharmacology and toxicology research materials.

20. Pharmacodynamics research data.

21. Pharmacology research data.

22. Acute toxicology research data.

23. Long-term toxicology research data.

24. Research data and references on irritability (topical, systemic, phototoxicity), hemolysis and topical irritation (blood vessels, skin, mucous membranes, muscle), and other special safety experiments as appropriate.

25. Genotoxicity research data.

26. Reproduction toxicity research data.

27. Carcinogenicity research data.

28. Animal pharmacokinetics research.

Clinical research materials:

29. Summary of clinical research in China and other foreign countries.

30. Clinical research plan and protocol to be conducted in China.

31. Informed consent form; IRB approval document.

32. Clinical research report.

E. Technical Review Guidance for Registration Documents

In order to help the applicant better understand the requirements for each of the application documents, and to clarify the technical review process, the CFDA has issued a number of technical guidelines. The following technical guidelines exist:

1. Technical guidance on long-term toxicity studies for chemical drugs.

2. Technical guidance on non-clinical pharmacokinetics research for chemical drugs.

3. Technical guidance on bio-statistics for chemical and biological drugs.

4. Technical guidance on acute toxicity studies for chemical drugs.

5. Technical guidance on format and content for chemical drug clinical trial reports.

6. Technical guidance on research of impurities for chemical drugs.

7. Technical guidance on pharmaceutical research for chemical drugs.

8. Technical guidance on chemical drug specification development.

9. Technical guidance on analytical method validation for chemical drugs.

10. Technical guidance on research of residue reagents for chemical drugs.

11. Technical guidance on research of irritability, stimulation, and hemolysis for chemical drugs.

12. Technical guidance on bioavailability and bioequivalence research for chemical drugs.

13. Technical guidance on raw material production and chemical structure verification for chemical drugs.

14. Technical guidance on stability research for chemical drugs.

15. Technical guidance on general pharmacological studies for chemical drugs.

16. Technical guidance on clinical pharmacokinetics research for chemical drugs.

17. Technical guidance for compiling chemical drug research summary: format and content.

18. Technical guidance for compiling chemical drug research summary: objectives and basis for application.

19. Technical guidance for compiling chemical drug research summary: pharmaceutical research summary.

20. Technical guidance for compiling chemical drug research summary: pharmacology and toxicology research summary.

21. Technical guidance for compiling chemical drug research summary: clinical research summary.

22. Technical guidance for chemical drugs having National Standards.

23. Technical guidance on reproductive toxicity research.

24. Technical guidance on research of chiral drugs.

25. Technical guidance on non-clinical research of cytotoxic anti-tumor drugs.

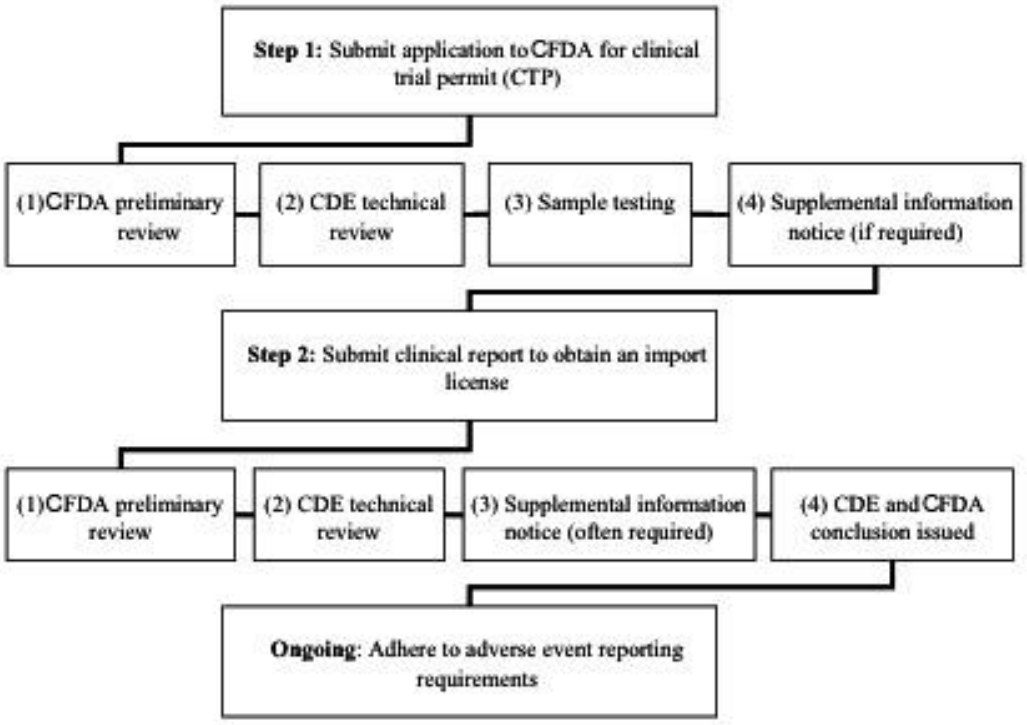
26. Technical guidance on non-clinical pharmacodynamics research of anti-HIV drugs.

27. Guidance for pharmacodynamic research of anti-HIV drugs.

**For detailed information regarding Technical Guidance, see Appendix 4.*

F. New Drug Registration Process

Summary Drug Registration Process:



The CFDA has issued a detailed documentation list for chemical drugs, biological products and traditional Chinese medicine. In addition, they have also issued technical guidance for some document sections. In 2010, they adopted the CTD submission format. If products are imported, the CFDA will also accept drugs prepared in accordance with ICH guidelines.

Data requirements are itemized according to drug classification designated by CFDA

(Sub-classes)	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6
Pharmaceutical Research Data (incl. CMC)						
Pharmacology and Toxicology Data						
Clinical Data (incl. size of trials)						

Step 1: Submit application to CFDA for clinical trial permit (CTP)

Application requirements:

a. Certified documents should be submitted, including all summary materials, pharmaceutical, pharmacological, toxicological, and clinical research data.
b. The draft clinical research protocol and investigator brochure should also be submitted.
c. 3 batches of samples should be prepared for sample testing.

Timeframe for CFDA review: minimum of 125 working days.

1. After the application (requirements listed above) has been submitted, the CFDA, will conduct a preliminary review. The preliminary review checks that the required documents have been submitted and the format of the dossier. This review will be completed within 5 days of the CFDA's receipt of the application, at which point the CFDA will issue an acceptance or non-acceptance notice to the applicant.

2. After preliminary review acceptance, the submitted dossier, inspection reports (if required) and review opinions of the CFDA are then transferred to the Center for Drug Evaluation ("CDE") of the CFDA for a technical review. A number of experts in pharmaceutical, pharmacological, and clinical areas will be responsible for the technical review. The technical review will be completed within 90 working days. For fast-track review, this timeframe is 80 working days.

3. During the technical review, the CFDA also collects samples and submits them to the appropriate certified testing center for drug registration tests to verify the sample and its claimed standards. The results of these sample tests are also submitted to the CDE. The timeframe for sample testing is 30 working days, or 60 days for special drugs and vaccines. It is possible to save time and money by using the same product batches for sample testing and clinical trials (once the CTP has been issued).

4. If the applicant needs to provide additional information based on the technical review or sample testing, the CDE will issue a formal supplement notice, and a 2-month period will be granted to gather and submit the information to the CDE. After submission, the review of supplemental documents will be completed within 40 working days.

Step 2: Submit clinical report and other relevant dossiers to obtain an import license

Application requirements:

a. All documents related to clinical research.
b. Updated summary information.
c. Other updated research data, such as the latest stability data, etc.

Timeframe for CFDA review: minimum of 175 working days.

1. The CFDA will conduct a preliminary review after they have received submission documents. The preliminary review will be completed within 5 days and the CFDA will issue an acceptance or non-acceptance notice to the applicant.

2. The CDE will be responsible for the technical review for the submission documents. A technical review will be completed within 150 working days. For fast track review, this timeframe is 120 working days.

3. If the applicant needs to provide additional information, the CDE will issue a formal supplement notice, and a 4-month period will be granted to gather and submit the information to the CDE. After submission, the review of supplemental documents will be completed within 40 working days.

4. When technical review is complete, the CDE will forward their final evaluation report to the CFDA. If the conclusion is an approval, the CFDA will grant an import license within 20 working days.

The CFDA must follow this timeline for each step of the new drug registration process. In addition, the application process is now tracked electronically and applicants can check their progress on the CFDA or CDE website. This electronic tracking system pressures the CFDA to comply with the specified timeline. Experts at the CDE receive a deadline for each task and any delay in the completion of the task will be recorded on the

internal computer system. Because CFDA and CDE officials do not want a poor annual performance evaluation, the tracking system pressures them to complete more cases within the prescribed timeline.

In practice, most applications require a supplement notice. An application dossier rarely passes through the CDE in one step. If the application documents are prepared in accordance with the regulations and technical guidance, the CDE's questions in the supplement notice will be somewhat easier for the applicant to answer. However, the CDE usually tries to ask all necessary questions at once, lowering the risk of delays through back-and-forth communications.

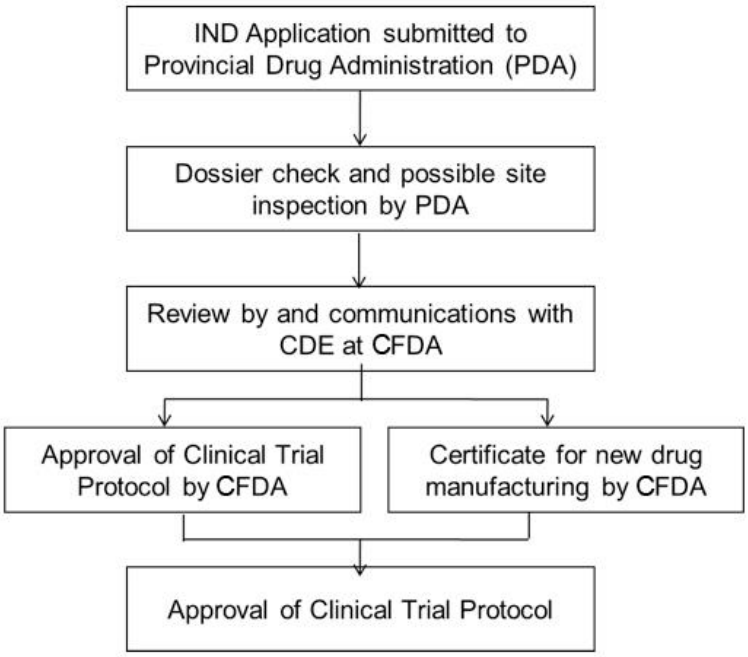
G. Clinical Trials

Companies should not encounter problems with different data requirements in China and other foreign countries. Chinese registration documents now follow ICH guidelines, so the requirements are fairly similar for China versus the United States or the European Union. Problems arise when drug companies do not wish to submit sensitive, confidential data for drug registration in China.

Before any questions arise, the applicant should discuss each registration informally with experts from the CDE. This will help them ascertain the minimum requirements for their therapeutic area.

Typical IND review and approval takes 7 - 9 months. The process is carried out in parallel with new drug manufacturing certificate approval. For locally produced drugs, the application process begins at the PDA level and approvals are issued by the CFDA. For imported drugs, the process begins with the CFDA. The standard review time is 3 - 4 weeks longer than for local products, but the actual time may vary greatly. It depends in large part on the complexity and quality of foreign clinical data.

Application and approval procedure for clinical trials in China



Clinical Trial Requirements on Chemical Products

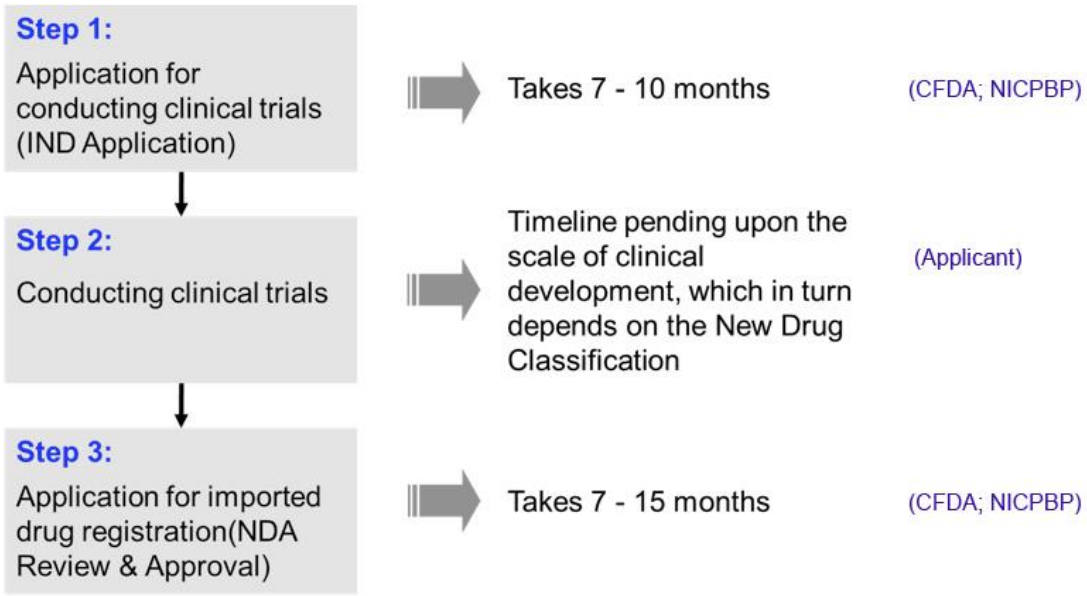
Cat. 1	**Phase I: 20 – 30 cases** **Phase II: 100 cases**
Cat. 2	**Phase III: 300 cases** **Phase IV: 2000 cases**
Cat. 3	**Minimum 100 pairs randomized, controlled trial + PK study,**
Cat. 4	**Minimum 60 pairs per indication**
Cat. 5	**1. Bioequivalence study, 18 – 24 cases, or** **2. Clinical trial, 100 pairs**
Cat. 6	**1. Bioequivalence study, 18 – 24 cases**

Note: The number of cases is the minimum requirement for a clinical study.

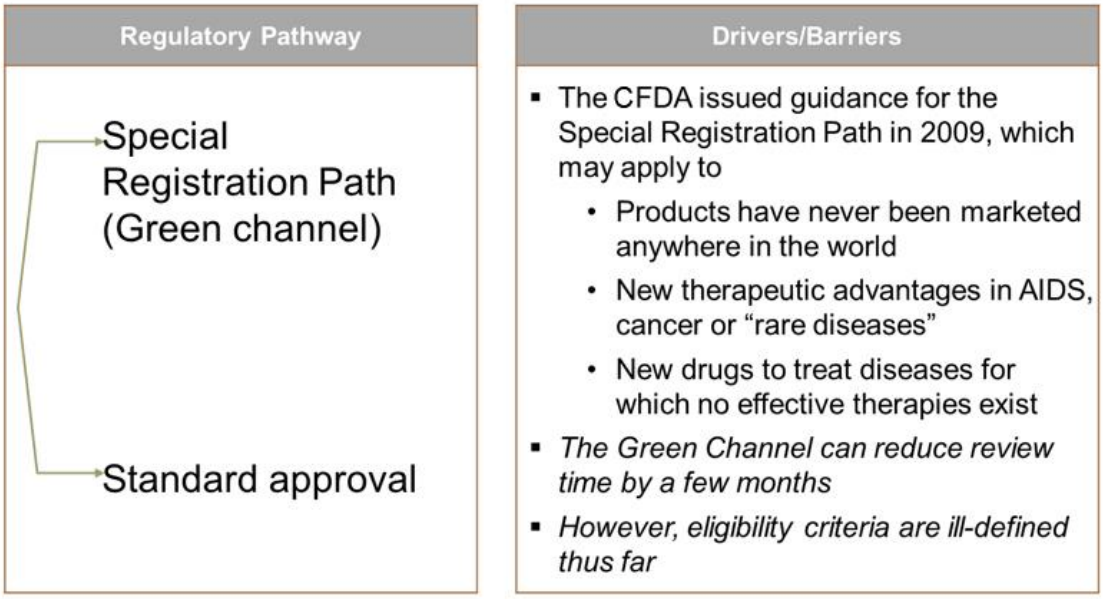
As of 2011, the CFDA had certified 433 clinical trial sites. All of them were affiliated with hospitals. Many changes in the clinical trial process have taken place in recent years, including the adoption of CTD format in 2010. By 2015, all local manufacturers will have to obtain GMP certification. Other changes being explored by the CFDA include reducing IND review and approval timelines, encouraging international multi-center clinical trials and exploring regional collaboration for clinical trials in Japan and South Korea.

H. Timeframe to get an Imported Drug Approved

For an imported new drug, it takes approximately 36 - 42 months from IND submission to NDA approval.



Expedited Approval is now possible in China, with eligibility criteria poorly defined



I. OTC New Drug Registration Process

In the following situations, drug companies can apply directly for an OTC drug registration application:

1. OTC drugs for which a national specification and testing method have already been established.

2. New dosage forms of currently marketed OTC drugs that do not change the drug indication, dosage amount, or administration route. For example, if a product is only changed from capsule form to tablet form, it can be registered with an OTC application, since the dosage is the same and administration is still oral.

3. New OTC combination drugs which are made up of ingredients which are already on the approved OTC list.

Except for the drug insert and package design, all other technical dossiers for OTC drug applications are the same as for prescription drug applications. The review process is also the same, and normally takes the same amount of time. Therefore, the advantage of OTC approval is not usually faster or easier approval, but the ability to market over-the-counter and without price controls.

For more details on drug registration information, dossier specifics, technical guidance and registration documents, please refer to Appendices 1 and 4-13.

J. Drug Registration Re-examination

After the CFDA approves or denies drug registration applications, drug manufacturers can appeal the decision and request a re-examination of their application. Historically, this process has been poorly defined. To standardize and improve the process of registration re-examination, the Center for Drug Evaluation (CDE) issued the Working Procedures for Drug Registration Re-examination (interim), which went into effect on February 27, 2009.

In the past, a drug manufacturer could appeal the CFDA's decision, but the re-examination was usually completed by the original reviewers. With the new Working Procedures, the CDE established a specialized working group to oversee the specific process of drug registration re-examination. The working group will organize the re-examination of chemical drugs, Traditional Chinese Medicines (TCM), and biological products. A special section has also been established on the CDE's official website to report re-examination progress and conclusions.

The re-examination working group will develop review plans for new drugs, generic drugs, imported drugs, and supplementary applications. The review plans will be made available to the public on the CDE's website once they are completed.

The re-examination working group will discuss original review conclusions in weekly meetings. These meetings will include both the re-examiners and the original reviewers. If necessary, applicants may also be invited to attend via conference call. The re-examination working group is responsible for planning the meeting and sending out notifications, meeting agendas, and necessary documents, including the registration application and original review conclusion. Meeting minutes will be taken to record their discussions and conclusions in detail. The agenda and conclusions of re-examination meetings should be published on the CDE's website.

The re-examination meeting will usually reach one of the following four conclusions:

1. The original review conclusion should be overturned. The re-examination working group will provide its opinions and return the application to the original reviewers for re-evaluation. The original reviewers should then complete the review process, taking those opinions into account.

2. The original review conclusion is supported. The re-examination working group will submit its decision supporting the original conclusion to the CDE for approval before sending it to the Department of Drug Registration in the CFDA.

3. A supplementary statement is required from the applicant. In this case, the re-examination working group has questions or issues have been raised that require further explanation from the applicant. The re-examination working group will ask the applicant for supplementary documents or supporting materials. Such materials should be submitted in a timely manner.

4. No conclusion can be reached. In this case, the re-examination working group should call a three-party review meeting with the applicant, outside experts, and the original reviewers. The three-party review meeting will generally end in a decision to either overturn or support the original review conclusion. Normally, the three-party review meeting will be held the month after the re-examination meeting. The agenda and conclusion of the three-party review meeting should also be published on the CDE's website.

K. Drug Registration Statistics

Since the new *Provisions on Drug Registration* went into effect on October 1, 2007, registrations for new drugs have dropped significantly. This is partly because verification standards have increased significantly, making fraudulent registrations more difficult. In addition, the simple fact that the Provisions have been overhauled has made the Chinese drug industry more uncertain about its ability to make submissions aggressively.

Comparison of Registrations Before and After the New Provisions:

	Drug registrations submitted (1/1/2006–12/31/2006, before new Provisions)	**% of total**	**Drug registrations submitted** (10/1/2007–9/30/2008, after new Provisions)	**% of total**
New Drugs	10,833	42.0%	4,572	48.2%
Drugs with National Standard	9,799	38.0%	267	2.8%
Imported Drugs	774	3.0%	844	8.9%
Supplement Registration	4,395	17.0%	3,798	40.1%
Total	25,801	100%	9,481	100%

The CDE, which reviews applications and then submits their recommendations for approval or rejection to the CFDA who grants the final approval, reviewed over 25,000 applications in 2008 including those for clinical trials, import, and production, but rejected over 60% of them. Western drug companies are being less affected by the new rules since their application material generally conforms to higher standards. In 2008, the results for foreign imported drug registration applications were as follows:

- 581 imported drug registration applications were approved by the CDE, which included import registration, supplemental applications, and clinical trials. This was about 37% of total imported drug applications and covered 215 specific chemical substances or compounds. Of these, 276 of the 581 applications were

approved for clinical trials. Also, 44 applications were approved for import. 261 supplemental applications were also approved.

In 2008, the results for locally-manufactured drugs were as follows:

- 710 registration applications were approved for clinical trials. Of these, 434 of the 710 applications were approved for clinical trials, and 276 applications were approved for bio-equivalence studies.

There were also 1,595 local drug registration applications that received production approvals from the CDE. Of these, 633 applications were recommended for new drug approval and 962 applications were approved as generic drugs. Additionally, 1,252 supplemental registration applications were approved for local drug products.

In 2009, a total of 6,428 drug registration applications were accepted. This represented a 30% drop from 2008 applications. Out of the 6,428 applications in 2009, 80% comprised domestic applicants. The rest were from overseas. New applications (both domestic and foreign) totaled 2,950, representing 46% of total drug registrations that year.

In 2009, the CFDA also reviewed and approved 792 registration applications for new drugs, different dosage forms, generic drugs and imported drugs in accordance with the new *Provisions for Drug Registration.* 69% of these approved applications were chemical drugs. 11% were traditional Chinese medicines and the remaining 20% comprised biological drugs and others.

In 2010, the CFDA reviewed and approved 609 registration applications for new drugs.

According to its 2011 annual registration report, the CFDA reviewed and approved 718 applications for new drugs, different dosage forms, generic drugs and imported drugs in 2011. Of the approved applications, 644 were for domestic drugs and 74 were for imported drugs. Of the 644 domestic drugs approved, 569 (88.4%) were chemical drugs, 50 (7.8%) were traditional Chinese medicines and the remaining 25 (3.8%) were biological drugs. Applications for innovative drugs increased significantly compared to 2009 and 2010. Of the approved domestic drugs, ten were considered new chemical drugs.

The CFDA has not published its registration report for 2012. But according to the CDE -- which issued its 2012 report at the end of February -- it reviewed and approved 615 applications for new drugs, different dosage forms, generic drugs and imported drugs in 2012. Of the approved applications, 518 were for domestic drugs and 97 were for imported drugs. Of the total 615 new drugs, 532 (86.5%) were chemical drugs, 37 (6%) were traditional Chinese medicines and the remaining 46 (7.5%) were biological drugs.

L. Classification of Combination Drug-Device Products

Combination drug-device products are currently regulated by CFDA Directive 94, the *Notice on Issues Relating to Registration of Combined Drug and Medical Device Products*, originally issued April 5th, 2004 and commonly referred to as "Directive 94." Under Directive 94, a combination product is registered as either a drug or a device depending on which part plays the key function and which part plays the supporting function. For example, syringes pre-filled with drugs are registered as drugs, since the drug plays the key function. On the other hand, drug-coated stents are registered as medical devices, since the device plays the key function. One exception to this general rule is bandages containing antibacterials or antibiotics, which are registered as drugs.

CFDA officials are currently developing an additional relevant regulation, the *Approval Procedures for Combined Drug and Medical Device Products*. It is not clear exactly how this will affect classification of combination products, but it is likely to increase scrutiny by bringing CFDA officials from both drug and device departments together into the same review processes.

M. New Regulatory Changes

The CFDA recognizes that advances in drug research and drug manufacturing technology will require continual changes to China's drug standards. The major plans and priorities for drug regulation were laid out by the CFDA deputy director, Wu Zhen, in early 2009. According to the CFDA's *Action Plan for Raising Drug Standards*, about 1,000 drug standards were revised during 2008 and beginning in 2009, the CFDA plans to revise or upgrade 2,000 drug standards each year. The government expects that Chinese standards for chemical drugs will be on a par with international standards in several years. The CFDA also aims to upgrade Traditional Chinese Medicine (TCM) standards and exert more control over the safety and efficacy of TCM. Additionally, standards management schemes will be established to eliminate drugs with potential safety risks or out-of-date prescriptions, production processes, and formulations.

In January 2009, CFDA clarified details on imported drug re-registration. Re-registration is applicable for certain drugs such as those where the manufacturing process, quality standards, excipient sources, labels, and packaging are the same as the previous application. Adding or improving safety instructions or shortening the drug shelf life will also mean re-registration.

Applicants will submit re-registration documents to the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP). NICPBP will check for all the appropriate documents and information within 40 working days. These re-registration documents will then be forwarded to the national CFDA for review.

If CFDA finds that the re-registration documents do not fulfill the requirements, the NICPBP will transfer all the technical documents to the Center of Drug Evaluation (CDE) for technical review. The evaluation timeframe is 100 working days.

NICPBP will automatically transfer re-registration documents to the CDE if the manufacturing process, prescription, quality standards, excipient source, inner packaging has changed. This transfer will also happen if the shelf life is extended or if there are any changes to the written content besides the safety instructions.

For imported drugs going through re-registration that are essential and innovative or treat serious illnesses, applicants can apply for a temporary import and re-packaging. Such drugs include cancer or HIV drugs with are serious, life-threatening, or urgently needed but not available in China. The drug should not have any serious adverse events, safety issues, or any record of marketing suspension by any CFDA body in the past five years. In addition, the drug company should not be under investigation or have been punished because of violating any regulations issued by the national CFDA.

The temporary import drug application must include reasons and basis for temporary import and state if there have been any serious adverse events or if the company is under investigation. Applicants will also submit a "Drug Re-Registration Acceptance Notice" with their seal (notice saying the re-registration documents have been accepted for review), the original drug approval documents and copy of appendix with the applicant's seal, any previous temporary import approval documents, and any other relevant documents.

The Administrative Acceptance Service Center of the national CFDA will check the documents within 5 days. If the documents meet the requirements, then the Registration Department will review the application within 20 days.

For the import drug temporary re-packaging, applicants should apply to the provincial FDA. The provincial FDA will check the documents within 5 days. Then the Registration Department of the national CFDA will review the re-package application within 20 days for final approval.

CFDA also implemented *Requirements on Special Approval of New Drug Registration* in January 2009. The Requirements promote the research and development of innovative drugs in China with priority reviews and multi-channel communication.

IV. DRUG PRICING REGULATIONS

A. Overview of Drug Pricing Policy

In China, the central and local governments have a vested interest in keeping drug costs down because the government bears the burden for the most widely used drugs. The Chinese government pays for almost all of the drugs on the National Reimbursement Drug List (NRDL). Between 1998 and 2008, authorities issued eighteen price cuts. These price cuts caused a cumulative total of RMB 29.5 billion (about US $4.1 billion) in lost sales, and extended to over 300 drugs. More price cuts are expected due to the healthcare reform. Vigorous efforts are made by the government to lower the prices of more expensive products, especially those sold by large foreign manufacturers.

B. Controls on Drug Pricing

Drug prices are regulated by the National Development and Reform Commission (NDRC) and provincial Pricing Bureaus (PB). After product registration, pharmaceutical companies are supposed to apply to the local provincial pricing bureau for pricing approval before the product is sold on the Chinese market. Documents regarding Cost of Goods Sold (COGS) and other costs are required as part of the submission. The pricing bureau will usually review the dossier and issue a price approval notification within 30 working days.

The NDRC commonly targets drugs on the NRDL for price cuts. Companies that are original developers or patent holders, however, can apply to the NDRC for *separate*

pricing for their drugs. This may let them receive a higher official price than the generic version.

Generally, government price cuts hit generic products the hardest. For example, in 2008 price cuts for generic products made by joint ventures (i.e. original-brand foreign products) had their prices cut by an average of 25%; patented JV products by 20%; and domestic generics by 60%.

For drugs that are not on the NRDL, pharmaceutical companies can suggest a retail price themselves. However, when the local government reviews price applications, they usually compare drugs in the same therapeutic area when determining pricing.

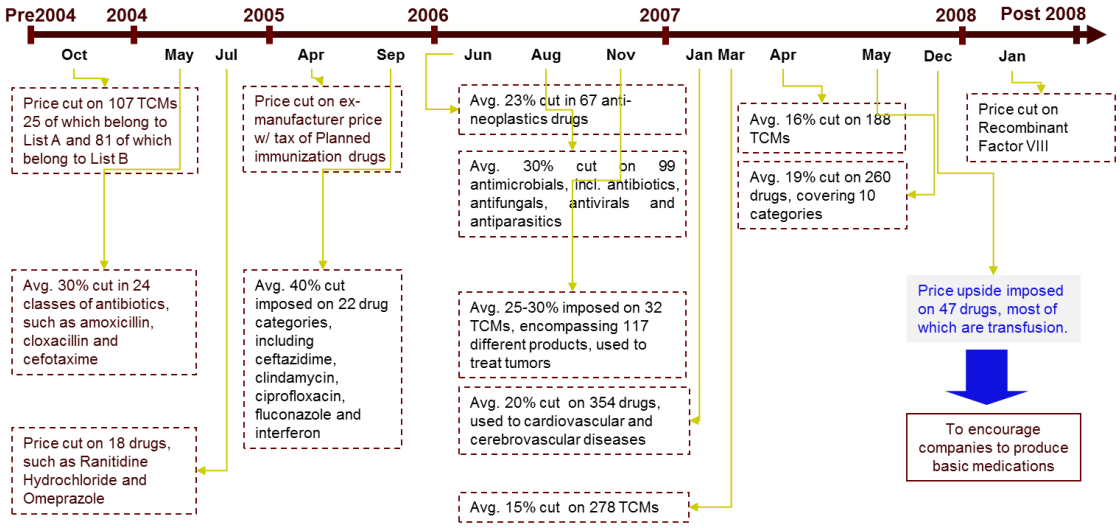
However, a significant development in December 2010 was a ceiling imposed by the NDRC on retail prices of selected drugs. These drugs previously had prices fixed independently by the manufacturers. Most of these manufacturers were foreign-invested enterprises and joint ventures. More than 100 kinds of drugs affected by this price ceiling were produced by at least 35 foreign pharmaceutical companies. Examples of affected drugs were Roche's *Cefatriaxone*, GlaxoSmithKline's *Cefuroxime* and Merck's *Simvastatin.* This policy was expected to save approximately $300 million on China's public healthcare expenditures. Nevertheless, not *all* essential medicines from foreign manufacturers that practiced independent price fixing were affected by the price ceiling.

The NDRC implemented two unusual price cuts in 2011. The first price cut, in late March, included 162 molecules and 1,300 dosage forms that dealt with infectious, cardiovascular and circulatory diseases (usually as antibiotics). These drugs experienced an average 20% cut in retail prices. The move was supposed to save China about $1.5 billion annually. In September 2011, the NDRC announced the second round of price cutting, which targeted 80 molecules dealing with hormone, endocrine and nervous system disorders. The average retail price cut for these drugs was 14%.

The prices of expensive drugs in China will gradually go down across the country. In specific provinces, such as Anhui, about 850 drugs already had prices cut by an average of 50% in September 2010.

Determining the price of an imported drug is different from the process of setting prices for domestically manufactured drugs. The price of an import drug is based on the Cost, Insurance, and Freight price, shipment documents, and invoices for customs tax and duty. Generally, a newly imported drug that has just entered the Chinese market will likely receive a price close to its free-market price, *unless* its original developer or patent holder is also selling the same substance in China. An imported generic drug will usually be given a price that is lower than the imported patented product but higher than the price for locally-made generics.

NDRC initiated several rounds of price adjustments, lowering the drug price about 25% since 2004 to 2010



C. Reimbursement Drug Lists

Drug pricing in China is based on a combination of free market and state control mechanisms. There are three major sets of drug reimbursement lists: the national Essential Drug List (EDL); the NRDL, List A and List B; and the Provincial Reimbursement Drug List (PRDL), which varies from province to province.

The EDL is issued once every three to five years by China's MOH. It includes drugs that are considered "essential" for public consumption, mostly old generic drugs. Drugs on the EDL are 100% reimbursed by the government. Few new or innovative drugs are on the list, though this has changed slightly with the 2013 version. For an updated version of the 2013 EDL, please see Appendix 15. The retail prices for EDL drugs are set by the NDRC.

The NRDL is issued once every four to five years by the Ministry of Human Resources and Social Security (MOHRSS). It is divided into two parts (1) List A and, (2) List B. Drugs on List A are mostly old, generic drugs, many of which are also on the EDL. Drugs on NRDL List A are 100% reimbursed by the government. The retail prices for NRDL List A drugs are set by the NDRC.

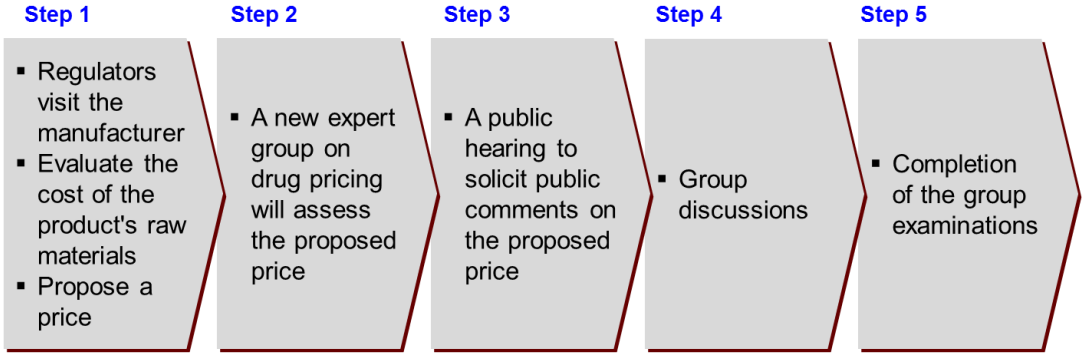
List B drugs include innovative and premium priced drugs, often for specialized purposes. The MOHRSS proposes NRDL List B, which is then forwarded to the provinces. Provinces have the option to replace up to 15% of drugs on NRDL List B. This substitution option is intended to address local needs, especially in regions that have high

incidences of rare or unusual diseases. The retail price for these drugs is set by the NDRC and the relevant Provincial Pricing Bureau. Patients' co-pays can be quite high, ranging from 10% - 90%.

List B drugs are officially categorized by active ingredient, not brand name. The same percentage of the price is always reimbursed by BMI *no matter the total price*. This system is not very advantageous for the government, which could reduce spending by encouraging the use of generic equivalents. However, the system makes Western versions of drugs much more affordable to many Chinese than they would be otherwise.

To illustrate this pricing policy, suppose that a China-made generic drug cost $10 for a month's supply, whereas an off-patent Western version of the same drug costs $20. The non-reimbursed (co-pay) percentage is 20%. In this situation, the patient would be responsible for a co--pay of $2 for the local generic product or $4 for the original Western product. The remainder of the price would be reimbursed. This greatly lowers the price differential between the generic and original Western versions of the drug, and makes Chinese more likely to choose the original Western version.

A 5-step price-setting process for NRDL drugs by NDRC has been in place since March 2007



- *The revised system is intended to secure the integrity of the pricing process, with regulators selected at random and rotated on a five-year basis to minimize conflicts of interest*
- *NDRC might be given expanded responsibility in the future to control prices of all prescription drugs and not just those on the NRDL*

If a drug is on the NRDL, public healthcare insurance will reimburse all or most of the drug's cost to patients. In theory, this review and decision process happens internally without the involvement of pharmaceutical companies. However, in reality, pharmaceutical companies attempt to influence doctors and experts on the review committee in order to get their product listed.

The latest NRDL was published in 2009. This list included 1,140 Western drugs and 987 Traditional Chinese Medicines (TCM). There are 23 therapeutic classes, from blood system drugs to digestive system drugs to biologics. The majority of drugs fall under the categories of specialist drugs, anti-microbial agents and circulatory system drugs. Of the Western medicines, 349 are on List A and 791 are on List B. For a complete list of Western medicines on the NRDL, please see Appendix 17. It is expected that an updated list will come out in late 2013 or 2014.

China's provinces can also pay for more drugs, using their own funds. These funds pay for drugs on the PRDL. For example, the Beijing government lists 113 more Western drugs and 131 more TCMs than on the NRDL. The PRDL also puts restrictions on how drugs can be used. For example, some antibiotics may only be used in hospitals above a certain size, or only for severe infections.

D. NRDL and PRDL Pricing

The development of the Reimbursement Drugs Lists is "top-down." Provincial level governments draw up their own PRDLs for actual implementation of the reimbursement system. List A drugs are fixed nationwide, and provinces may not alter them. List B drugs, on the other hand, may be altered within the above 15% limits. Provincial RDL revisions are usually made within two quarters of an NRDL revision and do not include the participation of drug makers.

The NRDL is set by central government entities including the MOHRSS, the NDRC and China's Ministry of Finance. Provincial RDLs are set by provincial government entities including the price bureau, the provincial bureau of MOHRSS and the provincial finance bureau.

In both cases, national and provincial expert committees and advisory boards are set up to review the prices. These boards consist of clinical key opinion leaders (KOL), pharmacy KOLs, health economics KOLs and pharmacology KOLs. Experts are randomly selected to participate in reviews from established expert databases. As soon as they are selected, the experts are grouped together and stay "quarantined" until the meetings are over.

Advocacy outreach to KOLs is crucial in moving products to the NRDL or PRDL.

When determining coverage, expert committees take into account clinical need above all other goals. The following are the criteria used when determining the inclusion of drugs on the NRDL or the PRDLs. The most important coverage is at the top of this list and items below are ordered by less important issues.

- Clinical need/utilization
- Efficacy and safety
- Reasonable prices (compared to other drugs in the same therapeutic area)
- Average total cost

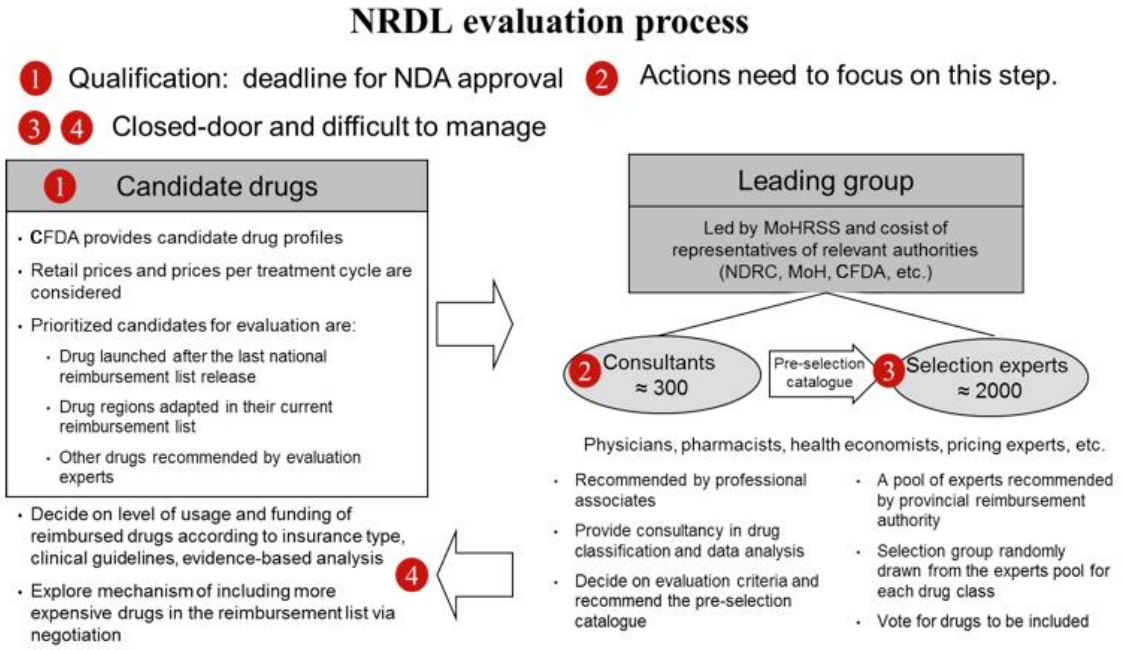
- Years on the market
- Cost effectiveness (in terms of health economics)

The MOHRSS updates the NRDL approximately once every four years, in a four step process. In the *first step*, government officials (including representatives of the CFDA, NDRC, MOH and MOHRSS) compile a list of NRDL candidates. Applications by drug makers are not necessary. In the *second step*, the Advisory Board reviews the list of pre-selected drugs. This is to categorize them and to confirm the rationale behind their therapeutic classifications. In the *third step*, KOLs in different therapeutic areas are randomly selected to participate in the voting. In the *fourth step*, the final list is finalized and published by the MOHRSS. The NDRC will then proceed to set prices for NRDL drugs and provincial MOHRSS offices will develop their own provincial PRDLs.

Materials required for NRDL and PRDL evaluation include information on:

- The disease being treated -- its epidemiology and the disease burden
- The product -- its general information, efficacy, safety, pharmacoeconomic data, budget impact and guideline recommendations
- The historical reimbursement status of the product -- domestic and international

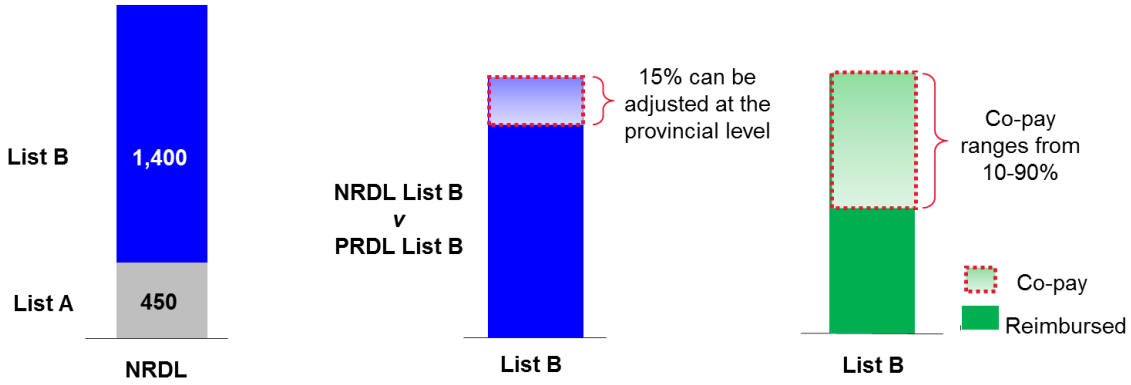
There is no official process for submitting the application materials. Therefore, drug companies should submit their application materials informally, to key reimbursement officials and experts involved in the process.



Consultants are very important in NRDL and PRDL listing. They serve as advisors for listing evaluation and are very important in the decision making process. These individuals include top pharmacists, top KOLs in different disease areas, health economists, health insurance experts, drug pricing experts and key reimbursement officials from MOHRSS.

Drug makers should plan and initiate their lobbying efforts to these consultants at least one year before the start of NRDL renewal.

The current NRDL was published in late 2009



- List A consists of mainly generic drugs, and are 100% reimbursed
- NRDL:
  - 2,127 drugs: 1,140 western drugs and 987 TCMs
  - In List A, 349 western products and 154TCMs
  - In List B, 791 western drugs and 833 TCMs

- List B can be adjusted at the provincial level – up to 15%
  - To meet unique need in that Province
  - Usually applied to "high profile" drugs such as for highly prevalent diseases, oncology, and rare diseases

- Reimbursement rate (reimbursed v. co-pay) for drugs on List B is not 100%
  - Provinces also have the freedom to adjust reimbursement rates
- Putting some drugs on List B is a symbolic gesture, as the provincial governments can make the co-pay as high as 90% for some drugs

If a drug fails to make it onto the NRDL, it is still possible to get it listed on the various PRDLs. However, drug makers and their advocates must approach all 31 provinces one by one. They may have an advantage in their host province, if they manufacture in China.

The process and materials required are similar to those for consideration on the NRDL. Consultants are mainly provincial top experts. Foreign drug companies would do best to focus on the 15% of NRDL List B that the provincial committees are allowed to adjust for local needs. For example, in 2009, the NRDL List B had 791 Western drugs listed. That means the provincial committees can add or remove up to 119 drugs from that list.

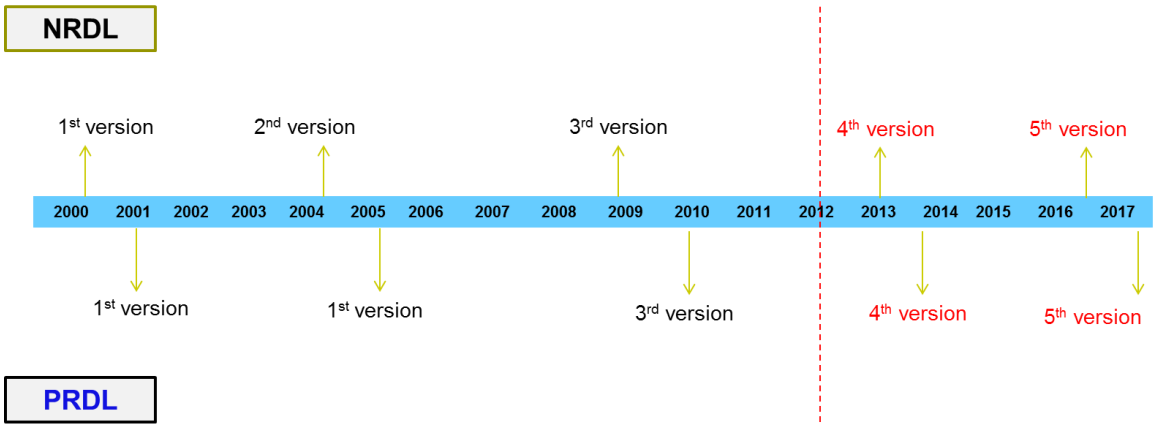
Although there is a tendency for physicians in China to overprescribe medicines, reimbursement is an important factor in making prescriptions affordable. Doctors do generally care whether patients can afford their prescriptions. Some patients will explicitly ask their doctor to give them a reimbursed prescription instead of a non-reimbursed one. This gives reimbursed drugs a strong competitive advantage in the market.

On the other hand, there is often an information gap between patients and doctors in China. Some patients may not even know that a different drug could be used for the same indication. In these cases, reimbursement may not affect their buying decision.

Also, if patients do not have BMI or other government insurance, or if their Individual Account is exhausted, their purchases cannot be reimbursed. Therefore, these patients will look only at drugs' actual prices.

NRDL/PRDL renewal timeline

- Estimation based on historical experience
- The N/PRDL is estimated to be renewed every 4 years.
- NRDL is followed by PRDL, e.g. if a product launched in 2013 and missed the NRDL renewal, it may have chance for 2014 PRDL



Pricing and reimbursement dynamics are complex. For example, the NRDL and PRDL are product specific, not brand specific. Regional differences in NRDL and PRDL reimbursement ratios can be significant. For several years, there has been talk of introducing NRDL List C, but nothing has yet materialized.

Another thing for drug companies to consider is the wisdom of seeking listing for their product. NRDL List B includes mainly innovative drugs that are partially reimbursed. Because the reimbursement ratio (reimbursement versus co-pay) can be as low as 10% for some very expensive drugs, certain premium drugs (such as oncologicals) may be better off under a cash-pay system.

For products not on the NRDL, manufacturers can set their own retail prices within reasonable levels, as long as the price is approved by the local Pricing Bureau. For certain very expensive drugs, getting onto the NRDL might not be a profit-maximizing strategy.

Materials required for a pricing application for non-NRDL drugs include:

- Product general information -- generic name, brand name, dosage, specification, indication, estimated annual sales, patent information (if any), drug license and country of origin
- Cost information -- CIF (cost, insurance and freight), exchange rate, tariff, VAT, port charges (drug testing fees, administrative fees, customs clearance fees and other costs), port price and applied retail price
- Retail price in the country of origin and surrounding countries (which include Hong Kong, Taiwan, Korea, Japan, Thailand and Singapore) -- country, brand, dosage, specification and retail price
- Competitors' prices in China -- brand, dosage, specification, retail price and place of production
- Backup materials (not officially required) -- efficacy, safety summary and product value dossier (including health economics data)

The price of imported drugs is calculated using a formula to arrive at a "reasonable" retail price, based on the CIF (cost, insurance, freight) price, which is registered with the pricing bureau of the first entry point of the product.

National Essential Drug List

In conjunction with the new healthcare reform plan, China released a list of medicines that are to be sold at government controlled prices starting in October 2009. This list of essential drugs reflects treatments for at least sixty percent of the current most common illnesses in China and includes Western drugs as well as traditional Chinese drugs. Most small public clinics and healthcare centers are required to purchase essential drugs, and larger hospitals must operate under a ratio of essential to nonessential drugs. China's target was to have approximately one third of the grassroots state-owned health facilities stocked with the medicines on the essential list by the end of 2009. By 2020, all state-owned facilities are expected to be fully equipped with medicines from the list.

In August 2009, the first part of the essential drug list was announced. This included 307 categories of Chinese and Western drugs. In October 2009, the price details and a list of 2,349 other routine drugs were announced. These were used for common medical procedures. There were lowered prices for 45% of the 2,349 drugs. On average, the price decreases were 12%. 49% of the items retained their prices while 6% had a higher price. The NDRC explained that the price increases were for medicines or drugs having a considerable shortage in the market and where past price increases have been small. The NDRC aimed to increase production of drugs and assure an adequate supply to meet demand. The price reform will affect more than 3,000 pharmaceutical companies, specifically those involved in marketing anesthesia drugs and Class 1 psychiatric drugs.

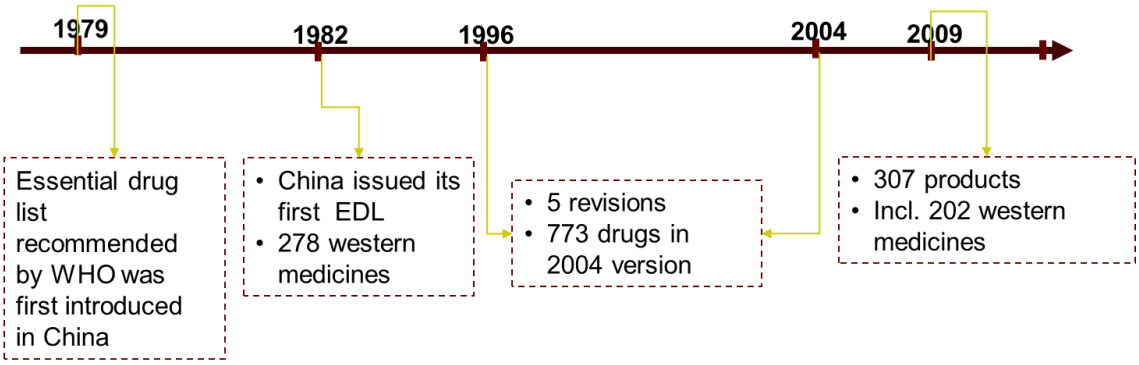
Under the new healthcare reform plan, there will be two main changes to the NRDL. All essential drugs will be added to the NRDL List A for basic medical insurance programs, and there will be a systematic method that determines which drugs should be on the NRDL.

The EDL system is also undergoing rapid changes and a new EDL was released in March 2013. The 2013 EDL includes 520 products, 317 of which are chemical and biological drugs. For a complete list, again, please see Appendix 15. The four guiding factors for including drugs on the EDL are: rational selection, affordable prices, sustainable financing and reliable health and supply systems. Drugs on the EDL have their prices set by the NDRC, but bidding and distribution is managed at a provincial level. The NDRC is currently considering a centralized bidding process. Other changes include more innovative drugs on the 2013 EDL.

Further priorities for China's essential drug reform include pressuring the CFDA for higher production standards for all national essential drugs. Additionally, an NDRC committee has been set up to examine the supply and demand of essential drugs. This will aid the government in adjusting drug prices to affordable levels.

Following this, the CFDA rolled out plans to place all essential drugs in China on a national digital monitoring network. This is to monitor the entire value chain of the drugs, encompassing manufacture, transportation, storage and sale of the products. The network includes all drugs on the EDL and involves the input of about 3,800 (or at least 70%) of drug manufacturers in China. Each drug package will bear a unique code, which the government may use to track and recall drugs in the network.

The Essential Drug List (EDL) is a key component under the new healthcare reform plan



- *Started as a recommendation to rational drug prescription/use*
- *More recently has become a way to control price for the very basic drugs*
- *EDL overlaps well with the medicines On RDL List A*

**The 2013 EDL was released in March 2013. It listed 520 products, including 317 western medicines.*

E. Bidding and Hospital Listing

The bidding process was first established in 2001, and its efficiency and transparency are improving over time. Once or twice a year, each province calls for foreign and local manufacturers to submit bids on specific drugs. A tendering committee of pharmacists, local government officials and NDRC representatives then decides which manufacturers may distribute their products in the province.

Price is one of the key factors in the decision making process. Having an advocate who can lobby committee members ensures a strong negotiating position for drug makers. Local distributors are the agents who usually help manufacturers in the bidding process. The tendering and bidding process takes place on a province-by-province basis, so approval in one province does not automatically guarantee approval in other provinces.

Tendering is generally conducted once or twice a year at the provincial level. The NDRC is considering centralized bidding for EDL drugs, but it has not yet announced a change to the current process.

The hospital listing of a brand is the pre-requisite step for prescribing by physicians in the hospital. Like the bidding process, hospital listing happens on an individual basis. Each large hospital forms a committee once or twice a year to approve new drugs for its formulary. These are the only products that the hospital purchases and prescribes to its patients.

The hospital pharmacy director leads the process within the hospital, aided by department chiefs who recommend drugs needed for their particular departments and specialties. Awareness and acceptance among physicians before pharmacy and therapeutics meetings is critical. The process of hospital listing is consensus based and takes 3 - 5 months.

V. PHARMACEUTICAL RESEARCH AND DEVELOPMENT AND RELATED REGULATIONS

A. China's Research and Development Climate

In the past few years, China has become an increasingly attractive place to conduct R&D. Many multinational pharmaceutical companies opened substantial R&D centers in China. GlaxoSmithKline (GSK), for example, established Clinical Research Centers in China with more than 200 drug development projects. These were done through collaboration with more than 30 leading medical institutions. In November 2009, Novartis announced spending of more than $1 billion on Chinese R&D centers. In the same year, Bayer also announced a 50 year investment plan worth $125 million in a new global R&D center in Beijing. Prior to that, AstraZeneca opened a $100 million research facility in Shanghai in 2007. Other global firms with substantial China R&D operations include Merck and Pfizer.

In addition to building their own facilities, many global firms also enter into research partnerships with Chinese firms which have specific expertise. For example, in August 2007, Eli Lilly made an agreement with the Shanghai-based Hutchison MediPharma to collaborate on discovering oncology and inflammation drugs. This agreement, extended in November 2008, gave a new level of responsibility to Hutchison MediPharma, specifying that it, and not Eli Lilly, would identify and select clinical candidates. Also, in November 2008, GlaxoSmithKline embarked on an R&D joint venture with a Shenzhen firm, Neptunus Interlong, targeting flu vaccines. Also, in July 2009, Pfizer announced a research partnership with the Shanghai Institute for Biological Sciences (SIBS) of Chinese Academy of Sciences (CAS) for fundamental research. More recently, in November 2010, Bristol-Myers Squibb announced a strategic partnership with Jiangsu-based company Simcere Pharmaceutical to co-develop BMS-817378, a preclinical small molecule MET/VEGFR-2 inhibitor.

There are other smaller-sized foreign firms which have partnered with Chinese firms. For example, in May 2010, OriGene Technologies, Inc announced plans to build one of the world's largest and most sophisticated monoclonal antibody production centers in Wuxi, China. This was through a collaboration with Wuxi Biopharmaceutical R&D Outsourcing Services Park (China). OriGene is a gene centric life sciences company based in Maryland, US.

China has many qualified researchers who can work at 20-30% of the cost of equivalent Western researchers. China has made many improvements to its R&D infrastructure, such as labs, equipment, etc. In addition, China's large population makes it relatively easy and quick to recruit clinical trial participants, including sufferers of rare diseases, which are difficult to recruit in the West. Some companies also feel that having R&D in China makes it easier to quickly design new or altered products to suit China market preferences and regulatory requirements. Although Chinese labor costs are expected to rise further in the future, this R&D advantage will remain salient in China for the foreseeable future.

B. Clinical Research

Before a clinical trial may be carried out in China, it must first be approved by the CFDA and receive a Clinical Trial Permit for New Drugs. The sponsor should prepare and submit the dossier and drug samples to the CFDA, which will consult with the Center for Drug Evaluation before issuing a clinical trial approval letter. This process takes approximately 6 – 8 months. Fast-track review is available for clinical trials of drugs that help serious or life-threatening illness, or for other life-saving drugs that are similar to drugs that have already been approved. For product registration, a complete summary of clinical data obtained worldwide must be submitted to the CFDA for technical review.

A new clinical trial must also receive approval from the Ethics Committee of the CFDA before the review of the clinical trial application is completed. On November 2, 2010, the CFDA formulated the *Guideline for Ethical Review of Drug Clinical Trials.* This was in accordance with the *Provisions for Drug Registration* and the *Good Clinical Practice (GCP).* The aims of the guidelines were to improve and to standardize the quality of ethical review of drug clinical trials as well as to strengthen the quality management of drug clinical trials.

IRB approval generally takes several months. Clinical trials are only permitted with doctors and hospitals that have been "approved" by the government and must be conducted according to Chinese Good Clinical Practice (GCP), which went into effect in 1999. No more than five hospitals can be selected in conducting a clinical trial.

Also, a draft of the clinical protocol should be submitted during the application for the Clinical Trial Permit for New Drugs. Clinical trial protocol can be independently designed in accordance with foreign data and drug characteristics. The CFDA rarely rejects design protocol if the design meets the minimum regulatory requirements. Phase I clinical trials are generally not recommended in China because lead times are long and cost savings are not that significant.

In April 2010, the CFDA developed the *Technical Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals.* This was in accordance to the *Provisions for Drug Registration* and was aimed at offering guidance to pharmaceutical R&D. The *Technical Guideline* describes the conditions under which carcinogenicity studies are required. This is to avoid the unnecessary use of laboratory animals, patients and other material resources. The *Technical Guideline* is applicable to pharmaceutical products mentioned in the *Provisions for Drug Registration.* Its basic principles can also be applied to Traditional Chinese Medicines, natural medicines, as well as biological products.

C. Good Clinical Practice (GCP)

The latest *Good Clinical Practice for Drugs* was promulgated on August 6, 2003 and became effective on September 1, 2003. GCP compliance is now mandatory for all clinical research for drug registration.

The GCP regulation defines the requirements as follows:

- Preparation for clinical trial
- IRB approval
- Clinical protocol design
- Responsibility of investigator, sponsor and monitor
- Data collection
- Data management and statistical analysis
- Clinical drugs administration
- Quality Assurance
- Multi-center clinical trial administration

D. GCP-Certified Clinical Research Centers

The Administrative Provisions for Clinical Research Center Certification (Trial) were initiated on March 1, 2004. According to this regulation, as of March 1, 2005, clinical trials in China could not be conducted in non-certified clinical research centers.

In March 2004, the CFDA started to implement the Measures for Qualification Certification of Drug Clinical Trial Institutions (Interim). Since August 2004, the CFDA has organized re-audits on those former National Bases for Drug Clinical Research, accepted new applications for qualification certification, and conducted document reviews and on-site inspections. Until January 2006, the CFDA issued a total of six CFDA Bulletins on Qualification Certification of Drug Clinical Trial Organizations, certifying a total of 108 medical institutions for conducting clinical trials for drugs. Most of these medical institutions are either prestigious medical school affiliated hospitals or major hospitals in the PLA (People's Liberation Army) system. Since 2006, there are increasing numbers of provincial and city-level hospitals or specialty hospitals of Class A of Grade III and even some hospitals of Class B of Grade III that have been qualified by the CFDA as institutions for drug clinical trials (Grade III hospitals are the most advanced and Grade I hospitals are the lest advanced). At the end of 2007, China had 178 GCP-certified drug clinical trial institutions.

In 2009, there were 251 hospitals which are certified to conduct clinical research for chemical and biological drugs in various appointed therapeutic areas. Most of these hospitals are the leading hospitals in certain therapeutic areas, principally teaching hospitals in larger cities.

To further strengthen the supervision and administration on drug clinical trials, improve the quality of drug clinical studies, and assure the rights and safety of clinical trial participants, the CFDA and the Ministry of Health (MOH) initiated a nationwide re-examination on institutions qualified for conducting drug clinical trials in 2009. On May 5, the CFDA and the MOH jointly issued the Working Plans for Re-examination on Institutions for Drug Clinical Trials in accordance to the Measures for Qualification Certification of Drug Clinical Trial Institutions (Interim).

The goal for re-examining the qualifications of institutions for drug clinical trials is for the CFDA and the MOH to learn about the current condition and status, objectively evaluate the implementation of drug Good Clinical Practice (GCP) among these institutions, and analyze existing problems or issues during drug GCP practice to determine potential risks in drug clinical trials. The re-examination will provide scientific evidence for establishing a standardized supervision and inspection system for drug clinical trials and continuously improving the quality of drug clinical trials.

Institutions authorized by the CFDA before January 1, 2007 for drug clinical trials should submit their application for re-examination before June 10, 2009. The CFDA and MOH will then organize the relevant inspections during 2009. Institutions for drug clinical trials authorized by the CFDA after January 1, 2007 should submit their applications for re-examination at least 6 months before the expiration of their Qualification Certificate for Drug Clinical Trials. Any institution that does *not* submit its application for re-examination within the required time period will be disqualified from conducting drug clinical trials. Before submitting applications for re-examination, institutions for drug clinical trials should conduct a comprehensive self-assessment or self-examination. They should review their own clinical trial practices and check their compliance with relevant requirements specified by the drug GCP since being last authorized by the CFDA.

Health administrative departments under the MOH will conduct verifications on applications based on relevant requirements specified by the Measures for Qualification Certification of Drug Clinical Trial Institutions (Interim). These departments will then forward those accepted applications to provincial food and drug administrations. The provincial food and drug administration will conduct formal examinations on the application forms and all the supporting documents, such as information about the institution's facility and staff. They will then transfer all the qualified applications for re-examination to the Administrative Acceptance Service Center of the CFDA before June 30, 2009.

Based on the results of the re-examination, the CFDA and MOH will select inspectors/auditors and experts from candidates recommended by provincial food and drug administrations. The CFDA and MOH will then organize comprehensive trainings for these auditors and experts on inspecting facilities for GCP compliance between July and September of 2009. In the meantime, the Certification Committee for Drugs (CCD) of the CFDA will be responsible for stipulating on-site inspection procedures, examination requirements, and the list of items for re-examination. The CFDA and MOH

will be responsible for developing the audit plans and organizing the on-site inspection by scheduling the audits and inspection personnel.

Based on the outcome of on-site inspection, the CCD will carry out comprehensive analysis and evaluation on the institutions' implementation of drug GCP. They will submit the re-examination reports, clinical trial on-site audit reports, and the Center's opinions on the re-examination to the CFDA. The CFDA and MOH will then conduct the final reviews of all the qualified applications for re-examination and make the final decisions accordingly. For those institutions which pass the re-examination, the CFDA will continue to grant them the qualification for drug clinical trials. The CFDA will disqualify those who have failed the re-examination. The agency will grant some institutions with minor non-conformances a 6-month rectification before re-considering their applications for re-examination. The outcome of re-examination will be published by the CFDA and a comprehensive summary meeting will be held by the agency later this year.

E. Good Laboratory Practice (GLP)

Drug Good Laboratory Practice was promulgated on August 6, 2003 and became effective on September 1, 2003. The CFDA created it to improve the quality of non-clinical drug research in China. This regulation follows the *Good Practice of Non-Clinical Drug Research* from 1999.

The GLP regulation includes standards for the organization and staff, facilities, experimental equipment and instruments, experimental materials, standard operating procedures, data collection, report and recording, and inspection and auditing.

In the latest *Administrative Provisions for Drug Registration* that became effective in May 2005, it was mandatory to comply with GLP for all drug safety evaluation research. However, this was not incorporated into actual drug registration procedures, so it was difficult to judge whether data submitted to the CFDA for new drug registration was GLP-compliant or not. Although the CFDA is gradually increasing its GLP requirements, obtaining GLP certification in China is still cumbersome. Currently, only 27 GLP-certified laboratories exist.

Since December 1, 2007, testing by GLP-compliant labs has been compulsory for the following selected drug categories:

1. Drug materials not previously marketed in China, or their formulations

2. Biological products

3. Active ingredients or materials, extracted from animals, plants, or minerals, not previously marketed in China, or their formulations

4. Active ingredients extracted from TCM or natural drugs, or their formulations

5. TCM injections

Research institutions applying for GLP certification should have already been GLP-compliant for at least 12 months and have completed relevant drug safety evaluation studies which can be examined. Once certified, institutions must submit annual GLP implementation reports, and the CFDA will do follow-up inspections every 3 years.

F. Adverse Event Reporting Requirements

China implemented the Provisions on *Adverse Drug Reaction Reporting and Monitoring* in 2004. The National Center for ADR Monitoring was founded in 1989 and put under CFDA authority in 1999. The National Center for ADR Monitoring collects and analyzes adverse event reports from all sources. There are also 34 provincial ADR monitoring centers that act as the first line of ADR monitoring.

The CFDA's National Adverse Drug Reaction Monitoring Center received a total of 602,000 ADR reports from January 1 to December 20, 2008. The number of ADR reports grew significantly from 2007 to 2008, which the Center attributes to improved monitoring and early warning capabilities. Among the total number of ADR reports in 2008, 85.7% came from medical institutions, 10.4% came from drug manufacturers and distributors, and 3.4% came from individuals. Reports for new and serious ADRs accounted for 13.3% of total ADR reports with 661 ADR deaths in 2008.

According to the current regulations, all drug manufacturers, distributors, and medical institutions are required to report all serious adverse drug reactions they learn of to the provincial ADR monitoring center within 15 days and non-serious reactions on a quarterly basis.

Manufacturers of imported drugs newly on the Chinese market have special reporting requirements. They must report all adverse reactions connected to their product, serious and non-serious, that occur in China in summary form to the CFDA. Manufacturers must also report all serious adverse events that take place outside of China to the CFDA within one month. After a product has been marketed for five years, manufacturers only need to submit these reports every five years.

Currently, manufacturers who fail to report adverse events could be fined from RMB 1,000 (about US$146) to RMB 30,000 (about US$4,400). The CFDA may increase these fines in the future to encourage reporting.

For detailed information regarding clinical trial regulations and clinical research organizations, please see Appendices 2 and 3.

VI. PHARMACEUTICAL MANUFACTURING REGULATIONS

A. Overview of Manufacturing in China

In 2009, there were about 4,000 pharmaceutical manufacturers in China. Most of these are manufacturers of preparations, while a minority produces active pharmaceutical ingredients (APIs). Local manufacturers comprised more than 85% of the total pharmaceutical manufacturers. The remaining percentage comprised foreign manufacturers.

The pharmaceutical manufacturing sector is fragmented and highly competitive. It is estimated that the top 20 pharmaceutical manufacturers in China account for less than a quarter of the country's total pharmaceutical market.

To regulate the product quality of the vast number of pharmaceutical manufacturers in China, the CFDA first issued the Good Manufacturing Practice (GMP) for Pharmaceutical Products in 1988. The GMP regulations were revised in 1992, 1998 and in 2010.

Manufacturers spent heavily on capital investment requirements to meet GMP standards since their promulgation. It was estimated that about RMB 400 billion (about US$58 billion) in capital investments was borrowed to finance GMP upgrades. Many manufacturers, especially small-scale enterprises, were shut down for noncompliance. With government-guided investment, China now has the world's largest manufacturing capacity for preparations and the second largest for API. The total sales volume of drugs and APIs increased 17% annually from 2002 to 2008. To further grow the API market, the Chinese government is believed to be planning investments of more than $750 million over the next 5 years. A formal announcement is expected in the middle of 2011. This is aimed at increasing production capacity of APIs for exports. By the year 2016, about 60 domestic API producers are targeted to reach international manufacturing quality standards.

However, intense competition and costs of business (especially energy costs) continue to pressure the medical industry. According to the National Bureau of Statistics, over one-fifth of domestic API manufacturers turned losses in 2007.

Although both production approval and Good Manufacturing Practice compliance has usually been required for API manufacturers since 2004, wide enforcement of this had only become a priority in 2008. Incidents such as the dangerous heparin exported the US, have been linked with API manufacturers not registered or approved by the CFDA. China's revised regulations should help re-organize and better control the API sector. As smaller companies are unable to keep up with new requirements or are acquired by larger companies, the government aims to have a market with fewer key players that are more easily regulated.

B. Good Manufacturing Practice (GMP) Regulations

In 1998, the CFDA introduced the Good Manufacturing Practice (GMP) Certificate in order to emphasize quality and safety of pharmaceutical production. However, the certification was optional and occurrences of medical accidents and legal issues continued to arise due to poor manufacturing practices. Since China announced the *Drug Good Manufacturing Practice (revision)* on July 2004, all drug manufacturing plants had to be GMP compliant, at least in theory. The CFDA forced manufacturers who failed to meet GMP standards by their respective deadline to stop production.

Following the July 2004 announcement, the CFDA continued to expand the scope of its GMP scheme. Manufacturers of IVD reagents (administered as drugs) were required to meet GMP standards by January 1, 2006. Beginning January 1, 2007, medicinal gas manufacturers required GMP certification. Beginning January 1, 2008, producers of cut crude drugs for TCM were added.

As of 2008, most Chinese drug manufacturers had obtained required GMP certification. However, widespread quality scandals, including deaths resulting from fake or mishandled drugs, have cast doubt on the integrity of GMP certifications, which have sometimes been obtained through bribery.

Drug GMP inspection criteria were significantly tightened under the *Inspection Standards for Drug GMP*, implemented from January 1, 2008. Under these standards, if a single defect classified as "severe" is found, certification will automatically be denied, with no opportunity for rectification. Previously, this was only the case if more than three severe defects were found. Also, failing over 20% of "general" inspection items will now lead to automatic failure, compared to the previous cutoff of 40%. These tightened standards may shake more small-sized domestic drug manufacturers out of the market.

Over 2008, Chinese officials significantly stepped up GMP inspections as part of new drug applications. Formerly, document review was prioritized over on-site inspections during the drug registration process. Now, inspections are more common as part of the review of each new drug application.

The CFDA never physically inspected drug manufacturing sites located outside of China. However, in 2008, the CFDA began training some of its inspectors in foreign standards and practices.

The GMP regulation was recently revised in 2010. This latest GMP regulation is known as the Good Manufacturing Practice for Pharmaceutical Products (2010 revised edition) or the "new version of GMP." This new version of GMP was implemented on March 1, 2011.

New pharmaceutical manufacturers are required to comply with the new standards. At a later point in time, existing drug manufacturing facilities will need to meet this new

regulation. The deadline to comply will be less than five years from the date of implementation.

The new version of the GMP was issued to improve the quality of manufactured drugs. For example, there are now more standards that distinguish between GMP hardware and GMP software used by drug manufacturing facilities. More specific clauses have also been added to better enforce the way records on manufacturing procedures are maintained. Other clauses improve the way the concept of risk management is addressed and enhance security measures. Additionally, changes have been made to allow for greater consistency with the World Health Organization's GMP.

Foreign manufacturers should note that Chinese GMP is not equivalent to US FDA GMP, and a company is not necessarily suited to be compliant with US FDA GMP just because it has this certification.

According to official statistics, China has about 2,700 drug GMP inspectors. Due to many various reasons, only 30% of these inspectors have participated in drug GMP inspections over the last 10 years. In addition, China does not have a stable staff of drug GMP inspectors and the management of inspectors has been quite lax, which, to a great extent, prevents the establishment of a high-caliber inspector team.

The CFDA has organized more than 20 drug GMP inspector trainings since 1998. There are about 2,700 inspectors in the CFDA's database of drug GMP inspectors. At the end of 2008, only 1,800 inspectors were under 50 years old and could be dispatched. Only about 800 inspectors, 28.5% of those listed in the CFDA database, have participated in more than one GMP inspection in the past 10 years.

Drug GMP inspectors currently handle certification-related on-site inspections and daily dynamic monitoring for approximately 4,000 drug manufacturers, 300 IVD enterprises, and more than 1,000 types of drug products. The majority of current drug GMP inspectors come from drug safety supervision departments of relevant food and drug administrations. Most of those inspectors are already over-loaded with their normal daily duties, preventing them from participating in drug GMP inspections. Therefore, they do not get the experience and practical knowledge they need on drug manufacturing.

To raise the overall capabilities of GMP inspectors, professional training demonstrates itself as an important and effective solution. The CFDA has been paying much more attention to leveraging the professional skills of drug GMP inspectors. The CCD has asked relevant departments of provinces, autonomous regions, and municipalities directly under the central government to recommend 900 drug GMP inspector candidates for systematic technical training within the next 3 years. The Center has selected 300 inspectors and arranged them for a series of 5 trainings in 2009. The remaining 600 inspectors were to complete their trainings in 2010 and 2011 based on the plan of 5 trainings per year.

From February 22 to March 2, 2009 the first training session was held in the city of Guangzhou in Guangdong province. The training had four modules: law and regulation, inspection requirements, professional techniques, and on-site simulation. Two-day simulated inspections were conducted within 5 drug manufacturers.

In November 2010, the CFDA initiated a joint inspection for drug safety by 6 government departments. After releasing the *Notice on Distributing Special Action Plan for Cracking Down on Violations of Intellectual Property Rights (IPR)* and the *Production and Distribution of Fake and Shoddy Products,* the CFDA launched a nationwide program running until March 2011. The program targeted at disreputable products that in the Chinese pharmaceutical market.

The joint inspections were executed by the Ministry of Health, the Ministry of Public Security, the Ministry of Culture, the State Administration of Industry and Commerce, the CFDA and the General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ).

The inspections commenced in the provinces of Zhejiang, Shandong and Sichuan and the Chongqing municipality. This was subsequently followed by 8 other provinces. The inspections focused on IPR protection, maintaining a fair market environment, false and misleading advertising, mail-order fake drugs, policy implementation and drug quality standard implementation.

C. GMP Certification

The Administration Provisions for the Certification of GMP were issued in 2002. The CFDA is responsible for granting GMP certificates for injectable products, radioactive drugs, and biological drug manufacturing. Local health authorities are responsible for GMP certification for all other kinds of drug preparations.

Newly-established drug manufacturers or established facilities with new dosage forms are required to undergo an inspection in order to receive GMP approval. The government inspection is generally carried out by a team of inspectors. The CFDA has a database of designated inspectors qualified to conduct GMP inspections. The timeframe for GMP certification approval from dossier submission, dossier review, and site inspection to final approval is about 90 working days.

Normally, when a pharmaceutical company wants to establish a new plant or make upgrades to an old facility, they must submit blueprints to the local government. Local health authorities will review the blueprints and then conduct an on-site inspection. Overall, GMP inspection is relatively non-problematic; the GMP certificate can often be granted within the prescribed timeline.

D. Drug Manufacturing Administration

The *Provisions for Supervision and Administration of Drug Manufacturing* was promulgated and became effective on August 5, 2004.

This provision explicitly stated that Original Equipment Manufacturing (OEM) is permissible in China. OEM for injectable and biological products requires approval from the CFDA at the national level. OEM for other chemical products only needs to be approved by a local food and drug administration.

E. Drug Manufacturing Certificate

A Drug Manufacturing Certificate is required in order to produce pharmaceuticals in China. Production should be carried out according to Good Manufacturing Practice (GMP), as established by the CFDA. The Drug Manufacturing Certificate is valid for 5 years. A company should apply for renewal six months prior to the certificate expiration date. Since 2005, a GMP certificate has also been required for the renewal of a Drug Manufacturing Certificate.

To obtain a Drug Manufacturing Certificate, a drug manufacturer must meet the following requirements:

1. Have the facilities, equipment, instruments, and sanitary environment necessary for production.

2. Employ legally-qualified pharmaceutical, technical and engineering professionals.

3. Employ personnel able to conduct the appropriate tests and ensure quality control.

4. Establish the rules and regulations necessary to ensure the quality of the drugs produced.

The applicant should submit an application to the local (province, autonomous region, or municipality) government office where the manufacturing site is located. The office will review the application within 30 working days and inform the applicant of their decision to approve or reject. Once an applicant receives approval, they may then apply to the same government office for a facility inspection. The inspection generally takes place within 30 days of making the request and a Drug Manufacturing Certificate is granted upon passing the inspection.

If a drug manufacturer plans to alter one or more of the items approved under the original Drug Manufacturing Certificate, the manufacturer will have to apply to the local government agency for approval for the planned change(s). The local government agency usually requires two weeks to approve or reject such changes.

Currently, local governments are actively encouraging investment in the pharmaceutical industry. As a result, Drug Manufacturing Certificates are relatively easy to obtain.

F. Biological Products

In response to deaths due to improperly prepared biological products, the CFDA instituted particularly strict safety regulations for these products in November 2007. Before specified biological products can be sold, *every batch* manufactured in China must be tested by a government testing lab. Currently, the specified products consist of 18 bacterial vaccines, 31 viral vaccines, 2 human serum albumins, 2 human immunoglobulins for intravenous injection, and 9 in-vitro diagnostic reagents.

The CFDA issued principles and procedures for quality management systems of in-vitro diagnostic reagents in late 2009. These principles explain the scope of coverage with one quality management system and when multiple quality systems are necessary. There are 16 classifications for the in-vitro diagnostic reagents as follows:

1. Enzyme-linked immunoasborbent assay (ELISA plate, beads, particles) reagents
2. Colloidal gold (Se, latex) reagents
3. Western blot reagents
4. Protein chip (microarray) reagents
5. Monoclonal antibody reagents
6. Polyclonal antibody reagents
7. Diagnostic serum (bacilli)
8. Hemagglutination reagents
9. Nucleic acid amplification reagents
10. Gene chip (microarray) reagents
11. Probe amplification (in situ hybridization) reagents
12. General biochemical reagents (100,000 grade including enzymes, chemical reagents, coagulation reagents, etc.)
13. General biochemical reagents (clean environment, general chemical reagents, blood gas electrolyte types, blood analyzer reagents, etc.)
14. Dry chemistry reagents
15. Sensitivity reagents
16. Medium

Imported vaccines and human serum albumins must come with official batch release documents from the regulatory authority of their country of origin.

Also in the future, the CFDA plans to require all blood to be quarantined for 90 days, then tested, before it may legally be processed into blood products.

To further enforce quality in supervision and examination of vaccine production, the CFDA and MOH jointly launched a program in June 2010. This program aimed to

enforce quality supervision of the biological vaccines, to improve the quality assurance in vaccine production, circulation and inoculation and ensure safety and effectiveness of the vaccines.

In early 2011, the CFDA issued the *Notice for Further Strengthening the Supervision of Quality and Safety of Vaccines*. This Notice outlined some important initiatives which affect the R&D, manufacturing and distribution of vaccines in China.

- The CFDA will be stricter with applications for capacity expansion in production of vaccines which are currently oversupplied in the market. At the same time, the CFDA also requires manufacturers to gradually upgrade quality standards for marketed vaccines.

- To provide guidance on vaccine R&D, manufacturing and regulatory approvals, the CFDA will form an expert panel. This panel will review industry policies, market demand, quality standards and quality assurance systems of manufacturers in order to assess the commercial value of vaccines to be approved.

- Detailed records regarding the source, history and biological characteristics of the microbial or pathogenic strains and cell lines used for vaccine development will be required by the CFDA in the regulatory dossiers.

- For changes in manufacturing locations, manufacturers are required to undertake full comparative analyses on the production technologies, quality control metrics, on-site operations and quality assurance systems. A supplemental regulatory approval with CFDA is also required to be filed. If the CFDA thinks that the change in the manufacturing location is material, it may require clinical studies and an on-site audit of the new manufacturing site. In particular, Phase IV study is required for newly-approved vaccines. Manufacturers of marketed vaccines are also required to conduct postmarket safety studies on their own initiative, if not already required by the CFDA.

- Vaccine manufacturers must comply with the GMP requirements and CFDA's *Opinion on the Supervision and Administration of Vaccine Operation.* Manufacturers are also required to register their vaccines in the CFDA's electronic database. It is mandatory to incorporate a bar code in the packaging materials of vaccines.

- Distributors of the vaccines must also comply with the *Administrative Rules for Vaccine Distribution and Prophylactic Vaccination,* as well as general GSP requirements.

- Provincial FDAs are expected to enhance the quality of onsite inspections during the regulatory approval process. High-risk manufacturers, in particular, need to have stricter routine supervisions. Provincial FDAs are required to order a production stop, demand recall of released vaccines, and suspension of batch

releases of vaccines which are manufactured with serious safety risks. Production can only be resumed once the safety issues are properly rectified.

It seems that tighter regulations on China's vaccine production bore fruit. In March 2011, an assessment by the World Health Organization (WHO) revealed that China's vaccine regulations are now complying with international standards. This implies that vaccine manufacturers in China can now submit applications to have their vaccine pre-qualified by WHO.

China is the 36th vaccine producing country where its regulatory system has been assessed as "qualified" by the WHO. The timeline for vaccines from China to be prequalified by WHO is between 1 and 2 years. China had previously failed WHO's vaccine regulatory system assessment in 1999, 2001 and 2005. Currently, China has 36 vaccine producing plants that produce 49 kinds of vaccines against 27 diseases. The new Good Manufacturing Practice (GMP) code adopted by the CFDA with effect from March 1, 2011, has also put in place stricter requirements for vaccine production to ensure production of quality vaccines.

VII. SELLING PHARMACEUTICALS AND RELATED REGULATIONS

A. WTO Agreement on Drug Sales

On November 15, 1999, China signed an agreement with the United States government regarding WTO accession. Within the agreement, China made five promises relating to the medical industry:

1. Improve intellectual property protection.

2. Reduce tariffs on imported drugs to less than 6%.

3. Reduce the restriction on the importation of large medical devices.

4. Gradually open the distribution channel for pharmaceutical products, including both wholesale and retail areas, starting January 1, 2003. For wholesale channels, it was to be completely opened to foreign companies by the end of 2004. By the end of 2005, wholesale companies could be fully owned by foreign investors as described above. For retail channels, after accession to the WTO, a Sino-foreign joint venture could be set up in the selected five Special Economic Zones (SEZ) and six big cities: Beijing, Shanghai, Tianjin, Guangzhou, Dalian, and Qingdao. In 2008, three years after the retail channels were opened, restrictions on foreign company franchising and opening chain stores were theoretically lifted. However, when there are large chain stores with over thirty branch stores, foreign investors cannot hold the majority of shares. In 2013, all restrictions on retail channels are expected to be lifted.

5. Open the healthcare services sector (hospitals) up to foreign competitors.

B. Drug Sales to Hospitals

In addition to price control policies, the government is strongly encouraging a fair bidding process for drug sales to hospitals. Presently, most pharmaceuticals (about $17 billion annually) are sold through hospitals, which make a majority of their revenue from drug sales.

Hospitals are supposed to encourage the use of generic drugs in order to reduce healthcare expenses. In practice, however, hospitals favor higher-priced drugs that will bring them more revenue. In some large cities, to keep healthcare expenses down, some of public hospitals' drug revenue must be handed over to city budgets.

According to an MOH regulation implemented in 2007, hospitals are required to purchase only two brands of any one drug. If the regulation is fully enforced, this would likely lead hospitals to purchase fewer brands of generic drug versions, creating more

downward price pressure. In the future, the MOH is also expected to require that more than 50% of commonly-used drugs be purchased through tendering.

C. Drug Purchasing System

In January 2009, six Chinese government agencies, including the CFDA, the MOH, and the National Development and Reform Council (NDRC), jointly issued the Opinions on Further Regulating Centralized Drug Purchases by Medical Institutions. These Opinions provide medical institutions with official guidelines for the centralized drug purchasing process. According to the Opinions, all non-profit hospitals at the county level or higher are now required to participate in centralized drug purchasing. Also, centralized drug purchasing is to be mandatory for prescription drugs, with some exceptions, including essential drugs, radioactive drugs, and narcotics.

Under the guidelines, centralized drug purchases are to be carried out by governments on the provincial level rather than the national level. Provincial governments are responsible for setting up drug procurement platforms, through which hospitals submit names, specifications, and volumes of their desired drugs. Provincial governments are required to formulate lists of drugs to be purchased through transparent processes such as open tenders or online bidding. As a measure to further increase transparency, China plans to move all centralized drug purchasing to the Internet over time.

To cut down on drug prices, pharmaceutical manufacturers (rather than distributors) will be the bidders in centralized drug tenders. Manufacturers are also supposed to contract only one layer of distribution. Successful tenders should be followed by formal purchase contracts between the purchasing medical institution and the drug manufacturer. These contracts should specify products, volumes, prices, etc., as well as penalties in case of contract violation. Furthermore, hospitals have been directed to strengthen their supervision of drug consumption by implementing systems to monitor drug prescriptions and use.

D. Selling Drugs in Drug Stores

In 2010, there were over 350,000 drug stores in China. The majority of these are small, independent stores. However, through mergers, acquisitions, and franchising, there has been a rapid increase in chain stores. Currently, there are almost 2,000 retail drug chains collectively operating about 100,000 individual drug stores. This implies that 1 retail drug chain in China operates an average of 50 individual drug stores.

China's retail drug stores, however, suffer from extremely low profit margins. An estimated 50% of retailers in China operated at a loss in the past year. Less than 500 retailers had sales exceeding $6.5 million annually. Although there are a number of chain stores in China, very few have a fully national presence. Nevertheless, long-term growth potential for the Chinese medicine retail market exists. As mentioned above, mergers and acquisitions are happening every day. Two Chinese companies have invested nearly $85

million to construct what will be two of the largest modern medicine distribution systems in China.

With the Chinese government proposing reforms for the current hospital medicine distribution system, the number of large, nation-wide drug chains should continue to grow. The sales of the top 100 drug chains grew by an average of 20% annually from 2003 to 2009, faster than the drug market as a whole, and now make up about 40% of the entire retail drug market.

E. Internet Drug Sales

Drug traders are only permitted to sell non-prescription drugs to individual consumers over the Internet. The new regulation, by the CFDA called *Interim Provisions on Examining and Approving Internet-based Drug Trading Services*, became effective on December 1, 2005. The regulation states that companies must be licensed as Internet drug traders before engaging in any such activities. Only 21 companies had been licensed as of November 2008, although this was up from 9 in July 2007.

In September 2010, Chinese government issued a circular to tighten restrictions on online transactions of drug precursor chemicals. This was a bid to counter Internet-enabled drug trafficking. This circular was jointly issued by five government departments including the Ministry of Public Security and the Ministry of Industry and Information Technology.
Only companies with licenses to produce and to sell these precursor chemicals (i.e chemical substances that are used to manufacture narcotics) are allowed to publish sales information online. Individuals are banned from selling precursor chemicals.

Four chemical substances on the strictest control list, such as ephedrine and lysergic acid are banned from online trading, either by companies or individuals.

Furthermore, business websites are required to perform strict checks of precursor chemical suppliers. Photocopies of the supplier licenses are required to be submitted to Internet service providers. The formal names of suppliers and their license numbers are required to be published on the business websites.

Between 2006 and 2009, Chinese police had cracked 1,554 cases of illegal trade in precursor chemicals and confiscated 3,814 tonnes of such chemicals.

F. Distribution Regulations

1. Current Developments in Drug Distribution

Currently in China, most distributors are local companies. These distributors, however, have low performance and service levels. The vast majority of them (over 80%) work on a small scale. Because of the inefficient distribution system in China, the cost of distribution services is high by world standards, and usually triples the price of the drug.

However, the ongoing opening of distribution channels should improve the situation substantially.

Although China had committed with accession to the WTO to open wholesale channels to foreign investment in 2004, this was delayed somewhat. Finally, in August 2005, a new regulation permitted foreign drug wholesalers and retailers (who do not manufacture in China) to engage in direct-selling to distribute drugs. Now, a few major foreign distributors have set up in China and also some local distributors been purchased by foreign companies. These local distributors are working on becoming more efficient.

Because of China's size, even distributors who are professional and well-funded are not able to operate in all regions of China. Therefore, it is standard for Western companies to establish networks with multiple distributors to sell their product across China.

2. Drug Distribution Policy

Drug distribution is regulated by the *Provisions on Supervision and Administration of Drug Circulation,* which were revised by the CFDA with effect on May 1, 2007.

When setting up a new drug supply company, either a wholesaler or retail drug store, the applicant should meet relevant requirements and submit an application to the provincial, regional and local governments. The local government will then review the application within 30 working days, and inform the applicant of an approval or rejection decision. Once they are approved, they may only sell drugs at the locations specified in their license. Companies licensed to manufacture drugs may not sell drugs made by other companies (including through contract manufacturing) without a wholesale drug distribution license.

In addition, *Drug Good Supplying Practice* regulations became effective in July 2000, and the *Promulgating Provisions for the Administration of Drug GSP Certification* were initiated in April 2003. A Good Supply Practice (GSP) certificate is valid for five years and a renewal application should be submitted three months before expiration. As of June 30, 2004, all pharmaceutical distributors needed to be GSP compliant. At the end of 2004, about 8,000 distributors had obtained GSP certification. According to the NDRC, about 1,000 other distributors were forced to exit the market due to the new requirements.

Local health authorities are responsible for GSP certification. Newly-established drug companies will be required to undergo an inspection in order to receive GSP approval. The inspection by the government agency is generally done by a team of inspectors. The CFDA has a database of designated inspectors qualified to conduct GSP inspections. The timeframe for GSP certification approval from dossier submission, dossier review, and site inspection to final approval is about 40 working days.

After revised regulations in May 2007, drug distributors and manufacturers have been banned from selling drugs on-site during fairs, exhibitions, trade shows, or other product promotion activities.

As of 2008, the CFDA is working on revising GSP to mandate the use of computer-based information management systems as well as stricter standards on environmental controls.

3. Renewal of Drug Distribution Licenses

The CFDA implemented the *Provisions on Drug Distribution Licenses* in April 2004 and all licenses were renewed around that time in accordance with the new regulations. As Drug Distribution Licenses are valid for five years, all such licenses came up for renewal in 2009. All distribution companies should demonstrate that they meet the standards required by the 2004 Provisions to renew their distribution license. Drug wholesalers should act in accordance with the Implementation Measures for Acceptance of Drug Wholesale Enterprises issued by the provincial food and drug administration with jurisdiction over their location. Similarly, drug retailers should renew their distribution license in accordance with the Implementation Standards for Acceptance of Drug Retail Enterprises issued by their provincial food and drug administration. Additionally, distributors of narcotics and psychoactive drugs need to meet requirements specified by the Regulations for Administration of Narcotic Drugs and Psychoactive Drugs and the Provisions on Distribution of Narcotic Drugs and Psychoactive Drugs, as well as the standards issued by their provincial food and drug administration.

An CFDA announcement in 2009 mandated that distribution licenses should be revoked and license renewal not be granted to the following types of distributors:

- Distributors who cannot meet the conditions for applying for a Drug Distribution License as specified by the Provisions on Drug Distribution Licenses after a three-month grace period;
- Distributors who have not obtained drug GSP certification;
- Distributors who have distributed fake and low-quality drugs with severe violations and/or consequences;
- Distributors who have transferred their Drug Distribution Licenses to others;
- Distributors who have not distributed drug products in more than six consecutive months;
- Distributors whose business licenses have not passed the 2009 review by the relevant industry and commerce administration;
- Distributors who have filed for bankruptcy; and
- Distributors whose renewal application materials are incomplete or contain false information.

If a drug distributor does not follow the necessary application and notification procedures in changing their location, they may also have their distribution license revoked. Currently, a drug distributor must file applications and follow certain procedures when they change locations. If the relevant food and drug administration is not notified and is unaware of their new location, the administration may make a public announcement asking the distributor to rectify the situation. After three months without the correct notification, the relevant authority will assume that the distributor voluntarily stopped drug distribution and revoke its distribution license accordingly.

Even if a distributor meets the requirements for license renewal, other changes can be made to the distribution license. During the distribution license renewal process, the relevant food and drug administration is to conduct a thorough verification of the distributors' range of products. Distributors that cannot meet certain requirements, including those regarding cooling, refrigeration storage, and transportation, will not be approved to sell drugs that require such storage and transportation conditions. Drugs will be removed from the scope of the license if:

- The distributor does not have the necessary conditions to distribute such drugs;
- The distributor has not distributed such drugs in six consecutive months within one year; or
- The distributor has not distributed such drugs in nine months total within one year.

The announcement also requested provincial food and drug administrations to send a copy of their Drug Distribution License renewal working plans to the CFDA. The CFDA will then be able to supervise the renewals across China and monitor the progress in a timely manner.

On May 1, 2010, the MOH issued the *Provisions for Pharmaceutical Precursor Chemicals (Order No.72 of the Ministry of Health).* Pharmaceutical precursor chemicals, such as lysergic acid, ergotamine, ergonovine, ephedrine and some ephedrine-related products, can be used to produce drugs illegally. The MOH's notice was aimed at strengthening the supervision of pharmaceutical precursor chemicals and to prevent the distribution of these chemicals into illegal markets. The CFDA later issued a notice on June 4, 2010, requiring businesses which were earlier approved by the CFDA (prior to May 1, 2010) to reapply for the production and distribution licenses for pharmaceutical precursor chemicals. The timeframe for the reapplication was less than 3 months from May 1, 2010.

G. OTC Drug Sales

Currently, China is actively promoting the use of OTC products. China's OTC market is now growing more rapidly than almost all other OTC markets in the world. OTC sales make up about 30% of all drug sales in China. OTC sales almost doubled from 2003 to 2009 to approximately $12 billion. Prescription sales grew at around 20% annually over the same period. More foreign drug companies are entering and/or expanding their presence throughout the country with OTC drugs. In 2007, Bayer AG spent over $140 million buying the rights to popular domestic OTC flu products belonging to Topsun Pharmaceuticals.

There are 2 kinds of OTC drugs, Class A and Class B. Drugstores can sell both classes, but general commercial stores such as supermarkets and convenience stores can only sell Class B OTC drugs, after receiving approval from local health authorities. Class A OTC drugs must be sold by qualified pharmacies. Also, like prescription drugs, Class A OTC drugs cannot be used as giveaways or prizes in promotional campaigns. The CFDA is responsible for arranging expert review meetings to evaluate and issue the OTC drug list.

As of now, about 4,500 drugs have been approved as OTC drugs. Over three-fourths of these contain Chinese medicines, while the rest are chemical drugs.

Furthermore, since 2004, the CFDA has restricted the sale of OTC antibiotics to patients who *have* received a doctor's prescription. Previously, no prescription was needed to purchase antibiotics in China. Moreover, before this new regulation there was *no* limit on the quantity of antibiotics that could be purchased by an individual. Many Chinese prefer to use antibiotics for all minor illnesses, including the common cold, and routinely purchased them over the counter. The CFDA's action seeks to regulate antibiotics misuse and to help educate the public about its consequences. The regulation also helps monitor antibiotic usage nationwide and suppress the production of illegal antibiotics.

In addition to regular OTC drugs, health food products are becoming increasingly popular in China. Other popular OTC products include beautification, aging prevention, and high calcium products. Slimming and weight loss products are also becoming more widely used.

H. Regulations on Importing Drugs

The latest *Administrative Provisions on Drug Importation* became effective on January 1, 2004. Drugs can only be imported into China after they obtain registration from the CFDA. For drugs imported for emergency healthcare needs and donations, the CFDA requires samples for registration for clinical research and testing, or a temporary drug import permit.

Drugs can only be imported into China through 18 cities. These cities are Beijing, Tianjin, Shanghai, Dalian, Qingdao, Chengdu, Wuhan, Chongqing, Xiamen, Nanjing, Hangzhou, Ningbo, Fuzhou, Guangzhou, Shenzhen, Zhuhai, Haikou, and Xi'an.

Every shipment of import drugs needs to pass quality analysis before the goods can clear customs for distribution. The quality analysis is conducted by the CFDA appointed drug testing centers. There are 16 appointed testing centers: the National Institute for the Control of Pharmaceuticals and Biological Products and 15 provincial Institutes for Drug Control. These testing centers will send people to conduct sampling for the imported goods, conduct analysis, and issue an analytical report according to the testing method and specification established during drug registration.

The National Institute initiates all sample testing for imported drug registration. If the registration agent has an established relationship with the Drug Institute, they can sometimes choose which drug control department will conduct sample testing. Testing is usually conducted in the province where sales will be made. The testing center will therefore be familiar with the product when they set up the specification for drug registration.

I. Drug Recalls

From December 10, 2007, the CFDA implemented the new *Provisions for Drug Recall*. These are a strengthened set of drug recall rules, largely in response to drug safety scandals over 2006 and 2007. Whereas so far the CFDA has generally ordered recalls itself, in the future it wants manufacturers to start recalling drugs voluntarily when the evidence calls for it. Reduction or elimination of administrative penalties is offered as encouragement.

Recalls are divided into three classes with different time requirements:

- Class I: Defective drugs that may cause serious health problems or death. Recall to be implemented within 24 hours.
- Class II: Drugs that may cause temporary, reversible health problems. Recall to be implemented within 48 hours.
- Class III: Drugs which are unlikely to cause adverse events, but which are in violation of CFDA regulations (for example, because of mislabeling). Recall to be implemented within 72 hours.

Foreign manufacturers have the same legal responsibility as domestic manufacturers to initiate recalls, and they are also obligated to report any recalls of their products outside of China.

J. Drug Safety

In January 2009, the CFDA vowed to crack down on the sale of counterfeit drugs. The thriving market for counterfeit drugs in China has hurt the international pharmaceutical industry for years. The volume of complaints prompted the CFDA to issue a notice in December 2008, directing local health and drug safety administrations to enhance their inspection and supervision of drug retailers.

Requirements specified by the December notice include the following:

- Drug retailers should establish an incoming inspection system for all the products they sell, including non-drug products. This system should include verification of vendor qualification, compliance certification, and product labels. Also, log books should be set up to record the product name, specification, quantity, supplier, and supplier contact information. The log books for incoming drugs and sales should be kept on file for at least two years.
- Drug retailers are not allowed to sell the following items:
    - Products that do not have drug registration numbers, compliance certification, or quality inspection certification.
    - Products that do not have the manufacturer's name, manufacturer's address, and a Chinese translation of the product name.

- Non-drug products (i.e., products not approved by the CFDA) whose packaging or naming is similar to CFDA-approved drugs, or which are claimed to have therapeutic effects.
- Food and drug administration at all levels should intensify the supervision and inspection of drug retailers and strictly punish violations. Drug Distribution Certificates should be revoked for severe violations.

Western companies should ensure that their products also comply with these requirements (e.g., Chinese translations for labeling) or risk having their products inadvertently acted on as "counterfeit drugs."

In December 2008, China's State Administration of Traditional Chinese Medicine also blacklisted 74 web sites for selling fake Chinese herbal medicine.

K. Authorized Quality Person

In January 2009, the CFDA vowed to crack down on the sale of counterfeit drugs. The thriving market for counterfeit drugs in China has hurt the international pharmaceutical industry for years. The volume of complaints prompted the CFDA to issue another notice in December 2008, directing local health and drug safety administrations to enhance their inspection and supervision of drug retailers.

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- Products that do not have drug registration numbers, compliance certification, or quality inspection certification.
- Products that do not have the manufacturer's name, manufacturer's address, and a Chinese translation of the product name.
- Non-drug products (i.e., products not approved by the CFDA) whose packaging or naming is similar to CFDA-approved drugs, or which are claimed to have therapeutic effects.
- Food and drug administration at all levels should intensify the supervision and inspection of drug retailers and strictly punish violations. Drug Distribution Certificates should be revoked for severe violations.

Western companies should ensure that their products also comply with these requirements (e.g., Chinese translations for labeling) or risk having their products inadvertently acted on as "counterfeit drugs."

VIII. MARKETING DRUGS IN CHINA AND RELATED REGULATIONS

A. Packaging Requirements

The Provisions for Drug Insert sheets and Labels became effective on June 1, 2006. The CFDA will review and approve all drug insert sheets and labels.

Product package requirements must be strictly followed, especially with imported drugs. Not only will the CFDA surveillance department check the packaging, but each party involved in the drug importation will also check the package requirements carefully. The drug testing center will check the package with the approved Import Drug Permit carefully when conducting the drug analysis. If there is any difference between the packaging approved by the CFDA and the packaging at the testing center, the testing center will issue a failing grade.

In addition, under Good Supply Practice (GSP) requirements, distributors and hospitals are obligated to check the package again before distributing the products. Distributors must reject products that fail to comply with packaging requirements.

For chemical and biological products, the package and label should contain the following information:

1. Label or inner package (in direct contact with the drug substance)
    a. Name of drug
        i. Generic name must be precisely as approved by CFDA
        ii. Unregistered trademark may not be displayed
        iii. Letters for trade name can be no more than half the size of generic name
    b. Strength
    c. Indications, contraindications
    d. Administration and dosage
    e. Storage specifics
    f. Manufacturing date
    g. Batch number
    h. Expiration date
    i. Manufacturer
    j. Approval number of import license

Label information must be supported by the insert sheet. Any language with implied therapeutic effects, misleading information on usage, or inappropriate promotion of the product will not be allowed. If there is not enough space, the adopted name in China, strength, batch number, and expiration date should be included at a bare minimum.

Insert sheets and labels must use the standardized Chinese characters published by the National Language Commission.

For products which have a limited package size, such as ampoule or injection bottles, the minimum requirements for the label content must show the name of the product, strength, and batch number.

2. Outer Package (boxes in direct contact with the inner package)
    a. Name of the product
    b. Ingredients
    c. Description
    d. Strength
    e. Indications
    f. Administration and dosage
    g. Storage specifics
    h. Adverse reactions
    i. Contraindications
    j. Precautions
    k. Package size
    l. Manufacturing date
    m. Product batch number
    n. Expiration date
    o. Manufacturer
    p. Approval number of import license

    For products which have limited package sizes, information on Adverse Reactions, Contraindications and Precautions must be indicated in the drug insert.

3. Large Package (containers for transport)
    a. Name of the product
    b. Strength
    c. Manufacturing date
    d. Product batch number
    e. Expiration date
    f. Storage specifics
    g. Package size
    h. Manufacturer
    i. Approval number of import license
    j. Special precautions and marks for transport

4. Drug Insert
    a. Name of the product
    b. Characteristics
    c. Pharmacology and Toxicology summary
    d. Pharmacokinetics summary
    e. Indication
    f. Administration and dosage
    g. Adverse reaction

h. Contraindications
i. Precautions
j. Use for pregnant and breastfeeding women
k. Use for children
l. Use for elderly patients
m. Drug interactions
n. Overdose warning
o. Strength
p. Storage specifics
q. Package size
r. Shelf life
s. Manufacturer and contact information
t. Approval number of the import license

All disease names, pharmaceutical terms, drug name need to use professional terms or names standardized and approved by the CFDA. Measurement units must also conform to national standards.

In addition, drugs classified as narcotics, psychotropic substances, toxic drugs for medical use, radioactive pharmaceuticals, drugs for topical use, and non-prescription drugs should be clearly indicated as such. OTC drugs have their own specific packaging requirements, including clearly displaying the OTC logo on the label. For injections and non-prescription drugs, insert sheets must list all excipients.

Some drugs also require standardized barcodes to be sold in China. The government-defined "Drug Supervision Code" contains data identifying the product, manufacturer, box, case, and lot. From October 1, 2007, narcotic drugs and Class I psychotropic drugs were required to have a Drug Supervision Code labeled on their inner package. From October 31, 2008, blood products, vaccines, Class II psychotropic drugs, and TCM injections also had this barcode required of them. The products requiring barcodes will expand over time to all drugs and medical devices.

IX. DRUG ADVERTISING REGULATIONS

In August 2005, the Chinese Ministry of Health (MOH) submitted a recommendation to the State Council to ban advertising for all medical services in China. Support for extending the proposed ban to include drug advertisements was also included in the proposal. The support for such a measure is a direct result of China's poor record of misleading and often illegal medical advertisements. Since then, pharmaceutical advertisements have not been banned, but a new law tightening restrictions on advertising took effect on May 1, 2007.

Currently, prescription drugs can be advertised only in CFDA-approved, professional medical publications. However, prior to advertising, approval from the local government is needed. The CFDA has listed a total of about 150 professional medical publications that were allowed to accept advertisements for prescription drugs.

Drug advertisements in China cannot contain names of medical or pharmaceutical institutions, experts, scholars, physicians or patients. All advertisements for prescription drugs must be submitted to the provincial-level government where the manufacturer or import company is located for approval. The local government office will review the advertisement materials and notify the applicant of the approval or non-approval decision within ten days. If approved, the advertisement will be assigned an approval number and a record will be filed with the CFDA. Some provinces have stricter limitations: for example, in Shanghai, the municipal government takes the submitted ads and passes them to the media itself.

Foreign drug manufacturers that sell their products in China through distributors should be careful of the advertising their distributors use, as penalties could affect them as well. Also, since May 1, 2007, manufacturers have been required to give their approval to each advertisement for it to be submitted.

Since many of China's small pharmaceutical companies do not have the resources to develop novel products, they rely heavily on advertising to market existing products. The medical industry is estimated to be the sixth-largest advertiser in China.

A 2005 study by the Chinese government found that more than 60% of drug advertisements on television, and more than 95% of newspaper and radio ads, violated the advertisement law. The MOH estimates that nearly 2.5 million Chinese misuse medications every year due to deceptive drug advertising. The current drug advertising law stipulates that advertisements cannot contain categorical assertions or guarantees. However, many drug advertisements make claims that their drug can cure cancer, obesity or other incurable diseases. With the constant appearance of new publications and broadcast stations in China, all of which depend on advertising, flouting of advertisement laws has often been the norm.

X. INTELLECTUAL PROPERTY PROTECTION AND PATENTS

A. Intellectual Property in the China Pharmaceutical Market

Currently, generic drugs (including branded generics) account for almost all of the pharmaceutical market in China. However, with increasing pressure from the WTO to comply with intellectual property regulations, and the increasingly affluent population, more and more patented drugs are entering the market.

The current *Regulation for the Implementation of Drug Administration Law of the People's Republic of China* includes clauses which state that undisclosed data from drug research submitted for drug registration will be protected. The protection period is six years from the date the pharmaceutical company obtains registration approval for the drug. For drugs which already hold patents in China, the *Administrative Provisions for Drug Registration* state that generics will not be approved to market until the patent expires.

Although the law states that intellectual property will be protected, the reality is quite different. In the past, Chinese pharmaceutical companies simply copied one another's drugs and there was no incentive to develop new medicines. Today, patent-violating drugs are a rampant problem and weak enforcement mechanisms often let their makers go unpunished. Also, pharmaceutical companies face problems with drug patents in China. Often significant patent life is lost during the clinical testing period. China does not restore patent life lost during the R&D and clinical testing process, even though R&D for a drug can sometimes take up to 15 years to complete.

China's *Patent Law* was revised with a new amendment in October 2009 (it was last revised in 2000). The revisions have varying positive and negative effects on Western drug companies. On one hand, the novelty requirement would be changed to an absolute novelty requirement, meaning that it would be harder for Chinese companies to patent drugs already patented abroad. It would also increase infringement penalties. On the other hand, the amendments seem to open the door to compulsory licensing of drugs, in which the government permits a company to infringe on another company's patent for public policy reasons.

B. Pharmaceutical Companies Experiencing IPR Problems

Although China is making efforts to improve the intellectual property enforcement and patent structure, pharmaceutical companies must still be extremely careful in the Chinese market. Some large US pharmaceutical companies have faced significant IP challenges in China.

Foreign pharmaceutical companies claim that China favors domestic firms and allows greater leeway for domestic firms when producing and selling drugs. Foreign pharmaceutical firms must be careful when importing patented drugs to China because

the patented drug is at risk for counterfeit. Competition from counterfeits can keep patented drugs from being profitable after entering the market.

In July 2004, the China State Intellectual Property Office (SIPO) overturned Pfizer's patent on the drug Viagra. SIPO claimed that the patent was seized because Pfizer failed to disclose all information about the drug's ingredients. Pfizer challenged SIPO in the Beijing No. 1 People's Court, and in January 2007 it won its case.

This case illustrates the ambiguous IP situation in China. Copying remains rampant, and government enforcement is weak. At the same time, civil infringement lawsuits have become noticeably more routine and reliable over the past few years. Although great care will still be needed, the Chinese system appears to be moving in the direction of more reliable IP protection.

C. Administrative Protection (AP)

The *Drug Administrative Protection Provisions* were initiated on January, 1993. This provision provided intellectual property protection for imported drugs that obtained a patent outside of China from January 1, 1986 to January 1, 1993. However, AP automatically expires on the date of patent expiration. Within the patent protection period, the CFDA will not grant registration approval to generics.

According to the current *Administrative Provisions for Drug Registration*, a summary of patent status is required with the application documents as well as a letter of guarantee stating that the applicant will not infringe upon the patent rights of others. According to this regulation, direct IPR infringement on drugs in China is illegal. Usually, local pharmaceutical companies will choose products whose patents will expire in 2 years or whose patents are not well protected, such as manufacturing process patents. If slight changes are made to the manufacturing process, the company will evade patent infringement charges.

XI. SETTING UP YOUR BUSINESS IN CHINA

To take advantage of China's pharmaceutical market growth, foreign drug companies should consider establishing operations in China. Options include setting up the following entities:

- Representative office
- Branch office
- Joint Venture (JV)
- Wholly Foreign Owned Enterprise (WFOE)
- Drug manufacturing facility

A representative or liaison office is the simplest business structure, and it usually consists of one person with an assistant. Job functions of a representative office include market research and advertising, but sales are specifically prohibited. A representative office is often set up in preparation for future expansion into a branch or subsidiary.

A branch office can earn income and remit that income to the parent company. It requires registration and the parent company must usually appoint an official representative responsible for local operations.

Joint ventures can be one of two varieties: a Chinese-foreign equity joint venture (EJV) or a Chinese-foreign cooperative joint venture (CJV). In an EJV, parties invest together, manage together and share risks, losses and benefits in proportion to their contributions of registered capital. An EJV is a limited liability company with Chinese legal person status. In a CJV, parties determine the manner of operation and management, obligations, risk and profit sharing through a contract at the beginning of the venture. Previously, joint ventures had to have 50/50 (foreign/Chinese) ownership splits, but now they can be 80/20 or even 90/10.

A wholly foreign owned enterprise (WFOE) allows for more management control and more autonomy in operations. It can be formed when operations rely heavily on advanced technology that benefits China, or when some of the annual output is exported. A WFOE is considered a Chinese legal entity and must abide by Chinese laws.

Setting up a WFOE requires submitting carefully prepared documentation in English and in Chinese. To gain the status of an "approved investor," a foreign investor must provide the following documentation:

- Articles of Incorporation or equivalent (copy)
- Business license, both national and local (copy)
- Certificate of Status (copy)
- Bank letter attesting to a sound banking relationship and the account status of the company (original)
- A description of the investor's business activities, including material such as an annual report, brochures, etc.

To be approved for incorporation, a foreign investor must provide the following documents in Chinese:

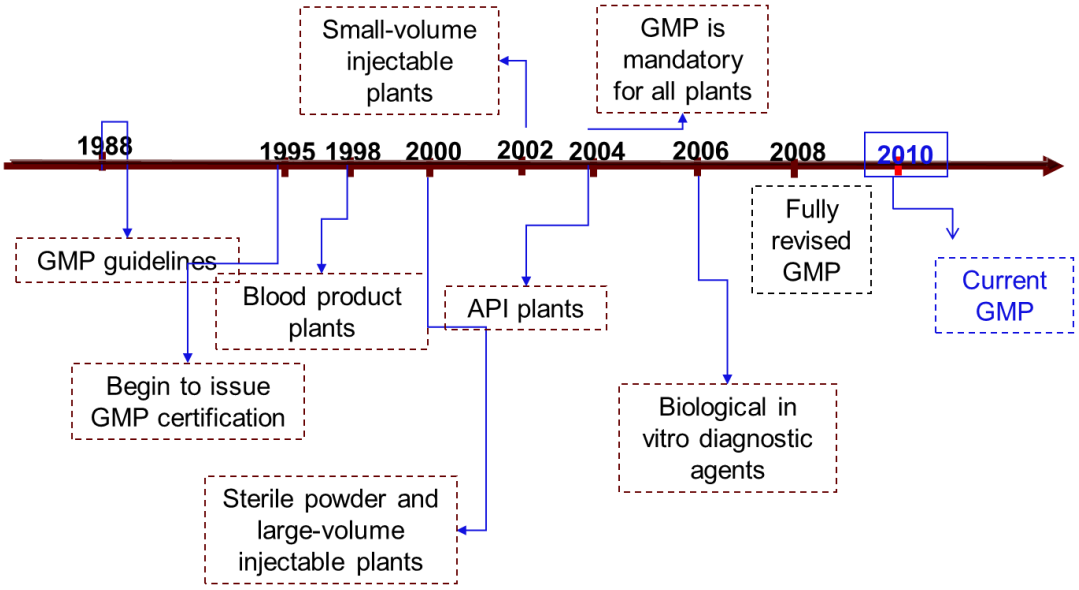
- Articles of Association: detailed information about the management and capitalization of the company
- Feasibility Study: a first year business plan and budget
- Leases: agreements for all required leases
- Proposed personnel salaries and benefits budget
- Additional documentation, as required

Setting up a drug manufacturing facility requires a drug manufacturing certificate and a Good Manufacturing Practice (GMP) certificate. The drug manufacturing certificate is issued by the local government office, after dossier review and on-site inspection. The certificate is valid for five years once issued.

Newly established drug manufacturers or established facilities with new dosage forms must undergo CFDA inspection for GMP approval. The timeframe for GMP certification approval (including dossier submission, dossier review, site inspection and approval) is 90 working days. When a pharmaceutical company wants to establish a new plant or upgrade an old facility, they must submit blueprints to the local government and undergo an on-site GMP inspection.

GMP has a relatively short history in China. Prior to the issuance of the fully revised guidelines, many plants operated without GMP certification. Some local manufacturers chose to pass GMP in order to sell to global markets, but many instead could not afford the expensive upgrades necessary to obtain GMP. From 2000 to 2010, the number of manufacturers went from more than 7,000 to just 4,500. Since 2005, a GMP certificate has been required for the renewal of a drug manufacturing certificate. By the end of 2013, facilities making sterile drugs will require GMP certification. By the end of 2015, *all* drug manufacturing facilities will require GMP certification.

GMP: the modernization of drug manufacturing in China



XII. WHAT OTHER COMPANIES ARE DOING IN CHINA

Many foreign pharmaceutical companies have entered the China market through joint ventures, acquisitions and licensing transfers. Below are several recent examples.

A. Joint Ventures

- In September 2012, **Merck** (NYSE: MRK) announced the creation of a joint venture with China's **Simcere Pharmaceutical Group**. The two companies have created Shanghai based center to develop and market advanced drugs for cardiovascular diseases in lower-level medical institutions in China.

- In February 2012, **Pfizer** (NYSE: PFE) announced the creation of a joint venture with China's state-owned **Zhejiang Hisun Pharmaceutical** for $295 million. **Hisun-Pfizer Pharmaceuticals Co., Ltd.** will develop, manufacture and commercialize off-patent pharmaceutical products for cardiovascular disease, infectious disease, oncology, and mental health.

B. Acquisitions

- In April 2012, **AstraZeneca** (LSE: AZN) completed its acquisition of privately-held **Guangdong BeiKang Pharmaceutical** for an undisclosed sum. China-based Guangdong BeiKang Pharmaceutical is a manufacturer of generic injectable antibiotics. The acquisition added five new medicines to the portfolio of AstraZeneca, which is now -- after Pfizer -- the second biggest foreign drug company in China in terms of sales.

- In March 2011, **Novartis** (NYSE: NVS) completed its acquisition of privately-held vaccine company **Zhejiang Tianyuan** for $124 million. Zhejiang Tianyuan is one of the largest vaccine manufacturers in China, with sales of $25 million in 2008. It produces a range of products focused on preventable viral and bacterial diseases.

- In February 2011, **Sanofi-Adventis** (NYSE: SNY) acquired **BMP Sunstone Corporation** for approximately $520 million. BMP Sunstone is a Plymouth-based company that manufactures and sells over-the-counter pharmacy products for women and children in China. The company generated sales of about $147 million in 2009.

- In January 2011, **Shanghai Fosun Pharmaceutical (Group) Co. Ltd.** (SSE: 600196) acquired a 75% stake in **Aleph Biomedical Co. Ltd.** for approximately $102 million. Aleph Biomedical is a vaccine maker based in Liaoning Province, while Shanghai Fosun is a leading drug retailer in China.

- In December 2010, **GlaxoSmithKline** (NYSE: GSK) entered into an agreement to acquire Nanjing **MeiRui Pharma Co. Ltd** for approximately $70 million in cash. MeiRui is a leading Chinese pharmaceutical business with a strong portfolio of urology and allergy products, including Prostat for benign prostatic hyperplasia and Sheniting for overactive bladder syndrome.

- In November 2010, **Cardinal Health** (NYSE: CAH) acquired privately-held **Zuellig Pharma China** for $470 million. Zuellig is a leading healthcare distributor in China, known locally as Yong Yu. It is also China's largest pharmaceutical importer.

C. Licensing

- In February 2013, **Dyax Corp.** (NASDAQ: DYAX) announced an exclusive license agreement with **Cvie Therapeutics** (a subsidiary of Lee's Pharmaceutical Holdings Ltd.) to develop and commercialize its drug Kalbitor in China, Hong Kong and Macau. Kalbitor is used to treat hereditary angioedema, a rare, genetic condition. Under terms of the agreement, Dyax will receive an undisclosed upfront payment and is eligible to receive future payments as well as royalties on product sales.

- In February 2012, **Cumberland Pharmaceuticals** (NASDAQ: CPIX) announced it had entered into an exclusive agreement with **Harbin Gloria Pharmaceuticals Co., Ltd.** for the commercialization of Acetadote, an injectable drug used to treat acetaminophen overdose and Caldolor, an injectable drug used to treat pain and fever. The agreement provides Harbin Gloria with exclusive rights to register and commercialize both drugs in China. In exchange, Cumberland receives undisclosed upfront and milestone licensing payments as well as royalties on future sales.

- In June 2011, **Roche Pharmaceuticals** (OTC: RHHBY) announced an agreement with **Nycomed** to market its osteoporosis treatment Bonviva in key Asia-Pacific markets. The licensing and supply agreement includes China, Hong Kong, Malaysia, Australia, New Zealand, Philippines, Singapore, Taiwan and Vietnam and a future option to commercialize Bonviva in other Asia-Pacific territories. Nycomed has a majority stake in China-based Guangdong Techpool Bio-Pharma, and was itself acquired by Japanese pharmaceutical company Takeda in 2011.

- In November 2010, **Bristol-Myers Squibb** (NYSE: BMY) announced an innovative strategic partnership with **Simcere Pharmaceutical Group** to develop and market BMS-817378, a preclinical small molecule MET/VEGFR-2 inhibitor. Under the terms of the agreement, Simcere will receive exclusive rights to develop and commercialize BMS-817378 in China, while Bristol-Myers Squibb will retain exclusive rights in all other markets.

- In October 2010, **Pfizer** (NYSE: PFE) announced it had granted exclusive worldwide rights to China-based **MingSight Pharmaceuticals** to develop, manufacture, and commercialize two preclinical stage new chemical entities for the prevention and treatment of diabetic retinopathy. Under the terms of the agreement, MingSight agreed to pay Pfizer an upfront fee, as well as development and sales related milestone payments, and royalties on future sales.

XIII. CONCLUSION

As China develops its pharmaceutical industry policies, the market will continue to expand. In addition to selling drugs in China, China is becoming a reputable R&D center. Distribution channels are also opening up. Reports and statistics are frequently updated showing the growth of China's pharmaceutical market. As the Chinese population becomes more affluent, more consumers will be willing and able to purchase drugs.

However, it is important to understand that China is a unique market. Each region of China is different. Strategies and regulatory procedures employed in other countries will not always work when doing business in China. There are also significant challenges within the Chinese pharmaceutical market, including hospital sector problems, hospital procurement systems, government reimbursement hurdles, and intellectual property infringement. However, the Chinese government continues to make improvements to pharmaceutical regulations and enforcement mechanisms.

Foreign pharmaceutical companies must understand the key business and regulatory requirements for drugs in order to succeed in China. By patiently employing these strategies, a foreign pharmaceutical company can find success in the China market.

APPENDICES

APPENDIX #1:
Application Form for Pharmaceutical Products

State Food & Drug Administration

Registration Application Form

Original No:

021202 Reception No:

Statement

We certify:

(1) This application abides by the following laws, rules and regulations, such as the *Drug Administration Law of The People's Republic of China,* the *Implementing Regulation of the Drug Administration Law of The People's Republic of China,* and the *Drug Registration Provisions*;

(2) The contents, submitted materials, and samples are all true, have a legal origin, and have not infringed upon others' rights, including the methods adopted in testing and the data coming from such testing;

(3) The contents of electronic documents are completely consistent with the printed versions.

We will accept all legal consequences for any untruths.

Registration Item:

1. Classification of Application: O Import Registration
2. Application Stage: O Clinical Trial O Market Authorization
3. Registration Categories: O Traditional Chinese medicine; O Natural drug; O Chemical drug; O Therapeutic biological product; O Preventive biological product; O Pharmaceutical adjuvant

Medicine Details

4. Generic name:
5. Source of generic name: O National standard O CPC O Self-named
6. English name/ Latin name:_____.
7. HanYuPinYin:_____.
8. Chemical name:_____.
9. Other name:_____.
10. Trade name: O Not used O Used:_____.
11. Classification of drug: ☐ OTC ☐ Clinical trial exemption ☐ Multinational trial ☐ Special procedures for examination and approval ☐ Other: _____.
12. Dosage Form:
    ☐ Non-preparation: O Raw material O Chinese crude drug O Herbal drug in small pieces O Active Ingredient O Preparation intermediary O Pharmaceutical adjuvant
    ☐ Preparation: O ChP:____ O Non-ChP:____ O Special preparation: _____.
13. Drug specification:_____.
14. The other same Preparation, which has been registered, and its Strength: _____.
15. Packaging: Immediate packaging material:_____.
    Packaging size:
16. Shelf Life:_____Month
17. Formula (Label claim): Active Ingredient:_____.
    Excipient:_____.
18. Raw material origin:

No.	Raw material name	Validation No.	Manufacturer name	Standard

19. Chinese crude drug standard:

No.	Chinese crude drug name	Stipulated by laws (Yes / No)	Origin of standard	Standard

20. The basis of drug specification: **Origin:** O National standard_____ ; O Self standard_____ ;
O ChP_____edition; O Biological Product Regulations:_____;
O Pharmacopoeia of other countries and their editions:_____;
O Registration standard and its number: _____;
O Other_____.

21. The main indications or function-to-cure:

Related Situation

22. Patent: ☐ Chinese patent: ☐ Patent of drug ☐ Patent of process ☐ Patent of formula ☐ Other patent:
Patent No.:_____;
Owner of patent:_____;
Expiry date:_____;
☐ Foreign patent:
Patent No.:_____;
Owner of patent:_____;
Expiry date:_____;

23. Drug under special administration:
O no O yes: ☐ Narcotics ☐ Psychotropic drug ☐ Radioactive drug ☐ Medical-use toxic drugs
Assent Issue No._____.

24. Traditional Chinese Drug protection: ☐ Traditional Chinese Drug protection Expiry date:

25. Monitoring Period of New Drug: O no O yes, Expiry date:

26. This application is: O New application O Re-application, the first application was:
☐ withdrawn, because:

Applicant

27. Agency1: (Licensed Company) O None OYes ☐ This agency is responsible for paying expenses

Chinese name :

English name:

Company Code:

Legal representative: Position:

Registration Address: Post Code:

Manufacturing Address: Post Code:

Contact Address: Post Code:

Contact Person: Signature: Position:

Telephone: Fax:

E-mail: Mobile:

Manufacturing Licence Code:

GMP: O yes (No._____) O no (Reason:_____)

28. Agency 2 (Manufactuing plant of imported drug): ○ None ○Yes

☐ This agency is responsible for paying the expenses

Chinese name :

English name:

Company Code:

Legal representative: Position:

Registration Address: Post Code:

Manufacturing Address: Post Code:

Contact Address: Post Code:

Contact Person: Signature: Position:

Telephone: Fax:

E-mail: Mobile:

29. Agency 3 (Foreign packing plant of imported drug): ○ None ○Yes

☐ This agency is responsible for paying the expenses

Chinese Name:

English Name:

Company Code:

Legal representative: Position:

Registration Address: Post Code:

Manufacturing Address: Post Code:

Contact Address: Post Code:

Contact Person: Signature: Position

Telephone: Fax:

E-mail: Mobile:

30. Agency 4 (Agency for drug registration): ○ None ○Yes ☐ This agency is responsible for paying the expenses

Chinese Name:

English Name:

Company Code:

Legal representative: Position:

Registered Address: Post Code:

Contact Address: Post Code:

Contact Person: Signature: Position

Telephone: Fax:

E-mail: Mobile:

31. Agency for Research:

No.	Item	Agency	Legal representative	Tel

Relevant Reception Number:	
32. Relevant Application Reception Number:	
Through inspection, this formconform to the requirements:	**For office use only**
Inspection office: Signature of inspector: Date:	

APPENDIX #2:
Listing of CROs in China

1.1 China Clinical Trials Centre Ltd.

www.chinahealthcareltd.com

Established: 2004
 # Employees: 130
Services: Clinical trial support services

Address: Room 801，Building B, CEC Plaza,
No.3 Dan Ling Street, Hai Dian District,
Beijing 100080, China

Phone: +86 10 8260 4588
Fax: +86 10 6406 2955
Email: info@chinahealthcareholdings.com

Comments:

- China Clinical Trials Centre Ltd, located in Beijing, is a wholly-owned subsidiary of China HealthCare Holdings Limited (CHC), a Hong Kong-based company. CHC is a facilitating partner for emerging and leading international healthcare companies, products, technologies, services, and capital to gain access to the People's Republic of China healthcare sector.
- CCTC provides a range of pharmaceutical and medical device clinical trial services. It is supported by an alliance with a leading full service academic research institution and a niche clinic-based CRO. It conducts trials for both pharmaceuticals and medical devices.

1.2 Excel Pharmastudies Inc.

www.excel-cro.com

Established: 1999
Services: Clinical trial management for Phases I-IV

Address: 8/F, Tower B, Central Point
No. 11, Dongzhimen South Avenue
Dongcheng District
Beijing 100007, China

Phone: +86 10 5763 6250
Fax: +86 10 5763 6251
Email: account.development@ppdi.com

Comments:

- Excel Pharmastudies was acquired by US-based Pharmaceutical Product Development (PPD) in November 2009. PPD is a leading global CRO providing discovery and development services. Excel Pharmastudies itself is a leading CRO in China.
- Apart from providing services in regulatory affairs, clinical trial management and biometric services, Excel Pharmastudies also provides patient recruitment, protocol design, case report form (CRF) design, survey, feasibility study, GCP training and drug management services.
- Excel Pharmastudies has 18 branch offices throughout China, allowing it to conduct clinical trials across the country.
- Excel CRAs receive extensive training, and the monitoring staff is composed of English-speaking physicians trained in ICH-GCP.
- Excel has completed nearly 200 clinical trials since 2000 (covering more than 330 hospitals in 40 cities with 160,000 enrolled subjects). Its therapeutic expertise covers 28 areas, with a focus on cardiovascular, endocrinology, oncology, central nervous system, infectious disease, and vaccines. Approximately three-fourths of its clients are multinational companies.

1.3 Accelovance, Inc.

www.accelovance.com

Established: 1999
Services: Clinical trial support services for Phases II – IV

Address: Hanwei Plaza West Tower 7B20
No.7 Guang Hua Road
Chao Yang District
Beijing 100004, China

Phone: +86 010 5165 4686 x 22
Fax: +86 10 5165 4686 x21
Email: info@accelovance.com

Comments:

- Accelovance is based in Rockville, MD and has 7 clinical sites in the US
- Accelovance's China division was originally more focused on market research and business development. Accelovance opened its first China office in Beijing in May 2005, and it began conducting clinical trials in 2006.
- Accelovance provides a range of clinical trial support services including patient recruitment, investigator selection, and trial management. It focuses on assisting clinical plans with recruitment troubles, needing testing on certain demographics, or recruiting for very specific indications. It also facilitates market entry into China.

- Accelovance is a vaccine-focused CRO that has successfully completed Phase I-IV studies in general health and nutritional/OTC medications.
- Accelovance was awarded "Best CRO," a Vaccine Industry Excellence award, at the 2009 World Vaccine Congress.

1.4 PHDS Healthcare Research

www.cnphds.com

Services: Clinical trial support services

Address: #8 Dongxiang Road
Miyun Industry Developing Zone
Beijing, China

Phone: +86 10 8446 6227/8/9
Fax: +86 10 8446 6225
Email: customer@cnphds.com

Comments:

- PHDS Healthcare Research is a leading Chinese CRO offering services in international site selection and management, protocol design, subject recruitment, monitoring, data collection and analysis, and NDA submission. It is equipped to do trials from Phases I – IV, and also works in new drug development, pre-clinical research, bioequivalence and bioavailability studies, regulatory affairs, and market research.
- PHDS has conducted 97 clinical trials, many on behalf of foreign pharmaceutical companies, including Chiron (a Novartis subsidiary). 50 of these were global clinical trials, conducted in other countries simultaneously. Top therapeutic areas were oncology, anti-inflammatory, diagnostics, cardiovascular, gastroenterology, and respiratory.

1.5 Vivo Development Ltd.

www.vivodevelopment.com/En/index.html

Services: Clinical trial support services

Address: Suite 109, 518 Bibo Road
Zhang Jiang High Tech Park
Shanghai 201203, China

Phone: +86 21 5027 5346
Fax: +86 21 5027 5349
Email: contact@vivodevelopment.com

Comments:

- Vivo Development was founded by Chinese returnees with significant experience in global pharmaceutical companies in the US and Europe.
- Vivo offers clinical trial support services in phases I-III, including study design and planning, project management, and medical writing. It also has businesses in technology transfer and pharmaceutical consulting.
- Vivo's particular therapeutic specialty is in psychiatric medicine: it is partnered with the Shanghai Mental Health Center and has conducted 33 clinical trials for various psychiatric disorders, including four multi-national trials with large Western pharmaceutical companies. It also has experience in cardiology, clinical pharmacology, oncology, and biostatistics.
- Vivo is in partnership with Arianne Consulting, a California-based CRO with offices in Serbia, India, and Singapore.

1.6 Venturepharm Services CRO Group

www.venturepharm.com

Established: 2000
Services: Clinical trial support services for Phases I-IV

Address: Venturepharm Towers
No. 3 Jinzhuang, Si Ji Qing, Haidian District
Beijing 100089, China

Phone: +86 10 8850 0088 x397
Fax: +86 10 8850 0080
Email: CRS@venturepharm.net/ info@venturepharm.net

Comments:

- Venturepharm Services CRO Group, or VPSCRO, is a Sino-Canadian-American joint venture of Venturepharm Laboratories Limited, which also has operations in drug discovery and development, contract API manufacturing, and contract drug sales and marketing.
- VPSCRO has completed over 100 clinical trials and has about 70 trials ongoing. Its therapeutic specialties include oncology, central nervous system, cardiovascular, gastrointestinal, respiratory, allergy and immunology.
- VPSCRO has had GlaxoSmithKline, Novartis, and other major drug companies as clients.
- VPSCRO has alliances with over 200 hospitals in 20 Chinese provinces.
- In April 2008, VPSCRO formed a partnership with ACT, a noted Indian CRO, to conduct trials in both China and India.

1.7 Newsummit Biopharma

www.newsummitbio.com

Established: 2001
Services: Clinical trial support services for Phases I-IV

Address: Building 7, Lane 67
LiBing Road, Zhangjiang Hi-Tech Park
Shanghai 201203, China

Phone: +86 21 5079 8788
Fax: +86 21 5079 8766
Email: ibd_information@newsummitbio.com

Comments:

- Newsummit Biopharma supports conducting international multi-center trials, as well as trials for traditional Chinese medicine and biological drugs. Its therapeutic specialties include cardiovascular, pulmonary, anti-infection, rheumatism, and gastroenterology. It also offers pre-clinical studies, laboratory services, contract manufacturing consulting, and NDA filing.
- Newsummit is also developing its own new biopharmaceutical products, with several dozen candidates at various pipeline stages.
- Newsummit has a partnership with the Harvard Medical School Department of Cell Biology.

1.8 Giant Med-Pharma Services, Inc.

www.giantcro.com

Established: 2001
Services: Clinical trial support services for Phases I-IV

Address: Room 2002, Jianguo Wuhao Plaza
No.5 JianGuoMen North Street
Dongcheng District
Beijing, 100005, China

Phone: +86 10 5128 1119
Fax: +86 10 6611 2200
Email: giant@giantcro.com

Comments:

- Giant offers services in clinical trial management, clinical monitoring, biostatistics, study report writing, quality control, healthcare market research, and translation services.

- Giant has successfully completed 20 clinical trials and currently has 10 more under way. It has worked for clients including GlaxoSmithKline, AstraZeneca, Novartis, and Wyeth.
- Giant is led by Dr. Winston Wu, a medical doctor who has investigated psychiatric drugs at Peking University and also has management experience with Watson Pharmaceuticals.

1.9 Shanghai SLG CRO Co., Ltd.

www.china-cro.com

Established: 2005
Services: Clinical trial support services for Phases I – IV

Address: 1289 Yi Shan Road
Fosun Medical Plaza
Shanghai, 200233 China

Phone: +86 21 6495 2868
Fax: +86 21 6495 5288
Email: bd@china-cro.com.cn, slgcro@yahoo.com.cn

Comments:

- SLG offers a variety of clinical trial support services, including clinical trial management for Phases I-IV, biostatistics, clinical data management, pharmacovigilance, and development and marketing consulting.
- SLG has provided services for Novo Nordisk, Pfizer, Wyeth, Roche, Eli Lilly, AstraZeneca, and GlaxoSmithKline.
- SLG is partnered with three Western CROs (Monitoring Force, based in Washington, DC; ReSearch Pharmaceutical Services, based in Fort Washington, PA; and ResearchPoint, based in Austin, TX) and one SMO (Global Rank Team, based in Lombard, IL). It is also a business partner of the major Chinese pharmaceutical firm Fosun.
- SLG has branch offices in Beijing and Shijiazhuang (in Hebei province).

1.10 Tigermed Consulting

www.tigermed.net

Established: 2002
Services: Clinical trial support services for Phases I – IV

Address: Hangzhou (registered headquarters)
Room 810, No. 388 Wensan Road
Hangzhou 310012, China

Phone: +86 571 89986792
Fax: +86 571 88211196
Email: bd@tigermed.net

Shanghai (operational headquarters)
Address: Room 813-815, No. 999 West Zhongshan Road
Shanghai 200051, China

Phone: +86 21 32503700
Fax: +86 21 32503707

Comments:

- Tigermed's services include management of clinical trials in all phases, as well as biostatistics, manufacturing and quality consulting, regulatory affairs, and medical translation.
- Tigermed has grown quickly since its founding in 2002, now having over 300 staff in total, 21 branch offices across China, and one subsidiary in the US with two offices.
- Since 2002, Tigermed has completed 110 clinical trials. It has worked with drugs, medical devices, diagnostic reagents, and functional food products. Its therapeutic areas include oncology, HBV, vaccines, and cardiovascular.
- In November 2008, Tigermed formed partnerships with two foreign CROs, OCT in Russia and LSK in Korea. The aim was to create a global clinical trial network together with these two companies.
- In April 2010, Tigermed signed a collaboration agreement with Ireland-based ICON to offer pharmaceutical and biotechnology companies better access to Chinese patients. ICON is a global provider of outsourced development services to the pharmaceutical, biotechnology and medical device industries.

1.11 MedKey Med-Tech Development Co., Ltd.

www.medkey.cn

Established: 1999
Services: Clinical trial support services for Phases I – IV

Address: 15th Floor, Zhongyi International Commercial Plaza
No.88 Guangxin Road
Shanghai 200061, China

Phone: +86 21 5187 7189
Fax: +86 21 6266 2999
Email: bd@medkey.cn

Comments:

- MedKey conducts clinical trials in Phases I through IV, including project planning, protocol design, CRFs, informed consent forms, and site selection. It

also offers data management, statistical analysis, regulatory affairs, and market research services.
- MedKey's past clients include large multinationals such as GlaxoSmithKline, Merck, AstraZeneca, Sanofi-Aventis and Medtronic.

1.12 Guangzhou Boji Clinical Research Center

www.gzboji.com/boji_en/Index.aspx

Established: 1998
Services: Clinical trial support services for Phases I – IV

Address: 1707-1708, Hui Hua Ge, Huabiao Plaza
609, Tianhe Bei Road, Guangzhou
Guangdong 510635, China

Phone: + 86 20 3847 3208
Fax: + 86 20 3847 3053
Email: lcyj@gzboji.com, boji588@163.com

Comments:
- Guangzhou Boji was one of the earliest CROs in China. It is a subsidiary of the Boji Medicinal Service Group.
- The company has conducted more than 500 trials over the last 10 years. Currently, more than 100 trials are being conducted.
- Guangzhou Boji has 25 other offices in China, including Beijing, Xi'an, Shanghai, Wuzhou and Chongqing.

1.13 Huaxipharm Group

www.huaxipharm.com/en/

Services: Clinical trial management for Phases I-IV

Address: Advanced Materials Building
No.7 Fenghuizhong Road
Haidian District
Beijing, 100094, China

Phone: +86 10 8072 0737
Fax : +86 10 8072 0803
Email: manage@huaxipharm.com, market-2@huaxipharm.com

Comments:

- Huaxipharm is a research-based pharmaceutical company in Beijing. The company is focused on the discovery, development and marketing of medicines, active pharmaceutical ingredients and CRO services in China.

1.14 WuXi PharmaTech (WuXi AppTec)

www.wuxiapptec.com/index.html

Established: 2008
Services: Clinical trial support services for Phases I-III

Address: WuXi AppTec (Shanghai) Co Ltd
288 Fute Zhong Road
Waigaoqiao Free Trade Zone
Shanghai 200131, China

Phone: +86 21 5046 1111
Fax : +86 21 5046 1000
Email: info@wuxiapptec.com

Comments:

- WuXi PharmaTech is a leading global contract research outsourcing provider. The company was a result of the merger between China's WuXi PharmaTech Inc, and US-based AppTec Laboratory Services Inc.
- The company is headquartered in Shanghai. It has operations in both China and the US.
- WuXi Pharma Tech has a trained workforce of about 4,500 employees, of which, about 3,500 are scientists.

1.15 Shanghai Pharma Engine Co., Ltd

www.pharma-engine.com/EN/index.asp

Services: Clinical trial support services

Address: 4F, 780 Cailun Road
Zhangjiang Hi-Tech Park
Pudong New Area
Shanghai 201203, China

Phone: +86 21 5855 5018
Fax : +86 21 5855 8075
Email: mail@pharma-engine.com

Comments:

- Shanghai Pharma Engine Co Ltd provides whole solutions and consulting services to bio-pharmaceutical companies in the area of new drug development and clinical research.

1.16 Shanghai ChemPartner Co. Ltd

www.shangpharma.com

Established: 2003
Services: Clinical trial support services

Address: No. 5 Building, 998 Halei Road
Zhangjiang Hi-Tech Park
Pudong New Area
Shanghai 201203, China

Phone: +86 21 5132 0088

Email: sales@chempartner.cn

Comments:

- Shanghai ChemPartner is one the leading CROs in China, serving more than 120 customers. The company provides chemistry, biology, pharmacology, DMPK, process R&D, pre-formulation, and analytical development services to global pharmaceutical and biotech companies.
- The company has more than 1,200 scientists in total, with branch offices in the US, Canada, Japan and Europe.

Local Offices of Large Foreign CROs

1.17 Covance

www.covance.com

Established: 1998
Services: Clinical trial support services

Address: Full Link Plaza, 18 Chaoyangmenwai Dajie (local office)
Chaoyang District
Beijing, China

Phone: +86 10 6588 1639
Fax: +86 10 6588 1640

Comments:

- Covance Inc. opened its Beijing office in 1998 and was the first company of its kind to test traditional Chinese medicines for the approval of the US FDA. This was done through a strategic agreement with the China Innovation Center for Life Sciences (CICLS), a department of the Chinese Ministry of Science and Technology, in conjunction with a number of Chinese pharmaceutical companies.
- In 2004, Covance Inc. partnered with Excel PharmaStudies Inc., the largest local Chinese CRO, to expand its clinical trial services in China. Covance also provides ongoing training to Excel PharmaStudies.
- To date, Covance has managed more than 2,200 patients and 100 investigator sites in China.

1.18 EPS International China Co., Ltd.

www.epscn.com / www.eps-inter.com

Established: 2001
Services: Clinical trial support services for Phases I – IV

Shanghai Office:
Address: 5th Floor, Building B, No.329 Tianyaoqiao Road,
Xuhui District
Shanghai, 200030, China

Phone: +86 21 3363 2793
Fax: +86 21 3363 2784
Email: contact@epscn.com

Beijing Office:
Address: Room 1012, Junefield Plaza
No.10, Xuanwumenwai Street
Xuanwu District
Beijing 100052, China

Phone: +86 10 6310 3193
Fax: +86 10 6310 4962

Guangzhou Office:
Address: Room 15A, ZhongQiao Building
No. 76 Xianlie Middle Road
Guangzhou 510070, China

Phone: +86 20 8732 4885
Fax: +86 20 8732 4887

Comments:

- EPS China Co. Ltd. is a branch of EPS Co., Ltd. of Japan.
- EPS China Co. Ltd. provides a range of clinical support services including patient enrollment, trial monitoring, test drug management, data management and statistical analysis, auditing, document preparation, site and investigator selection, and training.

1.19 CMIC (Beijing) Co., Ltd.

www.cmic.co.jp/corporate/group/beijing.shtml

Established: 1998
Services: Clinical trial support services for Phases I – IV

Address: B610-612, COFCO Plaza
No. 8 Jianguomennei Avenue
Beijing 100005, China

Phone: +86 10 6513 9211
Fax: +86 10 6513 9213

Comments:

- CMIC Beijing provides a range of clinical trial support services for Phase I to IV trials, including data management, strategic consulting, and post-market surveillance.
- CMIC Beijing is a subsidiary of CMIC Japan, a large Tokyo-based CRO.

1.20 Quintiles

www.quintiles.com

Established: 1997

Beijing Office:
Address: Office Tower 3, Unit 901-919
Sun Dong An Plaza
138 Wang Fu Jing Da Jie, Dong Cheng District
Beijing 100006, China

Phone: +86 10 5911 7888
Fax: +86 10 5911 7999
Email: clinical.info@quintiles.com, asia@quintiles.com

Shanghai Office :

Address: 68, Middle Yin Cheng Road,
Shanghai 200120, China

Phone: +86 21 5010 6680
Fax: +86 21 5010 6678

Comments:

- Quintiles Transnational opened its Beijing office in 1997 to expand its presence in the East Asian region. The Beijing office was the 9th Quintiles office in the Asia Pacific. It provides a range of clinical trial services, as well as health care consulting.
- Innovex China, a Quintiles subsidiary, was established in 1998 and provides a range of services to both local and international pharmaceutical companies, including commercial solutions, marketing, sales, and health management.
- In January 2008, Quintiles Transnational began consolidating its Global Clinical Laboratories and Clinical Development Services units into one new 17,000 square-foot facility in Beijing.

1.21 INC Research (previously MDS Pharma Services (China))

www.mdsps.com

Established: 1997
Services: Clinical trial support services and central laboratory

Beijing Office

Address: Suite 608, CBD International Mansion
No. 16 Yong An Dong Li, Chaoyang District
Beijing 100022, China

Phone: +86 10 5809 2300
Fax: +86 10 6588 9010

Shanghai Office:

Address: 11th Floor, Unit 2
Shanghai Times Square
93 Huaihai Zhong Road
Shanghai 200021, China

Phone: +86 21 6171 6800

Comments:

- US-based INC Research acquired MDS Pharma Services from MDC Inc in July 2009. Prior to the acquisition, MDC Pharma was the first global CRO to set up

offices in China. Its China office continues to offer the full range of clinical development services. It also provides regulatory consulting, product registration, recruiting, and consumer product services.

- The company conducted the largest global Phase II and III hepatocellular carcinoma trial ever in China. One hundred patients were recruited at 13 sites in China, and regulatory approval was obtained in 8 months.
- In 2002, the company's (then known as MDC Pharma) central clinical laboratory in Beijing became the first laboratory in China to receive accreditation from the College of American Pathologists.
- In addition to global central lab services, it also provides support and testing services including standardized assays and methodologies, remote data access, blood collection and hematology services, ECG services, and drug screening. All clinical sites are in compliance with GCP and GLP.
- The Beijing lab has also received Level II certification from the National Glycohemoglobin Standardization Program.

1.22 Beijing KendleWits Medical Consulting Co., Ltd.

www.kendlewits.com.cn

Established: 1997
Services: Clinical trial support services for Phases I – IV

Beijing Office:
Address: Room 1502-05, Tower B, Global Trade Center
No. 36 East, Third Ring North Road
Dongcheng District, Beijing 100013 China

Phone: +86 10 5825 6060
Fax: +86 10 5825 6055

Shanghai Office:
Address: Room 1608, Huasheng Business Mansion
No. 399 Jiujiang Road, Huangpu District
Shanghai 200001, China

Phone: +86 21 6361 9009
Fax: +86 21 6361 9006
Email: xieyb@kendlewits.com.cn

Comments:

- Beijing KendleWits is a Sino-American joint venture (formerly named Beijing AcerWits) between Beijing Wits Science and Technology Co., Ltd. and Kendle International Inc. It has conducted global clinical trials involving more than 50 sites and 3,000 patients.

- Beijing KendleWits has therapeutic expertise in range of areas including anti-infectives, oncology, immunology, cardiovascular, respiratory diseases, CNS diseases, gastroenterology, and endocrinology metabolism.
- The company's professionals hold either Bachelor's or Master's degrees in medicine, pharmacology, or other biological disciplines, and also undergo periodic training through seminars given by the State Food and Drug Administration of China and at Kendle College.
- Beijing KendleWits obtained the ISO 9001:2008 certification in March 2010.

1.23 Gleneagles CRC (China) Pte Ltd

www.gleneagleslescrc.com

Services: Clinical trial support services for Phases I – IV

Beijing Office:

Address: Room 0810, South Office Tower
Beijing New World Center
No. 3A, Chong Wen Men Wai Da Jie
Beijing 100062, China

Phone: +86 10 6708 0739 (40)
Fax: +86 10 6708 0737

Shanghai Office:

Address: Room 1309, Zhongchang Jincheng Building
1399 Haining Road
Shanghai 200070, China

Phone: +86 21 6381 0953 / 6381 0954
Fax: +86 21 5161 1309

Email: info@gleneaglescrc.com

Comments:

- This is the China branch office of Gleneagles CRC, an international CRO based in Singapore. Gleneagles CRC is a joint venture between Singapore's ParkwayHealth (a private healthcare network) and Mitsui Co Ltd.

1.24 PPD (China)

www.ppdi.com

Established: 1998
Services: Clinical development

Address: 8/F, Tower B, Central Point Plaza
No. 11, Dongzhimen South Avenue
Dongcheng District
Beijing 100007, China

Phone: +86 10 5763 6250
Fax: +86 10 5763 6251

Comments:

- This is the China branch office of PPD, a large global CRO based in Wilmington, NC.

1.25 PAREXEL International

www.parexel.com

Services: Clinical development for Phases I - IV

Shanghai Office:
Address: No. 2202-2206, 22F East Tower
Zhong Rong Heng Rui International Plaza
No. 620, Zhang Yang Road, Pudong
Shanghai 200122, China

Phone: +86 21 6160 9090
Fax: +86 21 6160 9193
Email: info@parexel.com

Beijing Office:
Address: Room 1115, 11F, Yi, Kuntai International Mansion Building
Chao Yang Men Wai Street
Chao Yang District
Beijing 100200, China

Phone: +86 10 5879 7676
Fax: +86 10 5789 7672

Comments:

- This is the China branch office of PAREXEL, a large international CRO headquartered in Waltham, MA.

1.26 Astrom Research International

www.astromresearch.com

Services: Clinical trial support services for Phases I – IV

Address: Research Park Ideon
SE - 223 70 Lund, Sweden

Phone: +46 70 863 4909
Fax: +46 46 286 2634
Email: stefan@astromresearch.com

Comments:

- Astrom Research is a CRO and specialized consultancy focusing on clinical trials and medical research in China for pharmaceutical, biotech, and medical device companies. Astrom provides complete service for clinical trials through a well-established local network of high quality university hospitals located in all major Chinese cities. It assists with the start-up, performance, and reporting of clinical trials in China, and also provides data management, ICH-GCP monitoring, and GCP training. In addition, it also assists with clinical trial applications and medical device product registration in China.
- Astrom's therapeutic expertise covers a variety of areas including cardiovascular, infectious diseases, neurology, respiratory, gynecology, rheumatology, nephrology, endocrinology, and hematology.
- The company's CEO, Dr. Stefan Astrom, previously served as CEO for Sweden-based Hylae Clinical Research and as Clinical Research Director for Astra in Toronto.

1.27 Protech Pharmaservices Corporation (PPC) (China)

www.ppccro.com

Established: 2003
Services: Clinical development for Phases 1- IV

Address: Room 2309, 1088 West Yan'an Road
Changning District
Shanghai, China

Email: contact@cro.asia, sha@ppccro.com, protech@protechlab.com.tw

Comments:

- This is the China office of PPC, an international CRO based in Taipei, Taiwan.

1.28 Omnicare Clinical Research

www.omnicarecr.com

Established: 2008
Services: Clinical trial support services for Phases I – IV

Beijing Office:
Address: Unit 1510, Beijing East Ocean Centre (local office)
JianGuoMenWai Street
ChaoYang District
Beijing 100004, China

Phone: +86 10 65156177
Fax: +86 10 65671916

Shanghai Office:
Address: Room 2001-2004
No. 83 Lou San Guan Road
New Town Center
Shanghai 200336, China

Phone: +86 21 6236 8678
Fax: +86 21 6236 8679

Comments:

- This is the China branch office of Omnicare Clinical Research, a large global CRO headquartered in the US.

1.29 ICON Clinical Research

www.iconclinical.com

Established: 1990 (Dublin headquarters)
Services: Clinical trial support services for Phases I – IV

Address: Floor 5 Tower B,
28, Jianguomennei Avenue
Minsheng Finance Centre
Dong Cheng District
Beijing 100005, China

Phone: +86 10 8529 5100
Fax: +86 10 8529 5199
Email: info@iconaus.com.au

Comments:

- This is the China branch office of ICON Clinical Research, an international CRO based in Dublin, Ireland. ICON has two other branch offices in Shanghai and Tianjin.

1.30 CCBR Beijing Center

www.synarc.com

Established: **1992**
Services: Clinical trial support services for Phase II - III

Address: **1st Floor Tower C, No. 29**
Life Science Park Road
Changping District
Beijing, China 102206

Phone: **+86 10 8072 9990**
Fax: +86 10 8070 5506

Contact: Pengchang Ha, GM
Mobile phone: +86 1342 601 9977
Email: pengchang.ha@ccbr.com

Comments:

- CCBR is a Danish CRO, founded in 1992 with multiple clinical centers mostly in Eastern Europe. In 2006, CCBR was acquired by Synarc, a pharmaceutical services company based in San Francisco, but kept its name.
- CCBR Beijing offers services in clinical trial management (phases II and III only), biostatistics, clinical data management, trial design, and trial registration with the CFDA. It works in partnership with the Beijing Friendship Hospital, which is one of Beijing's well-reputed hospitals and is often used by foreigners.
- CCBR Beijing's therapeutic specialties include osteoporosis, arthritis, women's health, cardiovascular, and obesity.

1.31 PRA International China

www.prainternational.com

Established: 1981 (US headquarters)
Services: Clinical trial management for Phases I - IV

Address: Unit 4907-03, 49F, Raffles City
268 Xi Zang Middle Road
Shanghai 200001, China

Phone: +86 21 6340 4425
Fax: +86 21 6340 4763
Email: trials@praintl.com

Comments:

- This is the China branch office of PRA, an international CRO headquartered in Raleigh, NC with over 3,500 employees worldwide.

1.32 Beijing Medpace Medical Science & Technology Ltd.

www.medpace.com

Established: 2002 (US headquarters)
Services: Clinical trial management for Phases 1 - IV

Address: No 23, East Business Tower
Sheng Shi Long Yuan
No 1005, Gao Bei Dian Xiang Xi Dian
Chaoyang District
Beijing 100022, China

Phone: +86 10 8770 6877
Fax: +86 10 8770 6422
Email: info.cn@medpace.com

Comments:

- This is the China office of Medpace, a large global CRO based in Cincinnati, Ohio.

1.33 Beijing CRO Bio-Pharmaceutical Development Co., Ltd.

www.b-cro.com

Established: 2004
Services: Clinical trial support services for Phases I – IV

Address: Outside Guangqumen Street
Shi Court No. 8 U A-1711-12
Chaoyang District, Beijing

Phone: +86 10 5861 2515
Fax: +86 10 5861 2519
Email: info@cro.co.jp

Comments:

- Beijing CRO is a subsidiary of Tokyo CRO, Inc., a Japan-based CRO.

1.34 Shanghai InCROM Pharma Development Co.

www.incrom.com/English/china/

Established: 2005
Services: Clinical trial support services

Address: Room 603, Building C, Hi-Tech Building
900 Yishan Road,
Shanghai, China 200233

Phone: +86 21 5423 4291
Fax: +86 21 5423 4292
Email: china-info@incrom.com

Comments:

- Shanghai InCROM is a unit of Japan InCROM (International Clinical Research Organisation for Medicine). Japan InCROM was one of the first clinical research providers in Japan. It also has offices in Beijing, Chengdu and Guangzhou.

APPENDIX # 3:

Regulatory Specifics for Clinical Trials in China

Note: All numbers given are for the number of subjects in the trial group only unless otherwise specified.

Traditional Chinese Medicine:

Phase I	20-30
Phase II	100
Phase III	300
Phase IV	2000
Bioequivalence:	18-24

Chemical drugs:

Categories 1 and 2

Phase I	20-30
Phase II	100
Phase III	300
Phase IV	2000

Categories 3 and 4 -Human pharmacokinetic study (except for topical products with only topical effects and oral preparations that are not absorbed)
-Clinical trial with 100 pairs of subjects, or 60 pairs per indication if more than 1 indication

Category 5:

Oral solid preparations:	Bioequivalence, 18-24 cases
Oral non-solid preparations:	Clinical trial, 100 pairs
Sustained or and controlled-release preparations:	Clinical trial, 100 pairs
Injections, single active component:	Clinical trial, 100 pairs
Injections, multiple active components:	Clinical trial, 300 pairs
Injections, microcapsules, microemulsions or liposomes	Same as for categories 1 and 2 above

Category 6 (generics)

Oral solid preparations:	Bioequivalence, 18-24 cases
If quality of drug needs to be controlled by processes and standards:	Clinical trial, 100 pairs

Therapeutic biological drugs:

Phase I	20
Phase II	100
Phase III	300

Preventive biological drugs:

Phase I	20-30
Phase II	300
Phase III	500

APPENDIX # 4

Administrative Provisions for Drug Registration
*(SFDA Order No. 28)**

*****In March 2013, the SFDA changed its name to the China Food and Drug Administration (CFDA).*

Chapter 1: General Principles

Article 1: This Regulation is promulgated according to the *Drug Administration Law of The People's Republic of China* (*Drug Administration Law*), the *Administrative Licensing Law of The People's Republic of China* (*Administrative Licensing Law*), and the *Implementing Regulation of the Drug Administration Law of The People's Republic of China* (*Implementing Regulation*) to ensure the safety, efficacy and quality control of drugs and standardize drug registration.

Article 2: This Regulation shall apply to all drug research and clinical studies, application for clinical studies, drug production and/or importation, drug examination and approval, registration inspection, and drug administration in the People's Republic of China (PRC).

Article 3: Drug registration means the legal process by which a decision is made by the SFDA, upon application for registration, to either approve or not approve the conducting of a drug clinical trial, production, or importation of a drug for marketing, based on a systematic evaluation of the drug's safety, efficacy, and quality control.

Article 4: The State shall encourage research and development of new drugs and implement special examination and approval for innovative new drugs and drugs for difficult-to-treat and life threatening diseases.

Article 5: The State Food and Drug Administration (SFDA) is the competent national authority for drug registration, responsible for the examination and approval of clinical studies, production, and importation of drugs.

Article 6: Drug registration should follow the principles of openness, equality, fairness, and public convenience. During drug registration, the SFDA shall be the principal responsible party, and will implement systems of transparency of relevant staff, conflict-of-interest avoidance, and responsibility investigation, with major procedures such as application acceptance, inspection, review, approval, and delivery subject to public scrutiny.

Article 7: During drug registration, should the drug administrative authority consider a license an issue of significant interest to the public, the issue should be announced to the public and a public hearing should be held.

Should the administrative permission involve any significant interests between the applicant and other parties, before any decision is made, drug administration authorities should notify the applicant and the other parties of their entitlement to request hearings, statements, and defense.

Article 8: Drug administration authorities shall provide the applicant with accessible information regarding the progress and conclusion of drug registration acceptance, inspection, testing, evaluation, approval, etc.

Drug administration authorities should publicly disclose the following information at their official website and/or office location.

1. Drug registration application items, procedures, fee standards and basis, timeline, table of contents of all required dossiers, as well as reference application documents.
2. List of names and related information for relevant staff at each step though acceptance, inspection, testing, review, and approval.
3. General information on drug registration, such as the formulary of approved drugs.

Article 9: The drug administration authority, units, and involved staff shall assume the responsibility of protecting trade secrets and experimental data provided by applicants during the process of drug registration.

Chapter 2: Basic Requirements

Article 10: A drug registration applicant (hereinafter referred to as "applicant") is an institution that makes drug application for drug registration and assumes corresponding legal liabilities.

A local applicant shall be a legally registered institution in China and shall be competent to independently assume legal liability. A foreign applicant shall be a legally established pharmaceutical company outside of China. In making application for an imported drug registration, the foreign applicant shall use its office in China or authorize an agent in China to handle the application.

The person(s) handling the drug registration application shall have technical expertise and be familiar with drug administration laws, regulations, and technical requirements.

Article 11: Drug registration application includes new drug applications, generic drug applications, imported drug applications, supplemental applications, and re-registration applications.

A local applicant shall apply according to application procedures for new drug or generic drug applications; a foreign applicant shall apply according to the application procedures for imported drugs.

Article 12: A new drug application means a registration application for a drug that has not been marketed in China. Applications for a changed dosage form, changed route of administration, or additional indication of a drug shall be made according to the new drug registration procedure.

Generic drug application means an application for registration of a drug for which the SFDA has already issued formal standards; however, biological products shall follow the new drug registration procedure.

Import drug application means an application for a drug produced outside China to be marketed in China.

Supplemental application means an application for the change, addition, or cancellation of any item or contents in the original registration after approval of a new drug, generic drug, or imported drug.

A re-registration application means an application to continue drug production or importation after the expiration of drug approval certification.

Article 13: Applicants should provide sufficient and reliable research data as evidence for the safety, effectiveness and quality control of their drugs, and assume liability for the truthfulness of their entire dossier.

Article 14: In citing literature and materials submitted for a drug registration application, the name of the work(s) and journal(s) as well as the volume, issue, and page number shall be provided in the application dossier submitted for drug registration. For unpublished literature and materials, an authorization letter from the owner must be provided. For any foreign language materials, a Chinese translation should be provided in accordance with relevant requirements.

Article 15: The SFDA shall implement the National Pharmaceutical Industry Development Plan and Policy, and may organize an assessment of the value of introduction of drugs to the market.

Article 16: During drug registration, drug administration authorities should conduct site inspection and specific inspections for pre-clinical studies and clinical trials, as well as conduct site inspection of the production site prior to any marketing approval, in order to confirm the truthfulness, accuracy, and completeness of the application dossier.

Article 17: If two or more institutions jointly apply for drug registration, the application shall be made to the provincial drug authority (PDA) where the drug manufacturer is located. If all the applicants are manufacturers, the application shall be made to the PDA where the manufacturer of the preparation is located. If none of the applicants are manufacturers, the application shall be made to the PDA where the drug sample is pilot manufactured.

Article 18: Regarding the drug or its formula, production process, indication, etc., the applicant shall submit documents explaining its patent status and ownership rights in China. If another party holds patent in China, the applicant shall submit a letter stating that the drug will not infringe on the patent rights of others. This statement or announcement submitted by the applicant shall be made public by drug administration authorities on the Administration Organization Website. If an infringement dispute occurs during registration application, the parties shall resolve the matter according to relevant laws for patent administration.

Article 19: For a drug that has obtained patent protection in China, another applicant may apply for registration within the two years preceding its patent expiration. The SFDA shall review the application according to this Regulation and, after expiration of the patent, issue a Drug Approval Number, *Imported Drug License* or *Drug Product License*, for an application that meets requirements.

Article 20: According to Article 35 of the *Implementation Regulation*, for a period of 6 years from the date of the original applicant's approval, the SFDA shall not approve a subsequent application that uses, without the express consent of the original applicant, the undisclosed R&D data or other data generated by the original applicant for submission of application of manufacturing or marketing of a drug containing new chemical ingredients, unless the submitted data is generated by the subsequent applicant itself.

Article 21: The scope of pre-clinical laboratory study (pre-clinical study) of a drug for registration includes synthesis process, extraction methods, physical-chemical properties and purity, dosage form selection, screening of formulas, preparation process, inspection methods, quality specification, stability, pharmacology, toxicology, and pharmacokinetics. For TCM preparations, information such as the source and the processing of raw materials should also be included. For biological products, information such as source, quality standards, storage condition, biological identity, genetic stability, and immunological study of strain, cell strain, and biological tissue should also be included.

Article 22: Pre-clinical study of a drug shall be conducted in accordance with relevant regulations, where the drug safety evaluation must be conducted in accordance with *Good Laboratory Practice for Pre-Clinical Laboratory Studies (GLP).*

Article 23: Institutions engaged in drug research and development shall have the necessary personnel, facility, equipment, instruments, conditions, and management system necessary for to the research project, and shall guarantee the authenticity of all data and materials. The animals, reagents and raw materials used in experiments shall comply with relevant national regulations and requirements.

Article 24: If an applicant authorizes another institution to conduct the study of drugs, or to conduct any single experiment, inspection, or pilot production or manufacture, the applicant shall sign a contract with the authorized party, and note this contract in the

registration application. The applicant is responsible for the truthfulness of the drug study data used in the application dossier. .

Article 25: When an application is made for registration of a preparation only, the raw materials of the investigative drug substance used for this preparation must have a Drug Approval Number, *Imported Drug Certificate* or *Drug Product Certificate,* and must have been obtained from legal channels. Any investigative drug substance which does not have a *Drug Approval Number*, *Imported drug Certificate* or *Drug Product Certificate* must be approved by the SFDA.

Article 26: If an applicant uses drug study data from a foreign drug study for a drug registration application, an explanation of the study items, referencing the page numbers issued by the institution, shall be provided, and a notarized certificate of the institution's overseas legal registration shall be attached. Only after the documents are authenticated by the SFDA may they be included in the registration documents. The SFDA may send people to conduct on-site inspections, if necessary.

Article 27: During the verification of drug studies, drug authorities may request the applicant or the institute that conducted the research to repeat an experiment for any item(s) using the methods and data listed in the application dossier. The SFDA may also designate other drug control institutes or drug research institutions to repeat the experiments or to validate the methodology.

Article 28: Drug studies shall be conducted in accordance with relevant technical guidelines issued by the SFDA. If the applicant conducts the experiments according to other methods and techniques, the applicant shall provide information as evidence that the methods and techniques are scientific.

Article 29: After obtaining a Drug Approval Number, the applicant should produce the drug according to the process approved by the SFDA. Drug administrations shall monitor production according to the approved production process and standards.

Chapter 3: Clinical Trials of Drugs

Article 30: Clinical trials of drugs, including bioequivalence trials, must be approved by the SFDA, and must be conducted in accordance with *Good Clinical Practice (GCP).* Drug administrations shall monitor and inspect the approved clinical trials.

Article 31: Clinical trials should be conducted for the registration of a new drug. For registrations application of generic drugs and supplemental application, clinical trials should be conducted in accordance with provisions specified in Appendix of this Regulation.

Clinical trials are divided into Phase I, Phase II, Phase III and Phase IV.

Phase I: Basic clinical pharmacology and human safety evaluation studies. The purpose is to observe tolerance in human bodies and pharmacokinetics, providing a basis for a drug administration program.
Phase II: A preliminary exploration of therapeutic efficacy. The purpose is to evaluate the safety and efficacy of a new drug on patients within the target indication of the drug, to provide the basis for designing a Phase III clinical trial, and to determine a drug administration program. A Phase II clinical trial may be conducted in many ways, including randomized blind controlled clinical trials, in accordance with the purpose of the study.
Phase III: The phase to confirm therapeutic efficacy. The purpose is to further verify the safety and efficacy of a new drug for patients with the targeted indication, to evaluate the risk and benefit relationship, and finally to provide sufficient data to support the registration approval of the drug. Such trials are usually randomized, blind and controlled with a large number of sample subjects.
Phase IV: A new drug study after the drug's marketing, conducted by the applicant. The purpose is to investigate the efficacy and adverse reactions under conditions of wide use, to evaluate the risk and benefit relationship when used by ordinary or special groups of patients, and to improve drug dosage.
Bioequivalence trials: Human trials determining if there is any statistical difference in absorption and absorption speed of the active component between the same or different dosage forms of the same drug under the same test conditions, using the methodology of bioavailability studies and with pharmacokinetic parameters.

Article 32: The number of human subjects in the clinical study of a drug should be decided in accordance with the objective of the clinical trials and shall meet both the statistical requirements and the minimal cases required by this Regulation for a clinical study. For a drug used for the treatment of rare and special diseases or in other special circumstances, any application for reduction in the number of human subjects in the clinical study, or exemption of the clinical study, should be made at the same time as clinical trial application and should be approved by the SFDA.

Article 33: For vaccines and other special drugs prepared during the strain selection stage, if there are indeed neither suitable animal experimental models nor a way to evaluate the efficacy of the drugs in laboratory studies, application for clinical trials may be made to the SFDA, provided that safety of the subjects can be ensured.

Article 34: After approval of a clinical study, the applicant shall select from the institutions qualified for drug clinical trials to conduct the clinical study.

Article 35: The investigational drugs shall be produced in a workshop which meets *Good Manufacturing Practice (GMP)* requirements; the production process shall be strictly in accordance with the requirements of GMP. The applicant is responsible for the drug quality of the investigational drugs

Article 36: The applicant may inspect the investigational drug itself in accordance with the drug's standards for its selected drugs for the clinical trial, or authorize a drug control

institute designated by this Regulation to conduct the quality test. Vaccines, blood products, and other bio-products designated by the SFDA must be inspected by a drug control institute designated by the SFDA.
The drug must not be used for clinical trials before it has passed inspection.
Drug administration authorities may conduct random inspections on the investigational drug.

Article 37: Before conducting the clinical study, the applicant shall file with the SFDA information such as the clinical study protocol, name of the principal investigator of the leading institution, participating institutions and their investigators, approval letter from the ethics committee, and a sample of the Informed Consent Form, also providing a copy to the PDA where the institutions are located and the PDA where the application was filed.

Article 38: If an applicant discovers that an institution conducting a clinical study is in violation of relevant regulations, or is not following the clinical study protocol, the applicant shall try to correct the situation. For serious violations, the applicant may request to suspend or stop the clinical study and shall submit a written report to the SFDA and the relevant PDA(s).

Article 39: Upon completion of the clinical study, the applicant shall submit a clinical study summary report, statistical analysis report, and database to the SFDA.

Article 40: A clinical study shall start within 3 years of its approval. Otherwise the approval certificate shall automatically become null and void. A re-application must be submitted to resume the study.

Article 41: Should any serious adverse event occur during clinical trials, the institution should report to the PDA, SFDA, and the applicant within 24 hours of occurrence, and report to the Ethics Committee in a timely fashion.

Article 42: The SFDA may request the applicant to amend the clinical study protocol or to suspend or stop the clinical study in any of the following circumstances:

1) The Ethics Committee has failed to perform its duty
2) The safety of the subjects cannot be effectively ensured
3) A serious adverse event was not reported in a timely fashion
4) Evidence exists that the investigative drug is not effective
5) Quality problems exist in the drug used for clinical trials
6) Fraud is committed in the clinical study
7) Other circumstances violating *GCP*

Article 43: During the clinical study, in case a large-scale or unexpected adverse reaction or serious adverse event occurs, or if there is evidence to prove that the investigational drug has significant quality problems, the SFDA or PDA may adopt emergency mandatory administrative measures to suspend or stop the clinical study, and the applicant and institution must immediately stop the study.

Article 44: A foreign applicant who wants to conduct an international multi–center clinical study shall apply to the SFDA in accordance with the following provisions:

1) The investigational drug used for an international multi–center clinical study shall be one already registered in a foreign country or already in phase II or phase III clinical trials. An application for an international multi–center clinical study of a new preventive vaccine from a foreign applicant that is not registered outside China shall not be accepted by the SFDA.
2) In approving an international multi–center clinical study in China, the SFDA may request the applicant to first conduct Phase I clinical trials in China.
3) During a study conducted in China, the applicant shall, in accordance with the relevant regulations, report to the SFDA any serious adverse events or unexpected adverse events which occur in any countries.
4) Upon completion of the study, the Applicant shall submit the complete clinical study report to the SFDA.
5) Data generated from an international multi–center clinical trial, if used for drug registration in China, shall be in accordance with the relevant provision of this Regulation, and the applicant shall submit complete research information from the study.

Chapter 4: Application and Approval of New Drugs

Article 45: The SFDA may use special examination and approval processes for the following new drugs:

1) New drug material and its preparations; active ingredients and their preparations extracted from plants, animals, or minerals, which have not been marketed in China
2) Chemical drug raw materials or their preparations, and/or biological products that have not been marketed domestically or outside China;
3) New drugs for AIDS, cancer, or orphan diseases that are superior to marketed drugs.
4) New drugs which treat diseases for which there is no effective therapy.

For those drugs meeting the above provisions of this Regulation, the applicant may apply for a special approval process during the drug registration. The SFDA shall organize a specialist meeting to decide whether to implement a special examination and approval process for the drug application.

Detailed provisions of the special examination and approval process shall be promulgated separately.

Article 46: When a new drug is jointly developed, the application shall be made by one of the parties, and other parties shall not apply in repetition. When a joint application needs to be made, the application shall be signed by all parties. After approval, all the new drugs, including different strengths of the same drug, shall only be manufactured by one party.

Article 47: For registration applications with a change in a drug's dosage form but with no change in the route of administration, new technology should be used to improve drug quality and safety, having obvious clinical advantages in comparison with original dosage form.

Except for targeted-delivery preparations or sustained or controlled-release preparations, a registration application for change in a drug's dosage form but with no change in the route of administration should be made by the company with production condition.

Article 48: During the review process for a new drug, even if another drug with the same active component is approved for marketing overseas, the registration category and technical requirements of the drug shall remain unchanged in the review process in China.

During the review process for a new drug, even if another domestic drug with the same active substance is approved for marketing in China, the registration category and technical requirements for the same kind of drug shall remain unchanged in the review process in China.

Article 49: A drug application dossier should be submitted at one time. The applicant shall not self-submit supplemental technical material to the SFDA once any application is accepted, except for new information related to the drug safety or for a special approval process. If the applicant believes that new technical materials must be added, the applicant should withdraw the application. When the applicant re-applies, the application procedures of this Regulation should be met and the same drugs should not already be approved [by another applicant] and in the monitoring period.

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Section 1: Clinical Trials for New Drugs

Article 50: Upon the completion of the pre-clinical study, the applicant shall complete the *Application Form for Registration of New Drugs*, and submit the authentic dossier to the local PDA.

Article 51: The PDA shall examine the format of the application dossier, and if the requirements are met, the application will be accepted and an acceptance notification of drug registration application should be issued. If the requirements are not met, the application will not be accepted and a non-acceptance notification of drug registration application should be issued, including an explanation of reasons for rejection.

Article 52: The PDA shall, within 5 days upon acceptance of the application, organize and conduct on-site inspection of the drug research and the original data, conduct preliminary review of the application dossier, and propose the review comments. If the drug to be registered is a biological product, the PDA shall take sample drugs from 3 batches of products, and notify the drug control institute for the registration inspection.

Article 53: The PDA should, within the prescribed time period, submit the examination recommendation, verification report, and application dossier to the Center for Drug Evaluation (CDE) of the SFDA, and notify the applicant.

Article 54: A drug control institute having received registration inspection notification should inspect the sample according to the drug standards submitted by the applicant, verify the drug standards, and submit the inspection report to the CDE within the prescribed time limit, and copy the submission to the applicant.

Article 55: Upon receipt of the application dossier, the CDE shall, within the prescribed time period, organize pharmaceutical, medical, and other technical staff to conduct technical examination of the application dossier, and may request, with explanation of reasons, the applicant to provide supplemental information and drug samples if necessary.

After completing the technical examination, a technical examination recommendation will be issued and submitted to the SFDA along with related application information. The SFDA shall make an approval decision based on the technical examination recommendation. When the SFDA considers the requirements to be met, *Approval for Drug Clinical Study* will be issued. When the SFDA does not consider the requirements to be met, *Notification of Approval Opinion* will be issued with explanation.

Section 2: Production of New Drugs

Article 56: After completion of clinical studies, the applicant shall fill out the *Drug Registration Form* and submit the production application dossier to PDA where the applicant is located. At the same time, the applicant shall submit the raw material and research data related to the standard substance for the preparation of the standard substance to the NICPBP.

Article 57: PDA shall examine the application dossier for form, and if the requirements are met, the application will be accepted an acceptance notification of drug registration application will be issued. If the requirements are not met, the application will not be accepted and a non-acceptance notification of drug registration application will be issued, including an explanation of reasons for rejection.

Article 58: The drug supervision and administration departments of all provinces, autonomous regions, and municipalities of China shall, within 5 days of application acceptance, organize and conduct on-site inspection for the clinical trial and relevant original data, conduct a preliminary review, and issue review comments. For those drugs other than biological product, samples of 3 batches of the drugs must also be taken, and the drug control institute must be notified to verify the standards.

The PDA shall, within the prescribed time limit, submit its recommendations, inspection report, and the application dossier to the CDE, and notify the applicant.

Article 59: The drug control institute should verify the drug standards, and then submit the verification recommendation to the CDE within the prescribed time limit and simultaneously copy the PDA that issued the notification for verification, and also copy the applicant.

Article 60: Upon receipt of the application dossier, the CDE shall, within the prescribed time, organize pharmaceutical, medical, and other technical staff to conduct technical examination of the application dossier, and may request, with explanation of reasons, the applicant to provide supplemental information and drug samples if necessary.
After the examination, if the related provisions are met, the CDE shall notify the applicant to file application for production site inspection, and notify the Center for Certification Administration (CCA) of SFDA.

After the examination, if the relevant provisions are not met, the CDE shall submit the recommendation and application dossier to the SFDA. The SFDA shall make the decision not to approve based on the technical examination recommendation, and a *Notification of Review Opinion* will be issued with explanation.

Article 61: Upon receipt of notification of production site inspection, the applicant should file application to the CCA for production site inspection within 6 months.

Article 62: Upon receipt of the application for production site inspection, the CCA shall, within 30 days, organize site inspection of the batch production process of the samples, confirm the feasibility of the verified production process, take 1 batch of samples (or 3 batches of samples for biological products), submit them for inspection to the drug control institute where the drug standards were verified, and submit the production site inspection report to the CDE within 10 days of completion of site inspection.

Article 63: The sample product shall be manufactured in a workshop with GMP Certificate. For a newly established drug manufacturing enterprise or workshop, or for the manufacture of additional drug dosage forms, the production process of the sample product should comply with GMP requirements.

Article 64: The drug control institute shall test the sample product in accordance with the verified drug standards, submit the drug test report to the CDE within the prescribed time period, and send copies to the relevant PDA and the applicant.

Article 65: The CDE shall conclude a general examination recommendation based on the technical examination recommendation, sample production site inspection report, and sample test report, and submit its recommendation to the SFDA along with related data. The SFDA shall make an approval decision based on the general recommendation. If the requirements are met, a new drug certificate will be issued. If the applicant already holds a *Drug Manufacturing License* and meets the production requirements, a drug approval number will be issued at the same time. If the requirements are not met, a *Notification of Approval Opinion* will be issued with explanation.

With the exception of special dosage forms such as targeted-delivery preparations and sustained or controlled-release preparations, after approval, no new drug certificate will be issued for the registration application of a change in the dosage form with no change in route of administration, or any application for an additional indication.

Section 3: Monitoring Period of New Drugs

Article 66: Based on requirements to ensure public health, the SFDA may implement a monitoring period for approved new drugs so as to continue to monitor the safety of the new drug. The drug-monitoring period shall start from the date of production approval and shall not exceed 5 years.

For new drugs under the monitoring period, the SFDA shall not approve production, dosage form change, or importation of the drug by other enterprises.

Article 67: During the monitoring period of a new drug, the enterprise manufacturing the drug shall regularly inspect its production process, quality, stability, efficacy, and adverse reactions, and annually report to the local PDA. The PDA should order a correction if the enterprise fails to perform the duties required during the monitoring period.

Article 68: When a serious quality problem, or serious or unexpected adverse reaction, is discovered by relevant institutions during the manufacture, distribution, use or inspection, or administration of the drug, it shall be reported to the PDA immediately. The PDA shall immediately organize an investigation of the drug with serious quality problems or serious or unexpected adverse reactions and report to the SFDA.

Article 69: If a new drug under a monitoring period has not begun production within 2 years from the approval date, the SFDA may approve the production application for the new drug by another applicant and continue the monitoring period

Article 70: When a new drug enters its monitoring period, for an application whose clinical study has already been approved by the SFDA, the application shall continue in the regular review process. The SFDA may approve production or importation if the application meets the requirements, and monitor this new drug together with the previously approved new domestic drug.

Article 71: When a new drug enters its monitoring period, application of the same drug by others will not be accepted. An application which has been accepted, but whose clinical study has not been approved by the SFDA, shall be returned.

Upon the completion of the monitoring period, another applicant may make a generic drug or imported drug application.

Article 72: For an imported drug that has already received marketing approval, if an application has already has its clinical study approved, the application may continue in the regular review process. While the SFDA may approve the production of the drug if

the application meets the requirements, the applicant may withdraw the application and make a generic drug application. For an application which has been accepted but whose clinical study has not been approved, the application shall be returned, and the applicant may make a generic drug application.

Chapter 5: Application and Approval of Generic Drugs

Article 73: A generic drug applicant should be a drug manufacturer. The drug for which application is made shall be consistent with the production scope described in its *Drug Manufacturing License*.

Article 74: A generic drug should have the same active component, route of administration, dosage form, strength, and therapeutic effect as the drug it copies. When it copies drugs from many companies, a comparison study of the drugs it will copy should be conducted based on relevant technical guidance and principles.

Article 75: An applicant for generic drug registration should fill out the *Drug Registration Form* and submit the production application dossier and application for inspection of production site to PDA where the applicant is located.

Article 76: The PDA shall examine the application dossier for form, and if the requirements are met, the application will be accepted and an acceptance notification of drug registration application will be issued. If the requirements are not met, the application will not be accepted and a non-acceptance notification of drug registration application will be issued with explanation of reasons.

For TCM drugs under application for TCM protection, any application for a generic version of the same drug will be suspended from the date protection application is accepted to the date an administration decision is made.

Article 77: The PDA shall, within 5 days of application acceptance, organize and conduct on-site inspection of the drug research and original data, conduct site inspection of the production site according to the production process and quality standards provided by the applicant, take sample drugs of 3 consecutive batches on site, and notify the drug control institute for inspection.

Production of the sample drugs should comply with the provisions of Article 67 of this Regulation.

Article 78: The PDA should, within the prescribed time period, conduct examination of the application dossier and issue its recommendation. If the requirements are met, the examination recommendation, verification report, production site inspection conclusion, and application dossier will be submitted to the CDE, and the applicant will be notified. If the requirements are not met, a *Notification of Approval Opinion* will be issued, with explanation, and the drug control institute will simultaneously be notified to stop the registration inspection of the drug.

Article 79: The drug control institute shall test the sample product and submit the drug test report to the CDE within the prescribed time, and send copies to the PDA that requested the test and the applicant.

Article 80: The CDE shall organize pharmaceutical, medical, and other technical staff to examine the verification recommendation and the application dossier, and may request the applicant to provide supplemental information if necessary, with explanation of reasons.

Article 81: The CDE shall complete a general examination recommendation based on the technical examination recommendation, sample production site inspection report, and sample test report, and submit the recommendation to the SFDA along with related data. The SFDA shall make its approval decision based on the general recommendation. If the requirements are met, a drug approval number or *Clinical Trial Approval* will be issued. If the requirements are not met, the decision not to approve will be made and a *Notification of Approval Opinion* will be issued with explanation.

Article 82: Upon completion of clinical trials, the applicant should submit the clinical trial data to the SFDA. The SFDA shall, based on the technical examination recommendation, issue a drug approval number or *Notification of Approval Opinion*.

Article 83: For those drugs confirmed by the SFDA to be defective in terms of safety, the SFDA may decide to suspend acceptance or approval of the application of generic drugs.

Chapter 6: Application and Approval for Imported Drugs

Section 1: Registration of Imported Drugs

Article 84: The drug being applied for import should have obtained marketing approval in its country/region of manufacture. Without such marketing approval, a drug to be imported may still be approved if the SFDA confirms the safety and efficacy of the drug, and if there is a clinical need for the drug.

The production of drugs being applied for import should meet GMP standards in the foreign country/region as well as the requirements of GMP in China.

Article 85: For an imported drug application, the applicant shall complete the *Application Form for Drug Registration* and submit the relevant application dossier and product sample, and provide the relevant certified documents. The application shall be made with the SFDA.

Article 86: The SFDA shall examine the application dossier for form; if the requirements are met, the application shall be accepted, and an acceptance notification shall be issued. The SFDA shall notify the NICPBP for drug registration inspection of 3 batches of drug

samples. When the SFDA does not consider the requirements to be met, a Notification of Non-Acceptance will be issued with explanation.

The SFDA may organize on-site inspection of the research status and manufacturing status, and take samples.

Article 87: The NICPBP should, within 5 days of receipt of the data and samples, organize registration inspection.

Article 88: Within 60 days of receipt of data, samples, and related standard substance, the drug control institute undertaking import drug registration inspection should complete the registration inspection and submit the inspection report to the NICPBP.

Sample testing and drug standard verification for special drugs and vaccine products may be completed within 90 days.

Article 89: The NICPBP should, within 20 days of receipt of verified drug standards and the drug registration inspection report from the drug control institute, organize specialists to conduct a technical examination, and if necessary, conduct re-verification based on the examination recommendation.

Article 90: The NICPBP should, upon completion of import drug registration inspection, submit the verified drug standards, drug registration inspection report, and verification recommendation to the CDE, and copy to the applicant.

Article 91: The CDE should within a limited time organize pharmaceutical, medical, and other technical staff to conduct technical examination, and may request the applicant to provide supplemental information if necessary, with explanation of reasons.

Article 92: The CDE shall conclude a general examination recommendation based on the technical examination recommendation, sample production site inspection report, and sample test report, and submit to the SFDA along with the related data. The SFDA shall make approval decision based on the general recommendation. If the requirements are met, *Drug Clinical Trial Approval* will be issued. If the requirements are not met, a *Notification of Approval Opinion* will be issued with explanation.

Article 93: Upon approval of the clinical study, the applicant shall conduct the clinical study in accordance with the provisions of Chapter 3 of this Regulation.

Upon completion of the clinical study, the applicant shall, in accordance with relevant requirements, submit to the SFDA the clinical study report, relevant changes, and supplemental information, with detailed explanation and justifications, and the relevant certified documents.

Article 94: The CDE should organize pharmaceutical, medical, and other technical staff to conduct overall examination of the submitted clinical trial data, and may request, with explanation of reasons, the applicant to provide supplemental information if necessary. The SFDA shall make its approval decision based on the technical examination recommendation. If the requirements are met, an *Imported Drug Certificate* shall be issued to the applicant. Applications by companies from Hong Kong, Macao and Taiwan shall proceed under this Regulation, and if the requirements are met, a *Drug Product Certificate* shall be issued to the applicant. If the requirements are not met, a *Notification of Approval Opinion* will be issued with explanation.

Article 95: For an imported drug preparation application, documents to evidence the legal channels of the immediate packaging materials or containers of the drug and documents to evidence the legal channels of the drug raw materials and excipients must be provided. For drug raw materials and excipients that have not been approved by the SFDA, standardized research information of relevant production processes, quality specification, and inspection methods should be submitted.

Section 2: Approval of Repackaging of Imported drugs

Article 96: Repackaging of imported drugs means taking from offshore finished drug preparations in large packaging and putting them into smaller packaging, or taking drugs in smaller packaging and putting them into final (outer) packaging with an insert sheet, labeling, etc. in China.

Article 97: The application for repackaging of imported drugs shall comply with the following requirements:

1) An *Imported Drug Certificate* or *Drug Product Certificate* has already been obtained for the imported drugs;
2) The drugs are yet to be manufactured in China or, if manufactured, are not able to meet the clinical demand;
3) The drugs of one pharmaceutical company shall only be repackaged by one pharmaceutical production enterprise, generally for a period not exceeding the validity period of its *Imported Drug Certificate* or *Drug Product Certificate*.
4) With the exception of tablets or capsules, internal packaging of repacked drugs in all other dosage forms should be finished offshore;
5) The pharmaceutical production enterprise to accept repacking should hold a *Drug Manufacturing License.* When imported uncoated tablets or capsules are to be repacked, the enterprise to accept repacking should also hold a GMP Certificate consistent with the dosage form of the drug to be repacked.
6) Any application for repacking of imported drugs should be made one year prior to the expiration of its *Imported Drug Certificate* or *Drug Product Certificate*.

Article 98: The offshore pharmaceutical company shall sign a repackaging contract for imported drugs with an onshore pharmaceutical production enterprise, and complete the *Drug Supplemental Application Form*.

Article 99: An application for repackaging a drug shall be submitted by the onshore pharmaceutical production enterprise to the PDA where the party is located, and the *Drug Supplemental Application Form* signed by the offshore pharmaceutical company should be submitted with the relevant information and sample products. PDA shall examine the application dossier for form, and if the requirements are met, the application will be accepted and an acceptance notification of drug registration application will be issued. If the requirements are not met, the application will not be accepted and a non-acceptance notification of drug registration application will be issued, with explanation of reasons. The PDA should make a recommendation after completion of the review process and submit the application dossier and recommendation to the SFDA for approval, and notify the applicant.

Article 100: The SFDA shall review the submitted application dossier. When the SFDA considers the requirements to be met, an *Approval for Drug Supplemental Application* and Drug Approval Number will be issued. When the SFDA does not consider the requirements to be met, a *Notification of Approval Opinion* will be issued with explanation.

Article 101: The registration standards for the imported drug shall be applied to the repackaged drug.

Article 102: The package, label, and insert sheet of a repackaged drug shall be consistent with that of the imported drug to be repacked, and shall include the approval number for the drug to be repacked and the name of the drug repackaging manufacturer.

Article 103: The import inspection of finished drug preparations in large packaging should be conducted in accordance with SFDA regulations. The same drug standards shall apply to both the inspection of the repackaged drug and to import inspection.

Article 104: The offshore pharmaceutical company shall be responsible for the quality of the repackaged drug. If a quality problem arises, the SFDA may cancel the approval number of the drug repackaging, and if necessary, cancel the *Imported Drug Certificate* or *Drug Product Certificate* of the drug in accordance with Article 42 of the *Drug Administration Law*.

Chapter 7: Application of OTC Drugs

Article 105: For a generic drug in the OTC category, applicant should check "OTC" in the "supplemental application items" section of the *Drug Registration Form.*

***Article* 106:** For a generic drug falling in both the prescription and OTC categories, an applicant may file the application choosing to follow the requirements for either prescription drugs or OTC drugs.

Article 107: In the following circumstances, an applicant may check "OTC" in the "supplemental application items" section of the *Drug Registration Form.* If the

requirements of OTC drugs are met, OTC drug regulation and approval shall apply. If the requirements of OTC drugs are not met, prescription drug regulation and approval shall apply.

1) Change in dosage form of an OTC drug as designated by the SFDA, but without changes in indication, dosage, or route of administration.
2) New combination preparations developed from active OTC ingredients designated by the SFDA.

Article 108: For an OTC drug registration application, the insert sheet and label should comply with relevant requirements for OTC drugs.

Article 109: If an imported drug falls into the OTC category, the regulation and approval procedures for imported drugs shall apply, and technical requirements for those drugs shall be consistent with requirements for domestic OTC drugs.

Chapter 8: Supplemental Application and Approval

Article 110: A supplemental application should be filed for changes of items in the approval certificate or in the content of its attachment on new drug research, drug production, and drug importation.

The applicant shall assess the impact of the change to the drug's safety, efficacy, and quality control, with reference to applicable technical guidance, and conduct the necessary technical research.

Article 111: The applicant should complete the *Supplemental Application Form* and submit to the PDA where the applicant is located with relevant documents and explanations. The PDA shall examine the application dossier for form, and if the requirements are met, the application will be accepted and an acceptance notification of drug registration application will be issued. If the requirements are not met, the application will not be accepted and a non-acceptance notification of drug registration application will be issued, with explanation of reasons.

Article 112: For a supplemental application related to an imported drug, the applicant shall apply to the SFDA with relevant information and documents, as well as the approval document for the proposed change from the competent authorities of the foreign country or region where the drug is manufactured. The SFDA shall examine the application dossier for form, and if the requirements are met, the application will be accepted and an acceptance notification of drug registration application will be issued. If the requirements are not met, the application will not be accepted, and a non-acceptance notification of drug registration application will be issued, with explanation of reasons.

Article 113: For a supplemental application for a change in the production process that affects drug quality, for amendment of drug registration standards, or for change to excipients with medical purpose in the formula, after the PDA issues an examination

recommendation, the application shall be submitted to the SFDA for approval, and applicant should be notified at the same time
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For a supplemental application for amendments of drug registration standards, the drug standards should be verified by a drug control institute if necessary.

Article 114: For a supplemental application of internal change of the manufacturing location within the drug manufacturer, name change of domestic drug manufacturer, or amendment of the validity period of a domestic drug, the application shall be filed and accepted at the local PDA. When PDA considers all the requirements to be met, an *Approval of Drug Supplemental Application* will be issued and the approval will be filed for record at the SFDA. If the requirements are not met, a *Notification of Approval Opinion* will be issued with explanation.

Article 115: For a supplemental application of change to a drug label as required by regulations or insert sheet amendment as required by the SFDA, the changes shall be filed at the PDA for record.

Article 116: Any supplemental application related to an imported drug shall be approved by the SFDA. For some supplemental applications of imported drugs, such as change of manufacturing location of raw material used for import drug preparation, change in drug appearance with change in drug standards, amendment of insert sheet according to National Standards or SFDA requirements, supplementing and perfecting of safety-related contents of insert sheet, change of design of packaging or label of imported drug as requested by regulations, or change of registration agent, the application needs to be filed for record at the SFDA.

Article 117: For a supplemental application for a change due to drug technology transfer or change in formula or process that is assessed to likely affect product quality, PDA shall, in accordance with attachments to the *Drug Registration Approval Letter* or the verified production process, organize on-site inspection of the production site, and drug control institute should test 3 batches of the sample product taken for inspection.

Article 118: The SFDA shall examine the supplemental drug application, and may request the applicant to provide supplemental information if necessary, with explanation of reasons. When the SFDA considers the requirements to be met, *Drug Supplementary Application Approval* will be issued. When the SFDA does not consider the requirements to be met, a *Notification of Approval Opinion* will be issued with explanations.

Article 119: After the approval of any supplemental application, when the drug approval certificate needs to be renewed, the old drug approval certificate shall be canceled by the SFDA. When an additional drug approval certificate needs to be issued, the old certificate shall continue to be effective.

Chapter 9: Re-registration of Drugs

Article 120: The validity period of the Drug Approval Number, the *Imported Drug Certificate*, and the *Pharmaceutical Product Certificate* issued by the SFDA is 5 years. 6 months prior to expiration, application for re-registration shall be made, should there be a need for continuing its production and/or importation.

Article 121: While the Drug Approval Number, the *Imported Drug Certificate* or *Drug Product Certificate* is valid, the applicant should conduct systematic assessment of drug safety, efficacy, and quality control, including relevant study results during the monitoring period, adverse reaction monitoring, production control and product quality homogeneity, in order to present as evidence during re-registration.

Article 122: The holder of a drug approval number shall apply for re-registration of the drug with the local PDA by completing the *Application Form for Drug Re-Registration* according to relevant requirements and submitting relevant application materials.
The application for re-registration of an imported drug shall be submitted to the SFDA.

Article 123: The PDA shall examine the application dossier, and if the requirements are met, the application will be accepted and an acceptance notification of drug registration application will be issued. If the requirements are not met, the application will not be accepted an a non-acceptance notification of drug registration application will be issued, with explanation of reasons.

Article 124: The PDA shall, within 6 months, examine the re-registration application; if the requirements are met, the re-registration will be approved; if not, the re-registration shall be filed at the SFDA for record.

Article 125: The application for re-registration of an imported drug shall be accepted by the SFDA, which shall complete the review of the application within 6 months of receipt, and approve the re-registration if it meets the requirements. If it does not, notification of non-approval will be issued with explanation of reasons.

Article 126: A re-registration shall not be accepted in any of the following situations:

1) Failure to apply for re-registration of the drug within the prescribed time
2) Failure to meet the relevant SFDA approval requirements for marketing
3) Failure to complete Phase IV clinical trials according to relevant requirements
4) Failure to monitor drug adverse reactions according to relevant requirements
5) The drug considered is of disputed efficacy, has high adverse reactions, or has other factors harmful to human health, based on SFDA re-evaluation
6) The drug considered should have its approval withdrawn according to the requirements of *Drug Administration Law*
7) Production conditions fail to meet the requirements of the *Drug Administration Law*
8) Failure to fulfill relevant responsibilities during the monitoring period
9) Other situations in which relevant requirements have not been met.

Article 127: After receipt of the PDA recommendation, if the drug to be re-registered fails to meet the requirement by examination, the SFDA shall issue a notification of rejection for re-registration with explanations.

For those drugs whose re-registration has been rejected, except for those certified drug approval documents that have been canceled by lawful enforcement, the drug approval number, *Imported Drug Certificate,* or *Pharmaceutical Product Certificate* of the drug shall be canceled upon the expiry of their validity period.

Chapter 10: Inspection During Drug Registration

Article 128: Drug registration inspection includes inspection of sample products and verification of drug quality standards.

Inspection of sample products means the drug inspection conducted by a drug control institute according to the quality standards submitted by the applicant or the quality standards approved by the SFDA.

Verification of drug quality standards means laboratory inspection by a drug control institute to verify the feasibility and scientific validity of inspection methods described in the quality standards of the drug and to verify whether or not the assumed parameters can control drug quality.

Article 129: Drug registration inspections shall be conducted by the NICPBP or the provincial drug control institute; inspections for imported drug registration shall be conducted by the NICPBP.

Article 130: Drug registration inspection shall be conducted by the NICPBP or the drug control institute designated by the SFDA in the following cases:

1) Drugs belonging to the categories in Article 45.1 and 45.2 of this Regulation
2) Biological products or radioactive drugs
3) Other drugs designated by the SFDA

Article 131: When arranging inspection of sample products and verification of drug quality standards, the drug control institute shall give priority to drugs accepted for special approval.

Article 132: A drug control institute engaged in drug inspection for registration shall be staffed and equipped according to requirements of the Good Laboratory Practice of Drug Control Institutes and National Measurement Certification, and shall comply with the requirements of the quality assurance system and the technical requirements of drug registration inspection.

Article 133: The applicant shall provide the drug control institute with information needed for drug registration inspection, submit sample products or co-operate in taking

sample products used for inspection, and provide the standard drug substance used for inspection. The amount of sample products supplied shall be three times the amount of the drug needed for inspection. For a biological product, the record of preparation and inspection of the corresponding batches shall also be provided.

Article 134: During the verification of drug standards, in addition to inspection of the sample products, the drug control institute shall also issue a verification recommendation regarding the drug standards of the drug, items to be inspected, and verification methods, based on the drug research data, the drug standards of similar domestic and foreign products, and national requirements.

Article 135: In re-making a drug's standards, the applicant shall not authorize the drug control institute that issued the recommendations to conduct the research work. Similarly, the institute shall not accept such authorization.

Chapter 11: Drug Registration Standards and Insert Sheets

Section 1: Drug Registration Standards

Article 136: "National Drug Standards" refers to drug registration standards, other drug standards, and the *PRC Pharmacopoeia* issued by the SFDA, covering technical requirements including quality parameters, inspection methods, and production process.

"Drug registration standards" means the drug standards approved by the SFDA for a specific applicant, which is the basis for drug production and the monitoring and administration of drugs.

Drug registration standards must not deviate from the standards of the current Pharmacopoeia.

Article 137: The determination of items and inspection methods for drug registration standards shall meet the basic requirements of the current Pharmacopoeia, the requirements of the technical guidance principles issued by the SFDA, and national rules for compiling national drug standards.

Article 138: An applicant should select representative sample products for the study of standards.

Section 2: Drug Standard Substance

Article 139: Drug standard substance, including standards, control products, raw material control products, and reference products, means a substance with specific values, which is to be used in physical and chemical inspection and biological method inspection needed for drug quality standards, and used to calibrate equipment, evaluate measuring methods, or assay inspection drugs.

Article 140: The NICPBP shall be responsible for standardization and administration of national drug standard substances.

The NICPBP may organize the relevant provincial drug control institutes, research institutions, or pharmaceutical production enterprises for cooperation in standardization and administration.

Article 141: The NICPBP shall be responsible for comprehensive technical review of standard substances regarding the selection of raw materials, production methods, standardization methods, standardization results, accuracy of assay values, tracing of origin of various values, stability, and conditions for repackaging and packaging, in order to conclude whether they can be used as national standard substances.

Section 3: Drug Name, Insert Sheets, and Labels

Article 142: Applications for drug names, insert sheets, and labels should comply with SFDA regulations.

Article 143: The drug insert sheets shall be proposed by the applicant, and the CDE shall examine the insert sheet contents, other than information related to the company itself, against the application dossier, and the insert sheets should be approved by the SFDA upon approval of production.

Applicants shall be responsible for the scientific validity, correctness, and accuracy of insert sheets and labels.

Article 144: The applicant shall monitor the drug's safety and efficacy during the post marketing period, and make timely application to amend insert sheets when necessary.

Article 145: The applicant shall print the insert sheet and labels according to the content of the approved insert sheet, and in accordance with the SFDA format requirements.

Chapter 12: Prescribed Timeline

Article 146: Drug administration authorities should adhere to the requirement of the prescribed timeline as specified in the *Drug Administration Law*, *Administrative Licensing Law*, and *Implementing Regulation*. The prescribed timeline for drug registration referred to in this regulation means the maximum allowed time for the relevant acceptance, examination and approval, etc, excluding the time legally required in suspending the approval and the time for the applicant to submit a supplemental dossier. Timeline for examination and drug regulation inspection should be according to this regulation. Necessary time extensions in special cases should be made with explanation of reasons, and receive approval from the SFDA, and the applicant should be notified in writing.

Article 147: Upon receipt of any application, drug administration authorities shall examine for form, and take action as follows:

1) If there is no need for administrative permits for the application items, inform the applicant of non-acceptance immediately.
2) If the application items falls outside of the legal jurisdiction of the division, come to a decision of non-acceptance immediately and then refer the applicant to the relevant authority.
3) Allow the applicant to make corrections on-site, if the defects in the application dossier can be corrected on-site.
4) If the application dossier is incomplete or fails to meet the legal format requirement, the applicant should be notified of the missing data to be supplemented in one notification, on-site or within 5 days; if no notification is made within this timeline, the application dossier shall be deemed as accepted on the date of receiving the dossier.
5) When the application items fall into the legal jurisdiction of the division, the application dossier is completed and in lawful form, or the applicant has supplemented all missing information, the drug registration application should be accepted.

When any drug administration authorities accept or do not accept a drug registration application, a written notification should be issued with the special drug registration seal and the date.

Article 148: Upon acceptance of the application, the PDA shall, within 30 days, complete its inspection of research status and original data, examination of the application dossier, taking of sample products, notification of the drug control institute for inspection of sample products, and submission of the recommendation and inspection report together with information submitted by the applicant to the SFDA, and at the same time, notify the applicant of the inspection recommendations.

Article 149: The timeline for drug registration tests should be in accordance with the following prescribed timeline.

1) Sample tests: 30 days, or 60 days if the sample tests and verification of drug standards are conducted at the same time
2) Sample tests for special drugs and vaccines: 60 days, or 90 days if the sample tests and verification of drug standards are conducted at the same time

Article 150: The timeline for technical review should be in accordance with the following prescribed timeline.

1) 90 days for a new clinical study, or 80 days if a drug meets the requirements for special approval
2) 150 days for production of a new drug, or 120 days if a drug meets the requirements for special approval
3) 160 days for registration of a generic drug or change in dosage form of a marketed drug
4) 40 days for supplemental application if a technical review is needed

The above timeline shall be used as reference for the technical examination of import drug registration applications.

Article 151: During technical review, the SFDA should issue one notification regarding submission of all needed supplemental materials. The applicant may raise questions on the required supplemental materials, and explanations to the applicant should be conducted face to face if necessary. Except for applications meeting the requirements for special approval, where special requirements apply, the applicant shall submit all the supplemental materials required by the notification at one time within 4 months.
Upon receipt of the supplemental information, the technical review should not exceed one third of original prescribed time, for a drug meets the requirements of special approval, the time should not exceed one quarter of original prescribed time.
During the drug registration, if the applicant self withdraws the applicant, the approval process automatically terminates.

Article 152: The SFDA should conclude the administrative approval decision within 20 days. If it is not possible to conclude a decision within 20 days, a 10-day extension may be granted with approval by the leading department head, and the applicant should be notified with explanation of the reason for the extension.

Article 153: The SFDA should publish/deliver the relevant administrative licensing certificate within 10 days, once the administrative approval decision has been concluded.

Chapter 13: Reconsideration

Article 154: The SFDA shall not approve an application under any the following circumstances:

1) The same or similar data or research information is used in applications by different applicants without a justified reason
2) During the registration, the application dossier is found to be untrue, and the applicant cannot prove its truthfulness
3) The design and implementation of research items is unable to support the assessment of the quality control, safety, or efficacy of the drug to be registered
4) Significant deficiency in safety, effectiveness, or quality control of the drug is revealed through the application dossier
5) Failure to submit the required supplemental information within the prescribed time
6) Sourcing of raw material fails to comply
7) Site inspection of production site or sample product test fails to comply
8) Any other situation in which approval should not be granted based on laws and regulations

Article 155: Upon lawful conclusion of the non-acceptance or non-approval decision in writing, the reason should be stated, and drug administration authorities shall notify the applicant of their entitlement to apply for administrative re-consideration or appeal.

Article 156: When an applicant objects to the non-approval decision, the applicant may apply for reconsideration with the SFDA within 60 days of receiving notification of non-approval, by filling out the *Drug Registration Re-consideration Application Form* together with an explanation and reasons for re-consideration.

The scope of re-consideration is limited to the original application items and application dossier.

Article 157: The SFDA should conclude its re-consideration decision and notify the applicant within 50 days of receipt of the application for reconsideration. If the original decision is upheld, no further re-consideration will be accepted by the SFDA.

Article 158: When there is a need for technical review during the reconsideration, the SFDA shall organize technical experts to complete the review within the original prescribed time.

Chapter 14: Legal Liability

Article 159: If one of the provisions of Article 69 of the *Administrative Licensing Laws* occurs, the SFDA should proceed with the cancellation of the relevant drug approval document, based on requests from a related party or from a lawful authority.

Article 160: If any staff of drug administration authorities is found to violate the provisions of this regulation with one of the following actions, their supervising authorities or auditing authorities will request a correction. In the case of any serious violation, disciplinary actions will be imposed to the staff's directly responsible supervisor and other directly responsible people.

1) Did not accept a drug regulation that met lawful requirements
2) Did not publicly publish the required information items for drug registration
3) Failed to fulfill legal obligations to notify the applicant or related parties during the process of acceptance, examination, and approval
4) Failed to notify the applicant in one single notification of all the supplemental information that must be submitted, when information submitted by applicant is incomplete or does not meet the statutory form
5) Failed to explain reasons not to accept or approve
6) Failed to hold a hearing when lawfully required to

Article 161: During drug registration, if any staff of drug administration authorities asks for valuables from another party or seeks any other interest, criminal charges will be investigated if the acts constitute a crime. If the acts do not sufficiently constitute a crime, disciplinary action will be imposed.

Article 162: If any staff of drug administration authorities is found to violate the provisions of this regulation with one of the following occurrences, their supervising authorities or auditing authorities will request a correction, and disciplinary actions will

be imposed on the directly responsible supervisor and other directly responsible people. Criminal charges will be investigated if the acts constitute a crime.

1) Making an approval decision to any registration application not meeting the legal requirements, or making an approval decision of a registration application beyond their delegated authority
2) Making a non-approval decision to any registration application meeting the legal requirements, or failing to make an approval decision within the lawfully prescribed timeline
3) Failing to fulfill the non-disclosure obligation specified in Article 9 of this Regulation.

Article 163: If a drug control institute issues a fraudulent inspection report during performance of the duty of drug inspection during the drug registration process, sanctions shall be imposed according to Article 87 of the *Drug Administration Law*.

Article 164: If any drug administration authorities charge unauthorized fees, or fees beyond the lawful fee category or rate, their supervising authorities or auditing authorities will request the return of the illegally overcharged fees, and disciplinary action will be imposed on the directly responsible supervisor and other directly responsible people.

Article 165: If GLP or GCP requirements are not adhered to during drug registration, sanctions shall be imposed according to Article 79 of the *Drug Administration Law*.

Article 166: If an applicant is found to have provided fraudulent drug registration information and/or sample product of the drugs during the clinical study application process, the SFDA shall not accept the application, or shall not approve the clinical study, and shall warn the applicant. No more new applications for clinical trials from the same applicant will be accepted for one year thereafter. If the application has already been approved, the approval certificate shall be canceled, and a fine of RMB 10,000-30,000 shall be imposed. Any clinical trial application by this applicant shall not be accepted for 3 years.
A database of fraudulent conduct by applicants shall be maintained and published.

Article 167: If an applicant is found to have provided fraudulent drug registration information and/or sample product of the drugs during the drug production or import application process, the SFDA shall not accept or approve the application, and shall warn the applicant. No more new applications for clinical trials from the same applicant will be accepted for one year. If the drug production or import application has already been approved, the approval certificate shall be canceled, and a fine of RMB 10,000-30,000 shall be imposed, an application for the drug by this applicant shall not be accepted for 5 years.

Article 168: When the provisions of Article 27 call for an experiment to be repeated, if an applicant refuses to repeat the experiment according to relevant requirements, the applicant shall be warned and ordered to correct the situation. If the applicant definitively refuses to make corrections, their application shall not be approved.

Article 169: Under any of the following events, the drug approval number will be cancelled, and the cancellation will be published:

1) Applicant self-proposes to cancel the drug approval number before the expiration of the certified approval documents
2) Re-registration is rejected according to the provisions of Article 126 of this Regulation
3) The *Drug Manufacturing License* is revoked or withdrawn under legal enforcement
4) The Drug has high adverse reaction levels or other hazards to human health, where the certified approval documents are withdrawn according to Article 42 of the *Drug Administration Law* or Article 41 of the *Implementing Regulation*
5) An administrative decision to cancel or withdraw the certified approval documents is lawfully made
6) Other situations leading to lawful cancellation or withdrawal of the certified approval documents

Chapter 15: Miscellaneous

Article 170: The application dossiers and requirements for TCM and natural drugs, chemical drugs, biological products, supplemental applications, and re-registration applications are specified in Annexes 1, 2, 3, 4, and 5 of this Regulation respectively. Provisions for monitoring periods are specified in Annex 6.

Article 171: Format of the Drug Approval Number should read Guoyaozhunzi H(Z, S, J)+ 4-digit year + 4-digit serial number, where H denotes chemical drugs, Z denotes TCM, S denotes biological products and J denotes imported drug repacking.

Format of *Imported Drug License* should read H (Z, S)+ 4-digit year + 4-digit serial number, and format of *Drug Product License* should read H (Z, S)C+ 4-digit year + 4-digit serial number, where H denotes chemical drugs, Z denotes TCM, and S denotes biological products. For the registration certificate number of repacking of large packages from outside of China, B will be added as a prefix to the original certificate number. Format of *New Drug Certificate* should read Guoyaozheng H (Z, S) + 4-digit year + 4-digit serial number, where H denotes chemical drugs, Z denotes TCM, and S denotes biological products.

Article 172: Application acceptance, approval of supplemental application, and approval of re-registration undertaken by PDA as specified by this Regulation all fall into the category of delegated authority by the SFDA. The SFDA may delegate PDA with other technical examination or approval tasks during the drug registration process.

Article 173: The SFDA will adopt a drug coding management system for marketed drugs. Detailed regulations for drug coding management will be promulgated separately.

Article 174: In addition to this Regulation, applications for narcotics, psychotropic drugs,, medical-use toxic drugs, and radioactive drugs shall also be administered according to other relevant national regulations.

Article 175: The SFDA shall promulgate separate regulations for the registration of TCM material, TCM herbs, and imported TCM material that are regulated with approval numbers.

Article 176: Regulation for technology transfer and contract manufacturing shall be promulgated separately.

Article 177: This Regulation will become effective from October 1, 2007. The *Drug Registration Regulation* promulgated by the SFDA (SFDA Order No. 17) on February 28, 2005 shall be abolished accordingly.

APPENDIX #5

Registration Classifications and Application Dossier Requirements for Traditional Chinese Medicines and Natural Drugs

In this annex, Traditional Chinese Medicine (TCM) means medical substances and their preparation used under the guidance of Chinese traditional medical theory.
Natural Drugs means medical natural substances and their preparations used under the guidance of modern medical theory.

I. Registration Categories and Notes

a. Registration Categories

1. Active ingredients and their preparations extracted from plants, animals, or minerals, which have not been marketed in China.
2. Newly found drug materials and their preparations.
3. New TCM substitutes.
4. New parts of drug materials and their preparations.
5. New active parts of materials to be used as drugs and their preparations, extracted from plants, animals, or minerals, which have not been marketed in China.
6. TCM, natural drugs and their combination preparations not yet marketed in China.
7. Preparations with change to route of administration from TCM or natural drugs already marketed in China.
8. Preparations with changed dosage form from TCM or natural drugs already marketed in China.
9. Generic drugs

b. Notes

Drugs in categories 1-6 are new drugs, and the procedure for new drugs also applies to new drugs in categories 7 and 8.

1. Category 1, “Active ingredients and their preparations extracted from plant, animal, or mineral sources, which have not been marketed in China,” refers to a single component or its preparation, extracted from plants, animals, or minerals and has not yet been collected into the National Drug Standards. The content of this single component should be more than 90% of the extraction.
2. Category 2, “Newly found drug materials and preparations,” refers to drug materials and preparations not yet collected into the National Drug Standards or into provincial drug formularies (statutory standards).
3. Category 3, “New TCM substitutes,” refers to drug materials used to substitute for toxic drug materials contained in the formula in

the National Drug Standards or to substitute for endangered drug materials which are not yet collected in statutory standards.

4. Category 4, "New parts of drug materials and their preparations," refers to new parts of existing drugs of animals or plants, which are to be used as drugs, whereas the relevant existing drugs are already contained in statutory standards
5. Category 5, "New active parts of materials to be used as drugs and their preparations, extracted from plant, animal, or mineral sources, which have not been marketed in China," refers to active parts of similar or multiple components and their preparations, which are extracted from plants, animals, or minerals, and have not yet been collected in the National Drug Standards. The active part should be more than 50% of the extraction.
6. Category 6, "TCM, natural drugs and their combination preparations not yet marketed in China" includes:

    1. Combination preparations of TCM
    2. Combination preparations of natural drugs
    3. Combination preparations of TCM, natural drugs and chemical drugs

    Combination preparations of TCM should be formulated under traditional Chinese medical theory, including:

    - Combination preparations of TCM from ancient classical formulas
    - Combination preparations with indications in ancient terminology
    - Combination preparations with combined terminology

    Combination preparations of natural drugs should be formulated under modern medical theory, and the indication should be in modern medical terminology.

    Combination preparations of TCM, natural drugs, and chemical drugs include:

    - Combination preparations of TCM and chemical drugs
    - Combination preparations of natural drugs and chemical drugs
    - Combination preparations of TCM, natural drugs, and chemical drugs

7. Category 7, "Preparations with change to route of administration from TCM or natural drugs already marketed in China" refers to

preparations with change to route of administration or absorption location.

8. Category 8, “Preparations with changed dosage form from TCM or natural drugs already marketed in China” refers to preparations with changed dosage form but no changed route of administration.
9. Category 9, “generic drugs” refers to TCM or natural drugs already approved for marketing in China.

II. Application Information Items and Notes

a. Application Information Items

Summary Information

1. Drug name.
2. Certified documents.
3. Objectives and basis for application.
4. Summary and evaluation of main research results.
5. Sample draft of insert sheet, notes to draft, and literature.
6. Sample design for packing, label.

Pharmaceutical Study Information:

7. Summary of Pharmaceutical Study Information.
8. Source of drug and determination.
9. Ecological environment, identity, description, cultivation, growing method, local processing and preparing.
10. Draft of standards for drug material, notes on draft. Drug standard material and related information should be provided.
11. Sample of plant or mineral, including flower, fruit, or seeds.
12. Research information on production process, verification information and literature, source of excipients and standards.
13. Experimental data and literature from chemical content studies.
14. Experimental data and literature from quality studies.
15. Draft of drug standards, with notes on draft and verification. Drug standard material and related information should be provided.
16. Test report for sample.
17. Stability study experimental data and literature.
18. Basis for selection and quality standards of immediate packing material and container.

Pharmacology and Toxicology Study Information

19. Summary of pharmacology and toxicology study information.
20. Pharmacodynamic experimental data and literature.
21. Pharmacology study experimental data and literature

22. Acute toxicity study experimental data and literature.
23. Long-term toxicity experimental data and literature
24. Special safety studies and literature on hypersensitive reactions (topical, systemic, photo-toxicity), hemolytic and topical irritation reactions (blood vessels, skin, mucous membrane, and muscle) related to topical and systemic use of drugs.
25. Genotoxicity research data and literature.
26. Reproductive toxicity research data and literature.
27. Carcinogenicity research data and literature.
28. Animal pharmacokinetics research data and literature.

Clinical Study Information

29. Summary of clinical study.
30. Clinical study plan and protocol.
31. Investigator's Brochure.
32. Sample draft of Informed Consent Form, with ethics committee approval.
33. Summary report of clinical study.

b. Notes

1. Notes on Application Information Items

Summary Information

1. Item 1, "Drug Name," includes:

    a. Chinese name
    b. Phonetic name
    c. Drug nomenclature

2. Item 2, "Certified Documents," includes:

    a. Applicant's certified documents of legal registration, copies of *Drug Manufacturing License* and *GMP Certificate*. For new drug production applications, copies of the *GMP Certificate* for the workshop where the sample product was manufactured should be provided.
    b. Certified documents stating patent status and ownership of drug entity and formula, drug production process, and letter of guarantee stating that no infringement upon the patent rights of others has been committed.

c. Copies of official research proposal approvals in the case of narcotics, psychotropic drugs, medical-use toxic drugs, and radioactive drugs.
d. For new drug production applications, copy of *Approval of Clinical Study of New Drug.*
e. Copies of *Drug Packing Material and Container Certificate* or *Import Drug Packing Material and Container Certificate* for immediate packing material and container.
f. Other certified documents.

For imported drugs, the following documents are also required:

g. Notarized free sale certificate (FSC) issued by the competent authorities of the country or region where the manufacturer is located, as well as the manufacturer's *GMP Certificate*, with Chinese translations.
h. When a foreign drug registration is conducted by the drug manufacturer's office in China, copies of the manufacturer's *Registration Certificate of Resident Office of Foreign Enterprise* should be provided.
i. When a foreign drug manufacturer authorizes a domestic agent to conduct the registration, copies of the authorization document, notarized document, Chinese translation, and the domestic agent's Business License shall be provided
j. For safety study data, GLP certification should be provided. For investigative drugs for clinical trials, the drug's GMP certificate should be provided.

3. Item 3, "Objectives and Basis of Application," should include ancient and modern literature, the source of the formula and basis for the application, current research and development status in China and overseas, summary of current clinical use and production, and analysis of the drug's innovation, feasibility, and dosage rationale, including a comparison with similar drugs included in National Standards, for TCM and natural drug preparations. For TCM, traditional medical theory and ancient text sources should also be provided.
4. Item 4, "Summary and evaluation of main research results," includes the summary of main research results by the Applicant, as well as a comprehensive analysis of safety,

efficacy, and quality controllability of the drugs in the application.

5. Item 5, "sample draft of insert sheet, notes to draft, and literature," includes a sample of the draft packaging insert sheet, drafted in accordance with relevant regulations, notes on the drafting of items in the insert sheet were drafted, and the latest relevant literature.

Pharmaceutical Study Information

6. Item 16, "test report for sample," refers to the report of the applicant's self-test of their product. When applying for a clinical trial, testing results of at least one batch should be proved. When clinical trials are complete, testing reports of 3 consecutive batches of the product should be provided with dossier submission.

Pharmacology and Toxicology Study Information

7. Item 24, "Special safety studies and literature on hypersensitive (topical, systemic, photo-toxicity), hemolytic and topical irritation (blood vessels, skin, mucous membrane, and muscle) reaction related to topical and systemic use of drugs." Experiments information of the preparation's safety should be provided based on the details of the drug's route of administration and preparation. When there is a tendency to drug dependence, experimental data relating to drug dependence should also be provided
8. Item 25, "Genotoxicity research data and literature." If the formula includes drug materials not yet collected in statutory drug standards, or from an active part of drug materials not yet collected in statutory drug standards, new drugs to be used for childbearing patient with action on the reproductive system (such as contraceptives, sexual hormones, drugs for sexual function disorder, sperm maturation promoting drugs, new drugs with positive results in mutations testing, or drugs with cytotoxicity), genotoxicity test data should be provided.
9. Item 26, "Reproductive toxicity research data and literature." For new drug to be used for childbearing patient where it may act on the reproductive system (such as contraceptives, sexual hormones, drugs for sexual function disorder, sperm maturation promoting drugs, new drugs with positive results in mutations testing, or drugs with cytotoxicity), reproductive toxicity research data should be provided depending on specific situation.

10. Item 27, “Carcinogenicity testing data and literature.” During long-term toxicity tests of a new drug, if cytotoxic effects are shown or extraordinary activation of the growth of cells in certain visceral organs and tissues are caused, or if there is a positive mutagenicity test result, then carcinogenicity testing data and literature must be provided.

2. Application Dossier Requirements

    1. In applications for clinical trials on a new drug, information items 1-4 and 7-31 should usually be submitted.
    2. In applications for production upon completion of clinical trials, information items 1-33 should be submitted, as well as other changes, supplemental information, and a detailed explanation of the application’s reasons and basis
    3. In applications for generic drugs (except for TCM or natural drug injections needing clinical trials, information items 2-8, 12, and 15-18 should usually be submitted..
    4. All technical information and certified documents from relevant foreign authorities used in import applications should be in Chinese, with the original documents attached. The submitted Chinese version of quality standards should be compliant with the format specified by Chinese national drug standards.
    5. Due to the complexity and diversity of TCM and natural drugs, when applying, necessary research should be conducted according to the specific drug. If there is a need for reduction or exemption of tests, there should be sufficient justification.
    6. Technical requirements for TCM and natural drug injections should be separately promulgated.
    7. For drugs in Registration Category 1, “active ingredients and their preparations extracted from plants, animals, or minerals, which have not been marketed in China,” if the active ingredient is related to a known carcinogen, or if the metabolite of the new drug is similar to the known carcinogen, or if the expected consecutive treatment period is longer than 6 months, or if the drug is used for treatment of chronic and recurrent diseases, or is used intermittently for a regular period of time, then experimental information and literature related to carcinogenicity must be provided. Also, for the application of drugs in this category, if there exists a similar drug or preparation that has been marketed in China, then a comparison should be made between the drug and the existing product as evidence for the advantage of the new drug.

8. For Registration Category 3, "new TCM substitutes," in addition to the pre-clinical submission requirements of Registration Category 2, the pharmacodynamic testing comparison between the drug and the substituted drug should also be provided. Human tolerance and clinical bio-equivalence testing data of the related preparation should be provided as well. If the substitute is a single component, testing data and literature of pharmacokinetic testing may be provided. After the approval of the TCM substitute, application for changes to the substitute should follow the procedure of supplemental application, but must be strictly within the approved scope of substitution.
9. For Registration Category 5, "new active parts of materials to be used as drugs and their preparations, extracted from plants, animals, or minerals, which have not been marketed in China," in addition to the required application information, the following information must also be submitted:

    a. Research data or literature related to the screening of the active parts as required by information item 12 and research data or literature related to the major chemical content of the active parts, as required by information items 13.
    b. If the active part is comprised of multiple components, each of the components should be assayed, and there should be a lower limit of representative value for each component (for toxic components, an upper limit should be added as well).
    c. When applying in this category, if the drug is comprised of an active ingredient extracted from plants, animals, or minerals that is already marketed in China, pharmacodynamic and other comparison testing should be conducted with that active ingredient as evidence for the drug's advantage and merit.

10. The required information for items in Registration Category 6, "TCM, natural drugs and their combination preparations not yet marketed in China," depends on the situation as follows:

    a. For TCM combination preparations, some experimental data may be exempted according to

the formula source, indication, and preparation process.

b. For natural drug combinations and preparations, research and literature on multiple components' efficacy and interactions should be provided.
c. If the formula includes drugs not listed in the statutory drug standards, additional application information must be submitted according to the requirements of the corresponding registration category.
d. There must be statutory standards for any medical-use material used in combination preparations of TCM, natural drugs, and chemical drugs, and comparison experiment data and literature on efficacy and interactions (focusing on efficacy improvement, toxicity reduction, or complementing) between TCM, natural drugs, and chemical drugs, as well as bio-availability interaction between TCM, natural drugs, and chemical drugs, should be provided in clinical trial applications.

   When applying for production, clinical trial information should evidence the necessity of the formula, providing experimental data on interaction in bio-availability between the TCM, natural drug and chemical drug. Chemical drugs used in formulas (single or combined formula) must have been collected into the National Drug Standards.

11. For preparations in Registration Category 6 that have changes in dosage form from TCM or natural drugs already marketed in China, the advantage and merits of the new preparation should be explained. In principle, the indication of the new preparation should be the same as that of the old preparation. If there is no way to verify by efficacy or clinical trial, relevant information should be provided.
12. Drugs in Registration Category 9, generic drugs, should be consistent with the drug they are copying. If necessary, their quality standards should be improved.
13. Clinical Studies

    a. Number of patients in clinical trials should meet the statistical requirements and the minimum required cases.
    b. The minimum required cases (trial group) of clinical trials are as follows: 20-30 for Phase I, 100

for Phase II, 300 for Phase III, and 2000 for Phase IV.

c. Phase IV clinical trials should be conducted for new drugs of Registration categories 1, 2, 4, 5 and 6, as well as those of category 7 and any other drugs where there has been significant change in the process flow, solvent, etc.
d. Bioequivalence trials should normally be 18-24 cases.
e. Phase I clinical trials of the contraceptives should be conducted following this Regulation. In Phase II clinical trials, a randomized controlled clinical study should be conducted on at least 100 pairs of subjects for at least 6 menstruation cycles. In Phase III trials, an open trial on at least 1000 cases for 12 menstruation cycles should be conducted. In Phase IV trials, variable factors for this type of drug should be carefully considered to finish the trial with adequate numbers of cases.
f. For TCM substitutes with new indications, substitute preparations that can be sufficiently representative of the substitute's indication should be chosen from drug standards and used as a comparative drug for the comparison study. For each indication, more than two TCM preparations should be used for verification, and clinical cases for each preparation should be not less than 100 pairs.
g. For drugs with changes in dosage form, clinical trials may be exempted or be conducted with no less than 100 pairs of cases, depending on the specific drug and the change.
h. For generic drugs, clinical trials shall be conducted with no less than 100 pairs of cases according to the specific situation.
i. For imported TCM or natural drugs, application dossiers should be provided according to the requirements of the corresponding Registration Category. Research and clinical trial data provided should include human pharmacokinetic research conducted in China with no less than 100 pairs of cases. For multiple indications, cases for trials of each major indication should be not less than 60 pairs.

III. Application Information Item Table and Notes

	Information Items	Registration Categories 1	2	3	4	5	6 6.1	6 6.2	6 6.3	7	8	9
Summary Information	1	+	+	+	+	+	+	+	+	+	+	−
	2	+	+	+	+	+	+	+	+	+	+	+
	3	+	+	+	+	+	+	+	+	+	+	+
	4	+	+	+	+	+	+	+	+	+	+	+
	5	+	+	+	+	+	+	+	+	+	+	+
	6	+	+	+	+	+	+	+	+	+	+	+
	7	+	+	+	+	+	+	+	+	+	+	+
	8	+	+	+	+	+	+	+	+	+	+	+
Pharmaceutical Information	9	−	+	+	−	▲	▲	▲	▲	−	−	−
	10	−	+	+	+	▲	▲	▲	▲	−	−	−
	11	−	+	+	−	▲	▲	▲	▲	−	−	−
	12	+	+	+	+	+	+	+	+	+	+	+
	13	+	+	±	+	+	+	+	+	+	+	−
	14	+	+	±	+	+	+	±	±	±	±	−
	15	+	+	+	+	+	+	+	+	+	+	+
	16	+	+	+	+	+	+	+	+	+	+	+
	17	+	+	+	+	+	+	+	+	+	+	+
	18	+	+	+	+	+	+	+	+	+	+	+
	19	+	+	*	+	+	+	+	+	+	±	−
	20	+	+	*	+	+	±	+	+	+	±	−
	21	+	+	*	+	+	±	+	+	−	−	−
Pharmacology and Toxicology	22	+	+	*	+	+	+	+	+	+	±	−
	23	+	+	±	+	+	+	+	+	+	±	−
	24	*	*	*	*	*	*	*	*	*	*	*
	25	+	+	▲	+	*	*	*	*	*	−	−
	26	+	+	*	*	*	*	*	*	*	−	−
	27	*	*	*	*	*	*	*	*	*	−	−
	28	+	−	*	−	−	−	−	−	−	−	−
Clinical Trial Information	29	+	+	+	+	+	+	+	+	+	+	−
	30	+	+	+	+	+	+	+	+	+	*	−
	31	+	+	+	+	+	+	+	+	+	*	−
	32	+	+	+	+	+	+	+	+	+	*	−
	33	+	+	+	+	+	+	+	+	+	*	−

Notes:
+: The item must be submitted.
±: Literature may be used instead of test information, or may be exempted by regulation.
−: The item may be exempted.
▲: The item may be omitted for TCM or natural drugs listed in statutory standards; for drugs not listed, the information must be submitted.
*: Please see relevant requirements.

APPENDIX #6

Registration Classifications and Application Document Requirements for Chemical Drugs

I. Registration Categories:

1. New chemical entity never marketed in any country.

    1. Drug substance and its preparations made by synthesis or semi-synthesis.
    2. Chemical monomer (including drug substance and preparations) extracted from natural sources or by fermentation.
    3. Optical isomer (including drug substance and preparation) obtained by chiral separation or synthesis.
    4. Drug with fewer components derived from marketed multi-component drug.
    5. New combination product.
    6. Drug preparation already marketed in China but with a new indication not yet approved in any country.

2. Drug preparation with changed administration route and not marketed in any country.

3. Drug marketed outside China, including:

    1. Drug substance and its preparations, and/or with changed dosage form, but no change to route of administration.
    2. Combination preparation, and/or with changed dose form, but no change to route of administration.
    3. Preparation with changed administration route, already marketed outside of China.
    4. Preparation already marketed in China but with a newly added indication approved outside of China.

4. Drug substance and its preparations with changed acid or alkaline radicals (or metallic elements), but without any pharmacological changes, whose original drug entity is already approved in China.

5. Drug preparation with changed dosage form, but no change to route of administration, whose original preparation is already approved in China.

6. Drug substance or preparation following national standards.

II. Application Dossier Items

1. Summary Information

    1. Name of drug.
    2. Certified documents.
    3. Objectives and basis for research and development.
    4. Summary of main research work.
    5. Draft of package insert, notes on draft, and latest literature.
    6. Design of packaging and labeling.

2. Pharmaceutical Study Information

    7. Summary of pharmaceutical study information.
    8. Research information and relevant literature on the drug substance's production process, as well as research information and relevant literature of the formula and preparation process.
    9. Study information and relevant literature for chemical structure and determination of components.
    10. Study information and literature for quality specification.
    11. Draft of quality specification and notes, providing reference standard.
    12. Test report of drug sample.
    13. Source, test report, and quality specification of drug substance and excipients.
    14. Stability studies and relevant literature.
    15. Selection basis and quality specification of immediate packing material and container.

3. Pharmacology and Toxicology Study Information.

    16. Summary of pharmacology and toxicology study information.
    17. Primary pharmacodynamics study and literature.
    18. General pharmacology study and literature.
    19. Acute/single dose toxicity study and literature.
    20. Repeated-dose toxicity study and literature.
    21. Special safety studies and literature on hypersensitive reactions (topical, systemic and photo-toxicity), hemolytic and topical irritation reactions (blood vessels, skin, mucous membrane, and muscle) related to topical and systemic use of drugs.
    22. Study and relevant literature on pharmacodynamics, toxicity, and pharmacokinetic changes caused by interactions among multiple components in combination product.
    23. Mutagenicity research data and literature.
    24. Reproductive toxicity research data and literature.
    25. Carcinogenicity research data and literature.
    26. Drug dependence research and literature.

27. Pre-clinical pharmacokinetics research data and literature.

4. Clinical Study Information

28. Summary of global clinical study information
29. Clinical study protocol.
30. Investigator's Brochure.
31. Sample draft of Informed Consent Form, with ethics committee approval.
32. Clinical study report

III. Notes to Application Information Items

1. Item 1, "name of drug," includes International Nonproprietary Name (INN), Chemical name, English name, and Chinese phonetic name. Chemical structure, molecular weight, and molecular formula shall be noted. The nomenclature of the drug should be explained for any new name.
2. Item 2, "certified documents," includes:

    1. Certified documents of applicant's legal registration, *Drug Manufacturing License,* and *GMP Certificate*. For new drug production applications, copies of the *GMP Certificate* for the workshop where the sample product of the drug was manufactured should be provided.
    2. Certified documents stating patent status and ownership of the drug entity and formula, drug production process, and letter of guarantee stating that no infringement has been made upon the patent rights of others.
    3. For narcotics, psychotropic drugs, medical-use toxic drugs, and radioactive drugs, copies of official research proposal approvals.
    4. For new drug production applications, a copy of the *Approval of Clinical Study of New Drugs* and the investigational drug's quality standard should be provided for market authorization approval.
    5. For preparation production applications preparation, certified documents should be provided as evidence for the legal channels of the drug substance, including copies of the certified approval document of the drug substance, drug standards, test report, business licenses of drug substance's manufacturer, *Drug Manufacturing License, GMP Certificate,* sales invoice, and supply contract.
    6. Copies of the *Drug Packing Material and Container Certificate* or *Import Drug Packing Material and Container Certificate* for immediate packing materials and container.

3. Item 3, “objectives and basis” of the application, includes R&D, marketing status, and the relevant drug literature, as well as a summary of the use and production of the drug, both domestically and overseas.
4. Item 4, “summary of main research results,” includes a summary of the applicant’s research results, as well as a comprehensive analysis of safety, efficacy, and quality controllability of the applied drug.
5. Item 5, “draft of packaging insert, notes on draft, and latest literature,” includes the sample of the draft packaging insert sheet, drafted in accordance with relevant regulations, notes on the drafting of items in the insert sheet were drafted, and the latest relevant literature.
6. Item 7, “summary of pharmaceutical study information,” refers to the summary of research and global literature of pharmaceutical study of the applied drug (synthesis process, selection of dosage form, screening of formula, determination of structure, quality study, determination of quality standards, and stability studies).
7. Item 8, “research information on the drug substance’s production process,” includes technology process and chemical reaction equations, initial raw materials and organic menstruum, reaction conditions (temperature, pressure, duration, catalyst), operation procedures, refining method, and main physical-chemical constants. The raw material input and output yield, as well as possible impurities or other by-products produced or mixed during the production process, should be explained.
8. Item 10, “study information and literature for quality specification,” includes physical-chemical properties, purity inspection, dissolution, assay, and methodology validation, as well as the data and results collected at various stages.
9. Item 11, “Draft of quality specification and notes, providing reference standard.” Quality specifications shall comply with the format of the current version of the *Chinese Pharmacopoeia,* and the terminology and units of measure of the *Chinese Pharmacopoeia* should be used. Reagents, reagent solutions, buffer solutions, titrants and others used, including their concentration, should follow the current version of the *Chinese Pharmacopoeia.* In the event that a different reference was used, detailed explanations should be provided. The reference standard shall be provided with separate information attached to explain the source, physical-chemical constants, purity, content, and measurement methods and data of the drug. Notes to the draft of drug standards shall include the selection of items to be controlled, selection of method, inspection, purity, limitation range, and the basis of decisions for each item.
10. Item 12, “test report of drug sample,” means the applicant’s self-test report of samples of the applied drugs. Before clinical studies, a self-test report for at least one batch of the sample product should be provided. After clinical study completion, self-test reports for 3 consecutive batches of sample products should be provided for the market authorization approval.
11. Item 14, “stability studies and relevant literature,” includes stability studies conducted using of the immediate packing materials and container.

12. Item 16, “summary of pharmacology and toxicology study information,” means a summary of the research and global literature on pharmacology and toxicology of the applied drug, including pharmacodynamics, mechanism of action, general pharmacology and toxicology, and pharmacokinetics.
13. Item 27, “Pre-clinical pharmacokinetics research data and literature,” means a summary of research and literature on the pre-clinical pharmacokinetics (animal) of the drug in application (absorption, metabolism, distribution, and excretion).
14. Item 28, “summary of global clinical study information,” is a summary of global literature, with abstracts and latest updates, regarding clinical studies of the applied drug.
15. Item 29, “clinical study protocol,” should cover details of critical items including proposed indication, usage, and dosage, which should be supported by submitted of clinical study information. The clinical study protocol should be scientific, complete, and include a comprehensive summary of pre-clinical and clinical information related to the key analysis of potential risks and benefits of the proposed trials.
16. Item 29, “Investigator’s Brochure,” refers to the summary of existing pre-clinical and clinical information on the applied drug, in order to provide the investigator and other participants with information to aid them in understanding the characteristics of the drug and clinical study protocol. The Investigator’s Brochure should be concise and objective.

IV. Table of Application Information Items and Notes

1. Table

		Registration Categories					
	Information Items	1	2	3	4	5	6
Summary Information	1	+	+	+	+	+	+
	2	+	+	+	+	+	+
	3	+	+	+	+	+	+
	4	+	+	+	+	+	+
	5	+	+	+	+	+	+
	6	+	+	+	+	+	+
	7	+	+	+	+	+	+
	8	+	*4	+	+	*4	*4
Pharmaceutical Information	9	+	+	+	+	+	+
	10	+	+	+	+	+	+
	11	+	+	+	+	+	+
	12	+	+	+	+	+	+
	13	+	+	+	+	+	+
	14	+	+	+	+	+	+
	15	+	+	+	+	+	+
	16	+	+	+	+	+	+
Pharmacology and Toxicology	17	+	*14	±	*16	—	—
	18	+	*14	±	*16	—	—
	19	+	*14	±	*16	—	—
	20	+	*14	±	*16	—	—
	21	*17	*17	*17	*17	*17	*17
	22	*11	—	—	—	—	—
	23	+	±	±	±	—	—
	24	+	±	±	±	—	—
	25	*6	—	*6	*6	—	—
	26	*7	—	—	—	—	—
	27	+	*18	*18	+	*18	—
	28	+	+	+	+	+	+
Clinical Study Information	29	+	+	+	+	+	△
	30	+	+	+	+	+	△
	31	+	+	+	+	+	△
	32	+	+	+	+	+	△

Notes:
+: Information must be submitted.
±: Literature may be used instead of test information.
−: Information may be exempted.
*: Please refer to requirements.
*(number): Please refer to note (number) below.
△: Provisions #4 of "V: Requirements For Clinical Studies" shall apply.
"Literature" refers to literature and/or literature summary of all pharmacology and toxicology study information on the applied drug (including pharmacodynamics, mechanism of action, general pharmacology and toxicology, and pharmacokinetics).

2. Notes

    1. For application of drugs in Registration Categories 1-5, Items 1-30 (except for Item 6) of the above table should be submitted. Upon completion of clinical studies, Items 1-6, 12, 14, 28-32, and other changes and supplemental information shall be recompiled and submitted, numbered with their item numbers.

       For drugs in Registration Category 1, upon completion of clinical studies, all of Items 1-30 should be recompiled based on clinical trial results, and re-submitted. When registrations of a chemical drug substance and its preparation under Registration Category 3 or 4 are applied for simultaneously, drug substance registration should comply with the production requirements.

    2. For application of drugs in Registration Category 6, Items 1-16 and 28-30 shall be submitted. If clinical studies are required, upon clinical study completion, Items 28-32 and other changes and supplemental information shall be submitted and numbered with their item numbers.
    3. During the registration of drugs in Registration Category 6, there should be a comprehensive quality study of the process and formula of the drug, as well as a quality comparison with already-marketed drugs according to national standards. When it is not possible to conduct a quality comparison with already-marketed drugs according to national standards, a quality study should be conducted according to requirements for new drug registration, and if necessary, quality provisions in the national standards may be appended and/or revised.
    4. During application for a preparation drug only, the legal Certified Documents that evidence the legal sourcing of the drug substances shall be provided in two duplicates, which should be respectively included under Item 2 (Certified documents) and Item 13 (source, test report, and quality specification of drug substance and excipients). For applicants using domestic drug substances, the documents to be provided include copies of the drug substance's certified approval document, drug standards, test report, manufacturer's business license, *Drug Manufacturing Certificate, GMP Certificate*, supply contract signed with manufacturers, and purchasing receipts.

       When imported drug substances are used, it is necessary to provide copies of the supply contract signed with the drug substance's manufacturer or their legal domestic agent, *Import Drug Certificate* or *Drug Product Certificate*, test report from the Drug Control Institute of the local Customs authority, and drug standards.

During drug registration, use of investigative preparations of drug substances lacking *Import Drug Certificate,* or *Drug Product Certificate* must be approved by the CFDA.

5. Reproductive toxicity research data for drugs used for the people at childbearing age should be submitted based on the indications and characteristics of the new drug
6. For any drug with an expected treatment period longer than 6 months inclusive, or used for treatment of chronic and recurrent diseases, or used intermittently for a regular period of time, carcinogenicity testing data or literature should be provided. Carcinogenicity testing data or literature should also be submitted for the following new drugs, based on their indication and characteristic of action:

    a. New drugs with chemical structure related to known carcinogens, or whose metabolites are similar to known carcinogens.
    b. Drugs which, during long-term toxicity studies, have shown cytotoxic effects or extraordinary activation of the growth of cells in certain visceral organs and tissues
    c. Drugs with a positive mutagenicity test result.

7. For new drugs acting on the central nervous system, such as analgesics, depressants, stimulants, and drugs with chemical structure related to those compounds liable to cause drug dependence, experimental data on drug dependence should be submitted.
8. For new drugs in Registration Category 1, toxicokinetics research should usually be conducted during the repeated-dose toxicity study.
9. For optical isomers obtained from known drugs through chiral separation or synthetic method, and their preparations (part of Registration Category 1), research information and literature comparing the racemate and mono-isomer in terms of pharmacodynamics, pharmacokinetics, and toxicology (normally acute toxicity) should be provided to indicate the justification of its research and development. When the racemate safety range is narrow, and available information indicates that the unexpected toxicology (unrelated to pharmacology) is considerably high, the mono-isomer's repeated-dose toxicology study (normally lasting for 3 months) or other toxicology tests (such as reproductive toxicology) shall be provided based on comprehensive information such as the clinical course of treatment, dosage, and indications, as well as the people using the drug.

10. For drugs with fewer components derived from already marketed multi-component drugs (past of Registration Category 1), if the components do not include any substances listed in note 6 above, then Items 23-25 may be omitted
11. For new combination products under Registration Category 1, Item 22 should be submitted.
12. For new combination products in Registration Category 1, toxicity test data of repeated dosage compared with single dosage should be provided, and if the toxicity test of repeated dosage indicated no increase in toxicity and no change in the target tissue, Item 27 should be omitted.
13. For new combination products in Registration Category 1, if there is no significant change in animal pharmacokinetic study results, then Items 23-25 should be exempted.
14. For the new drugs in Registration Category 2, the route of administration during pharmacology and toxicology studies should be identical to that used in clinical studies. Generally, pharmacokinetics tests or the related toxicology study (such as topical and repeated-dose toxicity) compared with the original route of administration should be provided.
15. For new drugs in Registration Category 3, the preparations with change in route of administration and already marketed overseas, emphasis should be focused more on the drug absorption or topical toxicity influenced by the excipient, and if necessary, the pharmacokinetic test or other toxicology study should be provided.
16. For new drugs in Registration Category 4, pharmacokinetic, main pharmacodynamic, normal pharmacology, and acute toxicity test data compared with already-marketed drugs should be provided to reflect the difference before and after the changes. If necessary, research information on repeated-dose toxicity and other relevant pharmacology and toxicology research should be provided. If the preparation is made by changing the acidic or alkaline radicals (or metallic elements) of the salt of a marketed drug, and has already been marketed overseas, then the application information requirements under Registration Category 3 shall apply.
17. For drugs for topical use, in addition to the information required for the relevant Registration Category, the information of Item 21 should also be submitted; topical absorption testing should also be conducted, if necessary.
18. When there is an obvious safety concern in the immediate, sustained and controlled-release preparations (narrow safety range, significant increase in dosage), animal pharmacokinetic study data compared with the already-marketed immediate, sustained, and controlled-released preparations should also be provided in single doses.

V. Requirements for Clinical Studies

1. For new drugs in Registration Categories 1 and 2, clinical trials should be conducted.

    1. The number of subjects for clinical trials should meet statistical requirements and the minimum required cases.
    2. The minimum required cases of clinical trials are as follows: 20-30 for Phase I, 100 for Phase II, 300 for Phase III, and 2000 for Phase IV (trial group).
    3. Phase I clinical trials of contraceptives should be conducted following this Regulation. In Phase II clinical trials, a randomized controlled clinical study should be conducted on at least 100 pairs of subjects for at least 6 menstruation cycles. In Phase III trials, an open trial on at least 1000 cases for 12 menstruation cycles should be conducted. In Phase IV trial, variable factors for the relevant drug type should be carefully considered to finish the trial with an adequate number of cases.

2. For new drugs in Registration Categories 3 and 4, human pharmacokinetic studies and randomized controlled clinical trials on at least 100 pairs of subjects should be conducted. When there is more than one indication, cases for each main indication shall not be less than 60 pairs. For contraceptives, human pharmacokinetics study and an open trial on at least 500 cases for 12 menstruation cycles should be conducted. Human pharmacokinetics studies may be exempted in the following two cases:

    1. Preparations for topical use with only topical treatment effect.
    2. Oral preparation that are not absorbed.

3. Clinical studies for new drugs in Registration Category 5 should be conducted in accordance with the following principles:

    1. For oral solid preparations, bioequivalence trials should be conducted on 18-24 cases normally.
    2. When a bioequivalence trial is difficult to conduct for oral solid preparations, or for other non-oral-solid preparations, clinical trials should be conducted, and the clinical trials should have at least 100 pairs of cases.
    3. For sustained and controlled-release preparations, controlled human pharmacokinetic studies and therapeutic clinical trials should be conducted on single doses and repeated doses of the drugs, and the clinical trials should have at least 100 pairs of cases.
    4. For injections, necessary clinical trials should be conducted. When clinical trials are needed, clinical trials should have at least 100 pairs of cases for single active component injection, and at least

300 pairs for multiple component injection. For microcapsules, microemulsions, and liposomes, clinical trials should be conducted according to the requirements for Registration Categories 1 and 2.

4. For oral solid preparations in Registration Category 6, bioequivalence tests should be conducted on 18-24 cases normally. If drug quality needs process and standards control, clinical tests should be conducted on 100 cases normally.
5. Application for reduction or exemption of clinical trials should be made during the drug registration process, detailing the information and reasons for the reduction or exemption. If a clinical trial is already approved, its reduction or exemption generally should not be allowed, except where this Regulation already allows it. If there is actual difficulty in completing the clinical trial, an application for reduction or exemption should be made with detail of the reasons and plans. The rationale should be justified in terms of clinical statistics and the status of patients in clinical trials.
6. The comparative drug used for controlled clinical trials shall be a drug already marketed in China. If the comparative drug must be imported, it must be approved by the CFDA. Priority in choosing the comparative drug for positive clinical research should be given according to the following:

    1. Drug from the original innovative manufacturer
    2. The same drug with definite clinical test data
    3. Drug with the same active substance and route of administration but different dosage form
    4. Other drug with the same indication and similar mechanism of action effect

VI. Requirements on Imported Chemical Drugs

1. Application Information Item Requirements

1. Application information should be submitted in accordance with requirements in the *Table of Application Information Items* for chemical drugs. For applications of new chemical entities not yet marketed in any country, application information should be submitted in accordance with Registration Category 1. For other drugs, application information should be submitted in accordance with Registration Category 3. Common Technical Document (CTD) data as specified by the ICH may also be submitted; however, summary general information should be submitted according to *Application Information Items* requirements. Drugs in Registration Category 1 should at least be at the stage of Phase II clinical trials outside China.
2. Item 5, “Draft of package insert, notes on draft, and latest literature” also includes the original package insert from the

country of manufacture, an actual commercial sample of the package insert used in the country of manufacture, and the Chinese translation. The original commercial packaging and labeling should also be provided for drugs in Registration Category 6.

3. All clinical study information used for marketing approval in the original country of manufacture shall be submitted in Item 28.
4. All application information shall be in Chinese with the original text attached. Information in other languages (e.g., English) may be attached as reference. The Chinese translation shall be consistent with the original language.
5. The Chinese translation of quality specifications must comply with the format of the National Drug Standards of China.

2. Requirements and notes for Item 2, "certified documents"

    1. Item 2, "certified documents," includes:

        a. Notarized free sale certificate (FSC) issued by the competent authorities of the local country or region where the manufacturer is located, *GMP Certificate* of manufacturer, and Chinese translation.
        In applications for drugs in Registration Category 1, the above certified documents can be submitted together with the clinical study report upon the completion of clinical trials in China. However, when making the clinical trial application, the certified *GMP Certificate* of the manufacturer, issued by the competent local drug administration where the drug is manufactured, must be provided.
        b. When the registration of a foreign drug is conducted by the manufacturer's office in China, copies of their *Registration Certificate of Resident Office of Foreign Enterprise* should be provided. When a foreign drug manufacturer authorizes a domestic agent to conduct registration, copies of the authorization document, notarized document and Chinese translation, and the domestic agent's Business License shall be provided.
        c. Documents and explanations evidencing the patent status and ownership of the applied drug, the drug formula, the drug production technology and process, as well as a statement that the new drug will not infringe upon the patent rights of others.

    2. Notes

a. Certified documents (notarized FSC and manufacturer's *GMP Certificate*) should comply with the recommended format of the World Health Organization (WHO). Document in other formats must be legalized by the Chinese embassy in the original country.
b. When the manufacturing site and packaging site are separate, the certified *GMP Certificates* of the manufacturing and packaging sites issued by their respective countries should be provided.
c. In the event that the product is not yet approved in the manufacturing country or region, certified documents from the country where the products are being marketed and *GMP Certificate* from this country may be provided. The certified documents and *GMP Certificates* from the country where the products are marketed should be recognized by the CFDA.
d. For drug substances, the certified documents for the marketing approval of the drug substance or of its preparation, issued by the competent authorities of the original manufacturing country, should be provided, as well as the *GMP Certificate* of the manufacturer. A Drug Master File (DMF) or Certificate of Suitability to the Monographs of the European Pharmacopoeia for the drug substance may also be accepted.
e. To apply for an international multi–center clinical study, the certified *GMP Certificate* of the drug manufacturer issued by the local drug administration where the manufacturer is located must be provided.
f. For drug substances or preparations, whenever applicable, the certified *GMP Certificate* of the drug manufacturer issued by the local food and drug administration where the manufacturer is located, a ISO9000 quality assurance certificate issued by a competent organization, and/or free sale certificate (FSC) issued by the competent authorities of the country or region where the manufacturer is located should be provided

3. Requirements for clinical studies conducted in China

a. During application for drugs never marketed in any country, clinical trials should be conducted according to the clinical trial requirements of Registration Category 1.
b. During application for drugs that are marketed outside China but not in China, clinical trials should be

conducted according to the clinical trial requirements of Registration Category 3.

c. During application for drugs with the same route of administration but a different dosage form from the drug marketed in China, if Item 28 of the application meets requirements, clinical trials should be conducted according to the clinical trial requirements of Registration Category 5. If information item 28 of the application does not meet requirements, clinical trials should be conducted according to the clinical trial requirements of Registration Category 3.

d. During application for drug already with National Standards, if Item 28 of the application meets requirements, clinical trials should be conducted according to the clinical trial requirements of Registration Category 6. If Item 28 of the application does not meet requirements, clinical trials should be conducted according to the clinical trial requirements of Registration Category 3. No clinical trials are needed for drug substances already having National Standards.

e. During application for importation only of a drug substance without National Drug Standards in China, clinical studies shall be conducted with the use of the preparations of the drug substance.

VII. Application Information and Requirements for Radioactive Drug

1. Information Items

1. In applications for radioactive drugs, application information shall be prepared for the nuclide, drug substance, packing case, and preparations respectively, and shall be in accordance with the corresponding Category of chemical drugs, and Items 22 and 26 may be exempted.
2. In applications for diagnostic radioactive drugs, Items 24 and 25 may be exempted.
3. In applications for radioactive chemicals and packing cases, Items 17 and 18 may be exempted. Information required for preparations should also be provided with the application of packing cases.

2. Notes

1. Item 8 shall be submitted in accordance with the following:

a. Radioactive chemicals: nuclide production method selection, irradiation conditions, nuclear reaction

equation, chemical processing technology after target material irradiated (with the chemical reaction equation and production process attached), detailed operation procedure, possible nuclear impurities introduced, refining (purifying) method, specification, standards and analysis of other chemical reagents (in particular, target material), and relevant domestic and overseas literature and information from should be provided.

b. Packing case: Research basis for determination of packing case, preparation process, route, reaction conditions, operation steps, and quality standards of all components of the packing case shall be provided. If any components were made by the manufacturer, then basis for determination of detailed synthesis route, synthesis process flow, reaction equation, chemical equation, reaction condition, operation procedures, material input, output ratio, and possible impurities introduced and mixed, quality control of intermediate products at each step, refining (purifying) method of finished product, quality standard of raw materials, and relevant domestic and overseas literature and information from should be provided.

c. Preparation: basis for determination of preparation formula, preparation process, reaction conditions, operation procedures, refining or purifying method, quality standards, analysis and testing data of raw materials, and relevant domestic and overseas literature and information from should be provided.

2. Item 9 shall be submitted in accordance with the following:

a. Radioactive chemicals: global literature and experiment data (illustrating spectrum and comprehensive interpretation) used to determine the structure should be provided. If the radioactive nuclide of the radioactive drug is not yet listed in the *Chinese Pharmacopoeia*, then the decay illustrating chart of the nuclide, experiment data (or spectrum) to determine nuclear characteristics, as well as experiment information and literature compared with the nuclear characteristic of the nuclide widely recognized domestically and overseas should be provided.

b. Packing case: The detailed components and usage of the packing case should be provided, with explanation of the function of each component of the packing case. If any components were made by the manufacturer,

then global literature and detailed experimental data (illustrating spectrum and comprehensive interpretation) used to determine the structure should be provided.

c. Preparation: Experimental data to determine the chemical structure should be provided. If there is difficulty in providing this, the reasons should be explained and reasonable logic can be used to conclude the possible chemical structure or quote the relevant literature that can be used as a basis.

3. Item 10 shall be submitted in accordance with the following:

   a. Radioactive chemicals: research items for physical-chemical constants, items of purity testing, screening of method to measure content, and basis to determine the method should be provided with details of the measuring method, as well as measuring data.
   b. Packing case: analyzing and measuring methods, principles and data of characteristics, determination, clarity, and pH value of the solutions should be provided. Determination of the content measuring method, experimental data, testing method for bacteria, intracellular toxicity, and research data to decide the limitation should be provided.
   c. Preparation: determination method and experimental data of physical-chemical properties, characteristics, determination and principles, pH value, radioactive nuclear purity (including main nuclear impurity), radioactive chemical purity, radioactivity, and chemical purity of the drug should be provided. For injections, methods used to test for bacteria, intracellular toxicity, data, and the basis for determining the limitation of intracellular toxicity should be provided.

4. Information Item 17 shall be submitted in accordance with the following,

   a. For diagnostic radioactive drugs, information on testing and measuring methods, testing conditions and result explanation, target organ image and whole body planar image should be provided. The image picture or its copies at all test development phases, as well as the function measuring result, should be provided.
   b. For therapeutic radioactive drugs, experiment data of the animal experimental model within the main indications should be provided. Detailed global

literature of pharmacodynamic studies of the drug or other similar drugs should also be provided.

5. Information Item 19 shall be submitted in accordance with the following: acute toxicity testing should be conducted on mice for radioactive drug substances in Registration Categories 1 and 3, while packing cases and preparations should undergo abnormal toxicity testing. If there is only a limited quantity produced from refining and synthesis of the drug substance and there is only trivial clinical usage, then abnormal toxicity testing may also be used.
6. Information Item 20 shall be submitted in accordance with the following:

    a. For radioactive drugs under Registration Category 1, experimental data and literature on long-term toxicity testing and medical internal irradiation absorption dose (MIRD) on rats and dogs should be provided.
    b. For diagnostic and therapeutic radioactive drugs under Registration Category 1, internal irradiation absorption dose after full decay of the radioactive nuclide of the drug, estimation of the absorption dose of the human target organ and non-target organs, or domestic and overseas literature on the drug or similar drugs should be provided.

3. Clinical Study Requirements

   Clinical research of radioactive drugs should be conducted in accordance with the corresponding chemical drug Registration Category. In some special cases, clinical trials case numbers may be adjusted to an appropriate level subject to statistical requirements.

4. Definitions

   Radioactive chemicals, packing cases and preparations referred to in this provision have the following definitions.

   Radioactive chemicals: radioactive nuclide materials which will be directly used for radioactive drug preparations.

   Packing case: a collective name for unidentified ligand, reducing agent, oxidant, or separator which will be used in an auxiliary role to the radioactive chemicals for the purpose of quick preparation before any application.

Preparation: radioactive drugs made of radioactive nuclides and other substances.

APPENDIX #7

Registration Categories and Application Dossier Item Requirements for Biological Products

Part I: Therapeutic Biological Products

I. Registration Categories

1. Biological products not yet marketed domestically or overseas.
2. Monoclonal antibodies.
3. Gene therapy, somatic cell therapy and their preparations.
4. Allergen products.
5. Multi-component bioactive products extracted from, or by fermentation from, human and/or animal tissues and/or body fluid.
6. New combination product made from already-marketed biological products.
7. A product that is already marketed overseas but is not yet marketed domestically.
8. Cell strains used for preparing microbial products, including those not yet approved.
9. Products with not completely identical structure to already-marketed products, that are not yet marketed domestically or overseas (changes including amino acid locus mutation/absence, modification caused by a different expression system, deletion, changed interpretation, and chemical modifications of the product.
10. Products with preparation method different from an already marketed product (such as using a different expression system, host cells, etc.).
11. Products made for the first time with recombinant DNA technology (e.g., use of recombinant technology to replace synthesis, tissue extraction or fermentation)
12. Products transformed from non-injection into injection form, or topical use into systemic use, and not yet marketed domestically or overseas.
13. Already-marketed products with a change in dosage form but no change in route of administration.
14. Products with change in route of administration (excluding Category 12 above).
15. Biological products with National Standards.

II. Application Information Items

i. Summary Information

1. Name of drug.
2. Certified documents.
3. Objectives and basis for application.

4. Summary of main research work.
5. Sample draft of package insert, notes on draft, and latest literature.
6. Sample design of packaging and labeling.

ii. Pharmaceutical Study Information

7. Summary of pharmaceutical study information.
8. Research information on raw materials used for production:

    a. Research information on sourcing, collection, and quality control of animal or plant tissues or cells, unprocessed blood plasma.
    b. Research information on sourcing, collection or selection process, and determination of cells used for production.
    c. Information on establishment, determination, and storage of strain banks, as well as stability of culture transfer.
    d. Research information on sourcing and quality control of other raw materials used for production.

9. Research information on the production process of raw materials or unprocessed fluids.
10. Research information on the preparation formula and process, sourcing and quality standards of supplementives, and relevant literature.
11. Research information and literature on quality study of the product, including preparing and standardizing of standard material or controls, as well as comparative information with similar products already marketed domestically or overseas.
12. Records of manufacturing and testing of sample products for clinical study application.
13. Draft manufacturing and testing standards, with notes on draft and verification information for testing method.
14. Preliminary research information on drug stability.
15. Basis for selection and quality standards of immediate packing materials and container.

iii. Pharmacology and Toxicology Study Information

16. Summary of pharmacology and toxicology study data.
17. Pharmacodynamics research data and literature.
18. Regular pharmacology research data and literature.
19. Acute toxicity research data and literature.
20. Long-term toxicity research data and literature.

21. Animal pharmacokinetics research data and literature.
22. Mutagenicity research data and literature.
23. Reproductive toxicity research data and literature.
24. Carcinogenicity research data and literature.
25. Immunotoxicity and/or immunogenicity research data and literature.
26. Hemolysis and local irritation research data and literature.
27. Research data and literature on the efficacy, toxicity, and pharmacokinetics caused by interactions among multiple components in combination product.
28. Drug dependence research data and literature.

iv. Clinical Study Information

29. Summary of domestic and overseas clinical study information.
30. Clinical study plan and protocol.
31. Investigator's Brochure.
32. Sample draft of Informed Consent Form, with ethics committee approval.
33. Clinical study summary report

v. Others

34. Brief summary of pre-clinical research.
35. Experiment and study information and summary of production process improvement, quality perfection, pharmacology and toxicology studies, and other work conducted during the clinical studies.
36. Amendments to the approved manufacturing and testing standards, with basis for amendments
37. Stability test research and study information.
38. Manufacturing and testing records of 3 consecutive batches of sample products.

III. Application Information Requirements

i. Table of Application Information Items for Therapeutic Biological Products (Information Items 1-15, 29-38)

		Registration Categories														
	Items	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Summary Information	1	+	+	Refer to Technical Guidance	Refer to Technical Guidance	+	+	+	+	+	+	+	+	+	+	+
	2	+	+			+	+	+	+	+	+	+	+	+	+	+
	3	+	+			+	+	+	+	+	+	+	+	+	+	+
	4	+	+			+	+	+	+	+	+	+	+	+	+	+
	5	+	+			+	+	+	+	+	+	+	+	+	+	+
	6	+	+			+	+	+	+	+	+	+	+	+	+	+
	7	+	+			+	+	+	+	+	+	+	—	+	—	+
Pharmaceutical Information	8	+	+			+	—	+	+	+	+	+	—	—	—	+
	9	+	+			+	—	+	+	+	+	+	—	—	—	+
	10	+	+			+	+	+	+	+	+	+	—	+	—	+
	11	+	+			+	+	+	+	+	+	+	—	+	—	+
	12	+	+			+	+	+	+	+	+	+	—	+	—	+
	13	+	+			+	+	+	+	+	+	+	—	+	—	+
	14	+	+			+	+	+	+	+	+	+	—	+	—	+
	15	+	+			+	+	+	+	+	+	+	—	+	—	+
Clinical Trial Information	29	+	+			+	+	+	+	+	+	+	+	+	+	+
	30	+	+			+	+	+	+	+	+	+	+	+	+	+
	31	+	+			+	+	+	+	+	+	+	+	+	+	+
	32	+	+			+	+	+	+	+	+	+	+	+	+	+
	33	+	+			+	+	+	+	+	+	+	+	+	+	+
	34	+	+			+	+	+	+	+	+	+	+	+	+	+
Other Information	35	+	+			+	+	+	+	+	+	+	+	+	+	+
	36	+	+			+	+	+	+	+	+	+	—	+	—	+
	37	+	+			+	+	+	+	+	+	+	—	+	—	+
	38	+	+			+	+	+	+	+	+	+	—	+	—	+

Refer to Technical Guidance

Notes:
+: Information must be submitted.
—: Information may be exempted.
±: Information may or may not be required depending on the particular case.

ii. Table of Application Information Items for Pharmacology and Toxicology Information for Therapeutic Biological Products (Information Items 16-29)

		Registration Categories														
	Item	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Pharmacology & Toxicology	16	+	+	Refer to Technical Guidance	Refer to Technical Guidance	+	+	+	+	+	+	+	+	+	+	+
	17	+	+			+	+	+	+	+	+	+	+	+	+	+
	18	+	+			+	+	+	+	+	+	+	+	+	+	+
	19	+	+			+	+	+	+	+	+	+	+	+	+	±
	20	+	+			+	+	+	+	+	+	+	+	+	+	+
	21	+	+			±	±	±	—	+	±	+	+	±	+	±
	22	±	±			±	±	±	—	±	±	±	±	—	±	—
	23	±	±			±	±	±	—	±	±	±	±	—	±	—
	24	±	±			±	±	±	—	±	±	±	±	—	±	—
	25	+	+			+	+	+	—	+	+	+	+	—	+	±
	26	+	+			+	+	+	—	+	+	+	+	+	+	±
	27	—	—			—	+	—	—	—	—	—	—	—	—	—
	28	±	±			±	—	—	—	±	—	—	±	—	—	—

Notes:
+: Information must be submitted.
—: Information may be exempted,
±: Information may or may not be required depending on the particular case.

IV. Notes on Application Information

i. Items 1-31 are required for clinical trial application. Items 1-6, 15, and 29-38 are to be submitted after the completion of clinical trials.
ii. Notes on general information requirements:

1. Item 1, "name of drug," includes International Nonproprietary Name (INN), English name, Chinese adopted name, and Chinese phonetic name. The nomenclature of the drug should be explained for any new name.
2. Item 2, "certified documents," includes:

    a. Certified documents of applicant's legal registration, *Drug Manufacturing License* and change registration, and *GMP Certificate*.
    b. Certified documents stating patent status and ownership of the applied biological product, its formula and process, and letter of guarantee stating that no infringement has been made upon the patent rights of others.
    c. For new biological product production applications, a copy of the *Approval of Clinical Study of New Drugs* and the investigational drug's quality standard should be provided for market authorization approval.

d. Copies of the *Drug Packing Material and Container Certificate* or *Import Drug Packing Material and Container Certificate* for immediate packing materials and container.

3. Item 3, "objective and basis" of the application, includes the current status and relevant literature of research and development, production, marketing, and use of the product domestically and overseas. Should also include analysis of innovation and feasibility of the product.
4. Item 4, "summary of main research work," includes a summary of the applicant's main research results, as well as a comprehensive analysis of the safety, efficacy, and quality controllability of the product.
5. Item 5, "draft of packaging insert, notes on draft, and latest literature," includes the sample of the draft packaging insert sheet, drafted in accordance with relevant regulations, notes on the drafting of items in the insert sheet were drafted, the latest relevant literature, and the latest version of the insert sheet from the original manufacturer in the original language, with Chinese translation.

iii. Notes on pharmaceutical study information requirements:

1. For any production using raw materials sourced from cows, relevant materials required by the CFDA should be provided.
2. For products extracted from human and/or animal tissues and body fluid, or for recombination products by McAb and eukaryote expression, additional verification information on the virus deactivation process should be added.
3. For any potential material toxic to humans introduced during the production process, research information on the removal effect of the production process should be provided, standards for material control within the limit should be established, and the basis for the standards should be provided.
4. Item 11, information on quality study of the product, includes analysis of physical-chemical characteristics, structure determination, verification testing, purity measurement content measurement, and bioactivity measurement of the product. For purified products, additional research information on impurity analysis should be provided.
5. For biological products in Registration Category 15, in principle, the quality standard should not be lower than that of similar products already marketed.
6. The production scale during the production of 3 consecutive batches of sample products should be to the designed

production capacity. The production scale before and after marketing should be consistent. If there is significant change in production scale before and after marketing, a supplemental application should be submitted.

iv. Notes on pharmacology and toxicology study information:

1. Due to the diversity and complications of biological products, the requirement of pharmacology and toxicology study information may not be applicable for all therapeutic products. The applicant should provide information with reasonable scientific reference to relevant guiding principles, based on the particular characteristics of the biological product, to meet drug evaluation requirements of during application for a biological product. If the above requirements are not applicable for the product to be registered, the applicant should note this in the application dossier, and if necessary, provide other relevant information.
2. In principle, relevant animals should be used for pharmacology and toxicology studies. Attention should be paid during the study to how the product's immunogenicity may impact the design, results, and assessment of the animal experimentation. If some of the standardized research method is not applicable for the product to be registered, the applicant should note this in the application dossier, and if necessary, provide other relevant information.
3. The standardized genotoxicity study is generally not applicable for biological products, therefore, the study is usually not required. However, if there are any particular safety concerns in the products, related research data should be submitted.
4. For products used for child-bearing patients, the applicant should assess their reproductive toxicity, taking consideration of the specifications and indications of the product, and if necessary, provide reproductive toxicity research information.
5. The standardized carcinogenicity tests are generally not applicable for most of biological products. However, the registration applicant should assess carcinogenicity risks, taking into consideration bioactivity, clinical duration, and the group using the products. If there is any possibility of carcinogenicity caused by the product, relevant research information should be provided.
6. Topical irritation research information should be provided for injections, suppositories, ophthalmologic products, sprays, ointments, creams, and gels. Hemolysis tests should be conducted for injection and biological products with the tendency of hemolysis.

7. When there are any concerns with drug dependence (need for repetitive use, possibly acting on central nervous system), the applicant should assess the possibility of drug dependence based on the functioning mechanism of the product, and if necessary, provide drug dependence research data.
8. For products in Registration Category 2 (monoclonal antibodies):

    a. When there is antibody combination information to indicate that primates shall be the most correlated species, for the uncoupled monoclonal antibody test, primates shall be used to conduct the main pharmacology and pharmacokinetic study.
    b. For toxicology and pharmacokinetic studies, the test should best be conducted on the animal experimental model with the same target antigen with human. If there is neither suitable animal experimental model nor animal with relevant antigen, and the cross-reaction test result with human tissue is negative, then the toxicology study may be exempted.
    c. Immunotoxicity studies should focus on the potential toxicity reaction when combining the non-target tissues, such as the cross-reaction with human tissues/cells or the combination with non-target tissue. If there is a suitable experimental model, cross-reaction tests should be conducted with animal in vivo, in addition to being conducted in vitro. In particular, for immunity combination products with cytolysis or antibodies with Antibody Dependent Cell-mediated Cytotoxicity (ADCC), additional animal toxicity tests on more than one kind of animal at over-dosage or multi-doses should be considered.

9. For products in Registration Category 3 (gene therapy products), pharmacology and toxicology studies should focus on:

    a. Related animal should be used for study. In principle, the biological reaction of the related animal to the expression of gene therapy products should be relevant to that of the human body. When a virus carrier is used in the products, the animal should also be susceptible to the wild virus.
    b. Standardized pharmacokinetics studies are not applicable for gene therapy products, where the focus of pharmacokinetics study of gene therapy products should be the introduction, distribution, and elimination of the gene, whether or not the gene acts on the host cell and

reproductive cell group, the pharmacokinetic action of the gene expression, and the distribution and elimination of the carrier.

c. The possibility of genotoxicity, carcinogenicity, and reproductive toxicity should be assessed based on data on distribution and elimination of the introduced gene and its expression, and if necessary, relevant research data should be provided.

10. For human blood products in Registration Category 5, safety research information (Items 19-28) may be exempted, once related information or evidence is provided, if the dosage is not to exceed biological tolerance dosage, and if no special process is used to treat the product, and no special solution is used.
11. For biological products in Registration Categories 7, 10 and 15, consistency with already-marketed products should be first assessed for the areas of preparation process, quality standards, and bioactivity (and pharmacokinetics data if necessary), using the method of comparison study. If there is great similarity with the marketed product in the above areas, and if the marketed products have a definite clinical safety and effectiveness record, only one animal is required for the toxicology study, and the duration of the long-term toxicology study may be one month. A major pharmacodynamic study may just conduct 1-2 study items, or be part of the Activity Assays of quality standards in general. If the applicant can sufficiently prove the consistency of the product with marketed products, this can justify the reduction or exemption of related pharmacology and toxicology study items.
12. For products in Registration Category 8, the research information used for determining dosage and research information on the products' influence on normal bacteria should be provided.
13. For products in Registration Category 13, choosing of the items to be tested should be based on a comprehensive consideration of the characteristics of the product's changed dosage form and the relevant pharmaceutical and clinical requirements that may have arisen from such change.

    a. For transforming between injection, powder for injection, and intravenous infusion, if there is no change in clinical usage and dosage, usually only testing information on hemolysis and local irritation is needed. Subject to the change in formula, if necessary, other related toxicology study information should be provided.

b. For other special preparations such as liposomes, which can change the original pharmacokinetic behavior, pharmacology and toxicology studies should be designed based on comparison study data of animal pharmacokinetics between the old and new dosage, taking into consideration identity, safety tolerance, clinical indication, and patient group using the products, and the relevant data should be submitted.

14. For preparations in Registration Category 14, if there is sufficient reasons and/or literature to prove that the in vivo metabolite and product safety are similar before and after the change to route of administration, then reduction or exemption of some required informational items may be applied.

v. Other

1. Requirements for therapeutic biological products shall be applicable to in vivo diagnostic biological products; the data should be submitted under the applicable category.
2. For any new indications of biological products, registration should follow the new drug registration category with submission of the relevant dossier. If there is no change in pharmaceutical aspect, and there is no increase in clinical dosage and duration, the related pharmacokinetic, pharmacology and toxicology data may be exempted.

V. Clinical Study Notes

i. Clinical trials should be conducted for new drug applications.
ii. The number of subjects for clinical trials should meet statistical requirements and the minimum required cases.
iii. The minimum required cases for clinical trials are as follows: 20 for Phase I, 100 for Phase II, and 300 for Phase III.
iv. Clinical trials for products in Registration Categories 1-12 should be conducted in accordance with the requirements for new drugs.
v. Only Phase III clinical trials are usually required for products in Registration Categories 13-15.
vi. For innovative sustained-release preparations, a comparison study in human pharmacokinetics and clinical trials shall be conducted.

VI. Imported Product Requirements

i. Application Information Item Requirements

Application information shall be submitted in accordance with the *Registration Application Information Items.* In applications for preparations not yet marketed domestically or overseas, information shall be submitted in accordance with Registration Category 1. For application of products marketed overseas but not in China, information shall be submitted in accordance with Registration Category 7. For application of products already marketed in China, information shall be submitted in accordance with Registration Category 15.

ii. Requirement and Notes for Item 2, Certified Documents

1. Item 2, Certified Documents, includes:

   a. Notarized approval documents for the marketing of the product, issued by the competent local authority in the country or region of manufacture, and the *GMP Certificate* of the manufacturer, with Chinese translations. For products not yet marketed domestically or overseas, the above documents can be submitted together with the clinical study report upon the completion of clinical studies in China.
   b. When a foreign drug registration is conducted by the manufacturer's office in China, copies of the office's *Registration Certificate of Resident Office of Foreign Enterprise* should be provided. When a foreign drug manufacturer authorizes a domestic agent to conduct the registration, copies of the authorization document, notarized documents with the Chinese translation, as well as the Business License of the domestic agent shall be provided.
   c. Certified documents and explanations stating patent status and ownership of drug and formula, drug production technology and process, and letter of guarantee stating that no infringement upon the patent rights of others has been committed.

2. Notes

   a. The *GMP Certificate* and marketing approval for the product issued by the competent local authorities in the country or region of manufacture should be acknowledged by the Chinese embassy and by a notary public in that country.
   b. When a preparation is manufactured in one location and packed in another location, then the certified *GMP Certificates* of the preparation manufacturer and packing

manufacturer issued by the respective countries where the manufacturers are located should be provided.

c. In the event that the product has not yet been approved for marketing by the country or the region of manufacture, then the certified documents from the country where the products is approved to be marketed should be provided, and should be recognized by the CFDA. However, the *GMP Certificates* must be issued by the competent authorities from the country of manufacture.

iii. Requirements for other informational items

1. All clinical study information used in the application for marketing in the country or region where the manufacturer is located should be submitted under Item 29.
2. All application information should be translated into Chinese with the original language version attached. The Chinese translation shall be consistent with the original language.
3. The Chinese translation of biological product standards must comply with the format required by the National Drug Standards of China.

iv. Requirements for clinical studies conducted in China

1. In applications for biological products not yet marketed domestically or overseas, clinical studies should be applied for in accordance with Registration Category 1.
2. In applications for biological products marketed overseas but not domestically, clinical studies should be applied for in accordance with Registration Category 7.
3. In applications for biological products with National Standards, a clinical study should be applied for in accordance with Registration Category 15.

Part II: Preventive Biological Products

I. Registration Categories

2. Vaccine not marketed in China or overseas.
3. DNA vaccine.
4. A currently marketed vaccine with new adjuvant. Change of carrier of combined vaccine.
5. Unpurified vaccine or full cell vaccine (bacteria, virus) changed into purified vaccine, or combined vaccine.
6. Vaccine with strains not yet approved in China (except for vaccine for influenza or vaccine for leplospirosis).
7. Vaccine already marketed overseas but not marketed domestically.
8. Conjugate or combined vaccine prepared with vaccine already marketed domestically.
9. Recombination vaccine with protective antigen spectrum different from the marketed one.
10. Vaccine manufactured with a change of other approved expression or other approved cellular stroma. Vaccine using a new process, which has been proven to improve the safety and effectiveness of the vaccine based on lab data.
11. Vaccine with change in the method of deactivation or method of de-toxicity.
12. Vaccine with change in the route of administration.
13. A domestically marketed vaccine with a change in dosage form but no change in route of administration.
14. Vaccine with a dosage of immunity or immunity procedure..
15. Vaccine for an enlarged group of people (enlarged age range).
16. Vaccine admitted with National Standards.

II. Application Information Items

1. Summary Information

    a. Name of drug.
    b. Certified documents.
    c. Objectives and basis for application.
    d. Sample draft of insert sheet, notes on draft, and literature.
    e. Sample design of packaging and labeling

2. Research information summary and evaluation.
3. Research information of production bacterial and toxicity strains

    a. Source and characteristics and Certified Documents.
    b. Information on establishment and determination of batches of the strains.
    c. Information on stability during transfer of culture.

d. Test report from NICPBP of batches of bacterial and toxicity strains used for production.

4. Research information on cellular stroma for production.

    a. Information on source, characteristics and determination of cellular stroma.
    b. Information on establishment and determination of cell bank.
    c. Information on stability of transfer of culture.
    d. NICPBP test report on the production cell bank for cellular stroma used for manufacture.
    e. Sourcing and quality standards for culture fluid, additives, and others.

5. Research information on production process and technology.

    a. Research data of production process of original fluid of vaccine, with theoretical and experimental basis and verification data.
    b. Preparation formula and production process, as well as basis of determination.

6. Research information on product quality: non-clinical efficacy and safety research data.

    a. Research data on quality studies and registration standard studies.
    b. Research and verification information on test method.
    c. Comparison analysis with similar products.
    d. Analysis information on product antigenicity, product immunogencity, and animal testing protection.
    e. Research data on animal hypersensitivity testing.
    f. Information on animal safety evaluation.

7. Draft of manufacturing and testing standards, drafted in accordance with relevant regulations, with notes on drafting of items and relevant literature attached.
8. Record of manufacturing and testing of sample product to be submitted for clinical study application.
9. Preliminary stability test information.
10. Quality certificate of animals used for production, research and testing.
11. Draft of Informed Consent form and clinical study plans and protocol.
12. Summary of pre-clinical research.
13. Summary information of relevant domestic and overseas clinical studies.
14. Summary of clinical study report, including sample of Informed Consent form, and ethics committee approval.
15. Summary of work, experiment, and study information on improvement of production technology and perfection of quality standards during clinical research .

16. Stability research information to determine storage and validity period of vaccine.
17. Amendments to approved manufacturing and test standards, as well as basis for amendments.
18. Record of production and testing of the 3 consecutive batches of sample products.

III. Application Information Items, Table

	Registration Categories														
Item	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3	+	+	—	—	+	+	+	+	±	—	—	—	—	—	+
4	+	+	—	—	+	+	+	+	±	—	—	—	—	—	+
5(1)	+	+	+	+	+	+	+	+	+	+	—	—	—	—	+
5(2)	+	+	+	+	+	+	+	+	+	+	+	+	—	—	+
6	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
7	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
8	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
9	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
11	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
12	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
13	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
14	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
15	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
16	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
17	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±
18	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: The item must be submitted.
−: The item may be exempted.
±: The item may or may not be required based on the specific case.

IV. Application Information Items, Notes

1. Items 1-11 shall be submitted for the clinical study application. Items 1, 2 and 12-18 shall be submitted upon clinical study completion
2. Item 1, summary of information:

    a. “Name of drug” includes International Nonproprietary Name (INN), English name, Chinese adopted name, Chinese phonetic name, and basis for the name. The nomenclature of the drug should be explained for any new name.

b. "Certified documents" includes:

    a. Certified documents of applicant's legal registration, *Drug Manufacturing License* and change registration, and *GMP Certificate*.
    b. Certified documents stating patent status and ownership of the applied biological product, its formula and process, and letter of guarantee stating that no infringement has been made upon the patent rights of others.
    c. For new biological product production applications, a copy of the *Approval of Clinical Study of New Drugs* and the investigational drug's quality standard should be provided for market authorization approval.
    d. Copies of the *Drug Packing Material and Container Certificate* or *Import Drug Packing Material and Container Certificate* for immediate packing materials and container.

c. "Objective and basis" includes the current status and relevant literature of research and development, production, marketing, and use of the vaccine domestically and overseas. Should also include analysis of innovation and feasibility of the vaccine.
d. "Draft of packaging insert, notes on draft, and latest literature" includes the sample of the draft packaging insert sheet, drafted in accordance with relevant regulations, notes on the drafting of items in the insert sheet were drafted, the latest relevant literature, and the latest version of the insert sheet from the original manufacturer in the original language, with Chinese translation.

3. Item 3:

    a. "Source and characteristics": source of the production bacterial and toxicity strains, research information or certified documents to show the bacterial and toxicity strains can be used for production, history including history of separation, determination and detoxicity, characteristics, research information on the adaptability to cellular stroma, infective titer, antigenicity, immunogenicity, and toxicity.
    b. "Information on establishment and determination of batches of the strains": relevant information on initial batch of production bacterial and toxicity strains, primary generation batch, information on establishment of production batch bank, including generation numbers, preparation, storage of sub-batch of production strains, test report on each batch of production bacterial and toxicity strains, and items to be tested, including exogenesis factors, determination tests, characteristics, infective titer, antigenicity, immunogencity. For primary generation strain, the gene sequence should be determined.

c. “Information on stability during transfer of culture”: determination of the limitation of last generation number to be used. For items to be tested, refer to test strain batches.

4. Item 4:

   a. “Information on source, characteristics and determination of cellular stroma”: source of cellular stroma used for production, certified documents and research information showing that the cellular stroma can be used for production, history (including the history of cell system establishment, determination, and history of transfer of culture), biological characteristics, exogenesis factors testing, karyotype analysis, tumorigencity testing, and other research. For vaccines with changed cellular stroma, in principle, the safety risk of new cellular stroma should not be higher than that of the marketed vaccine.
   b. “Information on establishment and determination of cell bank”: information on the establishment of the production cellular stroma initial cell bank, primary cell bank, and production cell bank, including generation number, preparation, storage and administration of the various production cell banks, and comprehensive tests of cell banks. Items to be tested include biological characteristics, karyotype analysis, and exogenesis factors.
   c. “Information on stability of transfer of culture”: determination of the limitation of last generation number to be used. For items to be tested, refer to cell bank items to be tested (above), with the addition of tumorigencity.
   d. In the event that material sourced from cows is used, relevant information should be provided in accordance with CFDA requirements.
   e. The above information may be exempted for bacterial vaccines.

5. Item 5:

   a. “Research data of production process of original fluid of vaccine”: main technical parameters to optimize production process, including inoculation quantity of bacteria (or virus), culture conditions, fermentation conditions, de-activity and crack process conditions, extraction and purification of bioactive material, removal of the materials potentially toxic to humans, activation, coupling and combination technology of antigen and carrier for combined vaccine, research information on percentages of various bioactive components, compatibility of antigens, etc. Summary of the materials input, output of various intermediary products, production process quality, finished product output and quality should be provided. Quality of the products in the production process should be assessed and verified.

b. When a substance with potential harm to humans goes into the production process, verification data for the removal process shall be provided. Standards for limitations on the harmful substance and the basis for standards should be provided.

6. Item 6(a):

    a. For purified vaccines, the quality study should usually include measurement of antigen components, contents, molecular weight, purity, specificity determination, and measurement and testing of the content (or residuals) of the non-effective component.
    b. Quality standards and test results of the product should include quality standards and test results of each single component of the combined vaccine.
    c. After the production process is defined, the product registration standards should be defined based on test results on multiple batches of the trial product by using statistical analysis methodology.
    d. The quality for vaccines applied for as per Registration Category 15 shall not, in principle, be lower than that of the same variety of vaccine already marketed.
    e. For vaccines produced using DNA recombinant technology, it is necessary to provide corresponding information with reference to therapeutic biological products.

7. Item 6(c):

    If there is already a similar vaccine on the market, it is necessary to compare it with the new vaccine. If the new vaccine is developed based on the marketed one, the comparison study should be conducted based on the quality of the old vaccine. For a combined vaccine, the quality comparison should be conducted based on each single vaccine.

8. Item 6(f):

    a. For toxoid vaccines or vaccines using toxoids as carriers, toxicity reversion testing information should be provided.
    b. Toxicity testing information should be provided based on the group of people using the vaccine, characteristics of the vaccine, immunity dosage, and immunity procedure.

9. Items 9 and 16:

    Vaccine stability tests should be conducted in such way that at least 3 batches of product are stored under the proposed storage condition, the efficacy and activity of the vaccine is verified periodically and trends are

analyzed, and an overall inspection is conduced at a critical point in time. In addition, accelerated stability should also be conducted.

10. Item 18:

    Production scale during the production of 3 consecutive batches of trial products should be to the designed production capacity. The production scale before and after marketing should be consistent. If there is significant change in production scale before and after marketing, a supplemental application should be submitted.

V. Clinical Study Notes

i. The number of subjects for clinical trials should meet statistical requirements and the minimum required cases. The minimum cases requirement includes both a trial group and a control group.
ii. The minimum required cases for clinical trials are as follows: 20 for Phase I, 300 for Phase II, and 500 for Phase III.
iii. Clinical trials for vaccines in Registration Categories 1-9 and 14 should be conducted in accordance with the requirements for new drugs.
iv. For vaccines in Registration Category 10, if the research information provided shows no change in the safety and effectiveness of the vaccine after the deactivation or detoxicity of the vaccine, clinical trials may normally be exempted
v. For vaccines in Registration Category 11, clinical trials should normally be conducted in accordance with requirements for new drugs. However, for vaccines with the route of administration changed from injection to non-injection, Phase I clinical trials may be exempted.
vi. Only Phase III clinical trials are usually required for vaccines in Registration Categories 12 and 15.
vii. For vaccines in Registration Category 13 where the immunity procedure is changed, Phase I clinical trials may be exempted.
viii. For preventive products used in infants, in principle, the sequence of Phase I clinical trials should be adults first, then children and then infants.
ix. Each clinical trial phase should be conducted after the completion of the previous phase in accordance with the prescribed immunity procedures.
x. For vaccines applying for marketing for the first time in China, an Epidemiology Protective Test should be conducted

VI. Requirements for Imported Preventive Biological Products

i. Application Information Item Requirements

Application information shall be submitted in accordance with the *Registration Application Information Items.* In applications for vaccines not yet marketed domestically or overseas, information shall be submitted in accordance with Registration Category 1. For application of vaccines marketed overseas but not in China, information shall be submitted in accordance with Registration Category 6. For application of products already marketed in China, information shall be submitted in accordance with Registration Category 15.

ii. Item 1(ii), Certified Documents, includes the following:

a. Notarized approval documents for the marketing of the vaccine, issued by the competent local authority in the country or region of manufacture, and the *GMP Certificate* of the manufacturer, with Chinese translations. For products not yet marketed domestically or overseas, the above documents can be submitted together with the clinical study report upon the completion of clinical studies in China.
b. When a foreign drug registration is conducted by the manufacturer's office in China, copies of the office's *Registration Certificate of Resident Office of Foreign Enterprise* should be provided. When a foreign drug manufacturer authorizes a domestic agent to conduct the registration, copies of the authorization document, notarized documents with the Chinese translation, as well as the Business License of the domestic agent shall be provided.
c. Certified documents and explanations stating patent status and ownership of biological product and formula, production technology and process, and letter of guarantee stating that no infringement upon the patent rights of others has been committed.

Notes:

d. The *GMP Certificate* and marketing approval for the product issued by the competent local authorities in the country or region of manufacture should be acknowledged by the Chinese embassy and by a notary public in that country.
e. When a preparation is manufactured in one location and packed in another location, then the certified *GMP Certificates* of the preparation manufacturer and packing

manufacturer issued by the respective countries where the manufacturers are located should be provided.

f. In the event that the product has not yet been approved for marketing by the country or the region of manufacture, then the certified documents from the country where the products is approved to be marketed should be provided, and should be recognized by the CFDA. However, the *GMP Certificates* must be issued by the competent authorities from the country of manufacture

iii. Notes, other information items

1. All clinical study information used in the application for marketing in the country or region where the manufacturer is located should be submitted under Item 13.
2. All application information should be translated into Chinese with the original language version attached. The Chinese translation shall be consistent with the original language.
3. The Chinese translation of vaccine standards must comply with the format required by the National Drug Standards of China.

iv. Requirements for clinical studies conducted in China:

4. In applications for vaccines not yet marketed domestically or overseas, clinical studies should be applied for in accordance with Registration Category 1.
5. In applications for vaccines marketed overseas but not domestically, clinical studies should be applied for in accordance with Registration Category 6.
6. In applications for vaccines with National Standards, a clinical study should be applied for in accordance with Registration Category 15.

APPENDIX #8

Items and Application Documents Required for Supplemental Application of Drug Registration

I. Registration Items

i. Supplemental applications to be approved by CFDA

1. Application for Drug Approval Number of a new drug by the New Drug Certificate holder of the drug.
2. Application for use of a drug trade name.
3. Additional indications or functions of TCM or natural drugs, or the indications approved in China for chemical drugs or biological products.
4. Change in the usage or dosage of a drug, or the group of patients to use the drug, but without change in route of administration.
5. Change of strength of drug.
6. Change to supplementary (inactive) ingredients in the formula of the drugs, where there is a medical requirement for it.
7. A change in drug manufacturing technology and process that affects drug quality.
8. Amendment of drug registration standards.
9. Substitution or removal of drug material listed in National Drug Standards as toxic or endangered.
10. Change of immediate packaging material or container of import drugs, domestic injections, ophthalmological drugs, sprays, powder aerosols, or inhalers. Use of new immediate packaging material or container.
11. Application for combined packing of drug.
12. Transfer of new drug technology.
13. Addition or amendment of items in insert sheet of TCM or natural drug, such as pharmacology, toxicology, clinical trials, or pharmacokinetics.
14. Change in items within the import drug registration certificate, such as drug name, drug enterprise name, registered location, packing specification.
15. Change of location where imported drug is manufactured.
16. Change of location where imported drug is packed overseas.
17. Repacking of import drugs in China.
18. Other

ii. Supplemental applications to be approved by PDA and filed for record at CFDA, or directly filed for record at CFDA.

11. Change of name of domestic drug manufacturer.
12. Internal change to manufacturing facility of domestic drug manufacturer.
13. Change to immediate packaging material or container (if not included in item 10 above).
14. Change to validity period of domestic drug.
15. Change of manufacturing location where raw material for imported preparation is manufactured.
16. Change of appearance of drug without change in drug standards.
17. Amendment of drug insert sheet according to national drug standards or as required by CFDA.
18. Supplementing and improving of drug safety section of insert sheet.
19. Modification of design of drug packaging and labeling according to regulations.
20. Change of agent for imported drug registration.
21. Other

iii. Supplemental applications to be filed for record at PDA

22. Amendment to insert sheet of domestic drug according to national drug standards or as required by CFDA.
23. Supplementing and perfecting of the drug safety part of domestic drug insert sheet.
24. Modification of design of domestic drug packaging and labeling according to regulations.
25. Change to packing specification of domestic drug.
26. Change of manufacturing location of domestic drug
27. Change of appearance of domestic drug without change to drug standards.
28. Other

II. Application Information Items

i. Copies of drug approval certificate and appendixes. Include all the approval documents related to the application, such as drug registration approval, supplemental application approval, trade name approval, drug standards publishing document, approval for amendment of drug standards and uniformly renewed drug approval number, *New Drug Certificate, Import Drug License*, or *Drug Product License*. Annex should include all annexes to above approval, such as drug standards, insert sheets, design of packaging and labeling, and other annexes.

ii. Certified Documents:

1. If the Applicant is a drug manufacturing enterprise, copies of the drug manufacturing certificate, business license, and GMP Certificate should be provided. If the Applicant is not a drug manufacturing enterprise, copies of the Applicant's certified document of legal registration should be provided.

   If drug registration is conducted by the resident office of the foreign manufacturer, a copy of their *Registration Certificate of Resident Office of Foreign Enterprise* should be submitted.

   If drug registration is conducted by a Chinese agent with authorization from the foreign manufacturer, the certified documents of the authorization, notarized documents and Chinese translation should be submitted together with the copy of the domestic agent's Business License.

2. For different application items, certified document should be provided according to the respective Table of Application Information Items for each item.

3. For imported drugs, the certified documents and notarized documents of the approval of drug changes, issued by the competent local drug authorities in the local country or region should be provided, with Chinese translation. The form of the documents should comply with the requirements for certified documents set out in the Application Information Items for TCM, natural drugs, chemical drugs, or biological products.

   Except for change to strength of drugs, change of manufacturing location, or change of manufacturer name or legal location, if the local drug authority in the country or region cannot provide relevant certification documentation, explanatory notes should be provided according to local laws and regulations.

iii. Draft of amended design of the drug insert sheet, with detailed notes on amendments attached.

iv. Draft of amended design of the drug packaging and labeling, with detailed notes on amendments attached.

v. Pharmaceutical study information.

   Part or all of the research data from pharmaceutical studies and necessary global literature should be provided respectively for the relevant registration category. Information items should be provided according to the corresponding items listed in Annexes 1-3.

vi. Pharmacology and toxicology study information.

Part or all of the research data from pharmacology and toxicology studies and necessary global literature should be provided respectively for the relevant registration category. Information items should be provided according to the corresponding items listed in Annexes 1-3.

vii. Clinical Study Information:

If there is need for a clinical study, information items should be provided according to the corresponding items listed in Annexes 1-3.

Information should be provided respectively before and after clinical trials. If there is no need for clinical trials, the literature of clinical studies may be provided instead.

III. Table of Application Information Items

	Information Items								
Supplemental Application Type	1	2			3	4	5	6	7
		2.1	2.2	2.3					
Application for Drug Approval Number of a new drug by the New Drug Certificate holder of the drug.	+	+	—	—	—	+	*1	—	—
Application for use of a drug trade name.	+	+	*2	+	+	+	—	—	—
Additional indications or functions of TCM or natural drugs, or the indications approved in China for chemical drug or biological products.	+	+	—	+	+	+	—	#	#
Change in the usage or dosage of a drug, or the group of patients to use the drug, but without change in route of administration.	+	+	—	+	+	+	—	#	#
Change of strength of drug.	+	+	—	+	+	+	+	—	*3
Change to supplementary (inactive) ingredients in the formula of the drugs, where there is a medical requirement for it.	+	+	—	+	*4	*4	+	±	±
A change in drug manufacturing technology and process that affects drug quality.	+	+	—	+	*4	*4	+	#	#
Amendment of drug registration standards.	+	+	—	+	*4	*4	*5	—	—
Substitution or removal of drug material listed in National Drug Standards as toxic or endangered.	+	+	*6	+	+	+	#	#	#
Change of immediate packaging material or container of import drugs, domestic injections, ophthalmological drugs, sprays, powder aerosols, or inhalers. Use of new immediate packaging material or container.	+	+	—	+	*4	*4	*7	—	—
Application for combined packing of drug.	+	+	—	+	+	+	—	*8	*8

Transfer of new drug technology.	*9	+	*10	—	+	+	*1	—	*11
Addition or amendment of items in insert sheet of TCM or natural drug, such as pharmacology, toxicology, clinical trials, or pharmacokinetics.	+	+	-	±	+	+	-	±	±
Change in items within the import drug registration certificate, such as drug name, drug enterprise name, registered location, packing specification.	+	+	—	+	+	+	*4	—	—
Change of location where imported drug is manufactured.	+	+	—	+	+	+	+	—	—
Change of location where imported drug is packed overseas.	+	+	*12	+	+	+	*13	—	—
Repacking of import drugs in China.	+	+	*14	—	+	+	*15	—	—
Change of manufacturing location where raw material for imported preparation is manufactured.	+	+	—	+	—	—	+	—	—
Change of name of domestic drug manufacturer.	+	+	*16	—	+	+	—	—	—
Internal change to manufacturing facility of domestic drug manufacturer.	+	+	*17	—	*4	*4	*1	—	—
Amendment of drug insert sheet according to national drug standards or as required by CFDA.	+	+	*18	—	+	+	—	—	—
Supplementing and improving of drug safety section of insert sheet.	+	+	—	+	+	+	—	*19	*20
Modification of design of drug packaging and labeling according to regulations.	+	+	*21	+	—	+	—	—	—
Change to packing specification of domestic drug.	+	+	—	—	+	+	*4	—	*3
Change to validity period of domestic drug.	+	+	—	+	+	+	*22	—	—
Change of the location where raw material for domestic preparation is manufactured	+	+	—	—	—	*4	*23	—	—
Change of appearance of drug without change in drug standards.	+	+	—	+	+	*4	+	—	—
Change of agent for imported drug registration.	+	+	*24	—	—	—	—	—	—

Notes:

*1: Only test reports for 3 consecutive batches of sample product are needed.
*2: Certified documents for trademark retrieval should be provided.
*3: Report of literature on clinical use should be provided
*4: Should be provided if there is any amendment.
*5: Only the research information and literature during quality study, draft for drug standards, notes to draft, the test reports for 3 consecutive batches of sample product should be provided.
*6: Certified documents verifying toxic drug material, or endangered drug material, or certified document from authorities requesting substitution or removal.
*7: Only the research information during drug stability study and test reports for 3 consecutive batches of sample products should be provided.

*8: Information should be provided according to corresponding requirements for preparations marketed outside of China in the registration categories of TCM, chemical drugs, or biological products. For the pharmaceutical study section, only test reports for 3 consecutive batches of sample products, research information during drug stability studies, basis for selection of immediate packing and container of the drugs, and quality standards should be provided.
*9: Original new drug certificate should also be provided.
*10: Transfer contract signed by the parties of the technology transfer should be provided; the relevant documents should be provided if the original drug manufacturer abandons drug manufacturing.
*11: Required separately by CFDA during evaluation and if there is a need.
*12: The certified GMP certificate of the packing enterprise issued by the competent drug administration authority in the local country or region where the packing enterpriser is located should be provided.
*13: Only the re-packing technology and process, experimental information of drug stability, basis for selection of immediate packing and container of drug, and quality standard, as well as test reports for 3 consecutive batches of the sample product, should be provided.
*14: The re-packing contract for the imported drug (including authorization of use of trademark) should be provided.
*15: Only repacking technology and process, basis for the selection of immediate packing material for the drug and container, and quality standards should be provided.
*16: Approval from relevant authorities of the change of the name, business licenses, *Drug Manufacturing Certificate*, and the GMP Certificate before and after the name is changed should be provided.
*17: Certified documents from the competent administration to approve the manufacture of the drug in a different facility should be provided.
*18: New national drug standards or the documents from CFDA requesting amendment of the insert sheet should be provided.
*19: Toxicology research information or literature may be provided.
*20: Literatures may be provided.
*21: Relevant document should be provided for change of drug packing and label as required by regulations.
*22: Only research data on drug stability and test report of drug sample from 3 consecutive batches should be provided.
*23: Only drug substance approval and certified documents showing legal sourcing of the drug substance, as well as test report for 1 batch of the preparation, should be provided.
*24: Authorization document, notarization document of the foreign drug manufacturer authorizing the domestic agent to conduct drug registration on its behalf, with Chinese translation, business license of domestic agent, and agreement document or other certified document that the original agent has waived its agency right should be provided.
#: See corresponding numbers in "IV: Notes and Relevant Requirements of Registration Items and Application Information Items."

IV. Notes and Relevant Requirements of Registration Items and Application Information Items.

1. Registration Item 1 refers to the application for manufacture of a new drug when the manufacturing conditions for the new drug are ready, but the manufacturing conditions to manufacture were not ready when the research institution of the new drug obtained New Drug Certificate, and the new drug has not been transferred to another enterprise for manufacture.
2. For Registration Item 3, adding indications or functions of TCM, or for chemical drug or biological drugs with a domestic drug having the same indication, pharmacology and toxicology studies and clinical studies should be conducted as follows:

    a) If a prolonged treatment period or increased dosage is needed for the additional indications or functions of the drug, research information and literature on main pharmacodynamics, primary pharmacology, acute toxicity, and long-term toxicity should be provided. After their approval, clinical studies should be conducted as with a new TCM.
    b) For additional TCM indications, if the treatment duration and dosage remain unchanged, pharmacodynamic data and literature should be provided and a clinical trial should be conducted with at least 100 pairs of subjects.
    c) For additional indications or functions of drugs where the same indications of the same kind of drug have been approved overseas, research information and literature on main pharmacodynamics should be provided and randomized controlled clinical trials should be conducted with at least 60 pairs of cases.

3. For Registration Item 4, for change in drug usage, drug dosage, or group of people to use the drug, the safety study information and literature to support the changes should be provided. A clinical study should be conducted if necessary. The clinical trial should focus on the major indication with at least 100 pairs of subjects.
4. Registration Item 5, change of strength of drug, should meet the following requirements:

    a) The strength of the drug in the application should be consistent with that of already-marketed drugs. The principle of being scientific, reasonable and necessary should be followed and any inconsistency identified.
    b) The strength of the drug in the application should be reasonably decided based on the drug usage and dosage, where strength should be not less than single minimal use or greater than single maximal use.

c) If there are is change both in usage or dosage and in the group of people to use the drug, information required in Registration Category 4 should also be provided, and clinical trials should be conducted when necessary.

5. Registration Item 7, a change in the drug manufacturing technology and process, should not change the basis of the material's medical use. If it does, for TCM drugs, comparison pharmacology and toxicity testing data should be provided, and a clinical trial with at least 100 pairs of cases should be conducted with a specific objective based characteristic.
6. Registration Item 9, substitution or removal of a drug material listed in National Drug Standards as toxic or endangered, refers to the substitution or removal of the drug material as applied for by the applicant, but does not refer to situations where the State uniformly requires substitution or removal.

a) For application for use of an approved substitute to TCM material to replace the TCM material in any preparation, research information on the new preparation process, drug standards and stability should be submitted. Pharmacology and toxicology and clinical information may be exempted.
b) For application for use of TCM material collected in statutory standards as replacement, if the drug material is supplemental, research information on the new preparation process, drug standards, stability, pharmacology, toxicology, and clinical information may be exempted. If the substitute is toxic drug, information on drug safety should be provided, as well as toxicology comparison test and clinical test. If the drug material acts as a primary substance, in addition to the above information, a clinical equivalence test should be conducted with the preparation of the drug. If necessary, pharmacology and toxicology comparison tests should also be conducted. If the substitute is a toxic drug, pharmacology and toxicology comparison tests should be conducted.
c) For application to remove of toxic drug, research information on the new preparation process, drug standards and stability, pharmacology and toxicology should be provided, and clinical trials should be conducted.
d) Requirements for pharmacy, pharmacology and toxicology information and clinical trials are as follows.

Pharmacy:
(1) Production process: production process should be the same as original process before and after the substitute and removal of the drug.

(2) Drug standards: specificity and content determination should be established for the substitute. If it is not possible to establish specificity and content determination, experiment information should be provided.
(3) Stability: if stability will be affected due to the substitute, stability testing should be conducted.
Pharmacology and toxicology:
After the drug material is substituted, a comparison study between the new drug and the original drug on pharmacodynamics and acute toxicity should be conducted on the main indication. After a toxic drug material is removed, a on pharmacodynamic comparison study should be conducted on the main indication between the new drug and the original drug.
Clinical trials:
Clinical trials should be conducted focusing on the major indication with at least 100 pairs of subjects.

7. Registration Item 11, combined packing of drugs, refers to packing of 2 or more drugs with independent indications and/or dosage and usage, excluding the following:

    a) Marketing of preparation made of a component of the same active substance.
    b) Lack of internationally recognized, fully developed treatment protocol as supporting basis.
    c) Drug with different route of administration.
    d) Otherwise not meeting requirements.

    No separate drug approval number will be issued for combined packing of drugs, and no monitoring period or no trade name is allowed to be used. Combined packing of drugs should also meet the following requirements:

    a) The enterprise applying for combined packing of drugs should be hold a *GMP Certificate*. The drugs to be packed should be manufactured by the enterprise itself with their drug approval numbers available.
    b) The insert sheet and packing label should be decided based on pre-clinical study and clinical trials results, but not simply by combining all insert sheets. Regulations on insert sheets and packing label should be followed.
    c) The immediate packing material should be compatible with the drug packed.
    d) The specified validity period should be the validity period for the drug with the shortest validity period.

e) The storage conditions should be compatible with the drug packed.
f) The name of the combined packing should read X/Y/Z combined packing, where X, Y and Z are the INN of each drug.

8. Registration Item 13, addition or amendment of insert sheet items for TCM or natural drugs, includes amendment involving pharmacology and toxicology, clinical trials, pharmacokinetics, etc. It does not include the addition or amendment of indication, dosage, or usage.
9. Registration Item 19, change of the name of a domestic drug manufacturer, should be done after the change of enterprise name and name change of *Drug Manufacturing License* have already been approved.
10. Registration Item 20, internal change of the manufacturing facility of a domestic drug manufacturer, includes renovation of the existing location, expansion, and new construction at a different location.
11. Registration Items 25 and 30 refers to the amendment of some item of the drug insert sheet according to uniform requirements by the CFDA, such as adverse reactions, contraindications, and precautions, excluding change of indication, usage and dosage, strength, etc.
12. Registration Items 26 and 31, supplementing and improving the safety part of the drug insert sheet: only adverse reactions, contraindication, and precaution can be added. The addition or amendment of indications, dosage, or usage are not included.
13. Registration Items 27 and 32, modification of design of packing and label of drug according to regulations, refers to modification based on the relevant drug regulation, national standards, or the approved content of the drug insert sheet.
14. Registration Item 33, change of the packing specification of drugs manufactured domestically, should meet the following requirements:

    a) The packing specification of the drug should be economic and convenient. If there is a treatment period for the drug, the packing specification should be based on the treatment period.
    b) If a disposable syringe is used for injection, or if a special solvent is used for intravenous infusion and injection, no separate name is allowed. The syringe or solvent should be registered. The validity period of the syringe or solvent should not be shorter than that of the drug packed

15. Registration Item 23 and 34, change of manufacturing location, refers to change and/or addition to the location where the raw material for a preparation is manufactured. When a domestic drug manufacturer changes the manufacturer of the raw material it uses to make its preparation, the raw material must have a drug approval number or import drug registration

certificate, as well as other certified documents showing the legal sourcing of the raw material.

16. Testing in Registration Items 1, 5-10, 12, 15, 20, and 21 should be conducted with 3 batches of drugs. In Registration Item 34, testing should be conducted with 1 batch of drugs.

APPENDIX #9

Application Dossier Items for Drug Re-Registration

I. Drugs manufactured in China

a. Certified documents

i. Certified documents of drug approval with approval of sequential changes issued by food and drug administration.
ii. Copy of *Drug Manufacturing License*.
iii. Copy of business license.
iv. Copy of *GMP Certificate*.

b. Summary of production, marketing, and random inspection during the past five years, with explanation of cases where the product failed to pass quality certification.
c. Summary of clinical use and adverse reaction during the past five years;
d. Necessary documents or explanations should be provided for any of the following cases:

i. If there is any work to be completed as required in the certified document of drug approval or re-registration approval, a summary report of work completion should be provided, with relevant information attached.
ii. During the first-time application for re-registration, if there is a need for Phase IV clinical trials, the summary report of the Phase IV clinical trial should be provided.
iii. During the first-time application for re-registration, if there is a need for a new drug monitoring period, monitoring period summary report should be provided.

e. Drug formula, production process and standards should be provided. If there is any change in these since the last registration, the specific changes should be provided with their certified approval documents.
f. Source of the raw material used for drug preparation production should be provided. If there is any change in the source, certified approval documents should be provided.
g. Sample of the current packaging, label, and insert sheet of the smallest retail package should be provided

II. Imported Drugs

a. Certified documents

i. Copies of certified *Import Drug License*, and *Drug Product License*, and approval of supplemental applications from CFDA.
ii. Notarized documents for the marketing approval from the competent drug authorities in the country or region of manufacture, as well as the *GMP Certificate* of the manufacturer, with Chinese translation.
iii. Notarized documents for approval of sequential changes issued from the competent drug authorities in the country or region of manufacture, with Chinese translation.
iv. If the drug registration is conducted by a resident office of the foreign manufacturer, a copy of their *Registration Certificate of Resident Office of Foreign Enterprise* should be submitted.
v. If the drug registration is conducted by a Chinese agent with authorization from the foreign manufacturer, the certified documents of the authorizations and notarized documents with Chinese translation should be submitted together with the copy of the domestic agent's *Business License*.

b. Summary of drug's importation and marketing in China during the past five years, with explanation of any cases where product failed to pass quality certification.
c. Summary of drug's clinical use, and adverse reactions during the past three years of marketing, since importation.
d. Necessary document or explanations should be provided for any of the following cases:

    i. If there is a need for a Phase IV clinical trial, the summary report of the Phase IV clinical trial should be provided.
    ii. If there is any work to be completed as required in the certified document of drug approval or the re-registration approval, a summary report of work completion should be provided, with relevant information attached.

e. Drug formula, production process, standards, and validation methods should be provided. If there is has been any change since the last registration, the specific change should be provided with certified approval documents.
f. Source of the raw material used for drug preparation production should be provided. If there is any change in the source, certified approval documents should be provided.
g. Sample of the current packaging, label, and insert sheet of the smallest retail package used in China should be provided.
h. The current version of the insert sheet in the original language from the original manufacturer, approved by the competent drug authorities in the country or region of manufacture, should be provided, with Chinese translation.

APPENDIX #10

Monitoring Periods for Drug Types

Note: No monitoring period will be established for the drugs not listed below.

1) New drugs for which a 5-year monitoring period will be established:

    a. TCM and Natural Drugs:

        i. Active ingredients and their preparations, extracted from plant, animal, and mineral sources, which have not been marketed in China

    b. Chemical Drugs:

        i. Drugs not yet marketed domestically or overseas:

            1. Drug substances and their preparations made by synthesis or semi-synthesis
            2. Preparations of new active chemical monomers extracted from natural sources or by fermentation
            3. Preparations of optical isomers obtained from known drugs by chiral separation or synthesis

    c. Therapeutic Biological Products:

        i. Biological products not yet marketed domestically or overseas

    d. Preventative Biological Products:

        i. Vaccines not yet marketed domestically or overseas

2) New drugs for which a 4-year monitoring period will be established:

    a. TCM and Natural Drugs:

        i. Preparations of newly found drug material
        ii. Preparations of new parts of materials to be used as drugs
        iii. Preparation of active components extracted from plant, animal, or mineral sources, which have not yet been marketed in China
        iv. Compound formula preparations of TCM and natural drugs not yet marketed in China:

            1. Compound formula preparation of TCM
            2. Formula preparations of natural drugs

3. Compound formula preparations of TCM, natural drugs and chemical drugs

b. Chemical Drugs

i. Drugs not yet marketed domestically or overseas:

1. Drugs with fewer components derived from marketed multi-component drugs
2. New compound formula preparations

ii. Preparations with changes in route of administration but not yet marketed domestically or overseas
iii. Drugs marketed overseas but not domestically:

1. Preparations already marketed overseas, and/or preparations with changes in dosage form not in route of administration

c. Therapeutic Biological Products

i. Monoclonal antibodies
ii. Gene therapy, somatic cell therapy and their preparations
iii. Allergen products
iv. Multi-component bioactive products extracted from, or made by fermentation from, human and/or animal tissues and/or body fluid,
v. New combination products made from already-marketed biological products
vi. Product that are marketed overseas but not domestically
vii. Microbial products with unapproved strains
viii. Products with structure not completely the same as already-marketed products and not yet marketed at domestic or overseas. Changes include:

1. Amino Acid Locus Mutation / Absence
2. Modification caused by a different expression system
3. Deletion
4. Changed interpretation
5. Chemical modification

ix. Products with a method of preparation different from an already-marketed product (e.g., use of different expression system, host cells)
x. Products made for the first time with recombinant DNA technology (e.g., use of recombinant technology to replace synthesis, tissue extraction or fermentation)

d. Preventative Biological Products

i. DNA vaccines
ii. Already-marketed vaccines with new adjuvants, or change of carrier of combined vaccine
iii. Non-purified vaccines or full cell vaccines (bacteria, virus) changed into purified vaccines or combined vaccines
iv. Vaccines with strains not yet approved in China (except for vaccines for influenza, vaccines for leptospirosis, and others)
v. Vaccines marketed overseas but not domestically
vi. Combined vaccines prepared with vaccines already marketed domestically
vii. Re-combination vaccine with a protective antigen spectrum different from the marketed version

3) New drugs for which a 2-year monitoring period will be established:

a. TCM and Natural Drugs

i. Preparations with the route of administration changed from an existing TCM or natural drug preparation already marketed in China
ii. Preparations with the dosage form changed from the existing TCM or natural drug preparation already marketed in China by use of special technology, such as targeted delivery, sustained-release or controlled-release preparation.

b. Chemical Drugs

i. Drugs marketed overseas but not in China:

1. Combination preparations and/or preparations with changed dosage form, but no change to route of administration
2. Preparations with changed route of administration

ii. Drug substances and their preparations with changed acid or alkaline radicals (or metallic elements), but without any pharmacological change, where the original drug entity is already approved in China
iii. Change to dosage form of existing drugs already marketed in China, but without change in route of administration, where special technology is used to change dosage form, such as targeted delivery, sustained-release or controlled-release preparation.

c. Therapeutic Biological Products

    i. Biological products with change in route of administration (excluding category 12)

d. Preventative Biological Products

    i. Vaccines manufactured with change to the other approved expressions or to other approved cellular stroma. Vaccines using a new process, which is proved to improve the safety and effectiveness of the vaccine based on laboratory data.
    ii. Vaccines with change to de-activator (method of deactivation) or de-toxicitor (method of de-toxicity)
    iii. Vaccines with change to route of administration

APPENDIX #11

Application and Approval Procedures and Timeline for Imported Drugs

1. Submit application

2. Dossier Content and Format Checking/notification of quality testing and specifications verification by CFDA (35 days)
    a. If needed, proceed with samples testing and standards verification by NICPBP (65 days / 95 days for special drugs and vaccine products)

3. Technical evaluation for clinical trials by the CDE (90 days regular/80 days fast track review)
    a. If needed, submit complementary data (4 months)
    b. If needed, submit supplementary data for CDE evaluation (40 days)

4. Administrative approval by the CFDA (30-40 days)
    a. If CFDA does not approve, must begin application process again

5. Approval for Clinical Trials

6. Notification of clinical trial protocol and list of investigators to CFDA

7. Commencement of Clinical Trials

8. Submission of clinical trial results and other amended or supplementary data

9. Acceptance by CFDA

10. Technical evaluation by CDE (150 days regular/120 days fast-track review)
    a. If needed, then submit complementary data (4 months)
    b. If needed then submit supplementary data for CDE evaluation (40 days)

11. Administrative approval by CFDA (30-40 days)
    a. If CFDA does not approve, must begin application process again

12. Approval of imported drug application

APPENDIX #12

Application and Approval Procedures and Timeline for Clinical Trials Only

1. Application Submission

2. Organize and complete site inspection and sampling by drug administration at the provincial level. (35 days)
    a. If needed, conduct sample testing and standards verification with the drug testing institute (65 days, or 95 days for special drugs and vaccines)

3. Acceptance by CFDA (5 days)

4. Technical Evaluation by the CDE (90 days regular/80 days fast-track review)
    a. If needed, submit complementary data (4 months)
    b. If needed, submit supplementary data (40 days)

5. Final approval by CFDA (30-40 days)
    a. If application is not approved, must begin application process again

6. Notification of clinical trial protocol and list of investigators for the CFDA

7. Commencement of clinical trials

APPENDIX #13

Listing of CFDA-affiliated organizations in China

1. **National Institute for the Control of Pharmaceutical and Biological Products (NICPB)**
Address: 2 Tiantan Xi Li, Beijing 100050, P. R. China
Tel: 86-10-67095114
Fax: 86-10-67018094
Email: nicpbp@nicpbp.org.cn

2. **Pharmacopoeia Commission of People's Republic of China**
Address: Building 11, Fahua Nanli, Gymnasium Road, Beijing 100061, P.R. China
Tel：86-10-67154488 67079644
Fax：86-10-67152766
Email: chpc@chp.org.cn

3. **Center for Drug Evaluation, CFDA (CDE)**
Address: Jia-1, Fuxing Road, Haidian District, Beijing 100038, P.R. China
Tel: 86-10-68585566
Fax: 86-10-68584181; 86-10-68584193, 8610-68584189
Email: cde@cde.org.cn

4. **Drug Certification Center of CFDA**
Address: 3/F, No.11 Building, Fahuananli Chongwen District, Beijing 100061, P.R. China
Tel: 86-10-67102284 (87559000 automatic, 87559009)
Fax: 86-10-67152467
Email: service@newhealth.com.cn

5. **Center for Drug Reevaluation, CFDA**
Address: Building 6, No 3 Sanlihe Area 1, Western district Beijing 100045, P.R. China
Tel：86-10-68586296
Fax：86-10-68586295)
Email: webmaster@cdr.gov.cn

6. **National Committee on the Assessment of the Protected Traditional Chinese Medicinal Products**
Address: Building 15, Southern Sihuanxi Rd Beijing 100070, P.R. China
Tel: 86-10-63703355
Fax: 86-10-63703550
Email: zybh@zybh.gov.cn

7. **Center of Medical Device Evaluation, CFDA**
Address: B3, Floor 3-5, No 5 Building, No 9 Gongzhuang Street, Western Area, Beijing 100044
P.R. China
Tel: 86-10-68390606)
Fax: 86-10-68330377
Email: cmde@cmde.org.cn

8. **Information Center of CFDA**
Address: A38, Beilishi Road, Beijing 100810, P.R. China
Tel：86-10-88363205
Fax：86-10-88363205
Email: info_center@sda.gov.cn

9. **Training Center of CFDA**
Address: 16 Xi Zhan Nan Lu, Beijing 100073, P. R. China
Tel：86-10-63365012
Fax：86-10-63263390
Email: sdatc@sdatc.com

10. **Center for Qualification of Licensed Pharmacists, CFDA**
Address：A38, Beilishi Road, Beijing 100810, P.R. China
Tel：86-10-66161121
Fax：86-10-66162391
Email:cqlpsda@263.net

11. **China Pharmaceutical News**
Address: Haidian Wenhuiyuan Nanlu A2, Beijing 100088, P. R. China
Tel：86-10-62212356
Fax: 86-10-62213699
Email: yyb@263.net.cn

12. **China Medical-Pharmaceutical Science & Technology Publishing House**
Address: A-22, Northern WenHuiYuan Road, Haidian District, Beijing 100088, P. R. China
Tel：86-10-62217308
Fax：86-10-62217308
Email: weiwang@mpsky.com.cn

13. **China Center for Pharmaceutical International Exchange**
Address: Room 5301-5312, Building B, No.6, South Street, Xizhimen, Beijing 100035, P.R. China
Tel：86-10-66152975/66155603

Fax：86-10-66161160
Email: ChinaPharm@263.net

14. **CFDA Southern Medicine Economic Institute**
Address: Lizhu building 8F, Jichang Rd. 10#, Guangzhou 510405, P.R. China
Tel：86-20-86571888-8876; 86-020-86356363
Fax：86-20-86356360
Email: meinet_wj@163.net

15. **Chinese Pharmaceutical Association (CPA)**

Address: 18/F Tower 9, Jianwai SOHO, No. 4 Jianwai Street, Chaoyang District, Beijing .....100022, P.R.C
Tel: 0086 10 58699271
Fax: 0086 10 58699272
Email: int@cpa.org.cn

APPENDIX #14

Healthcare Statistics and Pharmaceutical Markets in Asia

SIZE OF ASIAN PHARMACEUTICAL MARKETS (2009)

Country	Pharmaceutical Market Size (US$)
China	$38 billion
Hong Kong	$920 million
India	$11 billion
Indonesia	$1.7 billion
Japan	$58 billion
Malaysia	$960 million
Philippines	$720 million
Singapore	$598 million
Korea	$8 billion
Taiwan	$2.5 billion
Thailand	$1.4 billion
Vietnam	$960 million

Compiled from various sources by PBM

HEALTHCARE STATISTICS IN ASIA (2010)

Country	Number of Hospitals Beds per 1000 People	Doctors per 1000 People	Per Capita Spending on Healthcare (USD)
China	**2.5**	**1.2**	**178**
Hong Kong	**3.7**	**1.6**	**1,798**
Philippines	**0.6**	**0.8**	**61**
Indonesia	**0.5**	**0.2**	**58**
Japan	**12.0**	**2.0**	**2,748**
Malaysia	**1.5**	**0.7**	**299**
Singapore	**2.3**	**1.5**	**1,498**
South Korea	**4.4**	**2.7**	**1,098**
Taiwan	**6.0**	**1.3**	**998**
Thailand	**1.9**	**0.3**	**126**

Compiled from various sources by PBM

APPENDIX #15

The National Essential Drug List (2013): Chemical and Biological Drugs

(Translated from Chinese)

Drug	Agent/Type
Acarbose	Oral dosage forms
Acetamide	Injection
Acetaminophen (Paracetamol)	Oral dosage forms, granules
Acetazolamide	Oral dosage forms
Acyclovir (Aciclovir)	Oral dosage forms, topical ointment-type, eye drops
Albendazole	Oral dosage forms
Alfacalcidol	Oral dosage forms
Allopurinol	Oral dosage forms
Alprazolam	Oral dosage forms
Aluminum hydroxide compound	Oral dosage forms
Amantadine	Oral dosage forms
Ambroxol	Oral dosage forms, oral solution
Amikacin	Injection
Aminomethylbenzoic acid	Oral dosage forms, injection
Aminophylline	Oral dosage forms, oral sustained release formulation, injection
Amiodarone	Oral dosage forms, injection
Amitriptyline	Oral dosage forms
Amlodipine	Oral dosage forms
Amoxicillin	Oral dosage forms
Amoxicillin clavulanate potassium	Oral dosage forms, injection
Ampicillin	Injection
Anisodamine	Oral dosage forms, injection
Anti-AIDS drugs	
Arginine	Injection
Aripiprazole	Oral dosage forms
Arsenious Acid (Arsenic Trioxide)	Injection
Artemisinin drugs	
Asparaginase	Injection
Aspirin	Oral dosage forms
Atenolol	Oral dosage forms
Atropine	Oral dosage forms, injection, eye drops, eye ointment
Azathioprine	Oral dosage forms
Azithromycin	Oral dosage forms, granules
Barium sulfate	Dry suspension

Beclometasone Dipropionate	Aerosol spray solution agents
Belladonna	Oral dosage form, tincture
Benzathine Benzylpenicillin	Injection
Berberine	Oral dosage forms
Betahistine	Oral dosage forms
Bifendate	Oral dosage forms, pills
Bismuth Potassium Citrate	Oral dosage forms, granules
Bisoprolol	Oral dosage forms
Bromhexine	Oral dosage forms
Bucinnazine	Oral dosage forms, injection
Bupivacaine	Injection
Busulfan	Oral dosage forms
Calamine	Lotion
Calcium Folinate	Injection
Calcium Gluconate	Oral dosage forms, injection
Captopril	Oral dosage forms
Carbamazepine	Oral dosage forms
Carboplatin	Injection
Cefazolin	Injection
Cefradine	Oral dosage forms
Ceftazidime	Injection
Ceftriaxone	Injection
Cefuroxime	Oral dosage forms, injection
Cephalexin (Cefalexin)	Oral dosage forms, granules
Chloramphenicol	Eye drops
Chloroquine	Oral dosage forms, injection
Chlorpheniramine (Chlorphenamine)	Oral dosage forms
Chlorpromazine	Oral dosage forms, injection
Chorionic Gonadotrophin	Injection
Ciclosporin	Oral dosage forms, oral solution
Ciprofloxacin	Oral dosage forms, injection
Cisplatin	Injection
Citicoline Sodium	Injection
Clarithromycin	Oral dosage forms, granules
Clindamycin	Oral dosage forms, injection
Clomipramine	Oral dosage forms, injection
Clonazepam	Oral dosage forms
Clopidogrel	Oral dosage forms
Clotrimazole	Suppository
Clozapine	Oral dosage forms
Cobamamide	Oral dosage forms

Codeine	Oral dosage forms
Colchicine	Oral dosage forms
Colloidal Bismuth Pectin	Oral dosage forms
Compound Amino Acid 18AA	Injection
Compound Hypoensive	Oral dosage forms
Compound Piphenoxylate	Oral dosage forms
Compound Reserpine	Oral dosage forms
Compound sodium chloride	Injection
Compound Sulfamethoxazole	Oral dosage forms
Contraceptives	
Cortisone	Eye drops, eye ointment
Cyclophosphamide	Oral dosage forms, injection
Cyproheptadine	Oral dosage forms
Cytarabine	Injection
Dapsone	Oral dosage forms
Daunorubicin	Injection
Deslanoside	Injection
Desmopressin	Oral dosage forms, injection
Dextran (40,70)	Injection
Diazepam	Oral dosage forms, injection
Diethylstilbestrol	Oral dosage forms
Difenidol	Oral dosage forms
Digoxin	Oral dosage forms, injection
Diltiazem	Oral dosage forms
Diphenhydramine	Oral dosage forms, injection
Dipyridamole	Oral dosage forms
Dirithromycin	Oral dosage forms
Dobutamine	Injection
Domperidone	Oral dosage forms
Dopamine	Injection
Doxepin	Oral dosage forms
Doxorubicin	Injection
Doxycycline	Oral dosage forms
Enalapril	Oral dosage forms
Ephedrine	Nasal drops
Epinephrine (Adrenaline)	Injection
Ergotamine and caffeine	Oral dosage forms
Erythromycin	Oral dosage forms, injection, topical ointment-type, eye ointment
Estazolam	Oral dosage forms
Ethacridine	External-use solution, injection
Ethambutol	Oral dosage forms

Etoposide	Injection
Famotidine	Oral dosage forms, injection
Fentanyl	Injection
Ferrous Succinate	Oral dosage forms
Ferrous Sulfate	Oral dosage forms, oral sustained-release formulation
Fluocinonide	Topical ointment-type
Fluconazole	Oral dosage forms, injection
Flumazenil	Injection
Flunarizine	Oral dosage forms
Fluphenazine Decanoate	Injection
Fluorouracil	Injection
Folic Acid	Oral dosage forms
Fosfomycin	Injection
Furosemide	Oral dosage forms, injection
Gentamicin (Gentamycin)	Injection
Glibenclamide	Oral dosage forms
Glimepiride	Oral dosage forms
Glipizide	Oral dosage forms
Glucose	Injection
Glucose and Sodium Chloride	Injection
Glycerine Enema or Sorbitol Enema	Enema
Glycyrrhizin (Compound Liquorice)	Oral dosage forms, oral solution
Haloperidol	Oral dosage forms, injection
Hemophilia drugs	
Heparin	Injection
Homoharringtonine	Injection
Huperzine A	Oral dosage forms
Hydrochlorothiazide	Oral dosage forms
Hydrocortisone	Oral dosage forms, injection, topical ointment-type
Hydroxycarbamide	Oral dosage forms
Hydroxyethyl Starch 130/0.4	Injection
Ibuprofen	Oral dosage forms
Ichthyol (Ichthammol)	Topical ointment-type
Indapamide	Oral dosage forms, oral sustained-release formulation
Indomethacin (Indometacin)	Suppository
Insulin	Oral dosage forms, injection
Iodinated Oil	Injection
Iohexol	Injection
Ipratropium Bromide	Aerosol spray solution agents
Iron Dextran	Injection
Isoflurane	Tincture

Isoniazid	Oral dosage forms, injection
Isoproterenol (Isoprenaline)	Injection
Isosorbide mononitrate (Isosorbide Dinitrate)	Oral dosage forms, injection
Ketamine	Injection
Lactasin	Oral dosage forms
Levodopa and Benserazide Hydrochloride	Oral dosage forms
Levofloxacin	Oral dosage forms, injection, eye drops
Levothyroxine Sodium	Oral dosage forms
Lidocaine	Injection
Lithium Carbonate	Oral dosage forms
Live Bacillus Licheniformis	Oral dosage forms, granules
Live Combined Bifidobacterrium, Lactobacillus and Enterococcus	Oral dosage forms
Lobeline	Injection
Loratadine	Oral dosage forms
Lorazepam	Oral dosage forms
Low Molecular Heparin	Injection
Macrogol	Oral powder
Maglumine Diatrizoate	Injection
Magnesium Sulfate	Injection
Mannitol	Injection
Medroxyprogesterone	Oral dosage forms
Meglumine Diatrizoate	Injection
Menadiol	Oral dosage forms
Mercaptopurine	Oral dosage forms
Mesna	Injection
Metaraminol	Injection
Metformin	Oral dosage forms
Methimazole (Thiamazole)	Oral dosage forms
Methotrexate	Oral dosage forms, injection
Methyltestosterone	Oral dosage forms
Methylthioninium Chloride	Injection
Methysergide (Ergometrine)	Injection
Metoclopramide	Oral dosage forms, injection
Metoprolol	Oral dosage forms, injection
Metronidazole	Oral dosage forms, injection, vaginal effervescent tablets, suppositories
Mexiletine	Oral dosage forms
Miconazole	Topical ointment-type, suppository
Midazolam	Injection
Mifepristone	Oral dosage forms
Misoprostol	Oral dosage forms
Mitomycin	Injection

Montmorillonite (Smectite)	Oral powder
Morphine	Oral dosage forms, injection, oral sustained-release formulation
Multidrug-resistant TB drugs	
Naloxone	Injection
Nandrolone Phenylpropionate	Injection
National Immunization Program vaccine	
Neostigmine	Injection
Nifedipine	Oral dosage forms
Nikethamide	Injection
Nilestriol	Oral dosage forms
Nimodipine	Oral dosage forms
Nitrendipine	Oral dosage forms
Nitrofurantoin	Oral dosage forms
Nitroglycerin	Oral dosage forms, injection
Norepinephrine (Noradrenaline)	Injection
Norfloxacin	Oral dosage forms
Nystatin (Nysfungin)	Oral dosage forms
Ofloxacin	Ear drops
Omeprazole	Oral dosage forms, injection
Ondansetron	Oral dosage forms
Oral Rehydration Salts	Oral powder
Oxacillin	Oral dosage forms, injection
Oxaliplatin	Injection
Oxytocin	Injection
Paclitaxel	Injection
Paroxetine	Oral dosage forms
Penfluridol	Oral dosage forms
Penicillin (Benzylpenicillin)	Injection
Pentoxyverine	Oral dosage forms
Peritoneal Dialysis Solution	Injection
Perphenazine	Oral dosage forms, injection
Pethidine	Injection
Phenobarbital	Oral dosage forms, injection
Phenolphthalein	Oral dosage forms
Phentolamine	Injection
Phenytoin Sodium	Oral dosage forms, injection
Pilocarpine	Injection, eye drops
Piperacillin	Injection
Posterior pituitary injection	Injection
Potassium chloride	Regular release dosage form of oral, sustained Oral dosage form, granules, injection
Pralidoxime Iodide	Injection

Pralidoxime Chloride	Injection
Praziquantel	Oral dosage forms
Prazosin	Oral dosage forms
Prednisone	Oral dosage forms
Primaquine	Oral dosage forms
Procainamide	Injection
Procaine	Injection
Progesterone	Injection
Promethazine	Oral dosage forms, injection
Propafenone	Oral dosage forms, injection
Propofol	Injection
Propranolol	Oral dosage forms
Propylthiouracil	Oral dosage forms
Protamine	Injection
Purified Protein Derivative of Tuberculin	Injection
Pyrazinamide	Oral dosage forms
Pyridostigmine Bromide	Oral dosage forms
Pyrimethamine	Oral dosage forms
Quetiapine	Oral dosage forms
Rabies Antiserum	Injection
Ranitidine	Oral dosage forms, injection
Ribavirin	Oral dosage forms, granules, injection
Rifampicin	Oral dosage forms, eye drops
Risperidone	Oral dosage forms
Salbutamol	Aerosol spray solution agents
Salicylic Acid	Topical ointment-type
Semustine	Oral dosage forms
Simvastatin	Oral dosage forms
Snake Antivenin	Injection
Sodium Aminosalicylate	Oral dosage forms, injection
Sodium antimony gluconate (Sodium Stibogluconate)	Injection
Sodium Bicarbonate	Oral dosage forms, injection
Sodium Chloride	Injection
Sodium Diclofenac	Oral dosage forms, oral sustained-release formulation
Sodium Lactate Ringer	Injection
Sodium Morrhuate	Injection
Sodium Nitroprusside	Injection
Sodium Thiosulfate	Injection
Sodium Valproate	Oral dosage forms
Spironolactone	Oral dosage forms
Streptomycin	Injection

Sulfadiazine	Oral dosage forms, injection
Sulfadiazine Silver	Topical ointment-type
Sulfasalazine	Oral dosage forms, suppository
Sulpiride	Oral dosage forms
Suxamethonium Chloride	Injection
Tamoxifen	Oral dosage forms
Tegafur	Oral dosage forms
Tamsulosin	Oral sustained-release formulation
Terazosin	Oral dosage forms
Testosterone Propionate	Injection
Tetanus antitoxin	Injection
Theophylline	Oral dosage forms, oral sustained-release formulation
Thrombin	Freeze-dried powder for external use
Thyroid Tablets	Oral dosage forms
Timolol	Eye drops
Tinidazole	Oral dosage forms
Tranexamic Acid	Injection
Tretinoin	Oral dosage forms
Triamterene	Oral dosage forms
Trihexyphenidyl (Benzhexol)	Oral dosage forms
Tripterygium Glycosides	Oral dosage forms
Urea	Topical ointment-type
Urokinase	Injection
Ursodeoxycholic acid	Oral dosage forms
Valsartan	Oral dosage forms
Vecuronium Bromide	Injection
Verapamil	Oral dosage forms, injection
Victoria A acid (Tretinoin)	Type of topical ointment, gels
Vincristine	Injection
Vitamin B_1	Injection
Vitamin B_{12}	Injection
Vitamin B_2	Oral dosage forms
Vitamin B_6	Oral dosage forms, injection
Vitamin C	Oral dosage forms, injection
Vitamin D_2	Oral dosage forms, injection
Vitamin K_1	Injection
Warfarin	Oral dosage forms
Zopiclone	Oral dosage forms

Source: Ministry of Health

APPENDIX #16

The National Essential Drug List (2009): Chemical and Biological Drugs

(Translated from Chinese)

Drug	Agent/Type
Acetamide	Injection
Acetaminophen (Paracetamol)	Oral dosage forms, granules
Acetazolamide	Oral dosage forms
Acyclovir	Topical ointment-type
Acyclovir	Eye drops
Acyclovir (Aciclovir)	Oral dosage forms
Albendazole	Oral dosage forms
Allopurinol	Oral dosage forms
Aluminum hydroxide compound	Oral dosage forms
Amantadine	Oral dosage forms
Ambroxol	Oral dosage forms, oral solution
Amikacin	Injection
Aminomethylbenzoic acid	Oral dosage forms
Aminophylline	Oral dosage forms, oral sustained release formulation, injection
Amiodarone	Oral dosage forms, injection
Amitriptyline	Oral dosage forms
Amoxicillin	Oral dosage forms
Amoxicillin clavulanate potassium	Oral dosage forms
Ampicillin	Injection
Anisodamine	Oral dosage forms, injection
Anti-AIDS drugs	
Artemisinin drugs	
Aspirin	Oral dosage forms
Aspirin	Oral dosage forms
Atenolol	Oral dosage forms
Atropine	Oral dosage forms, injection
Atropine	Eye drops, eye ointment
Azathioprine	Oral dosage forms
Azithromycin	Oral dosage forms, granules
Barium sulfate	Dry suspension
Belladonna	Oral dosage form, tincture
Berberine	Oral dosage forms
Bifendate	Oral dosage forms, pills
Bismuth Potassium Citrate	Oral dosage forms

Bromhexine	Oral dosage forms
Bupivacaine	Injection
Calcium Gluconate	Oral dosage forms, injection
Captopril	Oral dosage forms
Carbamazepine	Oral dosage forms
Cefazolin	Injection
Ceftriaxone	Injection
Cefuroxime	Oral dosage forms, injection
Cephalexin (Cefalexin)	Oral dosage forms, granules
Chloromycetin	Eye drops
Chloroquine	Oral dosage forms, injection
Chlorpheniramine	Oral dosage forms
Chlorpromazine	Oral dosage forms, injection
Chorionic Gonadotrophin	Injection
Ciprofloxacin	Oral dosage forms, injection
Citicoline	Injection
Clindamycin	Oral dosage forms, injection
Colchicine	Oral dosage forms
Compound Amino Acid 18AA	Injection
Compound Reserpine	Oral dosage forms
Compound Reserpine Triamterene	Oral dosage forms
Compound sodium chloride	Injection
Compound Sulfamethoxazole	Oral dosage forms
Contraceptives	
Cortisone	Eye drops, eye ointment
Cyproheptadine	Oral dosage forms
Dapsone	Oral dosage forms
Deslanoside	Injection
Dexamethasone	Oral dosage forms, injection
Dextran (40,70)	Injection
Diazepam	Oral dosage forms, injection
Diclofenac	Oral dosage forms, oral sustained-release formulation
Difenidol	Oral dosage forms
Digoxin	Oral dosage forms, injection
Diphenhydramine	Oral dosage forms, injection
Dipyridamole	Oral dosage forms
Dobutamine	Injection
Domperidone	Oral dosage forms
Dopamine	Injection
Doxepin	Oral dosage forms
Enalapril	Oral dosage forms

Enema	Enema
Ephedrine	Nasal drops
Epinephrine (Adrenaline)	Injection
Ergotamine and caffeine	Oral dosage forms
Erythromycin	Oral dosage forms, injection
Erythromycin	Topical ointment-type
Erythromycin	Eye ointment
Estazolam	Oral dosage forms
Ethambutol	Oral dosage forms
Famotidine	Oral dosage forms, injection
Fentanyl	Injection
Ferrous Sulfate	Oral dosage forms, oral sustained-release formulation
Fluconazole	Oral dosage forms
Folic Acid	Oral dosage forms
Fosfomycin	Injection
Furosemide	Oral dosage forms, injection
Gentamicin	Injection
Glibenclamide	Oral dosage forms
Glipizide	Oral dosage forms
Glucose	Injection
Glucose and Sodium Chloride	Injection
Glycyrrhizin	Oral dosage forms, oral solution
Haloperidol	Oral dosage forms, injection
Heparin	Injection
Hydrochlorothiazide	Oral dosage forms
Hydrocortisone	Oral dosage forms, injection
Hydrocortisone	Topical ointment-type
Ibuprofen	Oral dosage forms
Ichthyol (Ichthammol)	Topical ointment-type
Indapamide	Oral dosage forms, oral sustained-release formulation
Indomethacin	Suppository
Insulin	Injection
Iron Dextran	Injection
Isoniazid	Oral dosage forms, injection
Isoproterenol (Isoprenaline)	Injection
Isosorbide mononitrate (Isosorbide Dinitrate)	Oral dosage forms, injection
Ketamine	Injection
Lactasin	Oral dosage forms
Levofloxacin	Oral dosage forms, injection
Levofloxacin	Eye drops
Lidocaine	Injection

Lobeline	Injection
Magnesium Sulfate	Injection
Mannitol	Injection
Medroxyprogesterone	Oral dosage forms
Meglumine Diatrizoate	Injection
Metaraminol	Injection
Metformin	Oral dosage forms
Methimazole (Thiamazole)	Oral dosage forms
Methyltestosterone	Oral dosage forms
Methylthioninium Chloride	Injection
Methysergide (Ergometrine)	Injection
Metoclopramide	Oral dosage forms, injection
Metoprolol	Oral dosage forms, injection
Metronidazole	Oral dosage forms, injection
Metronidazole	Vaginal effervescent tablets, suppositories
Mexiletine	Oral dosage forms
Miconazole	Topical ointment-type
Miconazole	Suppository
Montmorillonite (Smectite)	Oral powder
Naloxone	Injection
National Immunization Program vaccine	
Neostigmine	Injection
Nifedipine	Oral dosage forms
Nikethamide	Injection
Nimodipine	Oral dosage forms
Nitrendipine	Oral dosage forms
Nitrofurantoin	Oral dosage forms
Nitroglycerin	Oral dosage forms, injection
Norepinephrine (Noradrenaline)	Injection
Norfloxacin	Oral dosage forms
Nystatin	Oral dosage forms
Ofloxacin	Ear drops
Omeprazole	Oral dosage forms
Oral Rehydration Salts	Oral powder
Oxacillin	Injection
Oxytocin	Injection
Penicillin (Benzylpenicillin)	Injection
Pentoxyverine	Oral dosage forms
Perphenazine	Oral dosage forms, injection
Pethidine	Injection
Phenobarbital	Oral dosage forms, injection

Phenolphthalein	Oral dosage forms
Phentolamine	Injection
Phenytoin Sodium	Oral dosage forms, injection
Pilocarpine	Injection, eye drops
Piperacillin	Injection
Posterior pituitary injection	Injection
Potassium chloride	Regular release dosage form of oral, sustained Oral dosage form, granules, injection
Pralidoxime Chloride	Injection
Praziquantel	Oral dosage forms
Prednisone	Oral dosage forms
Primaquine	Oral dosage forms
Procainamide	Injection
Procaine	Injection
Progesterone	Injection
Promethazine	Oral dosage forms, injection
Propafenone	Oral dosage forms, injection
Propranolol	Oral dosage forms
Propylthiouracil	Oral dosage forms
Pyrazinamide	Oral dosage forms
Rabies Antiserum	Injection
Ranitidine	Oral dosage forms, injection
Ribavirin	Oral dosage forms, granules, injection
Rifampicin	Oral dosage forms
Salbutamol	Aerosol spray solution agents
Salicylic Acid	Topical ointment-type
Simvastatin	Oral dosage forms
Snake Antivenin	Injection
Sodium Aminosalicylate	Oral dosage forms, injection
Sodium antimony gluconate (Sodium Stibogluconate)	Injection
Sodium Bicarbonate	Oral dosage forms, injection
Sodium Chloride	Injection
Sodium Lactate Ringer	Injection
Sodium Nitroprusside	Injection
Sodium Thiosulfate	Injection
Sodium Valproate	Oral dosage forms
Spironolactone	Oral dosage forms
Streptomycin	Injection
Terazosin	Oral dosage forms
Testosterone Propionate	Injection
Tetanus antitoxin	Injection
Theophylline	Oral dosage forms, oral sustained-release formulation

Thrombin	Freeze-dried powder for external use
Thyroid Tablets	Oral dosage forms
Timolol	Eye drops
Triamterene	Oral dosage forms
Trihexyphenidyl (Benzhexol)	Oral dosage forms
Tripterygium Glycosides	Oral dosage forms
Urea	Topical ointment-type
Ursodeoxycholic acid	Oral dosage forms
Verapamil	Oral dosage forms, injection
Victoria A acid (Tretinoin)	Type of topical ointment, gels
Vitamin B_1	Injection
Vitamin B_{12}	Injection
Vitamin B_2	Oral dosage forms
Vitamin B_6	Oral dosage forms
Vitamin C	Oral dosage forms
Vitamin D_2	Oral dosage forms, injection
Vitamin K_1	Injection

Source: Ministry of Health

APPENDIX #17

National Reimbursement Drug List (2009): Western Medicines

(Translated from Chinese)

Notes:

- Drugs in reimbursement Class A are reimbursed in full, at a low, fixed price. Drugs in Class B are reimbursed on a percentage basis, the exact percentage determined by the provincial government.
- In many cases, more than one reimbursement class will be listed for a drug, for example, "A, B." This means that the drug occupies different classes depending on its formulation. For example, Cefradine is a Class A drug when in oral form, and a Class B drug when in injectable form. The classes in the right-hand column are listed in the same order as the formulations of the drug in the left-hand column.
- In rare cases, the same preparation of the same drug may be in different reimbursement classes depending on its indication or other factors. For example, Lamivudine is a Class A drug when used for AIDS, and a Class B drug when used for hepatitis B. This is indicated with "A/B."
- For quick reference, this list is arranged alphabetically. However, for reference to the original list, the identifying number for each drug is included.

Number	Drug	Formulation/Type	Reimbursement class
1	Benzylpenicillin	Injection	A
2	Phenoxymethylpenicillin	Oral dosage forms	A
3	Benzathine Benzylpenicillin	Injection	B
4	Procaine Benzylpenicillin	Injection	B
5	Oxacillin	Injection	A
5	Oxacillin	Oral dosage forms	B
6	Cloxacillin	Injection	A
7	Amoxicillin	Oral dosage forms	A
7	Amoxicillin	Oral liquid agent	B
8	Ampicillin	Injection	A
9	Piperacillin	Injection	A
10	Azlocillin	Injection	B
11	Sulbenicillin	Injection	B
12	Mezlocillin	Injection	B
13	Amoxicillin and Clavulanate	Oral dosage forms	A
13	Amoxicillin and Clavulanate	Injection	B
13	Amoxicillin and Clavulanate	Oral liquid agent	B

14	Amoxicillin and Sulbactam	Injection	B
15	Ampicillin and Sulbactam	Injection	B
16	Mezlocillin and Sulbactam	Injection	B
17	Piperacillin and Sulbactam	Injection	B
18	Piperacillintazobactam		B
19	Sutbactam	Injection	B
20	Ticarcillin and Clavulanate	Injection	B
21	Cefalexin	Oral dosage forms	A
22	Cefradine	Oral dosage forms	A
22	Cefradine	Injection	B
23	Cefadroxil	Oral dosage forms	B
24	Cefazolin	Injection	A
25	Cephathiamidine	Injection	B
26	Cefuroxime	Oral dosage forms	A
26	Cefuroxime	Injection	A
27	Cefprozil	Oral dosage forms	B
28	Cefaclor	Oral dosage forms	B
29	Cefmetazole	Injection	B
30	Cefotiam	Injection	B
31	Cefoxitin	Injection	B
32	Cefdinir	Oral dosage forms	B
33	Cefixime	Oral dosage forms	B
34	Cefotaxime	Injection	A
35	Ceftriaxone	Injection	A
36	Latamoxef	Injection	B
37	Cefminox	Injection	B
38	Cefoperazone and Sulbactam	Injection	B
39	Ceftazidime	Injection	B
40	Ceftizoxime	Injection	B
41	Cefepime	Injection	B
42	Cefpirome	Injection	B
43	Biapenem	Injection	B
44	Faropenem	Oral dosage forms	B
45	Meropenem	Injection	B
46	Panipenem and Betamipron	Injection	B
47	Imipenem and Cilastatin	Injection	B
48	Amikacin	Injection	A
49	Gentamicin	Injection	A

49	Gentamycin	Oral dosage forms	B
49	Gentamicin	Eye drops	A
50	Spectinomycin	Injection	B
51	Netilmicin	Injection	B
52	Tobramycin	Injection	B
52	Tobramycin	Eye drops	B
53	Etimicin	Injection	B
54	Isepamicin	Injection	B
55	Chloramphenicol	Injection	A
55	Chloramphenicol	Eye drops	A
56	Doxycycline	Oral dosage forms	A
57	Tetracycline	Oral dosage forms	A
57	Tetracycline	Ointment	B
58	Oxytetracycline	Oral dosage forms	A
59	Minocycline	Oral dosage forms	B
60	Azithromycin	Oral dosage forms	A
60	Azithromycin	Injection	B
61	Erythromycin	Oral dosage forms	A
61	Erythromycin	Injection	A
61	Erythromycin	Ointment	A
61	Erythromycin	Eye ointment	A
62	Dirithromycin	Oral dosage forms	B
63	Erythromycin Ethylsuccinate	Oral dosage forms	B
64	Clarithromycin	Oral dosage forms	B
65	Roxithromycin	Oral dosage forms	B
66	Acetylspiramycin	Oral dosage forms	B
67	Norvancomycin	Injection	B
68	Teicoplanin	Injection	B
69	Vancomycin	Injection	B
70	Clindamycin	Oral dosage forms	A
70	Clindamycin	Injection	A
70	Clindamycin	Ointment	B
70	Clindamycin	External liquid agent	B
71	Lincomycin	Injection	A
71	Lincomycin	Oral dosage forms	B
71	Lincomycin	Ointment	B
71	Lincomycin	Eye drops	B
71	Lincomycin	Ear drops	A

72	Fosfomycin	Injection	A
72	Fosfomycin	Oral dosage forms	B
73	Aztreonam	Injection	B
74	Polymyxin B	Injection	B
75	Fusidic Acid	Injection	B
75	Fusidic Acid	Ointment	B
76	Colistin	Injection	B
76	Colistin	Oral dosage forms	B
77	Compound Sulfamethoxazole	Oral dosage forms	A
77	Compound Sulfamethoxazole	Injection	B
78	Sulfadiazine	Oral dosage forms	A
78	Sulfadiazine	Injection	A
79	Trimethoprim	Oral dosage forms	B
80	Sulfamethoxazole, Sulfadiazine and Trimethoprim	Oral dosage forms	B
81	Pipemidic Acid	Oral dosage forms	A
82	Ciprofloxacin	Oral dosage forms	A
82	Ciprofloxacin	Injection	A
82	Ciprofloxacin	Ointment	A
82	Ciprofloxacin	Eye drops	B
82	Ciprofloxacin	Ear drops	B
83	Norfloxacin	Oral dosage forms	A
83	Norfloxacin	Ointment	B
83	Norfloxacin	Eye drops	B
84	Ofloxacin	Injection	A
84	Ofloxacin	Oral dosage forms	B
84	Ofloxacin	Eye drops	B
84	Ofloxacin	Ear drops	A
85	Levofloxacin	Oral dosage forms	A
85	Levofloxacin	Injection	A
85	Levofloxacin	Eye drops	A
85	Levofloxacin	Eye gel	B
85	Levofloxacin	Ear drops	B
86	Fleroxacin	Injection	B
87	Gemifloxacin	Oral dosage forms	B
88	Lomefloxacin	Oral dosage forms	B
88	Lomefloxacin	Injection	B
88	Lomefloxacin	Ear drops	B
89	Maxifloxacin	Oral dosage forms	B

89	Maxifloxacin	Injection	B
90	Metronidazole	Oral dosage forms	A
90	Metronidazole	Injection	A
90	Metronidazole	Gel	B
90	Metronidazole	Vaginal Effervescent Tablets	A
91	Ornidazole	Injection	B
92	Tinidazole	Oral dosage forms	B
92	Tinidazole	Injection	B
92	Tinidazole	External liquid agent	B
92	Tinidazole	Vaginal Effervescent Tablets	B
93	Levornidazole	Injection	B
94	Nitrofurantoin	Oral dosage forms	A
95	Furazolidone	Oral dosage forms	A
96	Pyrazinamide	Oral dosage forms	A
97	Sodium Aminosalicylate	Oral dosage forms	A
97	Sodium Aminosalicylate	Injection	A
98	Rifapentine	Oral dosage forms	A
99	Rifampicin	Oral dosage forms	A
99	Rifampicin	Injection	B
99	Rifampicin	Eye drops	A
100	Streptomycin	Injection	A
101	Ethambutol	Oral dosage forms	A
102	Isoniazid	Oral dosage forms	A
102	Isoniazid	Injection	A
103	Protionamide	Oral dosage forms	B
104	Capreomycin	Injection	B
105	Rifabutin	Oral dosage forms	B
106	Rifamycin	Injection	B
107	Pasiniazid	Oral dosage forms	B
108	Ethambutol, Pyrazinamide, Rifampicin and Isoniazid Ⅱ	Oral dosage forms	B
109	Ethambutol Rifampicin and Isoniazid	Oral dosage forms	B
110	Isoniazid and Rifampicin	Oral dosage forms	B
111	Isoniazid, Rifampicin and Pyrazinamide	Oral dosage forms	B
112	Dapsone	Oral dosage forms	A
113	Acedapsone	Injection	A
114	Clofazimine	Oral dosage forms	B
115	Clotrimazole	Oral dosage forms	B
115	Clotrimazole	Ointment	A

115	Clotrimazole	Ear drops	B
115	Clotrimazole	Patch	B
115	Clotrimazole	Vaginal tablets	A
116	Miconazole	Oral dosage forms	B
116	Miconazole	Injection	B
116	Miconazole	Ointment	A
116	Miconazole	Suppository	A
116	Miconazole	Vaginal Effervescent Tablets	B
117	Fluconazol	Oral dosage forms	A
117	Fluconazol	Injection	B
117	Fluconazole	Eye drops	B
118	Voriconazole	Oral dosage forms	B
118	Voriconazole	Oral liquid agent	B
118	Voriconazole	Injection	B
119	Itraconazole	Oral dosage forms	B
119	Itraconazole	Oral liquid agent	B
119	Itraconazole	Injection	B
120	Nysfungin	Oral dosage forms	A
120	Nysfungin	Vaginal Effervescent Tablets	A
121	Amphotericin B	Injection	B
122	Caspofungin	Injection	B
123	Micafungin	Injection	B
124	Flucytosine	Oral dosage forms	B
124	Flucytosine	Injection	B
125	Terbinafine	Oral dosage forms	B
125	Terbinafine	Ointment	B
126	Aciclovir	Oral dosage forms	A
126	Aciclovir	Injection	B
126	Aciclovir	Ointment	A
126	Aciclovir	Eye drops	A
127	Ribavirin	Oral dosage forms	A
127	Ribavirin	Injection	A
127	Ribavirin	Eye drops	A
127	Ribavirin	Nasal drops	B
128	Valaciclovir	Oral dosage forms	B
129	Famciclovir	Oral dosage forms	B
129	Famciclovir	Injection	B
130	Ganciclovir	Oral dosage forms	B

130	Ganciclovir	Injection	B
130	Ganciclovir	Eye gel	B
131	Adefovir Dipivoxil	Oral dosage forms	B
132	Enfuvirtide	Injection	B
133	Emtricitabine	Oral dosage forms	B
134	Entecavir	Oral dosage forms	B
135	Lamivudine	Oral dosage forms	B
136	Zidovudine and Lamivudine	Oral dosage forms	B
137	Telbivudin	Oral dosage forms	B
138	Oseltamivir	Oral dosage forms	B
139	Rimantadine	Oral dosage forms	B
140	Saquinavir	Oral dosage forms	B
141	AntiAIDS drugs		A
142	Foscarnet Sodium	Injection	B
143	Berberine	Oral dosage forms	A
144	Houttuyfonate	Oral dosage forms	A
145	Garlicin	Oral dosage forms	B
145	Garlicin	Injection	B
146	Linezolid	Oral dosage forms	B
146	Linezolid	Injection	B
147	Praziquantel	Oral dosage forms	A
148	Bithionol	Oral dosage forms	A
149	Diethylcarbamazine	Oral dosage forms	A
150	Artemether	Oral dosage forms	A
151	Artemisinin drugs		A
152	Artemisinin	Suppository	B
153	Primaquine	Oral dosage forms	A
154	Quinine	Oral dosage forms	A
154	Quinine	Injection	B
155	Chloroquine	Oral dosage forms	A
155	Chloroquine	Injection	A
156	Pyrimethamine	Oral dosage forms	A
156	Pyrimethamine	Patch	B
157	Sulfadoxine	Oral dosage forms	B
158	Malaridine	Oral dosage forms	B
158	Malaridine	Injection	B
159	Piperaquine	Oral dosage forms	B
160	Hydroxychloroquine	Oral dosage forms	B

161	Mebendazol	Oral dosage forms	A
162	Albendazole	Oral dosage forms	A
163	Niclosamide	Oral dosage forms	B
164	Piperazine	Oral dosage forms	B
164	Piperazine	Tablets	B
165	Pyrantel Pamoate	Oral dosage forms	B
165	Pyrantel Pamoate	Ointment	B
166	Sodium Stibogluconate	Oral dosage forms	A
166	Sodium Stibogluconate	Injection	A
167	Pentamidine	Oral dosage forms	A
167	Pentamidine	Injection	B
168	Diiodohydroxyquinoline	Oral dosage forms	B
169	Emetine	Injection	B
170	Aspirin	Oral dosage forms	A
171	Ibuprofen	Oral dosage forms	A
171	Ibuprofen	Oral liquid agent	B
171	Ibuprofen	Suppository	B
171	Ibuprofen	Cream	B
172	Paracetamol	Oral dosage forms	A
172	Paracetamol	Slow release formulation	B
173	Diclofenac	Oral dosage forms	A
174	Indometacin	Suppository	A
174	Indometacin	Oral dosage forms	B
175	Metamizole	Oral dosage forms	B
176	Piroxicam	Oral dosage forms	B
177	Aceclofenac	Oral dosage forms	B
178	Flurbiprofen Axetil	Injection	B
179	Compound Aspirin Preparations	Oral dosage forms	B
180	Compound Paracetamol	Oral dosage forms	B
181	Ibuprofen Arginine	Granules	B
182	Lysine Acetylsalicylate	Injection	B
183	Lornoxicam	Injection	B
184	Loxoprofen	Oral dosage forms	B
185	Meloxicam	Oral dosage forms	B
186	Nabumetone	Oral dosage forms	B
187	Naproxen	Oral dosage forms	B
188	Sulindac	Oral dosage forms	B
189	Didofenac Diethylamine	软膏剂	B

190	Nimesulide	Oral dosage forms	B
191	Parecoxib	Injection	B
192	Celecoxib	Oral dosage forms	B
193	Compound Aminopyrine Phenacetin Tablets (Somedon)	Oral dosage forms	A
194	Glucosamine	Oral dosage forms	B
195	Glucosamine Indomethacin	Oral dosage forms	B
196	Peptide injection preparations of animal bones	Injection	B
197	Compound Chlorzoxazone	Oral dosage forms	B
198	Cold symptoms relief, OTC preparation of compound		B
199	Capsaicin	Ointment	B
200	Leflunomide	Oral dosage forms	B
201	Colchicine	Oral dosage forms	A
202	Allopurinol	Oral dosage forms	A
202	Allopurinol	Slow release formulation	B
203	Benzbromarone	Oral dosage forms	B
204	Probenecid	Oral dosage forms	B
205	Fentanyl	Injection	A
205	Fentanyl	Patch	B
206	Pethidine	Injection	A
207	Morphine	Oral dosage forms	A
207	Morphine	Injection	A
207	Morphine	Slow release formulation	B
208	Oxycodone and acetaminophen		B
209	Butorphanol	Injection	B
210	Methadone	Oral dosage forms	B
210	Methadone	Injection	B
211	Oxycodone	Oral dosage forms	B
212	Remifentanil	Injection	B
213	Sufentanyl	Injection	B
214	Dihydrocodeine	Oral dosage forms	B
215	Paracetamol and Codeine Phosphate	Oral dosage forms	B
216	Paracetamol and Tramadol	Oral dosage forms	B
217	Paracetamol and dihydrocodeine		B
218	Bucinnazine	Oral dosage forms	B
218	Bucinnazine	Injection	B
219	Bulleyaconitine A	Oral dosage forms	B
220	Propoxyphene Napsylate and Paracetamol	Oral dosage forms	B

221	Rotundine	Oral dosage forms	B
221	Rotundine	Injection	B
222	Ibuprofen and Codeine	Oral dosage forms	B
223	Tramadol	Oral dosage forms	B
223	Tramadol	Injection	B
224	Tetrahydropalmatine	Oral dosage forms	B
225	Enflurane	Liquid dosage forms	A
226	Isoflurane	Liquid dosage forms	A
227	Desflurane	Liquid dosage forms	B
228	Sevoflurane	Liquid dosage forms	B
229	Nitrous Oxide	Gas formulations	B
230	Propofol	Injection	A
231	Thiopental Sodium	Injection	A
232	Ketamine	Injection	A
233	Midazolam	Injection	A
233	Midazolam	Oral dosage forms	B
234	Propofol Medium and Long Chain Fat Emulsion	Injection	B
235	Sodium Hydroxybutyrate	Injection	B
236	Etomidate	Injection	B
237	Tetracaine	Injection	A
237	Tetracaine	Oral liquid agent	B
238	Procaine	Injection	A
239	Bupivacaine	Injection	A
240	Lidocaine	Injection	A
240	Lidocaine	External liquid agent	B
240	Lidocaine (Ⅰ)	Mortar agent	B
241	Compound Articaine Preparations	Injection	B
242	Ropivacaine	Injection	B
243	Levobupivacaine	Injection	B
244	Atracurium	Injection	A
245	Vecuronium Bromide	Injection	A
246	Rocuronium Bromide	Injection	B
247	Pipecuronium Bromide	Injection	B
248	Pancuronium Bromide	Injection	B
249	Cisatracurium Besylate	Injection	B
250	Suxamethonium Chloride	Injection	A
251	Baclofen	Oral dosage forms	B
252	Ephedrine	Injection	A

252	Ephedrine	Nasal drops	A
253	Esmolol	Injection	B
254	Vitamin A	Oral dosage forms	B
255	Vitamin B 1	Injection	A
255	Vitamin B 1	Oral dosage forms	B
256	Vitamin B 2	Oral dosage forms	A
256	Vitamin B 2	Injection	B
257	Vitamin B 6	Injection	A
257	Vitamin B 6	Oral dosage forms	B
258	Vitamin B 12	Injection	A
259	Nicotinic Acid	Oral dosage forms	B
259	Nicotinic Acid	Injection	B
260	Nicotinamide	Injection	B
261	Vitamin C	Injection	A
261	Vitamin C	Oral dosage forms	B
262	Vitamin D 2	Injection	A
262	Vitamin D 2	Oral dosage forms	A
263	Vitamin D 3	Injection	A
263	Vitamin D 3	Oral dosage forms	B
264	Compound Vitamin B	Oral dosage forms	B
265	Dried Yeast	Oral dosage forms	B
266	Watersoluble vitamin	Injection	B
267	Fatsoluble vitamin	Injection	B
268	Calcium Gluconate	Oral dosage forms	A
268	Calcium Gluconate	Injection	A
269	Calcium Chloride	Injection	B
270	Calcium Carbonate	Oral dosage forms	B
271	Vitamin D 3 and Calcium Carbonate	Oral dosage forms	B
271	Calcium Carbonate and Vitamin D 3	Granules	B
272	MultiTrace Elements (I, II)	Injection	B
273	Zinc Sulfate	Oral dosage forms	B
274	Selenious Yeast	Oral dosage forms	B
275	Compound Amino Acid (l8AA)	Injection	A
276	Compound Amino Acid (l9AA1)	Injection	B
277	Compound Amino Acid (9AA)	Injection	B
278	Compound Amino Acid (3AA)	Injection	B
279	Compound Amino Acid (6AA)	Injection	B
280	Compound Amino Acid (20AA)	Injection	B

281	Compound Amino Acid (15AA)	Injection	B
282	Compound Amino Acid (18AAⅦ, 18B)	Injection	B
283	Alanyl Glutamine	Injection	B
284	Fat Emulsion (C1424)	Injection	B
285	ω3 Fish Oil Fat Emulsion	Injection	B
286	Medium and Long Chain Fat Emulsion (C624)	Injection	B
287	Medium and Long Chain Fat Emulsion (C824, Ve)	Injection	B
288	Fat Emulsion Amino Acids and Glucose	Injection	B
289	Enteral Nutritional Powder (AA)	Oral powder	B
290	Enteral Nutritional Powder (TP)	Oral powder	B
291	Diseasespecific enteral nutrition agent	Oral powder	B
292	High Energy Enteral Nutritional Polymeric Diet	Oral powder	B
293	Compound αKetoacid	Oral dosage forms	B
294	Corticotrophin	Injection	A
295	Desmopressin	Oral dosage forms	A
295	Desmopressin	Inhalation	B
295	Desmopressin	Injection	B
296	Chorionic Gonadotrophin	Injection	A
297	Posterior Pituitary Powder	Inhalation	B
297	Posterior Pituitary	Injection	A
298	Gonadorelin	Injection	B
299	Goserelin	Sustainedrelease implants	B
299	Goserelin	Oral dosage forms	B
300	Leuprorelin	Injection	B
301	Menotropins	Injection	B
302	Triptorelin	Injection	B
303	Vasopressin Tannate	Inhalation	B
303	Vasopressin Tannate	Injection	B
304	Human recombinant Somatropin (Recombinant Human Growth Hormone)	Injection	B
305	Dexamethasone	Oral dosage forms	A
305	Dexamethasone	Injection	A
305	Dexamethasone	Ointment	B
305	Dexamethasone	Eye drops	A
306	Prednisone	Oral dosage forms	A
307	Hydrocortisone	Oral dosage forms	A
307	Hydrocortisone	Injection	A

307	Hydrocortisone	Ointment	A
308	Betamethasone	Oral dosage forms	B
308	Betamethasone	Injection	B
308	Betamethasone	Inhalation	B
309	Methylprednisolone	Oral dosage forms	B
309	Methylprednisolone	Injection	B
310	Cortisone	Oral dosage forms	B
310	Cortisone	Eye drops	A
311	Prednisolone	Oral dosage forms	B
311	Prednisolone	Injection	B
311	Prednisone	Eye drops	B
312	Triamcinolone Acetonide	Injection	B
312	Triamcinolone Acetonide	Ointment	B
312	Triamcinolone Acetonide	Inhalation	B
313	Triamcinolone	Oral dosage forms	B
313	Triamcinolone	Injection	B
314	Testosterone Propionate	Injection	A
315	Methyltestosterone	Oral dosage forms	A
316	Danazol	Oral dosage forms	B
317	Prasterone	Injection	B
318	Testosterone Undecanoate	Oral dosage forms	B
318	Testosterone Undecanoate	Injection	B
319	Nandrolone Phenylpropionate	Injection	A
320	Stanozolol	Oral dosage forms	B
321	Tibolone	Oral dosage forms	B
322	Diethylstilbestrol	Oral dosage forms	A
322	Diethylstilbestrol	Injection	A
323	Estradiol Benzoate	Injection	B
324	Estradiol	Gel	B
325	Conjugated Estrogens	Oral dosage forms	B
326	Conjugated estrogens and Medroxyprogesterone	Oral dosage forms	B
327	Nilestriol	Oral dosage forms	B
328	Ethinylestradiol	Oral dosage forms	B
329	Estradiol Valerate	Oral dosage forms	B
330	Allylestrenol	Oral dosage forms	B
331	Progesterone	Injection	A
331	Progesterone	Oral dosage forms	B
332	Medroxyprogesterone	Oral dosage forms	A

332	Medroxyprogesterone	Injection	B
333	Dydrogesterone	Oral dosage forms	B
334	Hydroxyprogesterone Caproate	Injection	B
335	Megestrol	Oral dosage forms	B
336	Norethisterone	Oral dosage forms	B
337	Gestrinone	Oral dosage forms	B
338	Mifepristone	Oral dosage forms	B
339	Insulin of animal origin	Injection	A
340	Recombinant Human Insulin	Injection	B
341	UltraShort acting I nsulin S imilitude	Injection	B
342	Longacting I nsulin S imilitude	Injection	B
343	Glibenclamide	Oral dosage forms	A
344	Glipizide	Oral dosage forms	A
344	Glipizide	Slow release formulation	B
345	Gliquidone	Oral dosage forms	B
346	Glimepiride	Oral dosage forms	B
347	Gliclazide	Oral dosage forms	B
348	Nateglinide	Oral dosage forms	B
349	Repaglinide	Oral dosage forms	B
350	Metformin	Oral dosage forms	A
350	Metformin	Slow release formulation	B
351	Acarbose	Oral dosage forms	B
352	Voglibose	Oral dosage forms	B
353	Pioglitazone	Oral dosage forms	B
354	Rosiglitazone	Oral dosage forms	B
355	αLipoic Acid	Injection	B
356	Epalrestat	Oral dosage forms	B
357	Thyroid Tablets	Oral dosage forms	A
358	Liothyronine	Oral dosage forms	B
359	Levothyroxine	Oral dosage forms	B
360	Propylthiouracil	Oral dosage forms	A
361	Compound Iodine Solution	Oral liquid agent	A
362	Thiamazole	Oral dosage forms	A
363	Carbimazole	Oral dosage forms	B
364	Calcitonin	Injection	B
364	Calcitonin	Inhalation	B
365	Alendronate Sodium	Oral dosage forms	B
366	Sodium Risedronate	Oral dosage forms	B

367	Clodronate Disodium	Injection	B
367	Clodronate Disodium	Oral dosage forms	B
368	Pamidronate Disodium	Injection	B
369	Etidronate Disodium	Oral dosage forms	B
370	Zoledronic Acid	Injection	B
371	Alfacalcidol	Oral dosage forms	B
372	Calcitriol	Oral dosage forms	B
373	Strontium Ranelate	Dry suspension	B
374	Glucagon	Injection	B
375	Bromocriptine	Oral dosage forms	B
376	Pancreatic Kininogenase	Oral dosage forms	B
376	Pancreatic Kininogenase	Injection	B
377	Ciclosporin	Oral dosage forms	A
377	Ciclosporin	Injection	A
378	Tripterysium Glucosides	Oral dosage forms	A
379	Azathioprine	Oral dosage forms	A
380	Mycophenolate Mofetil	Oral dosage forms	B
381	Mycophenolate Sodium	Oral dosage forms	B
382	Mizoribine	Oral dosage forms	B
383	Tacrolimus	Oral dosage forms	B
383	Tacrolimus	Ointment	B
384	Sirolimus	Oral dosage forms	B
385	Ubenimex	Oral dosage forms	B
386	Mycobacterium Phlei FU36	Injection	B
387	αInterferon	Injection	B
388	Peginterferon α2a [α2b]	Injection	B
389	Recombinant Human Interleukin2	Injection	B
390	Recombinant Human Interleukin11	Injection	B
390	Recombinant Human Interleukin11 (Ⅰ)	Injection	B
391	Total glycosides of paeony	Oral dosage forms	B
392	Human Immunoglobulin (pH4) for intravenous Injection	Injection	B
393	Thalidomide	Oral dosage forms	B
394	Thymosin α1	Injection	B
395	Doxorubicin	Injection	A
396	Busulfan	Oral dosage forms	A
396	Busulfan	Injection	B
397	Procarbazine	Oral dosage forms	A
398	Chlormethine	Injection	A

399	Cyclophosphamide	Oral dosage forms	A
399	Cyclophosphamide	Injection	A
400	Carboplatin	Injection	A
401	Daunorubicin	Injection	A
402	Thiotepa	Injection	A
403	Cisplatin	Injection	A
404	Mitomycin	Injection	A
405	Semustine	Oral dosage forms	A
406	Aclarubicin	Injection	B
407	Amsacrine	Injection	B
408	Oxaliplatin	Injection	B
409	Chlorambucil	Oral dosage forms	B
410	Pirarubicin	Injection	B
411	Epirubicin	Injection	B
412	Formylmerphalan	Oral dosage forms	B
413	Fotemustine	Injection	B
414	Meisoindigotin	Oral dosage forms	B
415	Carmustine	Injection	B
416	Altretamine	Oral dosage forms	B
417	Lobaplatin	Injection	B
418	Lomustine	Oral dosage forms	B
419	Melphalan	Oral dosage forms	B
420	Nedaplatin	Injection	B
421	Nimustine	Injection	B
422	Cisplatin Sodium Chloride	Injection	B
423	Temozolomide	Oral dosage forms	B
424	Nitrocaphane	Injection	B
425	Ifosfamide	Injection	B
426	Cytarabine	Injection	A
427	Fluorouracil	Oral dosage forms	A
427	Fluorouracil	Injection	A
427	Fluorouracil	Ointment	B
428	Methotrexate	Oral dosage forms	A
428	Methotrexate	Injection	A
429	Hydroxycarbamide	Oral dosage forms	A
430	Tegafur	Oral dosage forms	A
430	Tegafur	Injection	B
430	Tegafur	Suppository	B

431	Dacarbazine	Injection	B
432	Fludarabine	Injection	B
433	Fluorouracil and Sodium Chloride	Injection	B
434	Fluorouracil and Glucose	Injection	B
435	Gemcitabine	Injection	B
436	Carmofur	Oral dosage forms	B
437	Capecitabine	Oral dosage forms	B
438	Tioguanine	Oral dosage forms	B
439	Mitoxantrone	Injection	B
440	Mercaptopurine	Oral dosage forms	B
441	Doxifluridine	Oral dosage forms	B
442	Tegafur, Gimeracil and Oteracil Potassium	Oral dosage forms	B
443	Mitoxantrone Hydrochloride	Injection	B
444	Dactinomycin	Injection	A
445	Bleomycin A5	Injection	A
446	Bleomycin Hydrochloride	Injection	B
447	Hydroxycamptothecin	Injection	A
448	Hydroxycamptothecinum and Sodium Chloride	Injection	B
449	Topotecan	Injection	B
450	Irinotecan	Injection	B
451	Vincristine	Injection	A
452	Homoharringtonine	Injection	A
453	Etoposide	Injection	A
453	Etoposide	Oral dosage forms	B
454	Vindesine	Injection	B
455	Vinblastine	Injection	B
456	Vinorelbine	Injection	B
457	Estramustine	Oral dosage forms	B
458	Docetaxel	Injection	B
459	Homoharringtonine and Sodium Chloride	Injection	B
460	Harringtonine	Injection	B
461	Teniposide	Injection	B
462	Paclitaxel	Injection	B
463	Asparaginase	Injection	A
464	Flutamide	Oral dosage forms	B
465	Tamoxifen	Oral dosage forms	A
466	Raloxifene	Oral dosage forms	B
467	Clomifene	Oral dosage forms	B

468	Toremifene	Oral dosage forms	B
469	Aminoglutethimide	Oral dosage forms	A
470	Anastrozole	Oral dosage forms	B
471	Bicalutamide	Oral dosage forms	B
472	Letrozole	Oral dosage forms	B
473	Exemestane	Oral dosage forms	B
474	Sodium Glycididazole	Injection	B
475	Elemene	Injection	B
475	Elemene	Oral liquid agent	B
476	Mesna	Injection	B
477	Calcium Folinate	Oral dosage forms	B
477	Calcium Folinate	Injection	B
478	Dexrazoxane	Injection	B
479	Tretinoin	Oral dosage forms	B
479	Tretinoin	Ointment	A
480	Arsenious acid (Arsenic Trioxide)	Injection	B
481	Arsenious Acid and Sodium Chloride	Injection	B
482	Chlorphenamine	Oral dosage forms	A
482	Chlorphenamine	Injection	B
483	Diphenhydramine	Oral dosage forms	A
483	Diphenhydramine	Injection	A
484	Promethazine	Oral dosage forms	A
484	Promethazine	Injection	A
485	Hydroxyzine	Oral dosage forms	B
486	Decloxizine	Oral dosage forms	B
487	Cetirizine	Oral dosage forms	B
488	Levocetirizine	Oral dosage forms	B
489	Cyproheptadine	Oral dosage forms	A
490	Acrivastine	Oral dosage forms	B
491	Loratadine	Oral dosage forms	B
492	Mizolastine	Oral dosage forms	B
493	Ebastine	Oral dosage forms	B
494	Dimenhydrinate	Oral dosage forms	B
495	Triprolidine	Oral dosage forms	B
496	Ketotifen	Oral dosage forms	B
496	Ketolifen	Inhalation	B
497	Levodopa	Oral dosage forms	A
498	Levodopa and Benserazide	Oral dosage forms	B

499	Carbidopa	Oral dosage forms	B
500	Carbidopa and Levodopa	Oral dosage forms	B
501	Amantadine	Oral dosage forms	A
502	Memantine	Oral dosage forms	B
503	Pramipexole	Oral dosage forms	B
504	Piribedil	Slow release formulation	B
505	Selegiline	Oral dosage forms	B
506	Entacapone	Oral dosage forms	B
507	Trihexyphenidyl	Oral dosage forms	A
508	Neostigmine	Injection	A
509	Pyridostigmine Bromide	Oral dosage forms	A
509	Pyridostigmine Bromide	Injection	B
510	Neostigmine Bromide	Oral dosage forms	A
511	Galanthamine	Oral dosage forms	B
511	Galanthamine	Injection	B
512	Edrophonium Chloride	Injection	B
513	Phenytoin Sodium	Oral dosage forms	A
513	Phenytoin Sodium	Injection	A
514	Sodium Valproate	Oral dosage forms	A
514	Sodium Valproate	Slow release formulation	B
514	Sodium Valproate	Injection	B
515	Carbamazepine	Oral dosage forms	A
515	Carbamazepine	Slow release formulation	B
516	Oxcarbazepine	Oral dosage forms	B
517	Magnesium Valproate	Slow release formulation	B
518	Lamotrigine	Oral dosage forms	B
519	Primidone	Oral dosage forms	B
520	Topiramate	Oral dosage forms	B
521	Ethosuximide	Oral dosage forms	B
521	Ethosuximide	Oral liquid agent	B
522	Levetiracetam	Oral dosage forms	B
523	Gabapentin	Oral dosage forms	B
524	Ergotamine Caffeine	Oral dosage forms	A
525	Nimodipine	Oral dosage forms	A
525	Nimodipine	Injection	B
526	Almitrine and Raubasine	Oral dosage forms	B
527	Batroxobin (Defibrase)	Injection	B
528	Betahistine	Oral dosage forms	B

528	Betahistine	Injection	B
529	Vinpocetine	Injection	B
529	Vinpocetine	Oral dosage forms	B
530	Tanshinon IIA	Injection	B
531	Butylphthalide	Oral dosage forms	B
532	Buflomedil	Oral dosage forms	B
532	Buflomedil	Injection	B
533	Dihydroergotoxine	Oral dosage forms	B
534	Fasudil	Injection	B
535	Flunarizine	Oral dosage forms	B
536	Puerarin	Injection	B
537	Cinnarizine	Oral dosage forms	B
538	Cinepazide	Injection	B
539	Pentoxifylline	Oral dosage forms	B
539	Pentoxifylline	Injection	B
540	Nicergoline	Oral dosage forms	B
541	Aescine	Injection	B
542	Dihydroergotamine	Oral dosage forms	B
543	Edaravone	Injection	B
544	Donepezil	Oral dosage forms	B
545	Rivastigmine	Oral dosage forms	B
546	Huperzine A	Oral dosage forms	B
547	Citicoline	Injection	A
547	Citicoline	Oral dosage forms	B
548	Lobeline	Injection	A
549	Nikethamide	Injection	A
550	Piracetam	Oral dosage forms	B
550	Piracetam	Injection	B
551	Pyritinol	Injection	B
552	Doxapram	Injection	B
553	Dimefline	Injection	B
554	Aniracetam	Oral dosage forms	B
555	Meclofenoxate	Oral dosage forms	B
556	Methylphenidate	Oral dosage forms	B
556	Methylphenidate	Slow release formulation	B
556	Methylphenidate	Injection	B
557	Tomoxetine	Oral dosage forms	B
558	Phenobarbital	Oral dosage forms	A

558	Phenobarbital	Injection	A
559	Secobarbital	Oral dosage forms	B
560	Amobarbital	Injection	B
561	eszopiclone	Oral dosage forms	B
562	Zaleplon	Oral dosage forms	B
563	Zopiclone	Oral dosage forms	B
564	Zolpidem	Oral dosage forms	B
565	Rizatriptan	Oral dosage forms	B
566	Antipyrine and Caffeine Citrate	Oral dosage forms	B
567	Sumatriptan	Oral dosage forms	B
568	Zolmitriptan	Oral dosage forms	B
569	Mannitol	Injection	A
570	Glycerol Fructose	Injection	A
571	Oryzanol	Oral dosage forms	B
572	Mecobalamin	Oral dosage forms	B
572	Mecobalamin	Injection	B
573	Tizanidine	Oral dosage forms	B
574	Cobamamide	Oral dosage forms	B
574	Cobamamide	Injection	B
575	Eperisone	Oral dosage forms	B
576	Perphenazine	Oral dosage forms	A
576	Perphenazine	Injection	A
577	Chlorpromazine	Oral dosage forms	A
577	Chlorpromazine	Injection	A
578	Clozapine	Oral dosage forms	A
579	Trifluoperazine	Oral dosage forms	A
580	Fluphenazine	Oral dosage forms	B
580	Fluphenazine	Injection	B
581	Compound chlorpromazine hydrochloridein	Injection	B
582	Fluphenazine Decanoate	Injection	B
583	Thioridazine	Oral dosage forms	B
584	Pipotiazine	Injection	B
585	Haloperidol	Oral dosage forms	A
585	Haloperidol	Injection	A
586	Olanzapine	Oral dosage forms	B
587	Droperidol	Injection	B
588	Quetiapine	Oral dosage forms	B
589	Risperidone	Oral dosage forms	B

589	Risperidone	Oral disintegrating tablets	B
590	Penfluridol	Oral dosage forms	B
591	Risperidone for Depot Suspension	Injection	B
592	Flupentixol	Oral dosage forms	B
592	Flupentixol	Injection	B
593	Flupentixol and Melitracen	Oral dosage forms	B
594	Clopenthixol	Injection	B
595	Chlorprothixene	Oral dosage forms	B
595	Chlorprothixene	Injection	B
596	Sulpiride	Oral dosage forms	A
596	Sulpiride	Injection	A
597	Amisulpride	Oral dosage forms	B
598	Tiapride	Injection	B
599	Sultopride	Injection	B
600	Paliperidone	Oral dosage forms	B
601	Ziprasidone	Oral dosage forms	B
602	Aripiprazole	Oral dosage forms	B
602	Aripiprazole	Oral disintegrating tablets	B
603	Alprazolam	Oral dosage forms	A
604	Estazolam	Oral dosage forms	A
605	Diazepam	Oral dosage forms	A
605	Diazepam	Injection	A
606	Oxazepam	Oral dosage forms	B
607	Lorazepam	Oral dosage forms	B
608	Clonazepam	Oral dosage forms	B
608	Clonazepam	Injection	B
609	Nitrazepam	Oral dosage forms	B
610	Buspirone	Oral dosage forms	B
611	Tandospirone	Oral dosage forms	B
612	Amitriptyline	Oral dosage forms	A
613	Imipramine	Oral dosage forms	A
614	Doxepin	Oral dosage forms	A
614	Doxepin	Cream	B
615	Clomipramine	Injection	A
615	Clomipramine	Oral dosage forms	B
616	Maprotiline	Oral dosage forms	B
616	Maprotiline	Injection	B
617	Mianserin	Oral dosage forms	B

618	Escitalopram	Oral dosage forms	B
619	Fluvoxamine	Oral dosage forms	B
620	Fluoxetine	Oral dosage forms	B
621	Paroxetine	Oral dosage forms	B
622	Sertraline	Oral dosage forms	B
623	Citalopram	Oral dosage forms	B
624	Venlafaxine	Oral dosage forms	B
625	Mirtazapine	Oral dosage forms	B
626	Moclobemide	Oral dosage forms	B
627	Trazodone	Oral dosage forms	B
628	Duloxetine	Oral dosage forms	B
629	Reboxetine	Oral dosage forms	B
630	Chlormezanone	Oral dosage forms	B
631	Tianeptine	Oral dosage forms	B
632	Lithium Carbonate	Oral dosage forms	A
632	Lithium Carbonate	Slow release formulation	B
633	Bromhexine	Oral dosage forms	A
634	Ambroxol	Oral dosage forms	A
634	Ambroxol	Injection	B
635	Myrtol Standardized	Oral dosage forms	B
636	Chymotrypsin	Injection	B
636	Chymotrypsin	Injection	B
637	Carbocisteine	Oral dosage forms	B
633	Bromhexine	Injection	B
638	Acetylcysteine	Oral dosage forms	B
638	Acetylcysteine	Inhalation	B
639	Compound Liquorice (Glycyrrhiza) Preparations	Oral dosage forms	A
640	Pentoxyverine	Oral dosage forms	A
641	Dioxopromethazine	Oral dosage forms	B
642	Compound Codeine Phosphate	Solution Agent	B
643	Codeine	Oral dosage forms	B
643	Codeine	Injection	B
644	Codeine and Guaifenesin Syrup	Oral liquid agent	B
645	Dextromethorphan	Oral dosage forms	B
646	Aminophylline	Oral dosage forms	A
646	Aminophylline	Injection	A
647	Theophylline	Oral dosage forms	A
648	Doxofylline	Oral dosage forms	B

648	Doxofylline	Injection	B
649	Diprophylline	Oral dosage forms	B
649	Diprophylline	Injection	B
650	Compound Theophylline Preparations	Oral dosage forms	B
651	Tiotropium Bromide	Inhalation	B
652	Ipratropium Bromide	Inhalation	B
653	Salbutamol	Inhalation	A
653	Salbutamol	Oral dosage forms	B
653	Salbutamol	Injection	B
654	Bambuterol	Oral dosage forms	B
655	Procaterol	Oral dosage forms	B
656	Formoterol	Inhalation	B
657	Clenbuterol	Oral dosage forms	B
657	Clenbuterol	Suppository	B
658	Clorprenaline	Oral dosage forms	B
659	Salmeterol	Inhalation	B
660	Terbutaline	Oral dosage forms	B
660	Terbutaline	Inhalation	B
660	Terbutaline	Injection	B
661	Beclometasone Dipropionate	Inhalation	B
661	Beclometasone	Ointment	B
661	Beclometasone	Inhalation	B
662	Budesonide	Inhalation	B
663	Fluticasone	Inhalation	B
664	Montelukast	Oral dosage forms	B
665	Sodium Cromoglicate	Inhalation	B
665	Sodium Cromoglicate	Eye drops	B
665	Sodium Cromoglicate	Nasal drops	B
666	Zafirlukast	Oral dosage forms	B
667	Budesonide and Formoterol	Inhalation	B
668	Fluticasone and Salmeterol	Inhalation	B
669	Ipratropium bromide compound		B
670	Pulmonary surfactant of animal origin	Injection	B
671	Compound Methoxyphenamine	Oral dosage forms	B
672	Rnei and Sodium Bicabronate	Oral dosage forms	A
673	Compound Aluminium Hydroxide	Oral dosage forms	A
674	Bismuth Potassium Citrate	Oral dosage forms	A
674	Bismuth Potassium Citrate	Granules	B

675	Sodium Bicarbonate	Oral dosage forms	A
675	Sodium Bicarbonate	Injection	A
676	Compound Bismuth Aluminate	Granules	B
677	Gefarnate	Oral dosage forms	B
678	Colloidal Bismuth Pectin	Oral dosage forms	B
679	Sucralfate	Oral dosage forms	B
680	Hydrotalcite	Oral dosage forms	B
681	Rebamipide	Oral dosage forms	B
682	Teprenone	Oral dosage forms	B
683	Famotidine	Oral dosage forms	A
683	Famotidine	Injection	A
684	Ranitidine	Oral dosage forms	A
684	Ranitidine	Injection	A
685	Cimetidine	Oral dosage forms	A
685	Cimetidine	Injection	A
686	Omeprazole	Oral dosage forms	A
686	Omeprazole	Injection	B
687	Esomeprazole	Oral dosage forms	B
687	Esomeprazole	Injection	B
688	Lansoprazole	Oral dosage forms	B
688	Lansoprazole	Injection	B
689	Rabeprazole	Oral dosage forms	B
690	Pantoprazole	Oral dosage forms	B
690	Pantoprazole	Injection	B
691	Lactasin	Oral dosage forms	A
692	OryzAspergillus Enzyme And Pancreatin	Oral dosage forms	B
693	Pancreatin	Oral dosage forms	B
694	Atropine	Oral dosage forms	A
694	Atropine	Eye drops	A
694	Atropine	Injection	A
695	Belladonna	Oral dosage forms	A
696	Anisodamine	Oral dosage forms	A
696	Anisodamine	Injection	A
697	Scopolamine Butylbromide	Oral dosage forms	B
697	Scopolamine Butylbromide	Injection	B
698	Scopolamine	Oral dosage forms	B
698	Scopolamine	Injection	B
698	Scopolamine	Eye ointment	B

699	Pinaverium Bromide	Oral dosage forms	B
700	Trimebutine	Oral dosage forms	B
701	Propantheline Bromide	Oral dosage forms	B
702	Domperidone	Oral dosage forms	A
702	Domperidone	Suppository	B
703	Mosapride	Oral dosage forms	B
704	Itopride	Oral dosage forms	B
705	Itopride	Oral dosage forms	B
706	Metoclopramide	Oral dosage forms	A
706	Metoclopramide	Injection	A
707	Ondansetron	Oral dosage forms	B
707	Ondansetron	Injection	B
708	Granisetron	Oral dosage forms	B
708	Granisetron	Injection	B
709	Tropisetron	Injection	B
710	Bromosoval and Procaine	Injection	B
711	Apomorphine	Injection	A
712	Phenolphthalein	Oral dosage forms	A
713	Glycerine Enema	Solution Agent	A
714	Glycerini Enema	Enema	A
715	Magnesium Sulfate	Oral powder	A
715	Magnesium Sulfate	Injection	A
716	Castor Oil	Oral liquid agent	B
717	Polyethylene Glycol	Oral powder	
717	Polyethylene Glycol Electrolytes	Oral powder	B
718	Glycerin	Suppository	B
719	Liquid Paraffin	Solution Agent	B
720	Compound Diphenoxylate	Oral dosage forms	A
721	Smectite	Oral powder	A
722	Compound Camphor	Oral liquid agent	B
723	Rifaximin	Oral dosage forms	B
724	Loperamide	Oral dosage forms	B
725	Racecadotril	Granules	B
726	Bacillus Licheniformis	Oral dosage forms	B
727	Live Combined B. Subtilis and E. Faecium	Oral dosage forms	B
728	Live Combined Bacillus Subtilis and Enterococcus Faecium	Oral dosage forms	B
729			B
730	Live Bifidobacterium Preparation	Oral dosage forms	B

731	Glutamate	Injection	A
732	Arginine	Injection	A
733	Bifendate	Oral dosage forms	A
734	Hepatocyte GrowthPromoting Factors	Injection	B
735	Polyene Phosphatidyl choline	Oral dosage forms	B
735	Polyene Phosphatidyl choline	Injection	B
736	Glycyrrhizin		B
737	Diammonium Glycyrrhizinate	Oral dosage forms	B
737	Diammonium Glycyrrhizinate	Injection	B
738	Glutathione	Injection	B
738	Glutathione	Oral dosage forms	B
739	Marine	Injection	B
740	Tiopronin	Oral dosage forms	B
740	Tiopronin	Injection	B
741	Ornithine aspartate		B
742	Glucurolactone	Oral dosage forms	B
742	Glucurolactone	Injection	B
743	Lactulose	Syrup	B
744	Bicyclol	Oral dosage forms	B
744	Bicyclol	Injection	B
745	Silibinin	Oral dosage forms	B
746	Ademetionine	Injection	B
747	Magnesium Isoglycyrrhizinate	Injection	B
748	Ursodeoxycholic Acid	Oral dosage forms	A
749	Phenylpropanol	Oral dosage forms	B
750	Compound Azintamide	Oral dosage forms	B
751	Anethol Trithione	Oral dosage forms	B
752	Trepibutone	Oral dosage forms	B
753	Dehydrocholic Acid	Oral dosage forms	B
754	Melilotus	Oral dosage forms	B
755	Diosmin	Oral dosage forms	B
756	Compound Carraghenates Suppositories	Suppository	B
757	Sulfasalazine	Oral dosage forms	A
757	Sulfasalazine	Suppository	A
758	Octreotide	Injection	B
759	Dimethicone	Oral dosage forms	B
760	Gastrointestinal discomfort relieve OTC preparation of compound		B
761	Gabexate	Injection	B

762	Lauromacrogol	Injection	B
763	Mesalazine	Oral dosage forms	B
763	Mesalazine	Suppository	B
764	Somatostatin	Injection	B
765	Ulinastatin	Injection	B
766	Digoxin	Oral dosage forms	A
766	Digoxin	Injection	A
766	Digoxin	Oral liquid agent	B
767	Strophanthin K	Injection	A
768	Lanatoside C	Injection	A
769	Deslanoside	Injection	A
770	Milrinone	Injection	B
771	Amiodarone	Oral dosage forms	A
771	Amiodarone	Injection	A
772	Quinidine	Oral dosage forms	A
773	Mexiletine	Oral dosage forms	A
774	Procainamide	Injection	A
775	Propafenone	Oral dosage forms	A
775	Propafenone	Injection	A
776	Disopyramide	Oral dosage forms	B
777	Moracizine	Oral dosage forms	B
778	Bretylium Tosilate	Injection	B
779	Nitroglycerin	Oral dosage forms	A
779	Nitroglycerin	Injection	A
779	Nitroglycerin	Sublingual tablets	B
780	Isosorbide Dinitrate	Oral dosage forms	A
780	Isosorbide Dinitrate	Injection	A
780	Isosorbide Dinitrate	Slow release formulation	B
781	Isosorbide Mononitrate	Oral dosage forms	B
781	Isosorbide Mononitrate	Injection	B
782	Nitrendipine	Oral dosage forms	A
783	Verapamil	Oral dosage forms	A
783	Verapamil	Slow release formulation	B
783	Verapamil	Injection	A
784	Nifedipine	Oral dosage forms	A
784	Nifedipine	Slow release formulation	B
785	LAspartic Acid Amlodipine	Oral dosage forms	B
786	Amlodipine	Oral dosage forms	B

787	Benidipine	Oral dosage forms	B
788	Diltiazem	Oral dosage forms	B
788	Diltiazem	Injection	B
789	Felodipine	Oral dosage forms	B
790	Lacidipine	Oral dosage forms	B
791	Lercanidipine	Oral dosage forms	B
792	Nicardipine	Oral dosage forms	B
792	Nicardipine	Injection	B
793	Cilnidipine	Oral dosage forms	B
794	Levamlodipine	Oral dosage forms	B
795	Atenolol	Oral dosage forms	A
796	Metoprolol	Oral dosage forms	A
796	Metoprolol	Injection	A
796	Metoprolol	Slow release formulation	B
797	Propranolol	Oral dosage forms	A
797	Propranolol	Slow release formulation	B
797	Propranolol	Injection	B
798	Arotinolol	Oral dosage forms	B
799	Bisoprolol	Oral dosage forms	B
800	Carvedilol	Oral dosage forms	B
801	Labetalol	Oral dosage forms	B
802	Sotalol	Oral dosage forms	B
802	Sotalol	Injection	B
803	Phentolamine	Injection	A
804	Prazosin	Oral dosage forms	A
805	Terazosin	Oral dosage forms	A
806	Alfuzosin	Oral dosage forms	B
807	Doxazosin	Oral dosage forms	B
808	Phenoxybenzamine	Injection	B
808	Phenoxybenzamine	Oral dosage forms	B
809	Methyldopa	Oral dosage forms	B
810	Clonidine	Oral dosage forms	B
810	Clonidine	Eye drops	B
811	Urapidil	Oral dosage forms	B
811	Urapidil	Injection	B
812	Captopril	Oral dosage forms	A
813	Enalapril	Oral dosage forms	A
814	Benazepril	Oral dosage forms	B

815	Fosinopril	Oral dosage forms	B
816	Lisinopril	Oral dosage forms	B
817	Ramipril	Oral dosage forms	B
818	Imidapril	Oral dosage forms	B
819	Perindopril	Oral dosage forms	B
820	Cilazapril	Oral dosage forms	B
821	Irbesartan	Oral dosage forms	B
822	Candesartan	Oral dosage forms	B
823	Losartan Potassium	Oral dosage forms	B
824	Telmisartan	Oral dosage forms	B
825	Valsartan	Oral dosage forms	B
826	Compound Hypoensive Tablets	Oral dosage forms	A
827	Compound Reserpine	Oral dosage forms	A
828	Reserpine	Injection	A
828	Reserpine	Oral dosage forms	B
829	Sodium Nitroprusside	Injection	A
830	Indapamide	Oral dosage forms	A
831	Bendazol (Dibazol)	Oral dosage forms	B
832	Diazoxide	Injection	B
833	Hydralazine	Oral dosage forms	B
833	Hydralazine	Injection	B
834	Minoxidil	Oral dosage forms	B
835	Dopamine	Injection	A
836	Dobutamine	Injection	A
837	Metaraminol	Injection	A
838	Noradrenaline Bitartrate	Injection	A
839	Adrenaline	Injection	A
840	Isoprenaline	Injection	A
841	Midodrine	Oral dosage forms	B
842	Phenylephrine	Injection	B
843	Simvastatin	Oral dosage forms	A
843	Simvastatin	Pills	B
844	Atorvastatin	Oral dosage forms	B
845	Fluvastatin	Oral dosage forms	B
846	Lovastatin	Oral dosage forms	B
847	Pravastatin	Oral dosage forms	B
848	Rosuvastatin	Oral dosage forms	B
849	Acipimox	Oral dosage forms	B

850	Bezafibrate	Oral dosage forms	B
851	Fenofibrate	Oral dosage forms	B
852	Gemfibrozil	Oral dosage forms	B
853	Probucol	Oral dosage forms	B
854	Inositol Nicotinate	Oral dosage forms	B
855	Sodium Ferulate	Oral dosage forms	B
856	Piperazine Ferulate	Oral dosage forms	B
857	Ligustrazine	Injection	B
858	Coenzyme Q10	Injection	B
859	Cyclic Adenosine Monophosphate	Injection	B
860	Cycleanine Dimethobromide	Injection	B
861	Alprostadil	Injection	B
862	Trimetazidine	Oral dosage forms	B
863	Adenosine Triphosphate	Injection	B
864	Enalapril and Folic Acid	Oral dosage forms	B
865	Furosemide	Oral dosage forms	A
865	Furosemide	Injection	A
866	Bumetanide	Oral dosage forms	B
866	Bumetanide	Injection	B
867	Torasemide	Oral dosage forms	B
867	Torasemide	Injection	B
868	Hydrochlorothiazide	Oral dosage forms	A
869	Triamterene	Oral dosage forms	A
870	Spironolactone	Oral dosage forms	A
871	Amiloride	Oral dosage forms	B
872	Compound Glycerol	Injection	B
873	Flavoxate	Oral dosage forms	A
874	Epristeride	Oral dosage forms	B
875	Finasteride	Oral dosage forms	B
876	Naftopidil	Oral dosage forms	B
877	Prostat	Oral dosage forms	B
878	Tamsulosin	Oral dosage forms	B
879	Oxybutynin	Oral dosage forms	B
880	Calcium Acetate	Oral dosage forms	B
881	Peritoneal Dialysis Solution	Injection	B
882	Tolterodine	Oral dosage forms	B
883	Phenazopyridine	Oral dosage forms	B
884	Papaverine	Injection	B

885	Levocarnitine	Injection	B
886	Aminomethylbenzoic Acid	Oral dosage forms	A
886	Aminomethylbenzoic Acid	Injection	B
887	Tranexamic Acid	Oral dosage forms	B
887	Tranexamic Acid	Injection	A
888	Human Coagulation Factor Ⅷ, freeze Dried	Injection	A
889	Menadiol	Oral dosage forms	A
890	Thrombin	Freezedried preparations for external use	A
891	Vitamin K 1	Injection	A
891	Vitamin K 1	Oral dosage forms	B
892	Menadione Sodium Bisulfite	Injection	A
892	MenadioneSodiumBisulfite	Oral dosage forms	B
893	Protamine	Injection	A
894	Aminocaproic Acid	Oral dosage forms	B
894	Aminocaproic Acid	Injection	B
895	Hemocoagulase	Injection	B
896	Prothrombin Complex Concentrate (Human), freeze Dried	Injection	B
897	Etamsylate	Injection	B
898	Haemocoagulase Agkistrodon	Injection	B
899	Carbazochrome	Oral dosage forms	B
899	Carbazochrome	Injection	B
900	Human Fibrinogen	Injection	B
901	Hemocoagulase	Injection	B
902	Hemocoagulase Atrox	Injection	B
903	Recombinant Coagulation Factor Ⅷ	Injection	B
904	Heparin	Injection	A
905	Low molecular weight Heparin (Enoxaparin)	Injection	B
906	Warfarin	Oral dosage forms	A
907	Rivaroxaban	Oral dosage forms	B
908	Streptokinase (Recombinant Streptokinase)	Injection	A
909	Urokinase	Injection	A
910	Alteplase	Injection	B
911	Lumbrokinase	Oral dosage forms	B
912	Fibrinogenase	Injection	B
913	Ferrous Sulfate	Oral dosage forms	A
914	Iron Dextran	Injection	A

915	Ferrous Fumarate	Oral dosage forms	B
916	Ferrous Succinate	Oral dosage forms	B
917	Ferrous Gluconate	Oral dosage forms	B
918	Iron Sorbitex	Injection	B
919	Ferrous Saccharose	Injection	B
920	Folic Acid	Oral dosage forms	A
920	Folic Acid	Injection	B
921	Recombinant human erythropoietin		B
922	Inosine	Injection	A
922	Inosine	Oral dosage forms	B
923	Amino polypeptide	Oral dosage forms	B
924	Coenzyme A	Injection	B
925	Leucogen	Oral dosage forms	B
926	Batiol	Oral dosage forms	B
927	Vitamin B 4	Oral dosage forms	B
928	Recombinant Human Granulocyte ColonyStimulating Factor	Injection	B
929	Recombinant Human Granulocyte / Macrophage Colonystimulating Factor	Injection	B
930	Dipyridamole	Oral dosage forms	A
930	Dipyridamole	Injection	B
931	Ozagrel	Injection	B
932	Beraprost	Oral dosage forms	B
933	Clopidogrel	Oral dosage forms	B
934	Troxerutin	Oral dosage forms	B
934	Troxerutin	Injection	B
935	Ticlopidine	Oral dosage forms	B
936	Sarpogrelate	Oral dosage forms	B
937	Tirofiban	Injection	B
938	Cilostazol	Oral dosage forms	B
939	Recombinant Human Thrombopoietin	Injection	B
940	Glucose	Injection	A
941	Fructose	Injection	B
942	Fructose Diphosphate sodium	Injection	B
943	Invert Sugar	Injection	B
944	Compound Sodium Chloride	Injection	A
945	Oral Rehydration Salts	Oral powder	A
946	Potassium Chloride	Oral dosage forms	A
946	Potassium Chloride	Injection	A

947	Sodium Chloride	Injection	A
948	Potassium Citrate	Granules	B
949	Potassium Magnesium Aspartate	Oral dosage forms	B
949	Potassium Magnesium Aspartate	Injection	B
950	Sodium Lactate	Injection	A
951	Sodium Lactate Ringer's	Injection	A
952	Compound Sodium Lactate and Glucose	Injection	B
953	Compound Potassium Dihydrogen Phosphate	Injection	B
954	Dextran	Injection	A
955	Coated Aldehyde Oxystarch	Oral powder	B
956	Succinylated Gelatin	Injection	B
957	Hydroxyethyl Starch	Injection	B
958	Glucose and Sodium Chloride	Injection	A
959	Sodium Glycerophosphate	Injection	B
960	Sterile Water for Injection	Injection	B
961	Benzoyl Peroxide	Ointment	B
962	Sulfadiazine Zinc	Topical powder	B
963	Sulfadiazine Silver	Topical powder	B
964	Methylrosanilinium Chloride	External liquid agent	B
965	Crotamiton	Ointment	B
966	Lindane	Ointment	B
967	Boric Acid	External liquid agent	B
968	Sublimed Sulfur	Ointment	B
969	Neomycin	Ointment	B
970	Amorolfine Hydrochloride Liniment	Ointment	B
971	Benzoic Acid	Ointment	B
972	Butenafine	Ointment	B
973	Compound Sulfadiazine Zinc Pingment	Gel	B
974	Ciclopirox Olamine	Ointment	B
975	Bifonazole	External liquid agent	B
976	Mupirocin	Ointment	B
977	Econazole and Triamcinolone Acetonide	Ointment	B
978	Undecylenic Acid	External liquid agent	B
979	Ketoconazole	Ointment	B
980	Econazole	Ointment	B
980	Econazole	Suppository	B
981	Compound Polymyxin B	Ointment	B
982	Sulfur	Ointment	B

983	Penciclovir	Ointment	B
984	Selenium Sulfide	External liquid agent	B
985	Pix Fabate Nigrate	Ointment	B
986	Pityrol	Ointment	B
987	Coal Tar	External liquid agent	B
988	Salicylic Acid	Ointment	A
989	Ichthammol	Ointment	A
990	Dithranol	Ointment	B
991	Compound Salicylic Acid Liniment	External liquid agent	B
992	Fluocinonide	Ointment	A
993	Clobetasol Propionate	Ointment	B
994	Desonide	Ointment	B
995	Hydrocortisone	Ointment	B
996	Compound Triamcinolone		B
997	Halcinonide	External liquid agent	B
998	Mometasone Furoate	Ointment	B
999	Halometasone	Cream	B
1000	Halometasone / Triclosan	Ointment	B
1001	Hydroquinone	Ointment	B
1002	Calamine	External liquid agent	A
1003	Urea	Ointment	A
1004	Adapalene	Gel	B
1005	Acitretin	Oral dosage forms	B
1006	Compound Hibiscuse	External liquid agent	B
1007	Potassium Permanganate	Tablet	B
1008	Podophyllotoxin	External liquid agent	B
1009	Methoxsalen	Oral dosage forms	B
1009	Methoxsalen	External liquid agent	B
1010	Calcipotriol	External liquid agent	B
1010	Calcipotriol	Ointment	B
1011	Oil Seed Bruceae	External liquid agent	B
1012	Zinc Oxide	Ointment	B
1013	Ethacridine	External liquid agent	B
1013	Ethacridine	Injection	B
1014	Isotretinoin	Oral dosage forms	B
1015	Camphor	Ointment	B
1016	Recombinant Human Epidermal Growth Factor	Gel	B

1016	Recombinant Human Epidermal Growth Factor	Eye drops	B
1017	Chlortetracycline	Eye ointment	A
1018	Tetracycline and Cortisone Acetate	Ointment	A
1019	Fluorometholone and Gentamicin	Eye drops	B
1020	Sodium Sulfacetamide	Eye drops	B
1021	Natamycin	Eye drops	B
1022	Tobramycin and Dexamethasone	Eye drops	B
1023	Hydrobenzole	Eye drops	A
1024	Pilocarpine	Injection	A
1024	Pilocarpine	Eye drops	A
1025	Dipivefrine	Eye drops	B
1026	Brimonidine	Eye drops	B
1027	Timolol	Eye drops	A
1028	Carteolol	Eye drops	B
1029	Levobunolol	Eye drops	B
1030	Acetazolamide	Oral dosage forms	A
1030	Acetazolamide	Injection	B
1031	Brinzolamide	Eye drops	B
1032	Bimatoprost	Eye drops	B
1033	Latanoprost	Eye drops	B
1034	Travoprost	Eye drops	B
1035	Tropicamide	Eye drops	A
1036	Betaxolol	Eye drops	B
1037	Compound Tropicamide	Eye drops	B
1038	Homatropine	Eye ointment	B
1039	Fluorometholone	Eye drops	B
1040	Fluorometholone	Eye drops	B
1041	Prolonium Iodide	Injection	A
1042	Pranoprofen	Eye drops	B
1043	Dobesilate	Oral dosage forms	B
1044	Artificial Tear	Eye drops	B
1045	Diclofenac Sodium	Eye drops	B
1046	Sodium Hyaluronate	Eye drops	B
1046	Sodium Hyaluronate	Injection	B
1047	Tolazoline	Injection	B
1048	Deproteinised Calf Serum	Eye gel	B
1049	Deproteinised Calf Blood Extractives	Eye gel	B
1050	Emedastine	Eye drops	B

1051	Indocyanine Green	Injection	B
1052	Fluorescein Sodium	Injection	B
1053	Recombinant Bovine Basic Fibroblast Growth Factor	Eye gel	B
1054	Recombinant Human (Bovin) Basic Fibroblast Growth Factor	Eye drops	B
1055	Difenidol	Oral dosage forms	A
1056	Compound Borax Solution	Gargle	A
1057	Morrhuate Sodium	Injection	A
1058	Azelastine	Inhalation	B
1059	Ephedrine and Nitrofurazone	Nasal drops	B
1060	Compound Benzoin Tincture	External liquid agent	B
1061	Compound Triamcinolone Acetonide	Ear drops	B
1062	Compound Norfloxacin	Nasal drops	B
1063	Compound OxymetazolineOxymetazoline Hydrochloride	Inhalation	B
1064	Hydrogen Peroxide	Solution Agent	B
1065	Mometasone Furoate	Inhalation	B
1066	Chloromycetin in Glycerine	Ear drops	B
1067	Chloramphenicol Hydrocortisone	Ear drops	B
1068	Oxymetazoline	Nasal drops	B
1069	Xylometazoline	Nasal drops	B
1070	Levocabastine	Inhalation	B
1071	Rice Bran Sterol	Oral dosage forms	B
1072	Cetylpyridinium Chloride	External liquid agent	B
1073	Ergometrine	Injection	A
1074	Oxytocin	Injection	A
1075	Dinoprostone	Suppository	B
1076	Carbetocin	Injection	B
1077	Carboprost Methylate	Suppository	B
1078	Carboprost Tromethamine	Injection	B
1079	Misoprostol	Oral dosage forms	B
1080	Ritodrine	Oral dosage forms	B
1080	Ritodrine	Injection	B
1081	Compound Zedoary Turmeric Oil Suppositories	Suppository	B
1082	Compound Metrnidazole	Vaginal Effervescent Tablets	B
1083	Policresulen	External liquid agent	B
1084	Nifuratel	Vaginal tablets	B
1085	Nifuratel and Nysfungin	Suppository	B

1086	Alarelin	Injection	B
1087	Flufenamic Acid	Oral dosage forms	B
1088	Promestriene	Ointment	B
1088	Promestriene	Vaginal capsules	B
1089	Living Preparation of Lactobacillus	Vaginal capsules	B
1090	Dimercaprol	Injection	A
1091	Sodium Dimercaptopropane Sulfonate	Injection	A
1092	Sodium Dimercaptosuccinate	Injection	A
1093	Dimercaptosuccinic Acid	Oral dosage forms	A
1094	Calcium Trisodium Pentetate	Injection	A
1095	Penicillamine	Oral dosage forms	A
1096	Deferoxamine	Injection	A
1097	Calcium Disodium Edetate	Injection	A
1098	Sodium Thiosulfate	Injection	A
1099	Sodium Nitrite	Injection	A
1100	Amyl Nitrite	Inhalation	A
1101	Pralidoxime Iodide	Injection	A
1102	Pralidoxime Chloride	Injection	A
1103	Obidoxime Chloride	Injection	A
1104	LCysteine	Injection	A
1105	Bemegride	Injection	A
1106	Sodium Diethyldithiocarbamate; Trihydrate; Dithiocarb	Injection	A
1107	Flumazenil	Injection	A
1108	Sodium Sulfate	Oral powder	A
1109	Naloxone	Injection	A
1110	Mercaptamine	Injection	A
1111	Nalorphine	Injection	A
1112	Methylthioninium Chloride	Injection	A
1113	Medicinal Charcoal	Oral dosage forms	A
1114	Acetamide	Injection	A
1115	Methionine and Vitamin B 1	Injection	B
1116	Nalmefene	Injection	B
1117	Penehyclidine	Injection	B
1118	Maglumine adipiodone	Injection	A
1119	Iophendylate	Injection	A
1120	Iopanoic acid	Oral dosage forms	A
1121	Iodinated Oil	Injection	A
1122	Barium sulfate (I, II)	Dry suspension	A

1123	Meglumine Iotalamate	Injection	B
1124	Iobitridol	Injection	A
1125	Ioversol	Injection	A
1126	Iohexol	Injection	A
1127	Iopamidol	Injection	A
1128	Iopromide	Injection	A
1129	Maglumine diatrizoate	Injection	A
1130	Iodixanol	Injection	B
1131	Iomeprol	Injection	B
1132	Iotrolan	Injection	B
1133	Sodium Diatrizoate	Injection	B
1134	Compound Meglumine and Diatrizoate	Injection	B
1135	Gadodiamide	Injection	A
1136	Gadobenate Dimeglumine	Injection	B
1137	Gadopentetate Dimeglumine	Injection	B
1138	Gadoteric Acid Meglumine Salt	Injection	B
1139	Ferucarbotran	Injection	B
1140	Sulphur Hexafluoride Microbubbles	Injection	B
1141	Double contrast gas particles	Granules	B
1142	Brucellin	Injection	A
1143	Purified protein derivative tuberculin	Injection	A
1144	Old tuberculin	Injection	A
1145	Diphtheria Antitoxin	Injection	A
1146	Gasgangrene Antitoxin (Mixed)	Injection	A
1147	Antirabies Serum	Injection	A
1148	Preparation of antisnake venom serum for injection		A
1149	Anthrax Antiserum	Injection	A
1150	Tetanus Antitoxin	Injection	A
1151	Botulinum Antitoxin	Injection	A
1152	Botulinum antitoxin A	Injection	B
1153	Purified Antirabies Serum	Injection	B
1154	Refined AntiCobra Venom Serum	Injection	B
1155	Purified Anthrax Antiserum	Injection	B
1156	Purified Tetanus Antitoxin	Injection	B
1157	(Human Tetanus) Immunoglobulin	Injection	B
1158	Human Rabies Immunoglobulin	Injection	B
1159	Human lmmunoglobulin	Injection	B
1160	Human Serum Albumin	Injection	B

1161	Rabies Vaccine for Human use	Injection	B
1162	Mouse Nerve Growth Factor	Injection	B
1163	Botulinum Toxin A for Therapeutic Use	Injection	B
1164	Recombinant Human Basic Fibroblast Growth Factor	Freezedried preparations for external use	B

Source: Ministry of Human Resources and Social Security

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