The Global Health R&D

Capacity and Opportunities in China

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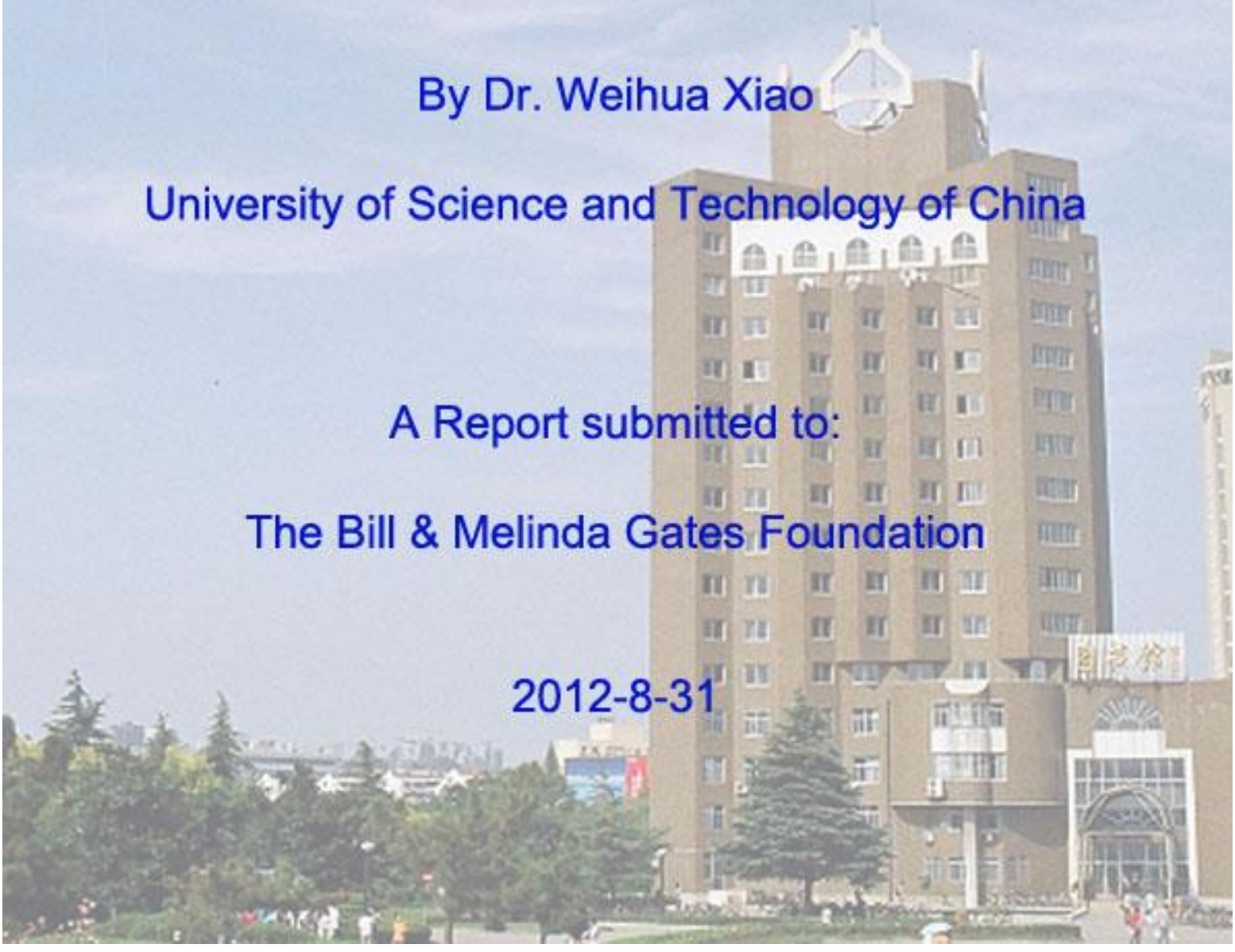

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Executive Summary

China is becoming an attractive player in global health R&D that is promoted by its rapid growth of economic development. This report is aimed to provide an evidence-based and deep analysis on the current status and future trends in the area of the BMGF defined global health R&D, especially in infectious diseases, in China. The data are carefully collected and evaluated from various sources including related research articles, patents, grant applications, interviews and on-site visiting, as well as from public news and third party review or commnets on some particular interested projects.

The first part of this report ,focuses on the achivements and major developments in each institute or laboratory, which provides an landscape of global health R&D from academic and industrial sectors The second part of this report describes in detail on recent R&D activities and achievements in the prevention, diagnosis and treatment for each of the major infectious diseases, including HIV, tuberculosis, malaria, diarrhea and pneumonia, which are priority areas of focus by BMGF; and hepatitis and influenza, which causes the major impact in China currently.

The report also highlights a number of potentially significant ongoing projects in global health R&D in China. These projects include but not limit to innovative vaccines such as therapeutic vaccine for hepatitis, recombinat BCG vaccine, DNA-viral vector combined HIV vaccine, transgenic plant diarrhea vaccine, as well as diagnostic reagents for drug-resistant MTB genotyping, hepatitis-HIV combined detection, rapid malaria detetion, pneumonia pathogen genotyping, et al.

The report also summarizes certain challenges in global health R&D which are currently exicting in China.

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Chapter 1

Landscape on Global Health R&D in China

1. 1 Overview on current Global Health R&D in China

The current features in the fields of medical and life sciences R&D in China which are tightly related to global health R&D are summarized as follows:

The social R&D resources are expanding. In 2009, China's total R&D expenditure is 580 billion RMB, which account for 1.7% of total GDP according to the statistic data from the Report for 2nd Invesigation on R&D Resources in China. In the filed of medical sciences, there are approximately 2200 R&D institutions, consisting mostly of government-affiliated research institutes, universities, and enterprises, which represent 5.1% of the total R&D institutions in China. There are 56 thousands of professional R&D persons, among them 8 thousands with doctoral degree and another 13 thousands with master degree. In addition, there are about 300 R&D institutions in the field of life sciences, consisting mostly of government-affiliated research institutes and universities.

The government is rapidly increasing its investment in R&D. The committee of Natural Science Foundation of China (NSFC) is the largest government funding agency for basic research. In 2011, NSFC has approved a total of 18 billion RMB researching funding, of which about 24 million in life sciences and 34 billion in medical sciences. The Ministry of Science and Technology is the largest government funding agency for applied research and technological development. In recent 30 years, the Ministry of Science and Technology has launched several major research projects such as the National Hi-Tech Research and Development Program (also referred to as the "863 Program"), the National Key Project for the Development of Basic Scientific Research (also referred to as the "973 Project"), and the Major Science and Technology Program.

Enterprises are becoming the dominant players in R&D. In 2009, 73.2% of the total R&D investment is input into industrial enterprises in China. The pharmaceutical companies have spent about 15 billion RMB in R&D investment, accounting for 1.48% level of total annual sales. This is much higher than the average level of 0.7% R&D investment of all industrial sectors. The R&D investment level of large or listed pharmaceutical companies is about 2-5%, which is relatively higher than small companies (typically less than 1%). In addition, more than 90% of the company R&D investment comes from the self-raised funds, government and other funding is less than 10%. However, in contrast to spending 15-20% of sales on R&D in the international top 10 phamaceutical companies, the spending on R&D in China local pharmarcompany is still too low.

1.2 Industry landscape on global health R&D

The pharmaceutical industry in China has been ushering in a golden age of development.

In 2010, the pharmaceutical industry achieved sales of 1.2 trillion RMB, of which chemical drugs accounted for 40%, traditional Chinese medicine accounted for 25%, biopharmaceuticals accounted for 10% and medical devices (including diagnostic reagents) accounted for 20%. In the last decade, the average annual growth rate for the pharmaceutical industry was approximately 15% and that of

the biopharmaceutical industry was 28%.

Currently there were a total of approximately 5,000 pharmaceutical companies in China. In 2010, the total sales of top 100 companies (as referred to as "Big Pharma" in this report) were about 440 billion RMB. The top 100 companies included approximately 90 domestic companies and 10 foreign-funded companies. The concentration ratio for the top 10 pharmaceutical companies in China was 18%, in contrast to 40% for the top 10 pharmaceutical companies worldwide.

The Chinese pharmaceutical market accounted for approximately 11% of the world pharmaceutical market in 2011 with average annual growth rate of nearly 15% in recent ten years.

China has become the world's largest vaccine producer and 3rd largest vaccine consumer.

Since 2007, China has become the world's largest vaccine producer with an annual production capability of one billion immunization vials (doses). In 2011, the Chinese vaccine market reached approximately 12 billion RMB, with an average annual growth rate of 15% in recent ten years. There are currently more than 30 domestic vaccine manufacturers in China, which can produce over 40 types of vaccines that prevent 26 types of infectious diseases. Currently, there are more than 20 new vaccine strains for infectious diseases in clinical trials approved by the SFDA.

The major vaccine manufactures in China are summarized in Table 1. According the annual sales of on-market vaccines and capabilities of new vaccine R&D, these pharmaceutical companies are generally classified as the following categories:

Big pharma with vaccines as main products. These companies have strong abilities in R&D of new vaccines. CNBG is the largest biopharmaceutical company in China. CNBG has committed 90% of its production tasks to the Expanded Program on Immunization (EPI) vaccines and does extensive vaccine R&D. Hualan Biol focuses on the development of influenza and hepatitis vaccines, which was of significant importance during the influenza pandemic in 2009 when the company rapidly developed the H1N1 influenza vaccine, thereby making an important contribution to the prevention and treatment of influenza.

Big pharma as new vaccine manufacturers. Most of them are traditional pharmaceutical for chemical medicines which stepped in development of biological products in recent years, including Huabei Pharm, Tianjin Jinlishi, Shenzhen Neptume, et al.

Small and medium enterprises (SMEs) with vaccines as main products. There are more than 20 domestic SMEs whose main business and R&D focus on infectious disease vaccines. Most of them reached the annual sales of more than 50 million RMB in 2011. Among them, Sinovac Biotech has the largest annual sales of vaccines with 800 million RMB.

Start-up companies with new vaccines in development. These companies are relatively small and typically collaborate with universities and academic institutes for development of novel vaccines with no similar products on market. Some of them have vaccine products in clinical trails such as Chongqing Jiachen Biologcial, Guangzhou Baidi Bio-Tech, Shenzhen Aokoo Biotech.

Table 1 Major vaccine R&D and manufacturing companies in infectious diseases in China

Company name[1]	Rank [2]	Products on the market[3]	Products in R&D[4]	Features and evaluations
China National Biotech Group[5]	11	hepatitis A/B/C, influenza (seasonal and H1N1), BCG, rotavirus, Hib, rabies, DTP combination, encephalitis, typhoid fever, diarrhea, hemorrhagic fever, plague, cholera, dysentery, anthrax, measles, rubella, mumps, varicella, et al.	AIDS (phase II), 3-valent rotavirus (phase I), hepatitis, influenza, typhoid, cholera and dysentery, et al.	China's largest manufacturer of human vaccines
Beijing Tiantan Biological[5]		hepatitis A/B, influenza (seasonal and H1N1), BCG, meningitis, typhoid Vi polysaccharide, DTP combination, hemorrhagic fever, et al.	hepatitis B, EV71 (phase II), yellow fever, MMR-varicella, pertussis, rabies, encephalitis B	
Northern China Pharma	7	hepatitis B (CHO)	N/A	
Tianjin Tasly Pharma	14	influenza subunit	N/A	
Changchun ChangSheng Life	180	hepatitis A, Influenza (seasonal and H1N1), rabies, DTP combination, varicella，Meningococcal Group A/C	Therapeutic hepatitis B DNA vaccine (phase II)	
Zhejiang Tianyuan Bio-Pharma	204	influenza (seasonal and H1N1), encephalitis, hemorrhagic fever，Meningococcal conjugate Group A/C or ACYW135	MF59-adjuvanted influenza, encephalitis coccus TT conjugate, pertussis triple vaccine	Acquired by Novartis in 2011
Yunnan Walvax Biotech	323	Hib, influenza Meningococcal Group ACYW135	23-valent pneumococcal, DTP-Hib, new adjuvant hepatitis B	leader in bacteria-conjugate technology
Beijing Sinovac Biotech	346	hepatitis A/B, influenza (seasonal, H5N1, H1N1), mumps	SARS (phase I), EV pneumococcal, Hib, meningitis, et al.	leader in hepatitis A vaccines
Beijing Wantai Biopahrma	409	hepatitis E	cervical cancer (phage I)	
Beijing Luzhu Biopharma	420	Hib, meningococcal Group A/C or A/C/Y/W135	EV71	
Institute of Medical Biology	483	hepatitis A, polio	inactivated polio (phase II)	leader in hepatitis A vaccine
Liaoning Chengda Biotech	N/A	rabies, meningitis	hemorrhagic fever(phase III), influenza (vero cells)	leader in rabies vaccine
Hualan Biological Engineering	N/A	hepatitis B, influenza (seasonal and H1N1), encephalitis ACYW135 group	EV71, DPT-Hib-hepatitis B, 9-valent pneumococcal	leader in Influenza vaccine
Changchun BCHT Biotech	N/A	varicella, rabies	Recombinant AIDS vaccine (phase II)	leader in varicella vaccine
Dalian Hissen Bio-pharm	N/A	hepatitis B (Hansenula yeast), influenza, rabies	Recombinant hepatitis E vaccine	leader in hepatitis vaccine

Zhejiang Pukang Biotech	N/A	hepatitis A (freeze-dried attenuated living)	cervical cancer, rabies	Leader in vaccine export
Jiangsu Ealong Biotech	N/A	influenza (seasonal and H1N1), rabies，mumps	N/A	N/A
Shenzhen Kangtai Biological	N/A	hepatitis B (*S. cerevisiae*)	therapeutic hepatitis B (phase II), rotavirus	leader in hepatitis B vaccine
Shenzhen Neptunus Bioengineering	N/A	influenza subunit	Next generation of influenza subunit vaccine	
Beijing Huaerdu Biotech	N/A	hepatitis B	N/A	
Beijing Minhai Biotech	N/A	Hib	N/A	
Dalian Aleph Biomedical	N/A	influenza (seasonal and H1N1)	N/A	
Shanghai Zerun	N/A	hepatitis A (Vero)	N/A	
Shanghai United Cell	N/A	cholera	N/A	
Guangzhou BaiDi Bio-Tech	N/A	N/A	Therapeutic hepatitis B vaccine (phase II)	
Chongqing JiaChen Biological	N/A	N/A	Therapeutic hepatitis B vaccine (phase II)	
Shenzhen Aokoo Biotech	N/A	N/A	DNA vaccines: AIDS, hepatitis B, lung cancer	

[1] The table lists major domestic companies with vaccine R&D or products for seven infectious diseases, including hepatitis, HIV, TB, malaria, pneumonia and influenza. Some small companies with vaccine R&D and production for rabies, encephalitis, varicella, measles, mumps, hemorrhagic fever, meningococcal, et al. are not listed here.

[2] Data source from 2010 Chinese Medical Statistical Report, the Chinese Ministry of Industry and Information. The top 500 pharmaceutical companies are ranked according to total annual sales in 2010 while some biotechnological or bioengineering companies are not included, we set are N/A.

[3]The main sources for the products listed above are the SFDA website (English version available at http://eng.sfda.gov.cn), keywords: drugs, biological products, the company's website, and publications. For some companies lacking accessible information we set as N/A.

[4] The main sources for R&D products are the SFDA website and each company's website. The R&D products are in pre-clinical study unless otherwise indicated.

[5] China National Biotech Group was established in 1998, currently consisting of six research institutes of biological products in Beijing, Shanghai, Chuangchun, Chengdu, Lanzhou, Shanxi as well as a subsidiary Beijing Tiantan Biological.

China is still in rapid development in the diagnosis of infectious diseases.

In China, the State of Food and Drug Administration (SFDA) has classified the diagnostic reagents of medical purposes into therapeutic medicines or medical devices for management. In 2011, the Chinese in vitro diagnostic reagent market was approximately 15 billion RMB, with an average annual growth rate of 15% in recent ten years. Currently, there are more than 400 domestic manufacturers for in vitro diagnostic reagents, approximately 100 of which involve infectious disease diagnostics and their products essentially covered all major infectious diseases.

The major diagnostic reagent manufactures for infectious diseases in China are summarized in Table 2. These companies are relatively strong in diagnostics reagent R&D and their products occupy a large share of the domestic market.

Two companies listed in the top 100 Big Pharma are involved in diagnostic reagent production and R&D for infectious diseases. China National Biotech Group is very powerful in diagnostic reagent R&D especially in diagnostic serum and antibody products for infectious diseases. Livzon Pharmaceutical mainly focuses on the development of diagnostic products for HBV, HCV and HIV.

Other companies are SMEs, most of which have their own advantages in specific diagnostic reagent R&D. For example, Beijing Wantai Biopharma is strong in EIA kits, Guangzhou Wanfu Biomedical is strong in ICG kits, and Da An Gene is strong in PCR kits. Most of the SMEs have annual sales of in vitro diagnostic products of more than 10 million RMB in 2011. Among them, Shanghai Kehua Biological has the largest annual sales of 200 million RMB.

Table 2 Major diagnostic reagent R&D and manufacturing companies in infectious diseases in China

Company/Group	Rank [1]	Products in the market[2]	Products in R&D[3]	Features and evaluations
China National Biotech Group	11	HIV, hepatitis B/C, diagnostic serum (intestinal bacteria)	N/A	Largest manufacturer of diagnostic serum
Beijing Tiantan Biological		hepatitis, syphilis, hemorrhagic fever, diagnostic serum (intestinal bacteria)	N/A	
Livzon Pharma	48	hepatitis A/B/C, HIV	HIV-p24 (4^{th} generation)	leader in hepatitis and HIV products
Huangzhou Acon Biotech	252	HIV, hepatitis B/C	N/A	
ABON Biopharm	279	hepatitis B/C, HIV, influenza A/B, RV	N/A	Leader of emulsion kits
Beijing Kinghawk Pharma	346	hepatitis B/C, HIV, influenza H1N1, EV71, tetanus, rabies, et al.	hepatitis, influenza, HIV	Leader of PCR kits
Xiamen Asiatec	381	hepatitis B/C, HIV, TB	N/A	
Beijing Wantai Biological	409	hepatitis A/B/C/E, HIV(4^{th} generation), TB, RV, influenza H1N1, syphilis	EV71	Leader of EIA kits
Shanghai Kehua Bioengineering	N/A	hepatitis A/B/C, HIV	kits for a variety of infectious diseases	Largest manufacturer of diagnostic reagents
Beijing Beier Bioengineering	N/A	hepatitis B/C//D/E, HIV, TB, EV71, pneumonia, syphilis, leptospirosis	N/A	leader in EV71 diagnostic reagents
Shanghai Rongsheng Biopharma	N/A	hepatitis A/B/C, HIV, TB	New ICG diagnostic kits Supersensitive TB kit	leader of EIA kits
Guangzhou Wondofo Biomedical	N/A	hepatitis A/B/C, HIV, Malaria	HIV, hepatitis C, influenza A/B	leader of ICG kits
Da An Gene	N/A	hepatitis B/C/D/E, HIV, TB, SARS	N/A	leader of PCR kits
NewScen Coast Bio-Pharma	N/A	hepatitis B/C, TB, HIV	N/A	leader of ICG kits
Beijing KeWei	N/A	hepatitis A/B/C/E, HIV(4^{th} generation),	N/A	leader of ECL kits

Diagnostic				
Beijing Chemclin Biotech	N/A	hepatitis B/C, HIV(4th generation), TB	N/A	
Beijing BGI-GBI Biotech	N/A	hepatitis B/C, TB, HIV, H1N1, EV71, SARS	N/A	Leader of PCR kits
Autobio Diagnostics	N/A	hepatitis B/C, TB, bacteria and virus (Hib, pneumonia, diarrhea et al.)	N/A	
Beijing Bioneovan Biotech	N/A	hepatitis A/B/C/E,TB, RV	N/A	
Weifang Kanghua Biotech	N/A	Hepatitis A/B/C/E, TB, HIV, hemorrhagic fever	N/A	
Boson Biotech	N/A	hepatitis B, TB, HIV	N/A	

[1] The table lists major domestic companies that manufacture in vitro diagnostic reagents for at least two of seven infectious diseases, including hepatitis, HIV, TB, malaria, pneumonia and influenza. Some small companies with diagnostic products for only one infectious disease or for other infectious diseases are not listed here.

[2] Data sources are from 2010 Chinese Medical Statistical Report, the Ministry of Industry and Information Technology. The top 500 pharmaceutical companies are ranked according to total annual sales in 2010 while some biotechnological or bioengineering companies are not included.

[3] Data sources are from the SFDA website for R&D products in clinical trails (English version available at http://eng.sfda.gov.cn), the state intellectual property office for patent searching (English version available at http://english.sipo.gov.cn), the company's website, and publications. For some companies lacking accessible information we set as N/A.

[4] The main sources for R&D products are the SFDA website and each company's website. The R&D products are either in pre-clinical study or clinical trails.

1.3 Academic landscape for global health R&D

In 2009, there are about 1200 academic research institutions in the field of medical science in China, including 314 government-affiliated research institutes, 967 colleges and universities, and a small number of independent research institutions. In the field of biological science, there are 86 government-affiliated research institutes and about 200 colleges and universities. Currently, these medical and biological research institutes undertake almost all of the basic and applied research activities in the field of global health R&D in China.

Universities are becoming the most powerful force in China's global health R&D in China.

There are a total of 2,200 public colleges and universities in mainland China according the statistic data from the Ministry of Education. There are approximately 110 "key" universities supported by the "211 Plan", which is mostly funded by the Ministry of Education. The key universities are the nationwide leaders in quality of the faculty, teaching standards and level of research.

More than 300 universities have established medical schools which typically include the department of basic medical sciences and ancillary clinical hospitals. These universities have certain research capabilities in the field of global health R&D. Among them, there are more than 70 universities have established graduate schools which are qualified to issue graduate degrees (master or doctoral). Also, there are about 200 universities have established graduate schools in life sciences which are

qualified to issue graduate degrees (master or doctoral). These universities with graduate schools in medical and life sciences have a strong presence in the field of global health R&D.

China's military system also includes a few universities and research institutes which have very strong programs in global health R&D. The military medical universities have unique funding and resource advantages as well as emergency production capacity in public health R&D, especially for major or emerging infectious diseases that may seriously affect national security.

Government-affiliated institutes have been contributed a lot in China's global health R&D.

The Chinese Academy of Medical Sciences (CAMS) was established in 1956 and has been ranked 1st among medical institutions for many years. It is the only national comprehensive medical science and technology center, and it includes Peking Union Medical College and a number of research institutions of higher education.

The Chinese Academy of Sciences (CAS) was established during the founding of P. R. China. It is the largest academic institution for natural science research and high-tech development. In the life sciences and biotechnology fields, CAS has more than 20 independent research institutes, with a team of 6,800 researchers and management staffs.

The Center for Disease Control and Prevention of the People's Republic of China (China CDC), which is directed by the Ministry of Health, is the national disease prevention and control center and public health management institution. It is actively involved in a variety of applied research programs in the field of public health prevention, diagnose, and therapy.

Table 3 summarizes the most powerful academic institutions in global health R&D in China. These R&D institutions include approximately 30 comprehensive universities, 5 medical universities, 7 military institutions, 4 CAS institutes, CAMS and CDC. They are at the forefront of the nation's academic institutions in terms of annual research grants, publications, patent applications, and high-tech achievements.

Table 3 Major academic institutions in Global Health R&D in China

Name[1]	Main research directions and projects[2]	Highlight achievements
Fudan University	1. Pathogenesis and vaccine development for pneumonia pathogens (mycoplasma and streptococci) 2. New TB vaccines and drugs; rapid diagnosis of drug-resistant TB 3. Molecular mechanism of hepatitis virus replication and intervention; anti-HBV immunotherapy 4. HIV vaccine and new drug development	Therapeutic hepatitis B vaccine in clinical phase II
Wuhan University	1. Separation and functional studies of natural flu drugs 2. Characteristics of hepatitis B virus genetics and the study of new treatment targets 3. Development of hepatitis C vaccines 4. Vaccine development of attenuated bacterial vector TB carrying the TB gene	Pre-clinical research

Peking University	1. Hepatitis B epidemiology, peptide treatment, drug development; hepatitis C pathogenesis and treatment plan optimization 2. Salmonella typhi pathogenesis of mycobacterium 3.TB-resistant molecular mechanism; new TB vaccine development	Pre-clinical research
Zhejiang University	1. Hepatitis targeting drug delivery system and stem cell therapy research 2. New methods of clinical treatment of severe viral hepatitis B 3. Panax saponin immunological adjuvant and vaccine formulations containing this adjuvant	Pre-clinical research
Jilin University	1. Development and mechanism hepatitis C virus nucleoside drug 2. Rapid diagnosis of MTB and screening of new drug target 3. Research on new viral vector AIDS vaccines	Laboratory research
Huazhong University of Sci & Tech	1. development of hepatitis targeting drug therapy 2. Mechanism study of rotavirus pathogenesis 3. The interaction between MTB and immune system and development of new gene therapy drugs	Laboratory research
Chongqing Medical University	1. New rotavirus oral vaccine development 2. *Strep*. pneumoniae infection mechanisms and drug development 3. Chronic hepatitis B clinical outcomes and associated factors	Laboratory research
China Medical University	1. Blocking method of malaria pathogen invasion of hosts 2. Study on factors related to AIDS disease progression 3. Development of HIV urine diagnostic reagents	Laboratory research
Sichuan University	1. Study of the biological treatment of viral diarrhea 2. Isolation and functional study of new natural TB drugs 3. Development of recombinant immunoadjuvant TB vaccines.	Laboratory research
Sun Yat-sen University	1. Test of hepatitis serum markers and stem cell therapy 2. Interactions of MTB and immune system and their treatment 3. Genetic engineering of hybrid yeast in AIDS vaccine research	Pre-clinical research
Tsinghua University	1. AIDS transmission and new transmission-blocking methods 2. Development of new HIV and influenza epitope vaccines	Laboratory research
Xiamen University	1. New hepatitis E vaccine and diagnostic reagent development 2. Research on drug-resistant TB diagnostic techniques and products	SFDA approved
University of Sci & Tech of China	1. Hepatitis immune and gene therapy 2. TB molecular targeting drug development	Laboratory research
Nanjing University	1. Mechanisms of malaria pathogen resistance 2. New biological technology in AIDS prevention and product development	Laboratory research
Hunan Normal University	1. Development of new types of influenza vaccine 2. New vaccine adjuvants from natural or synthetic compounds	Laboratory research
Capital Medical University	1. Development of new DNA vaccine for TB prevention and treatment 2. Study on prediction model for individualized treatment and clinical outcomes of chronic hepatitis B diseases	Laboratory research
China Agricultural University	1. Influenza virus molecular epidemiology and new transmission-blocking methods 2. Study of human and veterinary use of plant mucosal vaccines for the treatment of diarrhea	Laboratory research
Zhengzhou University	1. Development of new long-acting anti-viral α-interferon drugs	Laboratory

	2. Discovery of new anti-HIV chemical molecules	research
Central South University	1. development of new gene therapy for hepatitis	Laboratory research
Nanchang University	1. Vaccine development of new targeting gene carrier for TB therapy	Laboratory research
Nankai University	1. HIV genetic variation, pathogenic mechanisms, and targeting drug development	Laboratory research
Shandong University	1. Mechanism of liver cancer malignant transformation in the hosts of hepatitis virus infection	Laboratory research
Jiangsu University	1. Salmonella typhi bacteria pathogenic mechanism research and drug development	Laboratory research
Huazhong Agricultural University	1. Study of the molecular structure of MTB and its blocking method	Laboratory research
Shanghai Jiao Tong University	1. Mechanisms of hepatitis virus infection, drug resistance mechanisms and targeted therapy drug research	Laboratory research
Southern Medical University	1. New drug development and treatment of viral diarrhea 2. Rapid molecular diagnostic technology for malaria 3. Research on MTB molecular structure and development of new targeting drugs 4. Screening of traditional Chinese medicine for anti-HIV therapy	Laboratory research
Second Military Medical University	1. Development of new malaria vaccine and natural drugs 2. Development of therapeutic DNA vaccine for hepatitis 3. Study of new vaccine adjuvants based on heat shock proteins 4. Early diagnosis of hepatitis progressing to liver cancer, and development of new vaccines and biological therapeutics	Laboratory research
Third Military Medical University	1. Development of therapeutic hepatitis B polypeptide vaccine 2. Development of new rotavirus oral vaccine 3. Molecular mechanisms of plasmodium invasion of the host and development of multi-epitope DNA vaccine for malaria 4. Study of human anti-EHEC O157: H7 antibodies for diarrhea therapy and oral transgenic plant vaccine for infant diarrhea 6. Development of salmonella typhi vector vaccine for diarrhea	Therapeutic hepatitis B vaccine completed Phase II clinical trials.
Fourth Military Medical University	1. Study of MTB molecular structure and new vaccine development 2. Research on antibody targeting therapy fro viral hepatitis-related liver cancer	Pre-clinical research
Academy of Military Medical Science	1. New vaccines: influenza, malaria, cholera, dysentery, anthrax and plague combinations 2. New drugs: malaria, influenza, hepatitis, HIV 3. Detection reagent: Vibrio cholerae immune chromatography test paper 4. Important pathogenic bacterial micro-evolutionary studies	Shigella vaccines is phase II clinical trials
PLA Quartermaster University	1. Development of HIV recombinant fowlpox virus and multiple-epitope DNA vaccines 2. Research on new molecular adjuvant nasal vaccines	Pre-clinical research
PLA General Hospital	1. New diagnostic technology and product for TB	Pre-clinical research
PLA 302 Hospital	1. Research on pathogenesis, clinical warning signs and outcomes of severe	Laboratory

	hepatitis B. 2. Molecular mechanism of natural immunity against HIV	research
PLA 458 Hospital	1. Study of dual-plasmid gene vaccine hepatitis B virus	phase II clinical trials
Institute of Microbiology, CAS	1. Molecular pathogenesis of influenza virus and new treatments 2. Development of vaccinia virus and DNA epitope vaccine for avian influenza 3. Development of new anti-TB small molecule drugs. 4. Research on new immune adjuvant using heat shock protein gp96	Laboratory research
Institute of Biophysics, CAS	1. Development of new diagnostic techniques for infectious diseases such as HIV. 3. Study on MTB molecular structure and development of small molecule targeting drugs 4. Basic research on hepatitis C viral infection, prevention and treatment	Laboratory research
Shanghai Pasteur Institute, CAS	1. Biological characteristics and innovative treatment for refractory hepatitis C	Laboratory research
Wuhan Institute of Virology, CAS	1. Influenza virus molecular structure and new drug development 2. Molecular mechanism of MTB infection of the host and new blocking methods 3. Study on AIDS pathology and the immune protective mechanism 4. Development of new diagnostic reagent for HIV	New HIV diagnostic kit completed pre-clinical study
Chinese Academy of Medical Sciences	1. Development of inactivated rotavirus vaccines 2. Development of new HCV epitope peptide vaccine 3. Research on the influenza virus structure and development of broad-spectrum vaccines and small molecular targeting drugs. 4. Study of MTB pathogenesis and new diagnostic markers, and new TB drug screening 5. Study of adult AIDS patients with antiviral treatment and immune reconstruction, and innovative AIDS mucosal vaccine development 6. Development of new immune-adjutants for vaccines	Laboratory research
Center for Disease Control and Prevention	1. Cholera pathogenesis and testing 2. Rapid detection method of the malaria parasite 3. Development of new vaccinia virus vector HIV vaccine and antiviral treatment of childhood AIDS 4. Development of recombinant strains live rotavirus vaccine 5. Research on new viral hepatitis B immunization strategies 6. New detection methods of common diarrhea-associated viruses	HIV vaccine in phase II clinical trails

[1] Inclusion criteria for academic institutions: acquisition of at least a total of ten major research projects funded by NSFC; the 973 Project, the 863 Program, and the Major Science and Technology Program in the years of 2005 to 2011.

[2] The table lists only research projects in seven infectious diseases, including hepatitis, HIV, TB, malaria, pneumonia and influenza.

Chapter 2

Global Health R&D Status in Diseases

2.1 Hepatitis

The most common cause of hepatitis is viral infection by one of the five sub-groups of hepatitis viruses: hepatitis A (HAV), hepatitis B(HBV), hepatitis C(HCV), hepatitis D(HDV), or hepatitis E (HEV). HBV and HCV can lead to liver cirrhosis and liver cancer. There are an estimated 2 billion HBV carriers worldwide, of which 350 million have chronic infectious diseases. Each year, 500-700 thousand people die of hepatitis B diseases. Furthermore, approximately 130-170 million people are chronically infected with HCV and 350 thousand people die of liver diseases related to hepatitis C [WHO Viral Hepatitis Report, 2010]. According to the Ministry of Health statistics, there are approximately 120 million HBV carriers in China. In the last five years, the incidence of Chinese hepatitis cases has exceeded 1 million per year, with approximately 1,000 deaths from hepatitis each year [2010 Statutory Infectious Diseases Statistics, the Ministry of Health].

2.1.1 Hepatitis vaccines

Vaccines are the major means of prevention for viral hepatitis. The approved hepatitis vaccines currently in clinical use around the world can be classified into plasma-derived vaccines, live-attenuated vaccines, inactivated vaccines, genetically engineered recombinant vaccines, and others.

Table 3 summarizes the overall status of hepatitis vaccine production in China. The development of Hepatitis A and hepatitis B vaccines are relatively mature, and numerous vaccines are on the market. The development of Hepatitis C vaccine is relatively difficult and is therefore still in the laboratory research stage. Relatively little research is being conducted on hepatitis D vaccine because the commonly used hepatitis B vaccine also prevents hepatitis D infection. Hepatitis E vaccine was developed relatively quickly, and there is one product currently on the market in China.

Table 4 Major manufactures of hepatitis vaccines in China

Category	Company name	Total
Hepatitis A (live-attenuated vaccine)	China National Biotech Group, Institute of Medical Biology, Changchun Changshen Life, Zhejiang PuKang Pharma	4
Hepatitis A (inactivated vaccine)	Beijing Sinovac Biotech, Shanghai Zerun Biotech, Institute of Medical Biology of CAMS	3
Hepatitis B (recombinant vaccine)	China National Biotech Group, HuaLan Biology, Shenzhen Kangtai Phama, Beijing Tiantan Biological, Northern China Pharma, Beijing Huaerdung Biotech, Dalian Hissen Biopharma	7
Hepatitis E (recombinant vaccine)	Xiamen Innovax Biotech	1
Combined vaccine	Beijing Sinovac Biotech (hepatitis A and B)	

The first-generation hepatitis A vaccine was a live-attenuated vaccine, and it is currently produced

and marketed by four companies. The second-generation hepatitis A vaccine was an inactivated vaccine, and it is produced and marketed by three companies, although Beijing Sinovac has the major market share. Compared to the live-attenuated hepatitis A vaccine, the inactivated hepatitis A vaccine has a longer protection period and fewer side effects.

The first-generation hepatitis B vaccine was a plasma-derived viral vaccine made from the hepatitis B surface antigen (HBsAg), which was obtained from the plasma of asymptomatic HBV carriers. Because of the potential safety hazards and limited plasma sources, China prohibited the use of this vaccine in 2000. The second-generation hepatitis B vaccine was a genetically engineered recombinant vaccine obtained by expressing recombinant HBsAg in yeast or CHO cells. Six companies in China now produce the second-generation vaccine, and HuaLan Biology and China National Biotech Group have the major market shares.

Professor Linshao Xia's group at Xiamen University and Beijing Wantai Bio-pharmac jointly developed a hepatitis E recombinant vaccine (product name: Yikening). This vaccine was approved by SFDA in 2011 and is the first hepatitis E vaccine in the world to be approved. The joint research effort was the first to identify the two major immune dominant surface antigen epitope peptides on the hepatitis E virus, which contributed to more than 90% detection of human hepatitis E antibody. The hepatitis E recombinant vaccine was produced by expression and purification the recombinant antigen containing the two epitope peptide sequences from E.coli. The results of phase III clinical trials involving more than 10,000 volunteers (16-65 years old) indicate an inoculation efficiency of 100% with no or few side effects [Zhu FC].

Beijing Sinovac Biotech has developed a "hepatitis A and hepatitis B combined vaccine," which is the first combined hepatitis vaccine to be approved in China. This combined vaccine was developed by combining the hepatitis A inactivated vaccine and the hepatitis B recombinant vaccine. Clinical trials demonstrated that after injection of the combined vaccine, the positive rate of hepatitis A surface antibodies was 97.3%, the positive rate of hepatitis B surface antibodies was 100%, and the positive rate of hepatitis B protective antibodies was 97.3% [Chen YZ].

New hepatitis vaccine research in China is currently focused on the technical improvement of the available vaccines, the development of novel adjuvant vaccines, the combined hepatitis vaccines, multivalent antigen recombinant vaccines, polypeptide vaccines, nucleic acid vaccines, and therapeutic vaccines. Table 4 summarizes the major research and development efforts of new hepatitis vaccines in China in recent years.

Table 5 Major achievements of new hepatitis vaccine R&D in China

Protject name	Company/ Institute	Features and Innovative Characteristics	Patent Protection	Research Progress
Hepatitis A inactivated vaccine	Yunnan Walvax Biotech	A new type of HAV strain YN5, was obtained by screening and demonstrated high efficiency proliferation in vero cells. The virus was obtained after degradation and further purification.	CN021069 85.9	Phase I clinical trial
Hepatitis A inactivated vaccine	Beijing Minhai Biotech	A new type of HAV strain SH, was isolated from hepatitis A patients, and cultivated in MRC-5 human embryo lung cells with high efficiency. The virus was obtained after	CN201010 622268.0	Phase I clinical trial

		degradation and further purification.		
Novel adjuvant recombinant hepatitis B vaccine	Fudan University	This vaccine was produced from *Hansenula* yeast expressing HBsAg that were then heat-inactivated. *Hansenula* yeast cells were used as a novel adjuvant vaccine. Animal experiments demonstrated that this vaccine can induce relatively high titers of IgG antibody, enhance dendritic cell (DC) maturation, activate the Th1 and Th2 cellular immune responses, and enhance interferon γ (IFN γ) release levels.	CN200910196983.X	Pre-clinical research
Novel adjvant hepatitis vaccines	Beijing Hepo Biomed- Tech	A novel adjvant protein contaning human interleukin-2 (IL-2), human granulocyte-macrophage colony-stimulating factor (GM-CSF), and Tetanus toxin (TT)-derived peptide. This adjuvant can be used in new hepatitis B vaccine for disease prevention and treatment.	N/A	Pre-clinical research
Multivalent antigen recombinant hepatitis B vaccine	CP Guojian Pharma	This vaccine contains a fusion protein consistingof HBsAg, the human antibody Fc region and the adjuvant protein Flt3 ligand (FL). Animal experiments demonstrated that this vaccine can induce relatively high antibody titers in HBV transgenic mice and effectively reduce plasma HBsAg levels while activating the Th1 and Th2 cellular immune responses.	CN200710193859.9	Pre-clinical research
Hepatitis C polypeptide vaccine	Wuhan University	Using ribosome-polypeptide display technology, a hepatitis C glycoprotein antigen E2-specific binding peptide was obtained. *In vitro* experiments demonstrated that the polypeptide can prevent HCV E2 virus binding to the receptor CD81, thus inhibiting the HCV infection of human cells.	CN200710168887.5	Pre-clinical research
Hepatitis E protein-nucleic acid complex vaccine	Southeast University	This vaccine contains HEV recombinant protein and recombinant plasmid. Animal studies demonstrated that the combined vaccine can effectively induce animals to produce humoral and cellular immune responses simultaneously, indicating an effect that is superior to the protein vaccine or nucleic acid vaccine alone.	CN200910025685.4	Pre-clinical research
Hepatitis A/B/E combined vaccine	Southeast University	This vaccine contains inactivated HAV, recombinant HBsAg, and recombinant HEV antigen. Of these, the hepatitis E antigen has a better safety and immunogenicity profile.	CN200710024412.9	Pre-clinical research
Hepatitis and other infectious disease combined vaccine	Changchun Institute of Biological Products.	This vaccine was developed by combining hepatitis vaccines and other infectious disease vaccines, such as recombinant hepatitis B vaccine combined with hepatitis A vaccine, BCG vaccine, or varicella vaccine, or other vaccines, thereby simplifying the immunization process.	N/A	Pre-clinical research

Professor Jihong Meng's group at Southeast University has been developing combined hepatitis vaccines and conducting research on hepatitis virus infection and immune protection for many years. Meng's group was the first to express HEV containing a protein fragment with neutralizing antigen epitopes in prokaryotic cells. Subsequently, they constructed a genetically engineered recombinant HEV vaccine and initiated research and development of an oral hepatitis E vaccine, a hepatitis

A-hepatitis E combined vaccine, a hepatitis B-hepatitis E combined vaccine, and a hepatitis A-hepatitis B-hepatitis E combined vaccine.

At present, aluminum is the most widely used adjuvant for hepatitis vaccines the world. In China, adjuvant research includes the investigation of novel adjuvants containing CpG oligodeoxynucleotides, polyethylene glycol, and the adjuvant proteins. For example, Beijing Hepo Medical-Tech is developing a novel adjuvant protein that consists of human IL-2, GM-CSF, and TT-derived peptide. This adjuvant can be used in new hepatitis B vaccine for disease prevention and treatment.

CP Guojian Pharma is developing a multivalent antigen recombinant hepatitis B vaccine. The researchers constructed a recombinant fusion protein expression vector containing HBsAg, the fragment of the human antibody Fc region, and the protein adjuvant Flt-3. Two protein fusion patterns were used, including quadrivalent $(FL\text{-}CH\text{-}HBsAg\text{-}HBsAg)_2$ and octavalent $(HBsAg\text{-}HBsAg\text{-}CH\text{-}FL/\ HBsAg\text{-}HBsAg\text{-}CL)_2$. The fusions were subsequently expressed in CHO cells and purified to develop the new recombinant vaccine. Animal experiments demonstrated that this vaccine can induce a high antibody titer in HBV transgenic mice, effectively reduce HBsAg plasma levels, and activate Th1 and Th2 cellular immune responses. This vaccine is expected to be of particular value to hepatitis B virus tolerant individuals.

Professor Jihong Meng's group at Southeast University is developing a novel hepatitis E protein-nucleic acid combined vaccine consisting of recombinant HEV protein and recombinant plasmid expressing HEV viral gene. Animal experiments have shown that this combined vaccine can effectively induce organisms to produce humoral and cellular immune responses. The two components of this combined vaccine can act synergistically, yielding superior results to protein vaccines or nucleic acid vaccines acting alone.

3.1.2 Hepatitis diagnostics

The pathogenic features of the sub-groups of hepatitis viruses are different, as are the clinical diagnostic methods used to identify them. Hepatitis A is diagnosed by testing for anti-HAV-IgM antibodies. The diagnosis of hepatitis B, however, is relatively complicated. Depending on infection status and immune status, different antigens and antibodies must be tested, including the surface antibody, core antibody, e antibody, surface antigen, e antigen, pre-S1 antigen, and pre-S2 antigen. Patients infected with HCV have no obvious symptoms, and thus acute infection cannot be diagnosed in a timely fashion and a clinical diagnosis is made by testing for plasma anti-HCV-IgM antibodies viral RNA. The diagnosis of hepatitis D is made by testing for viral antigen and anti-HDV antibodies in blood plasma. HEV infection occurs through the intestinal tract, and thus a diagnosis is made based on epidemiological and clinical manifestations in combination with testing for plasma anti-HEV antibodies and viral RNA.

The most common techniques used to diagnose hepatitis can be grouped into three classes: 1) immunological techniques designed to test for antigens and antibodies associated with the hepatitis viruses, including enzyme-linked immunoassays (EIA), colloidal gold methods (ICG), chemiluminescence (ECL), chemical glow, and time-resolved immunofluorescence assays (IFA); 2) molecular biology techniques used to detect viral nucleic acids and genotypes, including the fluorescence probe PCR method and the PCR reverse dot blot hybridization method; and 3) newly

developed techniques such as the gene chip and microarray method.

Approximately fifty companies in China are currently approved by the SFDA to produce hepatitis diagnostic reagents, which are summaried in Table 5. These products cover all hepatitis subtypes and the technologies used include EIA, ICG, PCR, FIA, et al. More than ten companies dominate in the domestic market share and production technology, including Shanghai Kehua, Beijing Chemclin, Beijing Beier, Beijing Kewei, Beijing Blue Cross, Beijing Wantai, Zhengzhou Antu Luke, Guangzhou Wondfo, Zhongshan Daan Gene, and Zhuhai Livzon.

Table 6 Major manufacturers of hepatitis diagnostic reagents in China

Category	Company name	Total
Hepatitis A (EIA)	Weifang 3V Bioengineering, Shanghai Rongsheng Biotech, Shanghai Kehua Bio-engineering, Beijing KeWei Diagnostic, Zhuhai Livzon Diagnostics, Shanghai Huatai Hospital, Shenyang Huimin Biological, Xiamen Asiatec, Beijing Modern Gaoda Biotech, Beijing Wantai Biopharma, Autobio Diagnostics, Beijing Blue Cross, Beijing Bioneovan Biotech	13
Hepatitis A (ECL)	Beijing Yuande Bio	1
Hepatitis A (ICG)	Beijing Blue Cross, Weifang Kanghua Biotech	2
Hepatitis A (IFA)	Sym-Bio Life	1
Hepatitis B (EIA) combination	Beijing Beier Bioengineering, Beijing KingHawk Pharma, Beijing KeWei Diagnostic, Beijing Wantai Biopharma, Beijing Modern Gaoda Biotech, Beijing Bioneovan Biotech, Shanghai Fosun Pharma, Shanghai Huatai Hospital, Shanghai Kehua Bio-engineering, Shanghai Rongsheng Biotech, Shenzhen Huakang Biolical, Shenzhen Kang Sheng Bao, Shenzhen Mindray Bio-Medical, Shenyang Huimin Biological, Weihai Weigao Biotech, Weifang 3V Bioengineering, Xiamen Asiatec, Autobio Diagnostics, Livzon Diagnostics	21
Hepatitis B (ECL) combination	Beijing Chemclin Biotech, Beijing Yuande Bio, Shanghai Beyond Biotech, Fujian Hongcheng Biogical, Guangzhou Fenghua BioEngineering, Boson Biotech, Sichuan Maker Biotech, Weihai Weigao Biotech, Weifang Kanghua Biotech, Autobio Diagnostics, Chongqing Aifulang Biotech	11
Hepatitis B (ICG) combination	Guangzhou Wondofo Biomedical, Beijing Blue Cross, Shantou Runbio Biotech, NewScen Coast Bio-Pharma, Weifang Kanghua Biotech, Zhongshan Bio-Tech	6
Hepatitis B (IFA) combination	Guangzhou Fenghua BioEngineering, Sym-Bio Life, Da An Gene	3
Hepatitis B (EIA)	Beijing BGI-GBI Biotech, Guangzhou BGH Biomedical, Shanghai Alpha Biotech, Wuhan Aiengdi Biotech	4
Hepatitis B (fluorescent PCR)	Beijing KingHawk Pharma, Guangzhou Huayin Pharma, JiangSu Mole BioScience, Sansure Biotech, Shenzhen Qiagen Biotech, Amoy Diagnostics, Xiamen Amplly Bioteh, Shanghai Fosun Pharma, Shanghai Haoyuan Biotech, Shanghai Clone Biotech, Shanghai Shenyou Biotech, Shanghai Zj Bio-Tech, Shenzhen Yaneng Bioscience, Zhejiang Kuake Bioscience, Daan Gene, Zhuhai Sinochips Biotech	18
Hepatitis B (ICG)	Beijing Hepo Biomedical, Beijing Easyweet Biomedical, Shenzhen Relia Biotech, Zhengzhou Biocell Biotech	4
Hepatitis B (gene chip)	Zhuhai Sinochips Biotech, Shanghai Yulong Biotech	2
Hepatitis C (ICG and	Beijing Jingweikai Med-Biotech, Beijing Modern Gaoda Biotech, Beijing Bioneovan Biotech,	18

emulsion)	Beijing Easyweet Biomedical, Beijing Antai Diagnostic, Guangzhou Wondofo Biomedical, Beijing Blue Cross, Shenzhen Relia Biotech, Shantou Runbio Biotech, Shanghaih Chemtron, Shanghai Rongsheng Biotech, NewScen Coast Bio-Pharma, Weifang Kanghua Biotech, Xiamen Asiatec, Livzon Diagnostics	
Hepatitis C (ECL)	Beijing Yuande Bio	1
Hepatitis C (EIA for antigen)	Shandong LaiBo Biotech	1
Hepatitis C (fluorescent PCR)	Sansure Biotech、Shenzhen Qiagen Biotech、Xiamen Amplly Bioteh、Shanghai Haoyuan Biotech、Shanghai Kehua Bio-engineering、Shanghai Zj Bio-Tech	6
Hepatitis D (EIA)	Beijing Beier Bioengineering	1
Hepatitis E (ICG)	Beijing Modern Gaoda Biotech、Beijing Antai Diagnostic、Beijing Blue Cross	3
Hepatitis E (EIA)	Beijing Beier Bioengineering、Beijing KeWei Diagnostic、Beijing Wantai Biopharma、Beijing Modern Gaoda Biotech、Shanghai Huatai Hospital、Shanghai Kehua Bio-engineering、Shenyang Huimin Biological、Weifang Kanghua Biotech、Xiamen Asiatec	9

The research and development of hepatitis diagnostic reagents in China is currently focused on five areas. **Table 6 lists some of the major achievements of new hepatitis diagnostic reagents in recently in China.**

- **Improving the technology for products available on the market**
- **Incorporating the latest advancing technologies in immunology or molecular biology**
- **Using hepatitis virus genotyping technology to test for drug resistance**
- **Designing rapid detection methods for saliva or urine specimens**
- **Designing joint detection technologies for hepatitis and other infectious diseases such as HIV/AIDS**

Hunan Jingda Bioengineering Co., Ltd. is developing a new type of HCV antigen-antibody combined detection kit. This kit packages the HCV core antigen monoclonal antibody and recombinant chimeric antigen on one enzyme-linked plate. This kit can shorten the detection window for HCV infection from previous 10 weeks to current 2 weeks. A clinical trial involving 889 specimens revealed a specificity of 100% and a sensitivity of 98.8% [Zhang HQ].

Table 7 Major achievements of new hepatitis diagnostics R&D in China

Item name	Company	Features and Innovative Characteristics	Patent Protection	Research Progress
HCV antigen-antibody combined detection kit	Hunan Jingda Bio-engineering	HCV core antigen monoclonal antibody and recombinant chimeric antigen were packaged on one enzyme-linked plate to achieve simultaneous HCV core antigen and antibody detection, thus reducing the HCV testing window.	CN200810143274.0	Clinical trail

HBV diagnosis kit by nanometer luminescent particle technology	Shanghai Beyond Biotech	The kit uses nanometer luminescent particles to mark hepatitis B-specific antigens or antibodies; the sensitivity of a test using hepatitis B core antibodies, e antibodies, and surface antibodies was higher than that of the EIA method.	CN200810040118.1/CN200810205001.4/CN200810205002.9	Pre-clinical research
HAV rapid detection kit in saliva	HangZhou Alicon Pharma	The kit uses the colloidal gold labeling technique to detect HAV antigen in saliva and is rapid and easy to operate.	CN200910101038.7	Pre-clinical research
HBV drug-resistance mutation detection kit	Guangdong Kaipu Biotech	The kit was based on fluorescent PCR techniques by designing numerous specific primers. The kit can simultaneously test for 14 types of gene mutations for resistance to four hepatitis B drugs.	CN201110202903.4	Pre-clinical research
Hepatitis and HIV synchronous detection kit	Shanghai Kehua Bio-engineering	The kit adopts the specificity of immuno-bead separation instruments for the synchronous capture of HIV, HBV and HCV viral nucleic acids. The automation level is high, making it suitable for mass blood screening and clinical testing.	CN200610030229.5	Pre-clinical research

3.1.3 Hepatitis therapy

Currently available hepatitis treatment drugs in China inlcude nucleoside analog antiviral medicines, immuno-modulators, and traditional Chinese medicines. Nucleoside analogs can rapidly inhibit viral replication in the body, but many hepatitis viruses have become resistant to these drugs. Immuno-modulators mainly include IFNs and their derivatives, which can inhibit the translation of viral proteins by activating antiviral protein genes in liver cells. The disadvantages of immuno-modulators are their short half-life and immunogenicity. Traditional Chinese medicines are also used for clinical adjunctive therapy for hepatitis but typically cannot completely clear the hepatitis virus.

Among the five first-line nucleoside analog drugs for hepatitis B treatment, Chinese domestic companies are capable of producing three of these: lamivudine, adefovir dipivoxil, and entecavir. The other two drugs, telbivudine (Novartis) and tenofovir disoproxil fumarate (GSK), must be imported. The Beijing Union Pharmaceutical Factory, the China Academy of Medical Sciences, and the Peking Union Medical University have jointly developed a new drug for hepatitis treatment, shuanghuanchunpian (baisainv), which was approved by the SFDA in 2001. Approximately 20 dometic companies produce a variety of IFNs in China, of which Anke Bioengingger, China National Biotech Group, occupy the major marke share.

The research and development of new drugs to treat hepatitis is mainly focused in the following areas: **new derivatives of existing drugs, new synthetic or natural molecular compounds, therapeutic hepatitis vaccines, long-acting interferon preparations, and compound preparations of traditional Chinese and Western medicines.** In particular, several novel

therapeutic hepatitis vaccines are currently in clinical trials in China. **Table 7 summarizes the major achievements of the research and development of new hepatitis drug therapies in China.**

Table 8 Major achievements of new hepatitis drug R&D in China

Project name	Company/ Institute	Features and innovative characteristics	Patent protection	Research progress
Therapeutic antigen-antibody complex hepatitis B vaccine	Fudan University, Beijing Institite of Biological Products	This therapeutic vaccine contains HBsAg, Pre-S antigen, and specific antibodies. High-titer antigen-specific antibodies against hepatitis B can be induced in vaccine-immunized mice.	CN93112409.3	Phase III clinical trial
Therapeutic T cell surface polypeptide hepatitis B vaccine	The Third Military Medical University, Chongqing Beer Group	This therapeutic vaccine contains cytotoxic T lymphocyte (CTL) epitope peptides of the hepatitis B core antigen, the tetanus toxoid Th-cell epitope peptide, and hepatitis B Pre-S2 antigen B cell epitope peptides. Immunization of mice with this vaccine stimulates lymphocyte proliferation and activation, activates Th1 cells and a CTL response, and reduces blood serum HBV virus copy number, and the HBsAg/HBcAg titer.	CN02130738.5	Phase II clinical trial
Therapeutic double-plasmid gene hepatitis B vaccine	Chinese PLA 458 Hospital, Guangzhou Baidi Bio-medicine	This therapeutic vaccine uses a plasmid expressing the GM-CSF signal sequence and the HBV pre-S2 as an immunogen and another plasmid expressing human IL-2 and IFN-γ fusion protein as an immune adjuvant. Immunization of mice with this vaccine enhances CTL-specific immune responses and reduces HBV copy number through the synergistic effect of cytokines.	CN00107853.4	Phase II clinical trial
Therapeutic T cell surface hepatitis B vaccine	The Second Military Medical University	This therapeutic vaccine contains fusion peptides by connecting 21 selected CTL epitopes of HBV surface antigens and two general Th lymphocyte epitopes, the vaccine is then expressed and purified from *Saccharomyces cerevisiae*. The vaccine can activate or enhance cellular immune responses in chronic HBV infections, promoting the clearance of HBV from the body.	CN200710037962.4	Pre-clinical research
Carboxylic acid compounds with antiviral activity	Shenyang Pharmaceutical University	Numerous carboxylic acid ethyl ester compounds possess a wide spectrum of antiviral activity. Among them, 5-hydroxy-1H-indole-3-carboxylic acid ester significantly inhibits hepatitis virus and HIV replication activity in cultured human cells.	CN200410021364.4 PCT/CN2005/000301	Phase II clinical trial
peroxide quinic acid compound with antiviral activity	The Academy of Military Medical Sciences	DCQA (1, 5-Dicaffeoylquinic Acid) was extracted from the natural plant. *In vitro* and *in vivo* experiments demonstrated that the compound has a significant inhibitory effect on hepatitis virus replication activity.	CN200410080266.8	Phase I clinical trial

Flavonolignans with anti-HBV activity	Dali College	Flavonolignans (Scutellaprostin A) and their derivatives were separated from plants with anti-HBV activity, including benzyloxy flavonolignans, A-ring flavonolignans, and A-ring dioxane flavonolignans. *In vitro* experiments demonstrated that these compounds have significant inhibitory effects on HBV DNA replication and scavenging activity against HBsAg.	CN201010181312.9/CN201010181644.7/CN201010181892.1/CN201010181411.7/CN201010181362.7	Pre-clinical trial
Non-nucleoside compound with anti-HCV activities	Shanghai Institute of Materia Medica	The 2', 2-bithiazole non-nucleoside compound was obtained via chemical synthesis. *In vitro* cytological experiments demonstrated that the compound can inhibit HCV replication.	CN200910200581.2	Pre-clinical trial

Therapeutic hepatitis B vaccines

Professor Yumei Wen's group at Fudan University collaborated with the Beijing Institute of Biological Products to develop the first therapeutic hepatitis B vaccine (trade name: Yike) in China. The vaccine is composed of HBsAg, pre-S antigen, and a compound composed of specific antibodies and aluminum hydroxide adjuvant. Animal experiments have shown that mice immunized with the therapeutic vaccine have a clearly higher hepatitis B antigen specific antibody titer than mice immunized with the simple antigen plus adjuvant control. The vaccine is currently in phase III clinical trials in China. The initial results, which were published in 2011, revealed that there was no significant difference in the e antigen seroconversion rates between the vaccine group and the placebo group. However, among patients who did exhibit e antigen seroconversion after vaccination, 59.6% exhibited viral loads that had dropped to clinically negative levels, and 84.4% experienced a return to normal liver function.

Professor Yuzhang Wu's group at the Third Military Medical University has developed a novel synthetic peptide therapeutic hepatitis B vaccine. This vaccine contains a polypeptide fusion sequence formed from the hepatitis B core antigen CTL epitope peptide, the tetanus toxoid Th-cell epitope peptide, and the hepatitis B pre-S2 antigen B cell epitope peptide. Animal experiments demonstrated that immunization of HBV transgenic mice stimulates lymphocyte proliferation and activation, activation of Th1 cells and CTL responses, and reduces the viral copy number and HBsAg/HBcAg levels in the serum. The phase II clinical trial of this vaccine was completed in 2011 in China. When the vaccine was used alone to treat chronic hepatitis B patients, the effect was less than ideal. There was no significant difference in HBeAg/anti-HBe seroconversion between groups vaccinated with 600 or 900 μg hepatitis B vaccine and the placebo group. A second phase II clinical trial is currently in progress and its objective is to explore the therapeutic effects of this vaccine combined with entecavir in the treatment of patients with chronic hepatitis B. The results of this trial are not yet known.

Guangzhou Baidi Bio-medicine and Chinese PLA 458 Hospital have jointly developed a new type of therapeutic hepatitis B DNA vaccine. This vaccine was produced from two recombinant plasmids, one expressing the HBV envelope protein pre-S2 with the GM-CSF signal sequence and another expressing a human IL-2 and IFN-γ fusion protein. The vaccine is currently undergoing phase II clinical trials in China. The objective is to explore the efficacy of this vaccine in combination with lamivudine for the treatment of patients with chronic hepatitis B. The results of this trial are not yet

known.

Novel anti-hepatitis chemical compouds

Professor Ping Gong's group at Shenyang Pharmaceutical University has developed various carboxylic acid ethyl esters with wide-spectrum antiviral activity. These compounds include 5-hydroxy-1H-indole-3-carboxylic acid ethyl ester, 5-hydroxy-6-bromide-1H-indole-3-carboxylic acid derivatives, and 7-hydroxyquinoline-3-carboxylic acid ethyl ester. *In vitro* experiments have demonstrated that these compounds can effectively inhibit HBV replication activity in cells. The IC_{50} values were significantly lower than that of lamivudine [Liu YJ]. Of these compounds, 5-hydroxy-1H-indole-3-carboxylic acid ethyl ester (trade name: hydrochloride Aimi Erdo) is in phase II clinical trials, the results are not yet known.

The Academy of Military Medical Sciences has extracted a natural compound from honeysuckle herbs named 1, 5-dicaffeoylquinic acid (DCQA) that has broad-spectrum antiviral activity and the compound is abbreviated as IBC-5. *In vitro* and *in vivo* studies have shown that the compound has a significant inhibitory effect on HBV replication. The project has been transferred to the Jiangzhong Pharmaceutical Group for further development. Currently, phase II clinical trials are in progress. The phase I clinical trials demonstrated that the drug has good safety and tolerability in humans [Wei ZM].

2.2 Tuberculosis (TB)

Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis* (MTB) infection and is one of the three major infectious diseases worldwide. There are approximately 8.8 million new cases of tuberculosis worldwide and 1.1 million people died of this disease in 2010 [Global Tuberculosis Control Report, WHO, 2011]. In recent years, the diagnosis and appropriate treatment of multidrug-resistant tuberculosis have faced major challenges. In 2010, only 5% of new and former TB patients who had previously received treatment were tested for multidrug-resistant TB in most countries. China is one of 22 countries with the highest incidence of tuberculosis. In 2010, the yearly incidence of TB in China was roughly 1 million persons, and approximately 3,000 people died [Statistics of Notifiable Infectious Diseases, the Chinese Ministry of Health].

2.2.1 TB Prevention

Vaccination is an effective means of preventing tuberculosis. The BCG vaccine remains the only vaccine marketed for the prevention of TB in the world, which is produced from an attenuated strain of *Mycobacterium bovis*. In nearly 90 years of its clinical application, positive prevention effects have been achieved worldwide, but in some patecular regions or different populations, the immuno-protective effect is unstable. Furthermore, it is unclear if BCG provides protection for adults. In recent years, with the emergence of drug-resistant strains, TB prevention has become even more challenging.

The research and development of new TB vaccines in China is currently focused on these areas: recombinant or modified BCG vaccines, recombinant protein subunit vaccines, virus vector vaccines, and neucleic acid vaccines.

Of these, the recombinant BCG vaccine and the neucleic acid vaccine are regarded as the most promising vaccine candidates. While more than ten clinical trials of new TB vaccines are conducted internationally, China has no TB vaccine in clinical trials. **Table 9 summarizes some of the major achievements of new TB vaccine research and development in China.**

Table 9 Major achievements of new TB vaccine R&D in China.

Project name	Company/ Institute	Features and innovative characteristics	Patent protection	Research progress
Recombinant BCG vaccine	Fudan University	It contains the Ag85B, Mpt64 190-198 polypeptide, and the Mtb8.4 expression vector. Vaccine-immunized mice produce similar antibody levels and higher secretion levels of IFN-γ cytokines than BCG-induced mice.	CN200610116053.5	Pre-clinical research
Recombinant BCG vaccine	Sichuan University	It contains the CFP10/ESAT6 antigen and the cytokine GM-CSF gene expression vector. Vaccine-immunized mice have higher levels of T-cell activation and IFN-γ levels than BCG-induced mice.	CN201010140350.X	Pre-clinical research
Multicomponent antigen protein subunit vaccine	Shanghai Wanxing Bio-pharmaceutical Co.	It contains four sub types (A-D) of the rAg85 antigen protein. It yields greater induction of antibody titer and IFN-γ production capacity.	CN200710173372.4	Pre-clinical research
Multivalent antigen protein subunit vaccine	Fudan University	It contains the Ag85B and EAST antigens and the IFN-γ chimeric proteins composed of immune factors. Vaccine-immunized mice have a higher titer of MTB-specific IgG antibody than BCG-induced mice, as well as a higher level of IFN-γ secretion.	CN200610147665.0	Pre-clinical research
Vaccinia virus vaccine carring MTB antigens	Shanghai Haigui Bio-technology Limited Co.	It contains the Ag85A and Ag85B chimeric gene in combination with the adjuvant levamisole. It can also be used to treat TB infection. The integration of the ESAT6-Ag85A antigen fusion gene with the vaccine virus strain 752-1 provides better immune protection than the BCG vaccine.	CN201010191243.X	Pre-clinical research
Attenuated bacterial vector vaccine carrying MTB antigens	Wuhan University	An attenuated *Salmonella typhimurium* strain that stably expresses the ESAT6-Ag85B gene was constructed. The combined immunization of this vaccine and BCG in mice has a stronger immuno- protective effect.	CN200810236723.6	Pre-clinical research
Detection of MTB protective immune response epitope	The Second Military University	T-lymphocyte antigen epitope peptides were found for Ag85B antigens. These peptides can stimulate resistance to MTB protective immune response, aiding the development of new TB subunit and DNA vaccines.	CN200810058472.7	Animal experiments
Multivalent fusion gene DNA vaccine	Peking University	It contains the Ag85B, MPT-63, and MPT-64 antigen fusion genes. Vaccine immunization of mice in combination with a synthetic antimicrobial peptide provides better immune protection than a single dose of DNA vaccine or BCG, resulting in higher antibody titers, a greater number of activated T cells, and higher levels of	CN03153214.4	Pre-clinical research

		IFN-γ secretion.		
DNA vaccine based on T-cell epitopes	Fudan University	It contains a fusion gene of the heat shock protein (HSP) 65 and four T-cell epitope peptide antigens such as ESTA-6, Ag85A, Ag85B, and CFP-104. Intramuscular injection of the vaccine in mice can produce stronger multiple TB antigen-specific antibodies, a stronger TB-specific CTL and Th1 type immune response, and the secretion of higher levels of IFN-γ.	CN200710171416.X	Pre-clinical research
Double Fusion DNA Vaccine	The Fourth Military University	It contains the ESAT6 and CFP10 antigen fusion gene and induces mice to produce a higher specific antibody titer. The induction of IFN-γ production is comparable to BCG, but the IL-2 production capacity is less than BCG.	N/A	Pre-clinical research

Recombinant BCG vaccines

Through the appropriate genetic modification of MTB strains, recombinant BCG vaccines can express certain important MTB antigens to enhance the immunogenicity and protective efficacy of the BCG vaccine.

Professor Honghai Wang's group at Fudan University is developing a new type of recombinant BCG vaccine. They introduced an expression vector containing the MTB antigen genes such as Ag85B and ESAT associated with the immune cytokine genes (such as IFN-γ and TNFa) into BCG, thus forming a recombinant BCG vaccine. Animal experiments have shown that mice immunized with rBCG-Ag85B-ESAT6 and rBCG-Ag85B-ESAT6-TNF-a can be induced to produce higher levels of protective antibody than that induced by the traditional BCG vaccine. MTB antigen-specific IgG antibody titers in the fourth week were elevated more than 160-fold, and IFN-γ secretion levels in mouse spleen cells were increased more than 5-fold [Shen H].

Professor Lang Bao's group at Sichuan University has fused the GM-CSF gene and the MTB CFP10/ESAT6 gene to develop a novel recombinant BCG vaccine. Animal experiments have shown that the percentage of $CD4^+/CD8^+$T cells in the spleens of mice immunized with the rBCG-GM-CSF-CFP10/ESAT6 vaccine was twice that following immunization with the traditional BCG vaccine, and the levels of IFN-γ secreted by the immune cells also increased 1.5-fold [Yang XL].

Tuberculosis subunit vaccines

A tuberculosis subunit vaccine is composed of one or more MTB protein antigen components and an immune adjuvant. Of the currently identified MTB protein antigen components, Ag85, ESAT6, and MPT are most widely used. Furthermore, when these components are used in conjunction with an immune adjuvant, the Th1 response can be additionally enhanced. Many companies and research groups in China are currently developing tuberculosis subunit vaccines.

Shanghai Wanxing Bio-pharmaceutical is developing a multicomponent complex vaccine based on the rAg85 protein antigen. Animal experiments have shown that the antibody titer induced in mice with the multicomponent vaccine was 10-fold higher than that induced by rAg85A alone. The

production capacity of IFN-γ in separated mouse spleen cells increased 2-fold over the levels produced by traditional BCG.

Shanghai Haigui Bio-technology is developing a tuberculosis subunit vaccine based on the vaccinia virus. Researchers have integrated the ESAT6 and Ag85A antigen fusion gene into the vaccinia virus strain Tiantan 752-1 using vaccinia virus infection to produce an immuno-protective effect. Mouse experiments demonstrated that the subunit vaccine yielded a better immuno-protective effect than BCG. The combination of this vaccine with the Tiantan strain of vaccinia virus, which is incapable of replication, could improve vaccine safety [Li ZM].

Tuberculosis DNA vaccines

Tuberculosis DNA vaccines directly introduce specifically encoded protective antigens and recombinant DNA vectors with regulatory elements to control expression in the human body, thus inducing the body's protective cellular immunity and humoral immune responses. In China, many research groups are investigating tuberculosis DNA vaccines, but according to current publications, the immuno-protective effects of tuberculosis DNA vaccines alone generally do not exceed that of BCG.

Professor Hong Cai's group at Peking University is developing a polyvalent DNA vaccine containing the Ag85B, MPT-63, and MPT-64 genes. He is also studying the combined use of this vaccine with immunologic adjuvants, IL immune factors, or anti-TB drugs for the prevention and treatment of MTB infection. Mice immunized with this vaccine and a synthetic antibacterial peptide exhibited stronger immuno-protective effects, higher antibody titers, increased numbers of $CD4^+$/CD44-high and $CD8^+$/CD44-high T cells, and increased IFN-γ secretion levels by 1.5-1.8-fold than using the DNA vaccine or BCG alone [Li M]. In addition, the combined use of this vaccine with isoniazid or pyrazinamide in infected mouse models shortened the treatment period of the anti-TB drugs and produced a stronger IFN-γ response to the three antigens [Yu DH].

Professor Hai Zhang's group at the Fourth Military Medical University is developing an MTB ESAT6-CFP10 fusion gene DNA vaccine. Animal experiments have suggested that the vaccine induces specific antibody titers in mice of up to 1:800. The capacity to induce IFN-γ production is comparable to that of BCG, but the capacity to induce IL-2 production is less than that of BCG [Zhang H].

2.2.2 TB Diagnostics

The tuberculosis diagnostic methods currently in use or development can be divided into three categories. **The first category** consists of the direct MTB detection through cultivation and drug sensitivity testing, which is presently the gold standard for the diagnosis of active TB infection. In recent years, liquid-culture technology has been extensively applied throughout laboratories in China, and a variety of automated testing equipment and reagent kits are available, such as the MACTEC MGIT, Difco ESP, and MB/BacT systems. Liquid-culture methods have a higher testing sensitivity, and the detection cycle has been significantly reduced compared with the earlier solid-state culture method. **The second category** includes immunological methods such as EIA, ICG, and flow cytometry (FACS), to detect specific tuberculosis antibodies and antigens, human cytokines, and cell-mediated immune functions. Immunological methods are relatively simple and rapid and, consequently, have been fully developed. **The third category** consists of molecular

biology methods. Strains can be identified by specific amplification of MTB DNA using the isothermal amplification, quantitative PCR, and gene chip methods. Molecular biology methods have the advantages of short testing times, high reliability, and high repeatability. However, they require special equipment and trained technicians.

Approximately 30 companies are currently approved by the SFDA to produce TB diagnosis kits in China, which are summerized in Table 10. About ten of these companies have advantages in product market share and tehocnogical innovation, including Beijing Beier, Zhuhai Yingke, Tianjin NewScen Coast, Shanghai Upper, Hangzhou Innovation, Beijing Modern Gaoda, Beijing Wantai, Zhongsan Daan Gene, Beijing Kemei Dongya, and Shanghai Fosun.

Hangzhou Genesis Biodetection has developed the MTB diagnostic kit (ICG method). A specific antibacterial agent and standard sputum non-tubercle bacillus are added to the liquid medium, and the detection reagents use ICG techniques to conduct specificity testing on the MTB antigen MPB64. The sensitivity of the kit reaches 99%, and the specificity reaches 100%. The average detection time is 9.9 days, clearly superior to the improved Roche's culture [Gu XR].

Shanghai Upper Bio-Pharm has developed a new MTB diagnostic kit. This kit uses a colloidal gold-labeled standard H37RV membrane protein antigen and can be used to detect TB-specific antibodies in the blood. Studies have shown that the detection rate of the kit for the diagnosis of pulmonary tuberculosis reaches 76.5%, which is slightly lower than the 79.6% detection rate of the PCR method but significantly higher than the detection rate of sputum smear methods. This method is more suitable for use in basic-level hospitals with limited resources [Wang Y].

Table 10 Major TB diagnostic reagent manufacturers in China

Category	Company name	Total
Culture/drug sensitivity test	Wenzhou Kangtai Biotech, Nanjing Sinnova Medical, Hangzhou Weimao Biological, Henan Cellnovo Biotech, Shenzhen Yibaishi Biotech	5
ICG	Tianshui Fuyin Medical, Lanzhou Yahua Biotech, Jinan Jei Daniel Biotech, Beijing Beier Bioengineering, Shenzhen Piji Bioengineering, Zhuhai Encode Medical, NewScen Coast Bio-Pharma, Fujian Haitian Lanbo Biological, Hangzhou Acon Biotech, Boson Biotech, Beijing Antai Diagnostic, Shenzhen Huian Bio-Tech, Xiamen Asiatec, Bofeng Biolongical, Beijing Genesee Biotech, Shanghai Upper Bio-Pharma, Shanghai Mingyuan Health, Hangzhou Genesis Biodetect	19
EIA	Weifang Kanghua Biotech, Beijing Modern Gaoda Biotech, Beijing Wantai Biopharma, Shanghai Rongsheng Biotech, Shenzhen Anqun Biotech, Autobio Diagnostics, ChenDu Yongan Pharmaceutical, Haikou VTI Biological Institute	8
ECL	Beijing Chemclin Biotech	1
Fluorescent PCR	Shanghai Zj Bio-Tech, Shanghai Clone Biotech, hanghai Fosun, Fujian Triplex Biosciences, Daan Gene, Xiamen Amplly Bioteh, Beijing BGI-GBI Biotech, ChenDu Yongan Pharmaceutical, Shenzhen Qiagen Biotech	10
PCR reverse dot blot	Shenzhen Yaneng Bioscience	1
RNA isothermal	Shanghai Rendu Biotech	1

amplification		
Gene and protein chip	Shenzhen Yaneng Bioscience, Nanjing Potomac Bio-Tech, CapitalBio Corp	3

The research and development of new tuberculosis diagnostic reagents in China are currently focused on four areas. **Table 11 summarizes some of recent major achievement in research and development of TB diagnostic reagents in China.**

- **Technical improvement of existing tuberculosis diagnostic kits.**
- **Improving genotyping technologies to detect tuberculosis drug resistance.**
- **Developing new technologies to detect MTB DNA or live bacteria.**
- **Developing new technologies for tuberculosis nucleic acid sample extraction.**

Lei Shi's group at South China University of Technology has developed a rapid MTB detection kit. This method uses specific primers targeting the conserved region of the gyrB gene combined with in situ fluorescence loop-mediated isothermal amplification (LAMP) technology. The sensitivity for MTB complex DNA reaches 100 fg, the detection limit reaches 10 Cfu/ml, and the detection rate of the samples reaches 99%. In 100 sputum specimens collected from patients with suspected tuberculosis, the positive rates of smear acid-fast staining, the LAMP method, and the fluorescent real-time PCR method were 28%, 39%, and 38%, respectively [Shen HP].

Professor Qian Gao's group at Fudan University is committed to studying in MTB genotyping and identification of drug-resistant strains using rapid PCR technology. First, they developed a rapid diagnostic reagent kit for MDR MTB that includes specific primers targeting a variety of genes and oligonucleotide probes. The kit can detect at least 16 common MDR-related gene mutations. Second, they developed a rapid testing kit for the differentiation of MTB clinical strains. The kit contains 16 pairs of testing probes targeting the IS6110 insertion sequence, which can be used for the MTB genotyping and is particularly suitable for identifying Beijing-type MTB strains. Third, they developed a new real-time PCR technique to detect Chinese-specific MDR MTB. Six double-labeled probes and ten primers were designed to detect mutations in five drug resistance-associated genes. Among the 158 drug-resistant MDR strains obtained from the Shanghai Center for Disease Control, the detection specificity and sensitivity all reached 100%. Moreover, the technique can be used with single-channel PCR instruments [Zhang HQ].

Table 11 Major achievements of new TB diagnostic reagent R&D in China

Project name	Company/ Institute	Features and innovative characteristics	Patent protection	Research progress
MTB live bacteria detection kit by isothermal amplification	Shanghai Fosun Pharm, Fudan University Huashan Hospital	The kit uses NITAG technology to amplify MTB mRNA under isothermal conditions with specific primers and nano-gold-labeled probes to detect the amplicons. The test results are obtained through computed tomography hybrid color reactions. It is more sensitive than the NASBA and TMA kits and can eliminate MTB DNA interference.	CN101736078A	Pre-clinical research

MTB DNA detection kit (LAMP)	South China University of Technology	Four specific primers are designed based on the gyrB conserved gene region. Tubercle bacillus DNA is amplified by in situ fluorescence LAMP technology with a sensitivity 100 fg. The tubercle bacillus detection limit reaches 10 CFU/ml.	CN201010259678.3	Pre-clinical research
MTB DNA detection kit (LAMP)	Guangzhou Huafeng Bio-tech	Specific primers are designed based on the gyrB conserved gene region. Tubercle bacillus DNA is amplified by in situ fluorescence LAMP technology to enable the high-sensitivity detection of tubercle bacillus.	CN201010019454.5	Pre-clinical research
MTB DNA detection kit (LAMP)	Guangzhou Diao Bio-tech	Specific primers are designed by bioinformatics analysis. Tubercle bacillus DNA is amplified using LAMP technology and then visually identified by dye staining. The accuracy is greater than 99.9%. The tubercle bacillus detection limit reaches 10 CFU/ml and the detection rate for specimens reaches 97%.	CN200810219351.6	Pre-clinical research
MTB diagnostic kit targeting Rv1985c antigen protein	Fudan University	A newly discovered antigen protein Rv1985c can be used for rapid detection of MTB in serum samples in combination with ICG or EIA methods. The sensitivity reaches 59% and the specificity is 96% when using Rv1985c antigen alone. When combined with other antigens such as LAM/38kDa, the sensitivity increases to 75%.	CN200810042130.6	Pre-clinical research
New extraction method of bacterial nucleic acids from sputum	Capital Bio Corp, Tsinghua University	High-quality nucleic acids can be extracted from sputum samples using a special liquid reagent solution followed by cell lysis with the addition of solid particles. This method is rapid, easy to automate with high yield.	CN200810105172.X	Pre-clinical research
MTB Genotyping and drug-resistant strain identification	Fudan University	The kit includes a variety of specific primers and oligonucleotide probes for multidrug resistance (MDR) related genes. It can detect at least 16 common MTB MDR gene mutations. In addition, they developed a new Chinese-specific drug-resistant MTB detection method using a fluorescent RT-PCR technique. The accuracy and sensitivity are both 100%.	CN200810105172.X CN200910201104.8	Pre-clinical research

2.2.3 TB Therapy

The main treatment for tuberculosis infection (pulmonary tuberculosis) is the administration of anti-TB drugs. Current anti-TB drugs can be divided into five categries: first-line oral anti-TB drugs, anti-TB injections, fluoroquinolones, second-line oral antibacterial anti-TB drugs, and anti-TB drugs with uncertain efficacy [Guidelines for the Management of Multidrug-Resistant TB, WHO, 2011].

Table 12 summarizes the information on the production of anti-TB drugs in China. Chinese domesitc companies can produce approximately 14 of the 28 commonly used anti-TB drugs, most of which are generic drugs. Hundreds of companies are capable of producing the most commonly

used first-line oral medications, injection drugs and fluoroquinolones. But the research and development of new tuberculosis treatments is relatively slow in China.

Professor Honghai Wang's group at Fudan University is researching the mechanisms of anti-TB drugs and developing new treatments. They have developed a new anti-TB compound, I2906. In vitro and animal experiments in mice have shown that the drug has excellent anti-mycobacterial activity and low cytotoxicity towards ordinary and multidrug-resistant TB bacteria. This drug achieved better results when used in combination with isoniazid for 8 weeks, improving the survival rate of mice [Lu J]. In addition, Wang's group made a joint discovery with foreign research groups that pyrazinamide can specifically inhibit the translation process of the tubercle bacillus, thus providing an explanation for the underlying mechanism of how pyrazinamide eradicates persisting organisms [Shi W].

Table 12 Information on current production of anti-TB drugs in China

Category	Drug names and number of manufacturers*
First-line oral anti-TB drugs	Isoniazid (710); Rifampicin (856); Ethambutol (256); Pyrazinamide (123)
Injection anti-TB drugs	Streptomycin (67); Kanamycin (253); Amikacin (0); Capreomycin (0)
Fluorinated quinolone drugs	Ofloxacin(1278); Left-ofloxacin (0); Moxifloxacin (0); Gatifloxacin (0); Ciprofloxacin (0)
Second-line oral antibacterial anti-TB drugs	Ethionamide (0); Protionamide (16); Cycloserine (0); Terizidone (0), Aminosalicylic acid (0)
Anti-TB drugs with uncertain efficacy	Clofazimine (1, Liye Pharmacy), Amines linezolid (0), Amoxicillin/clavulanate potassium (886), Clarithromycin (224)
Other drugs (not listed by the WHO)	Rifapentine (10), Lifubuding (0); P-amino salicylic acid and isoniazid (0), Thioacetazone (1, East Health Pharma); Imine imipenem (13)

* Data from www.sfda.gov.cn with key word searching: drug-domestic, drug-chemical, drug-product.

2.3 HIV/AIDS

AIDS is a serious infectious disease caused by infection with HIV and is one of the three major infectious diseases worldwide. There are roughly 34 million people living with HIV/AIDS worldwide, with 2.7 million new HIV infections and estimated 1.8 million AIDS-related deaths [Progress report 2011:Global HIV/AIDS Response, a joint report from WHO, UNAIDS and UNICEF]. It is further estimated that in 2011, approximately 700 thousand people were living with HIV/AIDS in China, including 155 thousand AIDS patients, 48 thousand new HIV infections, and 18 thousand AIDS-related deaths [2011 Estimates for the HIV/AIDS Epidemic in China, a joint report from the Chinese Ministry of Health, WHO and UNAIDS]. Other statistics show that there were roughly 20,000 new AIDS cases and 9,000 deaths in 2011 [2011 Statistics of Notifiable Infectious Diseases, the Chinese Ministry of Health].

2.3.1 HIV/AIDS Prevention

The development of HIV vaccine is recognized as a difficult problem and thus far no HIV vaccine has been approved for the market worldwide. The ideal HIV vaccine must protect the majority of HIV-negative individuals from viral infection or at least reduce the viral load of HIV-infected

patients. Currently, there are dozens of HIV vaccines that are undergoing clinical trials around the world, but most trial results of these vaccines are not promising.

The most common types of HIV vaccines undergoing research and development in China include DNA vaccines, viral vector vaccines, recombinant protein subunit vaccines, and combined vaccines. Since 2010, the Chinese Ministry of Science and Technology has listed HIV vaccine development as one of the major funding directions. China has made certain progress in HIV vaccine R&D in recent years and several candidate vaccines are in phase I-II clinical trials. **Table 13 summarizes some of the major achvievements of new HIV vaccine R&D in China.**

Table 13 Major achievements of new HIV vaccine R&D in China

Project name	Company/ Institute	Features and innovative characteristics	Patent Protection	Research Progress
DNA-viral vector combination HIV vaccine	Changchun BCHT Biotech, Jilin University	It combines a DNA vaccine and a recombinant vaccinia virus vector vaccine designed to target CRF-07 B/C, a major epidemic HIV strain in China. It expresses the wild-type or artificially modified Gag Pol and Env antigens.	CN200410 011251.6	Phase II clinical trail
Recombinant vaccinia virus HIV vaccine	Center for Disease Control and Prevention	It targets a main epidemic strain, HIV-1 CN54. It expresses the Gag, PolΔ, and GP140TM antigens and uses the vaccinia virus Tiantan strain.	N/A	Phase II clinical trail
DNA-viral vector combination HIV vaccine	Beijing Institute of Biological Products, Nankai University	It targets a main epidemic HIV strain in China, CRF-07 B/C. It expresses Gag, Pol, Env, and Nef antigens and uses the replication-competent vaccinia virus Tiantan strain, which induces a stronger immune response than the traditional non-replication vectors.	N/A	Phase I clinical study
Lentiviral vector HIV vaccine	Center for Disease Control and Prevention	It combines immunization with a recombinant vaccinia virus containing the EIAV Env gene and its recombinant protein expressed by baculovirus. Compared to single-antigen vaccines, the neutralizing antibody titer has been increased 5- to 9- fold.	CN200810 097471.3	Pre-clinical study
Simian immuno-deficiency virus vaccine	CAMS, Tsinghua University	The joint use of modified vaccinia virus Tiantan strain (MVTT) mucosal vector vaccine and the adenovirus type 5 vector vaccine (Ad5) can induce sustained high levels of cellular immune responses in monkeys.	N/A	Pre-clinical study
Multi-epitope HIV subunist vaccine	Tsinghua University	It is based on multi-epitope HIV antigens for immunization which can induce relatively high levels of HIV-specific polyclonal antibodies.	CN011360 60.7	Pre-clinical study
Recombinant fowlpox virus HIV vaccine	Academy of Military Medical Sciences	The chimeric proteins of HIV structural proteins and cytokines can induce specific humoral and cellular immune responses in mice. The cytokines play the role of adjuvant.	CN200410 010754.1	Pre-clinical study
Multi-epitope HIV DNA vaccine	PLA Quartermaster University, Academy of	It uses multi-epitope HIV antigens to make a DNA vaccine. It induces a stronger and more extensive epitope-specific CTL cell response than vaccines containing the full-length HIV structural proteins.	CN031270 02.6	Pre-clinical study

	Military Medical Sciences			
Genetically engineered hybrid yeast HIV vaccine	Sun Yat-sen University, University of Hong Kong	Hybrid yeast simultaneously expressing Gag and IL-2 was obtained by yeast mating. Dried cell powder was prepared as a test vaccine and was found to induce a certain level of cellular immune response in mice and cynomolgus monkeys.	CN200410055579.8	Pre-clinical study

HIV viral vector vaccines

In viral vector vaccines, recombinant chimeric proteins that are synthesized from viral expression vectors inserted with HIV-specific protein antigens and expressed in animal cells or tissue cultures are used as vaccines to induce the animal to generate both humoral and cellular immune responses.

Professor Yiming Shao's group at the Chinese Center for Disease Control and Prevention is developing an HIV vaccine based on a recombinant vaccinia viral vector. The vaccine contains the Gag, PolΔ, and gp140TM genes, which are expressed by the major Chinese epidemic strain HIV-1 CN54, and uses the vaccinia virus Tiantan strain as the vector [Liu Y]. The phase I clinical trial was completed in 2006 and the results showed that the vaccine had a high level of safety. The vaccine entered phase II clinical trials in 2009, but results remain currently unavailable.

Professor Linqi Zhang's group in the Chinese Academy of Medical Sciences and Tsinghua University is developing an HIV vaccine based on vaccinia and adenoviruses. The group produced a combination vaccine using the modified vaccinia virus Tiantan strain (MVTT) mucosal vector and adenovirus type 5 (Ad5). Animal experiments showed that the vaccine induced a sustained high level of cellular immune response in rhesus monkeys and could completely prevent mucosal infection by the highly pathogenic SIVmac239 virus in rhesus monkeys.
[http://www.gov.cn/jrzg/2009-12/01/content_1477048.htm.].

The PLA Quartermaster University and the Academy of Military Medical Sciences are jointly developing a recombinant fowlpox virus (FPV) vaccine consisting of different combinations of HIV structural proteins (Env, Gag, Nef, Pol, Gp120, etc.) and cytokines (IL-6, IL-18, IFN-α, etc.) inserted into the expression vector of recombinant FPV [Zhang LS; Jiang WZ]. Animal experiments showed that the vaccine induced specific humoral and cellular immune responses in mice and that the cytokines served as immune adjuvants.

HIV DNA vaccines

For DNA vaccines, the nucleotide sequences of characteristic epitopes of HIV viral proteins are recombined to generate recombinant nucleic acid sequences, which can be used as transcription units for the in vivo biosynthesis of viral protein antigens to induce specific immune responses in vivo.

The PLA Quartermaster University and the Academy of Military Medical Sciences are developing a multi-epitope DNA vaccine against HIV. The vaccine preferentially chooses multiple highly conserved immunodominant epitopes in the HIV genome and covers the major structural and

regulatory proteins, such as Env, Gag, Nef, and Pol, for the targeted modification and design. The full-length multi-epitope DNA vaccine is then synthesized. Animal experiments showed that this vaccine could induce mice to produce CTL responses and neutralizing antibodies specific for the selected epitopes. Compared with DNA vaccines encoding the full-length HIV structural proteins, this vaccine can induce stronger and more extensive epitope-specific CTL responses [Li ZJ, Jing NY].

HIV combination vaccines using DNA and viral vectors

Professor Wei Kong's group at Jilin University and Changchun BCHT Biotech are developing a combination vaccine consisting of DNA and a poxviral vector. The DNA vaccine contains the artificially modified nucleotide sequences of Gag, Pol and Env. In the poxviral vector vaccine, Gag, Pol and wild-type Env have been used as antigens. Experiments in mice showed that both vaccines were capable of effective induction of specific anti-HIV-1 p24 antibodies [Teng HG]. The new vaccine uses the DNA vaccine for the initial immunization and the poxviral vector vaccine to enhance immunity. The phase I clinical trial was completed in 2006. The results showed that within the designed dose range, the vaccine was safe and well tolerated, and 90% of the subjects in the high-dose group were able to generate antibodies for specific immune responses against HIV in 15 days. The vaccine is undergoing phase II clinical trials, but experimental data are currently unavailable.

The Chinese Center for Disease Control and Prevention and the Beijing Institute of Biological Products are developing a combination vaccine consisting of DNA and a recombinant Tiantan vaccinia virus. For the vaccine, the four genes of Gag, Pol, Env, and Nef from the main Chinese epidemic HIV strain CRF-07 were selected as immunogens, and the replication-competent vaccinia Tiantan strain was utilized. The technical improvements were made specific for the Chinese population [Liu Q]. The vaccine is undergoing phase I clinical trials. The available results have shown that it has good safety features. Additionally, this vaccine can induce both humoral immune responses to produce antibodies and cellular immune responses to generate T-cell responses specifically against the virus.

2.3.2 HIV/AIDS diagnostics

The clinical diagnosis for HIV/AIDS can be generally divided into two categories: antibody detection and non-antibody detection. Currently, HIV antibody detection in blood plasma is still the most important basis for the early diagnosis of AIDS, generally consisting of primary screening followed by confirmatory assays. The common methods for primary screening include EIA, ECL, ICG, Dot-blot, and others. The common confirmatory assays include WB, LIATEK, RIA, IFA, and others. In addition, new techniques for detecting antibodies in urine or saliva are also being developed. Non-antibody detection methods typically detect HIV viral genes and protein markers. The common methods include virus isolation and culture, p24 antigen detection, virus nucleic acid detection, gene chip assay, and newly developed method based on human CD4/CD8 lymphocyte counting.

Currently, there are more than 50 domestic companies are approved by the SFDA to produce HIV/AIDS in vitro diagnostic reagents, which are summarized in Table 11. The commonly used

technologies include EIA, Dot-ELISA, WB, ECL, ICG, fluorescent PCR, TRFIA, CD4 cell counting, and others.

Over thirty companies manufacture EIA diagnostic kits for HIV, of which only three companies have the production capacity for the 4th-generation EIA kits. In the 4th-generation EIA kits, the HIV antigen and the anti-p24 antibody have been concurrently coated on the reaction plate to enable the simultaneous detection of HIV antibodies and p24 antigen. This method increases the detection accuracy and sensitivity and shortens the time frame for HIV diagnosis. It has been shown that the quality of the 4th-generation EIA kits produced by Beijing Kewei Clinical, Beijing Chemclin Biotech and Beijing Wantai Biol-Pharma are relatively stable. The detection sensitivity and accuracy rate of these kits have remained at 99% or above for three consecutive years from 2009 to 2011 [2011 National Clinical Quality Assessment Report of HIV Antibody Diagnostic Reagents, NCAIDS and Chinse CDC].

Fifteen companies manufacture ICG diagnostic kits for HIV. The technological differences arise in the use of distinct HIV membrane proteins or their combinations as coating antigens and gold-labeled testing antigens. For example, Shanghai Kehua Bio-engineering uses the recombinant EnV16 as coating antigen and EnV18 as testing antigen; NewScen Coast Bio-Pharma uses recombinant gp41, gp120, and gp36 as both coating and decting antigens; and Beijing Wantai Bio-Pharma uses the HIV-1+2 antigens.

There are three manufacturers of urine and saliva HIV diagnostic kits in China. Beijing Junhe Pharma has developed a "urine HIV type I antibody diagnostic kit (EIA)," which was approved by the SFDA in 2005. In the kit, the recombinant HIV-1 gp41 protein expressed in *E. coli* is used as the coating antigen. Urine can be directly tested without any special treatment with the sensitivity up to 100% and the specificity up to 98.5% [Zhang XG]. Beijing Wantai Biol-Pharma and Xiamen University have jointly developed a "cavity mucosa exudate HIV1+2 antibody diagnostic kit (Dot-ELISA)", which was approved by the SFDA in 2011. The kit has a test time of only 30 minutes. Compared with the imported HIV EIA diagnostic reagents, the positive, negative, and total coincidence rate of the kit is up to 99.1%, 99.8%, and 99.6%, respectively. Guangzhou Wondofo Biomedical has developed a "cavity mucosa exudate HIV antibody diagnostic kit (ICG)," which was approved by the SFDA in 2011.

The CD4/CD8 blood cell counting method is a newly developed HIV diagnostic approach that determines whether HIV infection has occurred by detecting the absolute values of CD4- and CD8-positive T cells in human blood and their percentages among the lymphocytes. The method is usually dependent on flow cytometry and other sophisticated and expensive equipment. However, the Central Hospital of Shanghai Xuhui District and Shanghai SemiBio Technology have developed a new type of "CD4 cell diagnostic kit", which was approved by the SFDA in 2008. The kit is based on a manual count of blood CD4 cells under regular optical microscope on glass slide. Its diagnostic cost is equivalent to only 1/3 of imported reagents. A clinical study involving more than 1,300 cases has proven that the kit provides accurate result, easy operation, room temperature storage, and the ability to permanently archive the specimens. The promotion of this product in poor countries and regions has been performed through cooperation with the Bill & Melinda Gates Foundation.

Table 14 Major HIV diagnostic reagent manufacturers in China

Category	Company name	Total
EIA (antibody)	Shenzhen Mindray Bio-Medical, Henan Sino-American Biotech, Shanghai Biology Myla, Autobio Diagnostics, Shanghai Yingmintai Biolog, Guangzhou Wondofo Biomedical, Weifang 3V Bioengineering, Hangzhou Acon Biotech, Zhuhai Livzon Diagnostics, Beijing KingHawk Pharma, Shanghai Rongsheng Biotech, Zhongshan Bio-Tech, Beijing BGI-GBI Biotech, Shanghai Yonghua Cell & Gene, Weihai Weigao Biotech, Xiamen Asiatec, Beijing Wantai Biopharma, Shanghai Kehua Bio-engineering, Beijing Beier Bioengineering, PKU Weiming Biotech, Wuhan Institute of Biological Products, Beijing Manuo Biopharma, Beijing United Biomedical, Beijing KeWei Diagnostic, Lanzhou Institute of Biological Products, Beijing Modern Gaoda Biotech, Beijing Junhe Pharma, Shenzhen Huakang Biolical, Tianjing Pusheng Tech, Henan Lili Biology, Zhongshan Bio-Tech, Shenzhen Huamei Shengke, Chengdu Institute of Biological Products, Beijing Yaohua Biotech	35
4^{th}-generation EIA (antibody+antigen)	Shanghai Biology Myla, Beijing Chemclin Biotech, Beijing Wantai Biopharma, Beijing KeWei Diagnostic	4
Enhanced ECL	Beijing Wantai Biopharma, Beijing Chemclin Biotech, Beijing Yuande Bio, Weihai Weigao Biotech, Beijing Chemclin Biotech	5
WB	Beijing Wantai Biopharma, Shanghai IMT Biotech, Hangzhou Ausia Biological	3
Dot-ELISA	Beijing Wantai Biopharma	1
ICG	Hangzhou Acon Biotech, T NewScen Coast Bio-Pharma, Guangzhou Wondofo Biomedical, Zhuhai Livzon Diagnostics, Nantong Egens Biotech, Beijing Blue Cross, Shanghai Rongsheng Biotech, E-Y Laboratories, Beijing Manuo Biopharma, Beijing KingHawk Pharma, Weifang Kanghua Biotech, Shantou Runbio Biotech, Shanghai Chemtron, Beijing Jingweikai Med-Biotech, Beijing Wantai Biopharma	15
Fluorescent PCR	Shanghai Kehua Bio-engineering, Shanghai Haoyuan Biotech, DAAN Genes, Shenzhen Qiagen Biotech, Shenzheng PG Biotech	5
TRFIA	Guangzhou Ruida Medical, Sym-Bio Life	2
Urine and saliva diagnostics	Guangzhou Wondofo Biomedical, Beijing Wantai Biopharma, Beijing Junhe Pharma	3
CD4 cell counting	Shanghai SemiBio Tech	1
Other methods	ABON Biopharma, Guangzhou Wondofo Biomedical, Shanghai Haoyuan Biotech, Hangzhou Acon Biotech	4

The research and development efforts for new HIV diagnostic reagents in China is currently focused on these areas**: 4^{th}-generation EIA, magnetic-bead based immunochromatography testing (MICT), CD4/CD8 cell cytometry, gene chip assay, saliva and urine antibody detection, and combined detection of HIV and other infectious diseases. Some of the major achievements of HIV diagnostic reagent R&D recently in China are summaried in Table 16.**

Professor Yifu Guan's group at China Medical University has developed a diagnostic strip for rapidly detecting HIV antibodies in urine. The HIV-1 gp41 antigen and colloidal gold solution with a diameter of 38 nm have been utilized to prepare the immune complexes. The detection time is only 10-20 minutes. A clinical study using 200 samples found that the sensitivity was up to 100% and the specificity was up to 98% [Li XN].

Table 15 Major achievements of new HIV diagnostic reagent R&D in China.

Project name	Company/ Institute	Features and innovative characteristics	Patent protection	Research progress
A test strip for HIV antibodies (MICT)	NewScen Coast Bio-Pharma	The kit uses nano-immunomagnetic beads labeled with HIV gp41 and gp36 antigens for detection of HIV antibodies and has a higher detection sensitivity and specificity than regular ICG kit.	CN200820 074598.9	Pre-clinical study
A test strip for HIV antibodies and p24 antigen (MICT)	Beijing Chemclin Biotech	The kit uses magnetic particles labeled with antibodies that specifically recognize HIV-1+2 antigens and p24 antigen. It introduces biotin-avidin system to amplify signals. It has higher sensitivity and accuracy than regular ICG kit.	CN200810 104825.2	Pre-clinical study
A gene chip for detection of HIV subtypes	Beijing Entry/Exit Inspection	Based on the analysis of the full-length HIV genome sequence, 75 oligonucleotide probes have been designed for the simple, rapid, and accurate determination of HIV genetic subtypes.	CN201110 077760.9	Pre-clinical study
A gene chip for detection of HIV drug-resistance	Tianjin Biochip	A total of 96 oligonucleotide probes were designed that cover the sites of major HIV reverse transcriptase inhibitor resistance mutations in China. The degree of drug resistance can be inferred based on the number of mutation sites.	CN200510 132118.0	Pre-clinical study
A gene chip for HBV/HCV/HIV-1 detection	Da An Gene	Eight oligonucleotide probes were designed targeting the specific sequences of HBV, HCV, and HIV. A single chip can simultaneously detect 38 samples.	CN200810 198011.X	Pre-clinical study
A multi indicator diagnostic kit for HIV (ICG)	Wuhan University	The kit contains five recombinant HIV antigen fragments – p24, gp41, gp36, gp120V3, and gp120C and uses nano-gold-labeled staphylococcal protein A (SPA) and anti-SPA antibody to amplify signal. The kit has the features of high sensitivity, strong specificity, and short detection time (five minutes).	CN200610 018769.1	Pre-clinical study
A rapid detection kit for HIV-1+2 in urine (ICG)	Wuxi Baijin Biotech	The kit uses the double-antigen sandwich principle and contains three colloidal gold-labeled recombinant antigen proteins HIV-1 p41/p42 and HIV-2 gp36 and specific mAbs for these proteins. The urine-concentrating pad can instantly concentrate urine 10- to 100-fold, thereby increasing the sensitivity of the diagnostic system.	CN201010 298777.2	Pre-clinical study

2.3.3 AIDS therapy

The current treatment for AIDS primarily consists of highly active antiretroviral therapy (HAART), also known as “cocktail therapy”. Current domestic and international anti-AIDS drugs that are either on the market or under development can be divided into the following categories: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors, fusion inhibitors (FIs), and CCR5 inhibitors.

In China, approximately 50 Chinese domestic companies are approved by the SFDA to produce anti-AIDS drugs, which are summarized in Table 16. These manufacturers can produce

nine of the twenty commonly used anti-AIDS drugs, most of which are generic drugs. The main manufacturers of anti-AIDS drugs include Desano Pharma, Henan Topfond Pharma, Northern China Pharma, Huahai Pharma and others. Most of these companies have the ability to produce two or more types of the commonly used anti-AIDS drugs with a relatively high share of the domestic market and product export.

Table 16 Information on current production of anti-AIDS drugs in China

Category	Drug name and number of manufacturers*
NRTIs	zidovudine (34), didanosine (12), stavudine (15), lamivudine (17), zalcitabine (0), abacavir (0), tenofovir disoproxil fumarate (0)
NNRTIs	nevirapine (25), delavirdine (1; Jilin Nova Pharmaceutical Co., Ltd.; clinical study), efavirenz (0)
PIs	saquinavir (1; Zhejiang Huahai Pharma), indinavir (6), ritonavir (1; Matrix Pharma Group (Xiamen), nelfinavir (0), amprenavir(0), abacavir (0), palinavir (0)
Integrase inhibitors	raltegravir (0)
FIs	enfuvirtide (0)
CCR5 inhibitors	maraviroc (0)

* Data from www.sfda.gov.cn with key word searching: drug-domestic, drug-chemical, drug-product.

The research and development of new anti-AIDS drugs in China is focused on these areas: **novel small-molecule chemical compounds, natural compounds from plants and animals, macromolecular biological products, and traditional Chinese herbal compounds. Table 17 summarizes the major achievements of new anti-AIDS drugs R&D in China.**

Table 17 Major achievements of new anti-AIDS drugs R&D in China

Project name	Company/ Institute	Features and innovative characteristics	Patent protection	Research progress
New anti-AIDS Chinese herbal preparations	Shanghai Hundreds' Ace Herbal	"Tang herb" was extracted from a combination of 20 different types of Chinese herbs. When used alone, this drug can inhibit HIV replication, increase the number of $CD4^+$ T cells, and promote the secretion of IL-2 and IFN-γ. When used together with HAART therapy, it can increase drug efficacy, reduce toxicity, and increase the number of white blood cells.	CN201010229396.9 CN200910048798.6	SFDA approved No. Z20050291
New anti-AIDS herbal medicine	Yunnan Shidea Pharma, Kunming Institute of Botany	"Si'aitesan" is composed of the active ingredients from more than ten natural plants, including safflower, and exhibits anti-HIV activity against multiple targets. When used alone, this drug has an effective rate of 89%. When used in combination with HAART therapy, it can significantly increase the drug efficacy and increase the number of $CD4^+$ T cells.	CN200510010999.9	Phase II clinical trial
CCR5 receptor antagonist nifeviroc	Shanghai Institute of Organic	Nifeviroc binds to the HIV CCR5 receptor with high specificity and affinity and shows no cross-resistance to maraviroc.	WO2005/121123	Phase II clinical trial

	Chemistry			
New membrane fusion inhibitor sifuvirtide	Tianjin Fusu Biological	Sifuvirtide can specifically block the fusion of the viral envelope and host cell membrane for a variety of HIV-1 genotypes. Its working mechanism is different from that of enfuvirtide (T20). When used in combination with other drugs, sifuvirtide achieves strong AIDS treatment effects.	CN200780021805.	Phase II clinical trial
New anti-AIDS drug polymannurog uluronate	Ocean University of China, Lantai Pharma	A sulfated polysaccharide anti-AIDS drug was obtained from seaweed through extraction and chemical modification. Its mechanism involves interfering with viral adsorption to cells and inhibiting reverse transcriptase activity.	CN00111372.0	Phase II clinical trial
Natural compounds with anti-AIDS activities	Kunming Institute of Zoology of CAS	A dozen natural compounds with significant anti-HIV activities in vitro were screened from plants and animals, including xanthohumol, concentricolide, schisandrin, and 2-(N-methyl-guanidino)-ethanesulfonic acid. A compound preparation called "Qishile" containing eight types of Chinese herbs was also developed with significant anti-HIV activity in vitro.	CN02113777.3/ CN200410040750.8/CN200310110784.5/CN200410082873.8	Pre-clinical study or applying for clinical trial
A new anti-AIDS chemical compound	Zhengzhou University	The compound asymmetric 6-hydroxy-biphenyl derivative is a non-nucleoside anti-AIDS drug. In vitro and in vivo studies have shown that it has strong anti-HIV and anti-hepatitis virus activities with less toxic side effects.	CN200310107029.1	Pre-clinical study
Natural compounds as HIV reverse transcriptase inhibitors	Chinese University of Hong Kong	A variety of biomolecules have been extracted from natural plants and animals, such as laccase from *Lentinus edode*s fruit, acaconin from Taiwan acacia seeds, lectin from the *Hericium* fruit, hexametric lectin from *Hibiscus* seeds, and lectin from green bean seeds. These biomolecules have good inhibitory effects on HIV reverse transcriptase *in vitro* ($IC_{50} < 1$ μM).	N/A	Laboratory study stage

Synthesis of small-molecule drugs

Professor Dawei Ma's group at Shanghai Institute of Organic Chemistry has developed a novel CCR5 receptor antagonist "nifeviroc", for which they have obtained Chinese and international patents. Nifeviroc is a small-molecule compound that binds to the CCR5 receptor with high specificity and affinity and shows no cross-resistance to the similar drug, maraviroc. In 2007, the patent for nifeviroc was transferred to Shanghai Targetdrug Ltd., and the Australian company Avexa for joint development. Nifeviroc is currently in phase II clinical trials in China.
[http://www.aidsmap.com/Chinese-company-to-develop-CCR5-inhibitor-with-Avexa/page/1427017/]

Professor Junbiao Chang's group at Zhengzhou University has engaged continually in the development of novel anti-AIDS compound drugs. The group has synthesized a new non-nucleoside compound, the asymmetric 6-hydroxy-biphenyl derivative. *In vitro* and *in vivo* studies have shown that the compound has strong anti-HIV and anti-hepatitis virus activities and few side effects. In 2011, the patent for this technology was transferred to Xingyu Zhongke Co. for further research and development; the compound is currently in pre-clinical studies.

Isolation of natural compound medicines

The Institute of Materia Medica at Ocean University of China has been engaged in the research and development of innovative marine-derived drugs against AIDS. Professor Huashi Guan's group has extracted, isolated, and chemically modified a seaweed sulfated polysaccharide called "polymannuroguluronate" from the ocean (trade name: Polishazi). The mechanism of this drug involves interfering with virus and cell adhesion and inhibiting reverse transcriptase activity. The patent for this compound has been transferred to Lantai Pharma for further research and development. Polymannuroguluronate was approved by the SFDA in 2003 for phase II clinical trials. It was reported that when used during the intermittent stage in AIDS patients under intermittent HAART regimens, polymannuroguluronate was well tolerated, safe, and nontoxic and that the viral load for the vast majority of patients either declined or did not rebound, and $CD4^+$ cells in nearly 50% of the patients were increased by more than 30% [Key Technology Research and Development Program during the "10th Five-Year Plan," AIDS treatment suitable for the national conditions of China, Serial number 2001BA705B01].

Professor Yongtang Cheng's group at the Kunming Institute of Zoology has been engaged in the research and development of natural compounds as anti-AIDS drugs. They have identified several natural compounds that have significant anti-HIV activities out of more than 3,000 compounds isolated from wild animals and plants, microbes, and marine organisms. These natural compounds include xanthohumol, concentricolide, schisandrin, 2-(N-methyl-guanidino)-ethanesulfonic acid, and others. In addition, they have invented a compound preparation called "Qishile," which is composed of eight types of Chinese herbal medicines. In vitro experiments demonstrated that "Qishile" could effectively inhibit various subtypes of HIV strains from infecting cells and replicating [Yang LM]. The pre-clinical studies of this drug have been completed, and application has been made to begin clinical trials.

Development of traditional Chinase medicines

Traditional Chinese herbal compounds may be promising in the treatment of HIV/AIDS. In 2010, China approved the first traditional Chinese herbal compound for the treatment of HIV/AIDS, "Tang herb." More than ten other Chinese herbal compounds are currently undergoing clinical trials, including Compound SH, Aining granule, Fufangsanhuangsan, Keaite, Aikefuzheng tablet, Qiankunning, Chuankezhi, and Aikeqing.

2.4 Diarrhea

Diarrhea is a gastrointestinal disease that can be caused by a variety of factors, although it can be divided into two major categories: infectious diarrhea and noninfectious diarrhea. Based on the difference in pathogens, infectious diarrhea can also be divided into bacterial, viral, fungi, and parasitic diarrhea. Bacterial pathogens associated with diarrhea include *Shigella*, *Vibrio cholerae*, *E. coli*, *Salmonella typhimurium*, and others. Viral pathogens associated with diarrhea mainly include rotavirus, Norwalk virus, and calicivirus. Parasites associated with diarrhea include amoeba, flagellates, and others. Rotavirus is the major pathogen that causes diarrhea in children. In China, roughly ten million infants and young children suffer from infectious gastroenteritis caused by rotavirus each year.

2.4.1 Prevention

Vaccines related to diarrheal diseases currently on the market in China include vaccines against typhoid, cholera, dysentery, and rotavirus. Cholera vaccine manufactures include Shanghai United Cell and Shanghai Institute of Biological Products. Typhoid vaccines are mainly manufactured by China National Biotech Group. Both dysentery and rotavirus vaccines are produced solely by the Lanzhou Institute of Biological Products.

The new diarrhea vaccines that are being developed in China cover the main pathogens that cause diarrhea, although more studies are focused on vaccines for typhoid, *E. coli*, rotavirus, and enterovirus type-71 (EV71). Table 18 summarizes the major achievements in research, development, and production of diarrhea vaccines in China.

Table 18 Major achievements of R&D and production of diarrheal vaccines in China

Project name	Company/ Institution	Features and innovative characteristics	Patent protection	Research Progress
Oral live RV vaccine	Lanzhou Institute of Biological Products	The attenuated strain of the Lanzhou lamb RV was used in the vaccine. it was prepared by using newborn calf kidney cells to culture and harvest virus solution.	N/A	SFDA approved
Trivalent reassortant RV vaccine	Lanzhou Institute of Biological Products	This vaccine includes the reassortment between the Lanzhou Lamb RV LLR and the G2, G3, and G4 strains of human RV to produce three human–ovine RV reassortant strains with both the safety of animal RV and the antigenicity of human RV.	CN200510041858.3	Phase II clinical trial
Hexavalent RV vaccine	Wuhan Institute of Biological Products	This project was launched in 2007 in collaboration with the United States Program for Appropriate Technology in Health. It has completed the processes of virus production in Vero cells, virus purification, and the liquid formulation preparation process.	N/A	Pre-clinical study
Oral RV by transgenic carrot and tobacco	Institute of Microbiology of CAS	Transgenic carrots that express RV VP4, VP6, VP7, and the CTB-EPEC CS3 fusion protein were constructed. In addition, transgenic tobacco was used to produce and purify RV virus-like particles (RV VLPs) containing the VP2, VP6, and VP7 proteins.	CN200610065167.1	Pre-clinical study
Oral RV vaccine by transgenic potato	Third Military Medical University	Transgenic potatoes that highly express the VP7 protein were generated. Animal experiments showed that oral administration of this vaccine can induce a relatively strong serum IgG response and a strong mucosal sIgA response.	CN200410021931.6	Pre-clinical study
Oral live RV vaccine by *Bifidobacterium* vectore	Chongqing Medical University	*Bifidobacterium* was transformed with the recombinant expression vector containing the human group A RV VP4 or VP7 to prepare the recombinant *Bifidobacterium* oral live vaccine containing VP4 or VP7.	CN200810300181.4 CN200810300177.8	Pre-clinical study
Recombinant RV vaccine	Chengdu Kanghua	Mouse myeloma cells have been used to amplify RV, with the advantages of low cost and high safety.	N/A	Laboratory study

	Biological			
Oral bivalent live vaccine for *Shigella flexneri*/*sonnei*	Lanzhou Institute of Biological Products	An attenuated dysentery strain (FSM-2117) that expresses *Shigella flexneri* 2a and *Shigella sonnei* bivalent somatic antigen (LPS) has been used in this vaccine. This strain is not kanamycin resistant.	CN00113985.1	SFDA approved
Genetically engineered multivalent vaccine for dysentery	Academy of Military Medical Sciences	The new FS-5416 dysentery strain contains the *Shigella* invasion plasmid antigen proteins A-D and the *Shigella flexneri* and *Shigella sonnei* bivalent LPS-O polysaccharide antigen. This vaccine is available as oral capsules and nasal drops. Multiple animal experiments have proven that the vaccine is safe and effective and can improve mucosal immunogenicity. The dosage for the nasal drops is 1% of the oral dosage.	CN200510089851.9	Phase II clinical trial
A conjugate vaccine for dysentery	Lanzhou Institute of Biological Products	This vaccine combines dysentery polysaccharides and recombinant rEPA to generate the *Shigella flexneri* 2a dysentery conjugate vaccine F2a-O-SP-rEPA and the *Shigella sonnei* conjugate vaccine S-O-SP-rEPA.	N/A	Phase III clinical trial
Oral vaccine for cholera	Academy of Military Medical Sciences	This vaccine was prepared by coupling the recombinant CTB expressed in *E. coli* and inactivated cholera bacteria (containing O antigen).	CN200910247594.5	SFDA approved
A conjugate vaccine for *Vibrio cholerae* O139	Beijing Minhai Biotech	This vaccine couples the *Vibrio cholerae* O139 capsular polysaccharide with recombinant CTB. The vaccine could effectively stimulate mice to produce anti-*Vibrio cholerae* O139 antibodies and anti-cholera toxin antibodies.	CN201010624059.X	Pre-clinical study
Typhoid Vi polysaccharide vaccine	China National Biotech Group	This vaccine is made by diluting the purified and refined Vi polysaccharide antigen of cultured *Salmonella typhi*. A Phase III clinical study enrolling more than 200,000 people has shown that this vaccine has good safety features. Its protection rate of people over age five is over 70%.	N/A	SFDA approved
Typhoid Vi polysaccharide-protein conjugate vaccine	Lanzhou Institute of Biological Products	This vaccine connects the *Salmonella typhi* Vi capsular polysaccharide and the recombinant *Pseudomonas aeruginosa* exotoxin A via adipic acid dihydrazide (ADH) to form conjugates. Primary immunization of mice with the vaccine results in higher levels of specific IgG antibodies than the regular typhoid vaccines, and secondary immunization has a strengthening effect.	N/A	Phase I clinical trial
Multivalent recombinant vaccine for EHEC	Third Military Medical University	This vaccine contains three recombinant antigens from the O157:H7 strain: Intimin, Stx2B, and EHEC hemolysin. After immunizing mice with a mixture of the three antigens, the antibody GMT was up to 1000 and the protection rate in mice was 91%.	CN200710078173.5	Pre-clinical study
A attenuated *Salmonella* vector vaccine for EHEC	Third Military Medical University	A recombinant vector expressing antigens from the O157:H7 strain (Intimin, Stx2B, and EHEC hemolysin) was constructed and transformed into attenuated mouse *Salmonella typhimurium* to prepare the vaccine. The	CN200810069320.7	Pre-clinical study

		combined immunization scheme of oral administration of the vaccine strain and subcutaneous or intramuscular injections of the recombinant proteins produced good immunogenicity and protective efficacy in mice.		
A bivalent inactivated viral vaccine for EV71	Academy of Military Medical Sciences	This vaccine contains the EV71 and coxsackie virus type A16 (Cox. A16). It is prepared from virus amplified and collected from vero cells.	CN200910236591.1	Pre-clinical study
An inactivated viral vaccine for EV71	Beijing Luzhu Biopharma	This vaccine was prepared from highly purified inactivated EV71 with an aluminum adjuvant. It has excellent immunogenicity.	CN201010127032.X	Pre-clinical study

Rotavirus vaccines

Lanzhou Institute of Biological Products has developed a live oral RV vaccine (trade name: Luotewei) that was approved by the SFDA for marketing in 1998. The vaccine uses the Lanzhou lamb RV attenuated strain (G10-LLR-85) and is made from virus solution cultured on the newborn calf kidney cells. Luotewei belongs to the first generation of univalent animal RV vaccines in the world. A phase III clinical study enrolling 4,000 children showed that the vaccine could trigger the production of neutralizing antibodies against RV serotypes G1-G4. The seroconversion rate was from 40% to 60%, and the protective effect against RV-induced diarrhea was 78% [Ju YY]. Although it has been widely used in China, this vaccine lacks strict phase IV clinical research data and monitoring measures for long-term adverse effects, and it remains unknown whether the vaccine will cause intestinal complications.

Lanzhou Institute of Biological Products is currently developing a trivalent reassortant RV gene vaccine. This vaccine uses the reassortment between LLR and the G2, G3, and G4 strains of human RV to obtain three human–ovine RV reassortant strains with both the safety of animal RV and the antigenicity of human RV. When injected into rats, this vaccine induced titers of specific antibodies against the antigens of the G2-G4 strains that were significantly higher than the antibody titers against antigens of the G1 and G10 strains. This vaccine was also shown to have good safety features [Han J]. The vaccine is currently undergoing phase II clinical studies, but results data remain currently unavailable.

The Wuhan Institute of Biological Products and the United States Program for Appropriate Technology in Health are collaborating to develop a hexavalent RV vaccine with funding from the Bill & Melinda Gates Foundation. Since this project was launched in 2007, it has completed the processes of virus production in Vero cells, virus purification, and preparation of the liquid formulation. The vaccine is currently undergoing pre-clinical studies.
[The development of multivalent rotavirus vaccine for human use, China Science and Technology Achievements, June 2010].

Professor Rongxiang Fang's group at Institute of Microbiology of CAS is investigating the production of RV vaccines by transgenic plants. The group has utilized the modified carrot invertase II gene promoter to generate transgenic carrots that express RV VP4, VP6, VP7, and the CTB-EPEC CS3 fusion protein. In addition, they have utilized transgenic tobacco to produce and purify RV virus-like particles (RV VLPs) containing the VP2, VP6, and VP7 proteins, which have

been made into an oral vaccine. Animal experiments showed that oral administration of the vaccine coupled with the cholera toxin immune adjuvant can produce specific antibodies at levels similar to the attenuated RV vaccine [Yang YM].

Professor Yuzhang Wu's group at the Third Military Medical University is developing a transgenic potato RV vaccine. The group has transferred the RV VP7 gene into the potato genome to obtain transgenic potatoes that express the VP7 protein at high levels. Animal pharmacodynamic tests and acute toxicology examinations have been completed, and the results showed that the oral administration of transgenic potato expressing RV genes can induce a relatively strong serum IgG response and a strong mucosal sIgA response. The sIgA antibody titers in fecal and saliva are approximately 1000 and 250 recpecttively, and there was almost no sIgA in the urine [Li JT].

Professor Yongping Ma's group at Chongqing Medical University is performing *Bifidobacterium* RV vaccine research. They have transformed *Bifidobacterium* with a recombinant expression vector containing the human group-A RV VP4 protein, followed by fermentation, to prepare the oral active *Bifidobacterium* vaccine containing RV-VP4. Animal experiments showed that after oral administration of the vaccine, the serum IgG antibody titers could be up to 700 and the fecal IgA antibody titers could be approximately 100.

Dysentery vaccines

The Lanzhou Institute of Biological Products and the Academy of Military Medical Sciences have jointly developed a freeze-dried oral *Shigella flexneri*/*sonnei* bivalent live vaccine, which was approved for the market by the SFDA in 2003. The vaccine uses an attenuated dysentery strain (FSM-2117) that expresses *Shigella flexneri* 2a and *Shigella sonnei* bivalent somatic antigen (LPS); the strain is not kanamycin resistant. Phase III clinical trials showed that the protection rate of the vaccine in children was 74.8%, the protection rate in adults was 58.33%, and the protection rate for the profiled dysentery was 47.82%. The rate of side effects was only 0.136%.

The Academy of Military Medical Sciences is developing a new generation of genetically engineered multivalent dysentery vaccines. The group has transferred the invasion plasmid antigen proteins (IpaA-D) shared by all groups of dysentery bacteria to the FSM-2117 dysentery strain to construct the new FS-5416 dysentery strain. This genetically engineered multivalent dysentery vaccine is available as oral capsules and nasal drops. Animal experiments have proven that the vaccine is safe and effective and can improve mucosal immunogenicity. In addition, the nasal drops can produce relatively good immunogenicity and protection even at a dosage that is 1% that of the oral dosage. A clinical study in volunteers demonstrated that the oral vaccine strains could provide a protection rate of 91.8% in children, 86.5% in adults, and 76.8% for the profiled dysentery strain.

The Lanzhou Institute of Biological Products is developing a new type of dysentery conjugate vaccine. The vaccine combines dysentery polysaccharides and the recombinant *Pseudomonas aeruginosa* exotoxin A (rEPA) to generate the *Shigella flexneri* 2a dysentery conjugate vaccine F2a-O-SP-rEPA and the *Shigella sonnei* conjugate vaccine S-O-SP-rEPA. The vaccine has completed phase II clinical trials, and the results show that the vaccine had good safety features. The seroconversion rates two weeks and 12 weeks after vaccination were 86.27% and 79.74%, respectively, and the geometric mean titer (GMT) increased 12.47-fold and 9.83-fold, respectively,

over pre-immunization levels [Zhou WZ].

Cholera vaccines

Professor Qingjun Ma's group at the Academy of Military Medical Sciences and Shanghai United Cell jointly developed the oral cholera vaccine in enteric-coated capsule formulation, rBS-WC (trade name: Ke Wei Shi). The vaccine was approved for marketing by the SFDA in 2000 and has now become one of the three cholera vaccines recommended by WHO. The vaccine was prepared by combining the recombinant cholera toxin B subunit expressed in *E. coli* (rBS) with inactivated cholera bacteria (containing the O antigen). Phase III clinical trials showed that the immune protection rate of this vaccine for the general population reaches more than 85%. Compared with similar products in other countries, this vaccine has few side effects, a high seroconversion rate, high antibody titer, and long duration.

Typhoid vaccines

The Chengdu Institute of Biological Products and Lanzhou Institute of Biological Products both affiliated with the China National Biotech Group have jointly developed a typhoid Vi polysaccharide vaccine approved by the SFDA for marketing in 1994. The vaccine is made by diluting the Vi polysaccharide antigen that has been purified and refined from cultured *Salmonella typhi*. Phase III clinical trials enrolling more than 200,000 people have shown that this vaccine has good safety features; its protection rate in people over the age of five is over 70%, but the protection rate for children under five years old is poor [Xie GZ].

The Lanzhou Institute of Biological Products is developing a next generation of typhoid Vi polysaccharide protein conjugated vaccine. The vaccine fuses the *Salmonella typhi* Vi capsular polysaccharide and the non-toxic recombinant *Pseudomonas aeruginosa* exotoxin A via adipic acid dihydrazide (ADH) to form conjugates. Pre-clinical studies have shown that the primary immunization of mice with the vaccine results in higher levels of typhoid-specific IgG antibodies than the regular typhoid vaccines, and secondary immunization has a strengthening effect, leading to the production of higher levels of antibodies, with the IgG antibody titer up to six thousands. Its immunogenicity is significantly weaker than the domestic typhoid Vi polysaccharide vaccine [Pu J]. In 2011, the vaccine was approved for clinical trails but the results are currently unavailable.

***E. coli* enteritis vaccines**

Professor Quanming Zou's at the Third Military Medical University is developing a new enterohemorrhagic *E. coli* (EHEC) vaccine. For this vaccine, three antigens – Intimin, Shiga toxin II subunit (Stx2B), and EHEC hemolysin (Hly) – were chosen for expression as recombinant proteins containing the respective immune protection fragments followed by the preparation of the O157:H7 multivalent genetically engineered vaccine. Animal experiments showed that mixed-immunization of mice with the three types of antigens – IntiminC300, Stx2B, and HlyAN43 – induced an antibody GMT of 1000 or more and a protection rate in mice of up to 91% [Cheng JP].

Professor Yongping Ma's group at Chongqing Medical University is currently using *Bifidobacterium* to produce vaccines against enterotoxigenic *E. coli* (ETEC).

2.4.2 Diarrhea diagnosis

Diagnosing the primary cause of diarrhea or its etiology requires a comprehensive analysis of the patient's disease history, clinical symptoms, and routine laboratory examinations. If necessary, examination methods such as B-ultrasound, X-ray barium meal, barium enema, and direct colonoscopy can also be used. Of these techniques, the detection of possible disease-causing pathogens, such as bacteria, viruses, or parasites, along with their identification in stool samples collected from diarrhea patients, is an important basis for the diagnosis of the clinical cause of diarrhea.

The commonly used diagnostic methods for bacterial diarrhea still rely on bacterial culture and drug susceptibility testing methods in addition to diagnostic serum used for bacterial typing. Most of the new testing methods currently under development are for the classification and typing of pathogens, including immunoassays, fluorescent probe PCR methods, loop-mediated isothermal amplification (LAMP) methods, and gene chip technology. The commonly used diagnostic methods for viral diarrhea are immunoassays (including colloidal gold assay, ELISA, and immunofluorescence) and fluorescent-probe PCR methods. The main new diagnostic methods under development are LAMP and gene chip methods.

Approximately 30 companies are currently approved by the SFDA to produce diarrhea diagnostic reagents, which are summarized in Table 19. These products essentially cover the common diarrhea pathogens. Some of the companies have the advantage in market share and production technology, including Shenzhen Hui An Biotech, Beijing Wantai Biological, Beijing Beier Bioengineering, Zhuhai Encode Medical; Lanzhou Institute of Biological Products; Zhengzhou Autobio Lvke Biological, Beijing Kinghawk Pharma, Da An Gene, and others.

Table 19 Major manufacturers of diarrhea diagnostic reagents in China

Category	Company name	Total
Rotavirus (ICG)	Shenzhen Huian Bio-Tech, Beijing Wantai Biopharma, Beijing Bioneovan Biotech, Hangzhou Acon Biotech, Sichuan Maker Biotech, Shantou Runbio Biotech, Zhuhai Encode Medical, Hangzhou Abon Biopharm, Beijing Beier Bioengineering, Hangzhou Acon Biopharm	10
Rotavirus (EIA)	Lanzhou Institute of Biological Products, Shenzhen Anqun Biotech	2
Rotavirus (Immunofluorescence)	Beijing Bohui Innovation	1
Enterovirus EV71 (ELISA and ICG)	Beijing Beier Bioengineering, Beijing Wantai Biopharma	2
Enterovirus EV71 (Fluorescent PCR))	Daan Gene, Shanghai Zj Bio-Tech, Beijing IPE Biotech, JiangSu Mole BioScience, Beijing KingHawk Pharma	5
Cholera (ICG)	Beijing Zhuangdi Biomedicine, Zhengzhou Wantai Bio-Science	2
Cholera (diagnostic serum)	Ningbo Tianrun Biopharma, China National Biotech Group	2
Cloacae (culture)	Autobio Diagnostics, Zhengzhou Biocell Biotech, Shanghai Kemajia Biotech, Hunan Tiandiren Biotech, Zhuhai Meihua Bio-Medical, HuiZhou Sunshine Biological, Shanghai Fosun Biolog, Bofeng Biolongical, Jinan Baibo Biotech, Wenzhou Kangtai Biotech	10

Typhoid fever (diagnostic broth)	Ningbo Tianrun Biopharma, Lanzhou Institute of Biological Products	2
Typhoid fever (culture)	Zhengzhou Biocell Biotech, Shanghai Kemajia Biotech, Autobio Diagnostics	3
Typhoid fever (Fluorescent PCR)	Shenzhen Mabsky Tech	1
Dysentery (culture)	Chongqing Pang Tong Medical, Beijing Aoboxing Biotech, Shanghai Yi-Hua Clinical, Nanjing Periong Medical, Shanghai Zenka Biotech	5

Presently, the research and development of new diagnostic reagents for diarrhea in China is focused these areas: **technical innovation of existing diagnostic kits; advancing molecular biology for detection of pathogen nucleic acids; new colorimetric labeling technologies for detection and typing of live pathogens; gene chip assays for pathogen genotyping and drug-resistance testing. Table 20 summarizes some of the major achievements in research and development of new diarrhea diagnostic reagents in China.**

Detection of rotavirus

Beijing Wantai Biopharma has developed an in vitro diagnostic kit for detection of group A RV that was approved for marketing by the SFDA in 2005. The kit utilizes the ICG technique and the double-antibody sandwich principle by coating with monoclonal antibody and labeling with polyclonal antibodies, thus achieving the specific detection of group A RV. A clinical study in multiple hospitals showed that the kit was consistent with imported EIA and ICG diagnostic kits at a rate of up to 97.2%. Compared with the EIA method, this kit has the advantages of high sensitivity, good specificity, and easy operation with the testing time for only a few minutes.

Shenzhen Huin Bio-Tech has developed an in vitro diagnostic kit for combined detection of rotavirus and adenovirus that was approved for marketing by the SFDA in 2005. The kit utilizes the ICG technique by coating specific antibodies against RV antigen VP6 and adenovirus antigen Hexon. The detection sensitivities for RV and adenovirus both reach 31ng/ml, and even up to a maximum of 8 ng/ml for RV and 4 ng/ml for adenovirus after 10 minutes.

Detection of *Vibrio cholerae*

Beijing Diho Biomedical has developed the *Vibrio cholerae* O1/O139 test kit that was approved for marketing by the SFDA in 2006. The colloidal gold labeling and the membrane chromatography technologies have been utilized to achieve rapid semi-quantitative detection of the possible existence of *Vibrio cholerae* serotypes O1/O139. A clinical study has shown that compared with the conventional bacterial culture and hemagglutination method, the sensitivity, specificity, and false-positive rate of this diagnostic kit in detecting *Vibrio cholerae* O1 was 93.33%, 98.132%, and 1.68%, repetitively [Wu DR].

Guangzhou Huafeng Biotech is developing a new diagnostic kit for detecting *Vibrio cholerae* O1/O139 by the LAMP method. Specific primers were designed using the RfbN gene of the O1 subtype and the wbfR gene of the O139 subtype as the targeting genes. The test can be completed in two hours with the sensitivity up to 10 Cfu/ml. The kit has good specificity with no cross-reactions

to other species of intestinal bacteria.

Daan Gene is developing a new diagnositic kit for detecting *Vibrio cholerae* O1/O139 by fluorescent PCR. The kit contains four pairs of specific primers targeting the genes of different *Vibrio cholerae* antigens, including the O antigen, hemolysin, and the CTX virulence genes. It is capable of simultaneous *Vibrio cholerae* strain typing and pathogenic toxicogenetic gene detection and is suitable for large-scale and rapid screening of human populations and food.

Detection of *E. coli*

EHEC is a subtype of *E. coli* that includes over 40 serotypes, although O157:H7 is its major serotype. Because EHEC causes serious harm and has a wide range of serotypes, the accurate and rapid detection of EHEC is of great importance.

Guangzhou Huafeng Biotech is developing a detection kit for EHEC by the LAMP method. The kit contains specific primers targeting the highly conserved regions of the Stx1 and Stx2 genes, which cover almost all of the EHEC serotypes. Its detection sensitivity is up to 10 Cfu/ml, and it shows no cross-reaction with other species of intestinal bacteria.

Tianjin Biochip is developing a gene chip detection kit for ETEC. The kit contains specific nucleic acid probes targeting the oligosaccharide unit (O unit)-processing enzyme genes, *Shigella dysenteriae* type I gene, and the heat-stable (ST) and heat-labile (LT) enterotoxin genes of the 19 most common serotypes of ETEC. The detection sensitivity reaches 10 ng DNA/sample, and it has very good accuracy and reproducibility.

Detection of dysentery and typhoid

Guangzhou Huafeng Biotech is developing a detection kit for *Salmonella* and *Shigella* by the LAMP method. The kit contains the specific primers targeting the *Salmonella* AgfA gene and the *Shigella* IphA gene. The detection sensitivities for the two intestinal bacteria both reach 10 Cfu/ml.

Table 20 Major achievements of new diarrhea diagnostic reagents R&D in China

Project name	Company/ Institution	Features and innovative characteristics	Patent protection	Research Progress
A multi-channel test strip for intestinal pathogens based on UCP technique	Academy of Military Medical Sciences	The kit contains a variety of UCP-labeled specific antibodies. It is capable of real-time rapid detection of ten types of foodborne intestinal pathogens, such as A/B/C paratyphoid *Salmonella, L. monocytogenes, V. parahaemolyticus, E. coli* O157, and *V. cholerae* O1/O139. The special sample handling solution ensures the detection sensitivity and specificity.	CN201010257697.2	Pre-clinical study
A kit for *V. cholerae* typing and virulence gene detection	Da An Gene	The kit contains four pairs of specific primers and fluorescence-labeled probes for the different antigen genes of *V. cholerae* (O antigen, hemolysin, and CTX virulence gene). It is capable of simultaneously typing	CN201010145729.X	Pre-clinical study

(fluorescent PCR)		and pathogenic virulence gene detection of cholera bacteria.		
A diagnostic kit for *V. cholerae* O1/O139 strains (LAMP method)	Guangzhou Huafeng Biotech	The kit contains specific primers targeting the O1 subtype RfbN gene and O139 subtype wbfR gene of *V. cholerae*. It has a detection sensitivity of up to 10 CFU/ml.	CN201010193228.9 CN201010193227.4	Pre-clinical study
A test strip for Cholera based on UCP technique	Chinese Center for Disease Control and Prevention	The kit contains UCP particles labeled with antibodies specifically against the cholera O1 and O139 strains and can be used for the rapid quantitative detection and typing of *V. cholerae*. It has high sensitivity and good specificity.	CN201020297996.4	Pre-clinical study
EHEC detection kit (LAMP method)	Guangzhou Huafeng Biotech	The kit contains specific primers targeting the highly conserved regions of the Stx1 and Stx2 genes and covers almost all of the EHEC serotypes. The detection sensitivity reaches 10 CFU/ml with no cross-reactivity with other species of intestinal bacteria.	CN201110211370.6 CN201110211377.8	Pre-clinical study
Gene chips for detecting diarrheagenic *E. coli* subtypes	Tianjin Biochip	The kit targets the EPEC eae gene, ETEC Lt, Stap and Stah genes, EHEC Stx1 and Stx2 genes, EIEC ipaH gene, and *E. coli* O157wzy gene. It can simultaneously detect multiple *E. coli* subtypes with simple operation, high accuracy, and strong repeatability.	CN200810176576.8	Pre-clinical study
Gene chips for detecting ETEC	Tianjin Biochip	The kit contains specific nucleotide probes targeting the oligosaccharide unit processing gene, *S. dysenteriae* type I gene, and the Lt and St enterotoxin genes of the 19 most common serotypes of ETEC. The sensitivity reaches 10 ng DNA/sample with high accuracy and strong repeatability.	CN200810189248.1	Pre-clinical study
A combination kit for *Salmonella* and *Shigella* (LAMP method)	Guangzhou Huafeng Biotech	This kit contains specific primers designed for the *Salmonella* AgfA gene and *Shigella* ipaH gene. The detection sensitivity for *Salmonella* and *Shigella* reaches 10 CFU/ml.	CN201010145716.2	Pre-clinical study
A diagnostic kit for *S. flexneri* by suspension microarray technology	Institute of Microbiology & Epidemiology	This kit contains microspheres labeled with different colors and specific nucleotide probes targeting the *S. flexneri*-specific rfc genes. The genomic DNA samples are amplified by PCR, labeled, and then hybridized. The intensity of the fluorescent signal is used to determine whether the tested specimen contains *S. flexneri*. The detection sensitivity can reach fg level of genomic DNA/sample.	CN200810181198.2	Pre-clinical study

2.4.3 Diarrhea therapy

Diarrhea therapy requires comprehensive treatments based on the cause (infectious or noninfectious) and the characteristics (acute or chronic, as well as severity). Medications for treating infectious diarrhea can be classified as follows: (1) appropriate antibiotics targeting the pathogenic bacteria,

such as fluoroquinolone antibiotics; (2) appropriate antiviral drugs targeting the pathogenic virus, such as ribavirin and recombinant interferon; (3) drugs for rehydration and supportive care, such as saline and glucose, for the maintenance of the body's normal supply of nutrients and electrolyte balance; (4) drugs belonging to the gastrointestinal mucosal protective agent family used to protect intestinal function, such as smectite powder; (5) anti-motility drugs used to alleviate the symptoms of diarrhea; (6) supplementation of probiotic drugs (probiotics), such as bifidobacteria and lactobacillus, which can maintain the balance of intestinal microbial populations and correct intestinal micro-ecological disorders.

Professor Baotian Chen's group at Southern Medical University found that the traditional Chinese medicine guava leaf had a significant therapeutic effect for viral diarrhea in children. They subsequently developed a Chinese herbal medicine compound preparation (trade name: "Lianfan Zhixie Jiaonang"), which was approved for marketing by the SFDA in 2005. A phase III clinical trail have shown that guava leaf and its compound preparation performed significantly better than the control group Smecta (montmorillonite) for the treatment of diarrhea in children caused by rotavirus and Norwalk virus as evaluated by several indicators, including clinical efficiency, antigen negative rate (81% vs. 47.6%, respectively), and intestinal sodium/glucose absorption rates. In addition, guava leaf combined with Smecta leads to a better treatment effect [Zhang XS]. Further studies showed that the active ingredients in guava leaves, such as quercetin and 2α-hydroxy ursolic acid, have good anti-RV effects and can kill RV and other pathogens while inhibiting intestinal movement to reduce symptoms of diarrhea [Zhang WJ].

Professor Yi Zeng's group at the Chinese Academy of Sciences and the Jiangxi Sino-German Joint Research Institute jointly developed an anti-RV immunoglobulin product, which was subsequently transferred to Huludao Eyck Biological for production and was approved for marketing by the SFDA in 2001. This drug is produced by extracting and purifying a variety of biologically active factors (including anti-RV IgY immunoglobulin) from the yolk of RV-immunized chicken eggs followed by sterilization and a freeze-drying process. After oral administration, the drug is resistant to protease degradation and the gastric acid barrier in the gastrointestinal tract of children, thereby maintaining long-term activity in the digestive tract. Clinical application showed that the drug can shorten the course of the RV diarrhea significantly with the total efficiency of 80% [Wang YM].

2.5 Malaria

Malaria is caused by *Plasmodium* protozoa and is one of the three major infectious diseases worldwide. In 2010, there were 216 million clinical cases of malaria worldwide, approximately 655 thousand malaria-related deaths, of these deaths, 91% occurred in Africa, and 85% occurred among children under five age [World Malaria Report 2011 Summary (Report), WHO]. Another study estimated that the number of malaria deaths in 2010 could have been as high as 1.24 million [Murray C]. According to statistics, the incidence of malaria in China has steadily declined over the past 10 years. In 2011, the number of new malaria cases was approximately 4,000 with 39 deaths [Statistics of Notifiable Infectious Diseases, the Chinese Ministry of Health].

2.5.1 Prevention

Preventing transmission by targeting the malaria vector (mosquito) is currently the primary method

of malaria control. Developing a safe and effective malaria vaccine is difficult because of the complex life cycle of the malarial parasite and its tendency to undergo antigenic variation. Currently, there is no malaria vaccine on the market, but a number of malaria vaccines are undergoing clinical trials. These vaccines are primarily pre-erythrocytic vaccines, which prevent blood-stage infection and transmission.

Currently, only a small number of academic institutes and companies in China are researching and developing malaria vaccines, which as summarized in Table 21.

Professor Weiqing Pan's group at the Second Military Medical University is developing a malaria vaccine based on a novel recombinant protein known as *P. falciparum* chimeric protein 2.9 (PfCP-2.9). This protein is a fusion of the terminal 19-kDa fragment of the massive surface protein I-C (MSPI-C), a candidate blood-stage vaccine antigen, and the III sub-region of the apical membrane antigen I (AMAI) through the P28 linker sequence. In 2009, this vaccine completed the phase II clinical trials. All of the volunteers in the vaccine group had produced antigen-specific antibodies in the blood, and most of their PfCP-2.9-specific antibody serum levels were much higher than the anti-MSPl-19 antibody and anti-AMAl (III) antibody titers combined. The mean serum antibody titer was $>3 \times 10^4$, and in some volunteers, the serum antibody titer was $>10^6$. This clinical trial was co-financed by WHO and Bill Melinda & Gates Foundation.

Table 21 Major achievements of new malaria vaccine R&D in China

Project name	Company/ Institution	Features and innovative characteristics	Patent protection	Research Progress
Pre-erythrocytic DNA vaccine	Third Military Medical University	Vaccine induces the production of antigen-specific antibodies and CD8 T-cell responses	N/A	Pre-clinical study
Recombinant malaria vaccine	Shanghai Wanxing Bio-Pharma, Second Military Medical University	Vaccine is a fusion of the terminal 19-kDa fragment of MSPI-C and the III sub-region of AMAI through the P28 linker sequence. Antigen-specific antibodies were produced in the serum of volunteers in two clinical trials, and the mean antibody titer was $>3\times10^4$.	N/A	Phase II clinical trial
DNA vaccine containing the cholera toxin B subunit	Military Academy of Medical Sciences	Vaccine contains multiple epitopes of the multiple life stages of *P. falciparum* and can be expressed in multiple organs, resulting in antibody production and CTL responses. Animal studies have shown a nearly 100% protection rate.	N/A	Applying for clinical trials

2.5.2 Diagnostics

Malaria diagnosis requires a comprehensive understanding of epidemiological investigations, clinical symptoms, and laboratory analysis. Currently, three methods of malaria laboratory diagnosis are being developed and applied. The first method is the blood smear microscopy method, which has been the gold standard for the diagnosis of malaria. However, the method's sensitivity is low and requires professional and technical personnel. The second method is serological detection

based on immunoassay technology, which is primarily used to detect the *Plasmodium* antigens in the blood and the antibodies produced by the host. Many companies worldwide are marketing rapid diagnostic kits for *Plasmodium*-specific antigen proteins. Finally, molecular biology diagnostic methods have become more common in recent years, such as PCR, LAMP, and gene chip. These methods are also currently the primary methods for testing malaria for drug resistance because they are accurate and highly sensitive, although they require specialized equipment.

Currently, the research and development of new malaria diagnostic kits in China is mainly focused on the ICG and PCR methods, and some of the major achievements are summarized in Table 22.

Guangzhou Wondofo Biomedical has developed a rapid diagnostic kit to detect *Plasmodium falciparum*, which was approved for marketing by the SFDA in 2011. This kit utilizes the ICG technique and the double-antibody sandwich principle by detecting the *Plasmodium* pan-lactate dehydrogenase (panLDH) levels in test samples. This method is relatively simple and fast to obtain results in 15 minutes. Furthermore, it requires only 5 μl of blood. A clinical study has shown that the kit has the sensitivity of 95% and the specificity of 100%, and its consistency rate with microscopic examination is 96.9%, with no cross-reaction with *vivax* malaria [Liu H]. Another study during the Waw peacekeeping mission in Sudan has shown that the kit has the sensitivity, specificity, and total effectiveness of 92.3%, 99.5%, and 98.3%, respectively. [Xue CJ].

Beijing Jin Wofu Biological is developing a rapid diagnostic kit by the ICG method which can distinguish between the *falciparum* and *vivax* malaria. This kit can simultaneously identify the *falciparum* and *vivax* malaria patients using two colloidal gold-labeled monoclonal antibodies that target the *P.vivax*-specific lactate dehydrogenase (pLDH) and the *P. falciparum*-specific histidine-rich protein 2 (HRP-2).

Table 22 Major achievements of new malaria diagnostic reagent R&D in China.

Project name	**Company/ Institution**	**Features and innovative characteristics**	**Patent protection**	**Research Progress**
A rapid diagnostic kit for *P. falciparum*	Guangzhou Wondofo Biomedical	The kit uses the ICG technique and the double-antibody sandwich principle by detecting the *Plasmodium* panLDH levels in test samples.	CN201010 620089.3	SFDA approved
A rapid test strip for *P. falciparum* and *P. vivax*	Beijing Jin Wofu Biological	The kit uses the ICG technique which contains colloidal gold-labeled HRP-2 and pLDH mAbs that detect *P. falciparum* and *P. vivax*, respectively.	CN200910 147608.6	Pre-clinical study
A rapid test strip for *P. falciparum* and *P. vivax*	Southern Medical University	The kit uses the ICG technique which contains three colloidal gold-labeled mAbs, including two binding to the LDH protein of *P. vivax* or *P. falciparum* and a third binding to their common antigens. This kit can identify whether one is infected with *P.vivax*, *P. falciparum*, or both.	CN201110 138524.3	Pre-clinical study
A single-tube, two-step malaria gene PCR diagnostic kit	Guangxi CDC	Multiple common primers and species-specific primers are designed to target the mitochondrial cytochrome oxidase (cox1) gene of human *Plasmodium*. The kit requires only 4 μl of blood collected on filter paper and can detect both *P.*	CN200710 303516.3	Pre-clinical study

		falciparum and *P. vivax*. The sensitivity reaches 1 *Plasmodium*/μl of blood.		

2.5.3 Therapy

Currently, three categories of anti-malarial drugs are used in clinical practice, including *Plasmodium* DNA replication and transcription inhibitors, folate metabolism inhibitors, and mitochondrial electron transport inhibitors. In most regions of the world, *Plasmodium falciparum* has become resistant to single use of malaria drug. Therefore, the WHO recommends artemisinin-based combination therapies as the frontline treatment for *Plasmodium falciparum* malaria.

Table 23 provides an overview of anti-malarial drug production in China. There are roughly one hundred companies that are approved for manufacture malaria drugs. The major manufacturers include Guilin Pharma (a subsidiary of Shanghai Fuxing Pharma), Kunming Pharma, Guangzhou New Southern, Chongqing Huali Pharma, Chongqing Tonghe Pharma, and Sichuan Xieli Pharma.

Guilin Pharma is China's largest manufacturer and exporter of anti-malarial drugs. In 1987, this company developed a patent drug artesunate. In 2007, the artesunate amodiaquine tablets and amodiaquine hydrochloride tablets obtained the pre-certification requirements to become the WHO anti-malarial drug supplier.

Table 23 Information on anti-malarial drug production in China

Category	Product name and number of manufactures
Heme detoxification inhibiors	Chloroquine class (43); Quinine (51); Mefloquine (0)
Molate metabolism inhibitors	Sulfadoxine (6); Pyrimethamine (15); Proguanil (0)
Mitochondrial electron transport inhibitors	Artemisinin (11); dihydroartemisinin (8); Artemether (18); Artesunate (6)
Other function	Lumefantrine (5)
Compound formulations	artemisinin piperazine tablet (1); dihydroartemisinin piperazine tablet (1); artesunate amodiaquine tablet (1); dihydroartemisinin + piperaquine phosphate + trimethoprim (1)

In recent years, the research and development of new anti-malarial drugs in China has mostly focused on new compound preparations for existing drugs, especially for artemisinin. The research on new molecules or compounds with anti-malarial activity has yielded few results. Table 24 summarizes some of the new anti-malarial drugs currently being developed in China.

Table 24 List of new malaria drug R&D in China.

Project name	Company/ Institution	Features and innovative characteristics	Patent protection	Research progress

Isolation and characterization of natural anti-malarial compounds	Guangzhou Institute of Biomedicine and Health Research, South China Botanical Garden	A β-Resorcylic acid lactone derivative and an isocoumarin compound were isolated from natural plants, and both were found to have strong anti-malarial activity. The half-inhibitory concentration of the latter is 20 nM.	CN200910197474.9 CN200910040215.5	Pre-clinical study
Isolation and characterization of natural anti-malarial compounds	Second Military Medical University, East China University of Sci & Tech	A variety of compounds with anti-malarial activity were isolated from natural plants, including cynanversicoside C, lithospermate esters, flavonoid glycosides, etc. These compounds all bind to and inhibit the enzyme activity of Falcipain-2 protease.	CN200910197474.9 CN200910197473.4 CN200910197472.X	Pre-clinical study
Development of new artemisinin-based compound combinations	Guangzhou University of Traditional Chinese Medicine	A variety of artemisinin derivatives have good anti-malarial activity, including the combination of artemisinin, naphthoquine, and primaquine compounds and the combination of artemisinin, piperaquine, and primaquine compounds.	CN03146951.5 CN200610110050.0	Pre-clinical study
Indinavir and its derivatives in anti-malarial drugs	Guangzhou Institute of Biomedicine and Health Research	When used in combination with chloroquine, Indinavir or hydroxyl Indinavir has good *in vitro* and *in vivo* synergistic inhibitory effects on *Plasmodium*, especially chloroquine-resistant *Plasmodium*. These compounds can be used to develop anti-malarial drug combinations.	CN200910039442.6 CN200710028696.9	Pre-clinical study
Three-layer formulation of artemisinin-based combination anti-malarial drugs	Guilin Pharma	A three-layer tablet of anti-malarial compounds contains a layer of artemisinin or its derivatives, a layer of another anti-malarial drug, and a barrier that prevents direct contact between the drugs and improves the stability of the formulations.	CN200610148830.4	SFDA-approved for marketing

2.6 Pneumonia

Pneumonia is the world's leading cause of infectious disease-related deaths. The WTO estimates that pneumonia causes approximately 2 million deaths each year [Rudan]. Pneumonia is also the leading independent cause of death in children under age 5, most of which occur in developing countries [Lack]. Although the Chinese Ministry of Health does not list pneumonia as an independently reported infectious disease in the national statistics on annual disease incidence and mortality, pneumonia remains one of the leading causes of death in adults and children in China. The WTO estimates that the incidence of pneumonia in children is approximately 0.22 person per year in China, but some studies have shown that this number has dropped to approximately 0.05 person per year, which is similar to those observed in developed countries [Guan X].

Pneumonia is typically classified into several categories according to its pathogen: (1) bacterial pneumonia (e.g., *Streptococcus pneumoniae*, *Staphylococcus aureus*, hemolytic *Streptococci*, *Haemophilus influenzae*, pneumonia *Klebsiella bacillus*); (2) viral pneumonia (e.g., respiratory syncytial virus [RSV], influenza virus, adenovirus, cytomegalovirus, herpes simplex virus); (3) atypical pneumonia (e.g., *Legionella*, *Mycoplasma*, *Chlamydia*); (4) fungal pneumonia (e.g.,

Candida albicans, *Aspergillus*, Actinomycosis); (5) other pathogen-induced pneumonias (e.g., *Rickettsia*, *Toxoplasma gondii*, protozoa, parasites); (6) pneumonias caused by other physical and chemical agents. The most impactful pathogen of pneumonia in adults and children is *Streptococcus pneumoniae*, followed by RSV and *Mycoplasma*. In China, respiratory diseases such as pneumococcal pneumonia are one of the leading causes of death in infants and children. Pneumococcal resistance to drugs has gradually increased, and multi-drug resistance has begun to appear.

2.6.1 Pneumonia prevention

Currently there are only two types of pneumonia vaccines on the Chinese market, including *Streptococcus pneumoniae* vaccine and *Haemophilus influenzae type b* (Hib) vaccine. Besides these two vaccines, the research and development of new pneumonia vaccines in China is also focused on novel vaccines for RSV, Severe Acute Respiratory Syndrome (SARS). However, the research and development of vaccines for other types of pneumonia is limited and slow. **Table 25 summarizes the major companies and institutes in research, development and production of pneumonia vaccines in China.**

Table 25 Major companies and institutes in R&D and production of pneumonia vaccines in China

Category	Products approved by the SFDA	Products in R&D
Pneumococcal polysaccharide vaccine (PSV)	Chengdu Institute of Biological Products	Beijing Sinovac Biotech, Yunnan Watson Biotech, Beijing Luzhu Biopharma
Pneumococcal conjugate vaccine (PCV)	N/A	Beijing Sinovac Biotech, Yunnan Watson Biotech
Hib vaccine (protein conjugate)	Lanzhou Institute of Biological Products, Yunnan Watson Biotechnology, Beijing Luzhu Biopharma	Lanzhou Institute of Biological Products
Hib combination vaccine	N/A	Beijing Minhai Biotech, Yunnan Watson Biotech, Beijing Luzhu Biopharma
RSV vaccine	N/A	Academy of Military Medical Sciences
SARS vaccine	N/A	Beijing Sinovac Biotech

***Streptococcus pneumoniae* vaccine**

Currently, two *Streptococcus pneumoniae* vaccines are being evaluated: a pneumococcal capsular polysaccharide vaccine (PSV) and a pneumococcal capsular polysaccharide-protein conjugate vaccine (PCV).

PSV uses the pneumococcal capsular polysaccharides as antigens. The vaccine is recommended for children over age 2 and for adults. Currently, most of the PSVs on the Chinese market are 23-valent PSVs manufactured by Merck (trade name "Pneumovax"), Sanofi-Pasteur (trade name "PNEUMO 23"), and Chengdu Institute of Biological Products. The 23-valent PSVs developed by Beijing Sinovac Biotech and Yunnan Watson Biotech have obtained SFDA approval for clinical trials recently. In addition, the 23-valent PSV developed by Beijing Luzhu Biopharma is mostly likely in

the process of submitting an application for the SFDA approval for clinical trials.

PCV is composed of a specific antigen protein which acts as an adjuvant and the capsular polysaccharide. It has better immunogenicity and efficacy than PSV. PCV is more suitable for children under age 2. Currently, there is only one 7-valent PCV on the Chinese market, which is manufactured by Wyeth. There are several domestic companies in research and development of PSV vaccines including Beijing Sinovac Biotech and Yunnan Watson Biotech. Their vaccines are all 13-valent PCVs, both of which have obtained SFDA approval for clinical trials in 2011.

Hib Vaccine

The majority of Hib vaccines currently being developed are capsular polysaccharide-protein conjugate vaccines. The products of three domestic manufacturers have been approved for marketing by the SFDA: Lanzhou Institute of Biological Products (trade name "he'er'bei"), Yunnan Watson Biotech (trade name "bangbeike"), and Beijing Luzhu Biopharma. All of these vaccines are produced with a covalent combination of isolated *Haemophilus influenzae* type b capsular polysaccharide and tetanus toxoid.

Beijing Minghai Biotech (now a subsidiary of Shenzhen Kangtai Biological) is the first company in China to develop a combination vaccine against acellular diphtheria, tetanus, pertussis, and *Haemophilus influenzae* type b. They have optimized the ratio of DPT antigen to Hib polysaccharide antigen through animal experiments, which have shown that the combination vaccine has good safety features [Li GF]. This vaccine is currently in clinical trials. Yunnan Watson Biotech is also developing the DTP and Hib combination vaccine which have obtained the SFDA approval for clinical trials in 2012.

Beijing Luzhu Biopharma is currently developing a meningococcus polysaccharide-*Haemophilus influenzae* type b polysaccharide conjugate vaccine. This vaccine is made using an appropriate proportion of the A/C/Y/W135 groups of epidemic cerebrospinal *cocci meningitis* capsular polysaccharide-protein conjugate and *Haemophilus influenzae* type b capsular polysaccharide-protein conjugate. This vaccine has completed the phase II clinical trials in 2012. The results showed that the meningococcal antibody-positive rate of the A and C groups were 100% and 92.6%, respectively, and that Hib-PRP antibody-positive rate and long-term protective antibody positive rate were 96.53% and 95.75%, respectively. Moreover, the incidence of severe adverse reactions was lower than that of the single-dose control vaccine [Li YP].

RSV Vaccine

Currently, RSV vaccines being developed in other countries have entered clinical trials, the majority of which are either attenuated recombinant vaccines or fusion protein particle vaccines. Most of the RSV vaccines being developed in China are in the laboratory research stage, and no vaccine has yet entered clinical trials.

Professor Xingguo Mei's group at the Institute of Pharmacology and Toxicology of the Academy of Military Medical Sciences is currently developing an RSV subunit vaccine. The group is using the thiol-disulfide oxidoreductase (DsbA) protein to fuse the 125-225 amino acid fragment of the RSV

G antigen protein and the M2:81-95 CTL epitope of the F protein. Animal studies have shown that this vaccine can induce balanced, long-lasting humoral and cellular immune responses in immunized mice. Furthermore, these responses can lead to a 700-fold reduction in the RSV virus titer in the lung and nasal cavities [Fan CF]. The use of CpG ODN as the vaccine adjuvant has been shown to further enhance the humoral and cellular immune responses of mice. This vaccine is currently undergoing further investigation in pre-clinical studies.

2.6.2 Pneumonia diagnostics

Clinical diagnosis of pneumonia is dependent on the integrated application of a variety of methods including the collection and identification of the pathogen specimen, routine blood and urine examination, tests of liver and kidney function, X-ray examination, humoral immune detection, computed tomography (CT), and endoscopic examination. Among these methods, the collection and identification of the pathogen specimen is the most common basis for the clinical diagnosis of pneumonia.

The specimen collection methods mainly include: (1) phlegm, blood, and pleural fluid specimen collection; (2) suction of the secretion of the lower respiratory tract via fiberoptic bronchoscopy or through an artificial airway (bronchial alveolar lavage, BAL); (3) percutaneous fine-needle aspiration (PFNA) after the injection of normal saline solution.

The pathogen identification methods vary according to the sources and characteristics of the causative pathogen. The most commonly used methods for diagnosing bacterial pneumonia are still the culture and drug sensitivity test, and most of the new detection techniques currently being developed are for the classification and typing of pathogens. These methods include immunoassay, PCR, LAMP, and gene chip assay. The most commonly used methods for diagnosing viral pneumonia are fluorescent labeling PCR, LAMP, gene-chip assay, et al. There are two commonly used techniques for diagnosing mycoplasma pneumonia. The first technique involves the culture and drug sensitivity test followed by fluorescence labeling PCR to detect antigens. The second technique is an immunological assay used to detect specific antibodies. This second technique is also the most commonly used method for diagnosing chlamydial pneumonia.

Currently, there are more than one hundred companies can manufacture pneumonia diagnostic reagents in China. These reagents cover the main pneumonia-causing pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Legionella*, *mycoplasma*, *Chlamydia,* and RSV. About 30 companies have products with the immunological and molecular biological methods. **Table 26 lists the major manufacturers of pneumonia diagnostic reagents in China.**

Table 26 Major manufacturers of pneumonia diagnostic reagents in China

Category	Company name	Total
Pneumonia streptolysin O antigen (immune turbidimetric method) [1]	Shanghai Fosun Pharma, Weifang Kanghua Biotech, Beijing Chemclin Biotech, Ningbo Rui Biotech, Anhui Daqian Bio-Engineering, Xiamen Asiatec, Shanghai Kehua Bio-engineering, Hunan Tiandiren Biotech, Shandong Biobase Biology, Sichuan Maker Biotech, Fudan-zhangjiang Bio-Pharma, Shenzhen Huian Biotech, et al.	>50
Hib (culture)	Autobio Diagnostics, Shanghai Biology Myla, Hunan Tiandiren Biotech, Ningbo Scientz	6

	Bio-tech , Wenzhou Kangtai Biotech, Huamei Lunxianghe Medical	
Mycoplasma pneumoniae (culture)	Quick Dabiology, Zhengzhou Langfeng Biotech, Zhuhai Encode Medical, Zhengzhou Vigorous Biotech, Weifang Hightop Biotech, Shaanxi Ruikai Biological, Autobio Diagnostics, Shanxi Cnbios Technology, Shanghai Enkang Biology, Wuhan Showtime Science, Zhengzhou Beida Biotech, Zhenghzhou Labscience, Zhengzhou Beiruite Bio-tech	13
Mycoplasma pneumoniae (fluorescent PCR)	Da An Gene, Huangzhou Acon Biotech, Shanghai Fosun Pharma, Shanghai Clone Biotech	4
Mycoplasma pneumonia (EIA)	JiangSu Mole BioScience, Zhuhai Livzon Diagnostics, Beijing HOB Biotech, Shenzhen Anqun Biotech, Shenzhen Yhlo Biotech	5
Mycoplasma pneumoniae (ICG)	Beijing Beier Bioengineering, Beijing Antai Diagnostic, Bofeng Biolongical, Weifang Kanghua Biotech, Fujian Haitian Lanbo Biological, Lanzhou Yahua Biotech	6
Legionella pneumoniae (immunoassay)	Tianjin Ruiaijin Bio-Tech	1
Chlamydia (immunoassay)	Weifang Kanghua Biotech, Livzon Diagnostics, JiangSu Mole BioScience	3
RSV (fluorescent PCR)	Da An Gene , Guangzhou Huayin Pharma	2

[1] There are more than fifty companies can manufacture *Pneumonia streptolysin* O antigen diagnostic kits. We only lists a number of companies with relatively high market share and strong R&D capacity.

The research and development of new pneumonia diagnostic reagents in China is currently focused on improving existing detection techniques and applying new detection techniques. **Among them, the newly developed molecular biology techniques such as the LAMP, NABSA and gene chip assays may be more promising in future. Table 27 summarizes some of the recent achievements in research and development of new pneumonia diagnostic reagents in China.**

Guangzhou Huafeng Biotech is developing a LAMP assay kit to detect a variety of pneumonia pathogens, including *Klebsiella pneumoniae*, *Legionella pneumoniae*, and RSV. The company has developed a patented reaction tube by integrating the gene amplification and detection steps in the same tube, which can effectively reduce the vulnerability of the sample to aerosol pollution. The oligonucleopeptide-binding protein (opp) A gene of *Klebsiella pneumoniae* acts as the targeting gene for nucleic acid amplification and detection, and the kit's sensitivity can reach 10^3-10^4 Cfu/mL.

Tianjin Biochip is developing a gene chip to detect pathogens in the lower respiratory tract. This chip uses a variety of specific oligonucleotide probes fixed on a solid phase carrier to rapidly identify a variety of pneumonia pathogens, including *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Legionella pneumophila*, and *Moraxella catarrhalis*.

Table 27 Major achievements of new pneumonia diagnostic reagent R&D in China.

Project name	Company/ Institution	Features and innovative characteristics	Patent Protection	Research Progress

A diagnostic kit for a variety of pneumonia pathogens	Beijing Haikang DNA Chips	The kit uses the NABSA technique. It contains multiple specific primers and probes that can simultaneously detect *Chlamydial, Mycoplasma, Streptococcu pneumoniae, Legionella pneumophila,* and *Haemophilus influenzae*. The sensitivity is higher than conventional PCR.	CN200910083897.8	Pre-clinical study
Gene chip assay for respiratory pathogens	Tianjin Biochip	The gene chip uses a variety of specific oligonucleotide probes fixed on a solid phase carrier to rapidly identify more than ten common pneumonia pathogens.	CN200810182565.0	Pre-clinical study
A diagnostic kit for *Mycoplasma* and *Chlamydia*	Zhuhai Encode Medical	The kit uses the LAMP technique. Specific primers are designed to rapidly amplify and quantitatively identify the nucleic acid sequences of *Mycoplasma pneumoniae* or *Chlamydia*. The sensitivity reaches 100 cfu/ml.	CN201010174440.0 CN200910039674.1	Pre-clinical study
A diagnostic kit for a variety of pneumonia pathogens	Guangzhou Huafeng Biotech	The kit uses the LAMP technique. Specific primers are designed to rapidly amplify and quantitatively identify a variety of pathogens including *Klebsiella pneumoniae, Legionella pneumoniae,* and RSV.	CN200910142762.4 CN201010114243.X	Pre-clinical study
A diagnostic kit to identify *Legionella pneumophila*	Shanghai Fosun Pharma	The kit uses the multi-wavelength fluorescence-labeled PCR. Specific primers that are designed for single-tube amplification and detection of non-*Legionella* and *Legionella pneumophila*. It is quick and easy to operate, the sensitivity is high, and the false positive and false negative rates are low.	CN200910199298.2	Pre-clinical study
A diagnostic kit for RSV	Beijing Ascle Bioengin	The kit uses the ICG technique. A novel anti-RSV N protein mAb is used to rapidly detect RSV. The specificity, sensitivity, and accuracy are high.	CN200610111650.9	Pre-clinical study

2.6.3 Pneumonia therapy

Two clinical approaches are commonly used to treat pneumonia: the first is to select appropriate drugs based on the pneumonia-causing pathogens, and the second is to perform appropriate adjuvant therapy to alleviate the pneumonia symptoms. Bacterial, mycoplasma, or chlamydial pneumonia currently treated with various antibiotics while viral pneumonia is typically treated with antiviral medicines. Because infants and children have relatively immature immune system, conventional drugs for treatment of adult pneumonia may be not always suitable.

China is a major producer of antibiotics and antiviral chemicals, but most of the drugs manufactured by Chinese domestic companies are generic. Currently, there are more than one thousand companies in China that can manufacture conventional antibiotics, such as penicillin, cephalexin, ofloxacin gatifloxacin, roxithromycin, azithromycin, and ribavirin. These drugs are frequently used to treat bacterial, mycoplasma, chlamydial, and RSV pneumonia. In addition, there are more than twenty interferon manufacturers and their products consist primarily of the 2a and 2b subtypes. Interferon is commonly used to treat viral pneumonia, and it has shown highly efficacious in treatment of atypical pneumonia caused by the SARS coronavirus.

Recently, the combined application of Chinese traditional medicine and Western medicine has shown promising results for the treatment of various types of pneumonia in infants and children.

Professor Weiming Wang's group at the Heilongjiang Academy of Traditional Chinese Medicine is currently developing a traditional Chinese medicine compound called "Qinbai Qingfei concentrated pellets" to treat pneumonia in children. Animal studies have shown that this drug has significant effects to treat mycoplasma pneumonia in mice with a minimal effective concentration approximately 100 ug/ml. The drug can also improve pneumonia symptoms such as high body temperature and immune system disorders [Wang WM]. Clinical studies have shown that the overall effect of this drug on mycoplasma pneumonia in children is comparable with that of azithromycin. However, it improves pneumonia symptoms more effectively during the course of treatment than azithromycin [Zhu T]. This drug has completed phase III clinical trials in 2012 and expected to approval for marketing by the SFDA in recent future.

Professor Shouchuan Wang's group at the Nanjing University of Traditional Chinese Medicine has been conducting research on the treatment of RSV pneumonia with traditional Chinese medicine. A study of approximately 300 pediatric RSV pneumonia patients showed that the total efficacy of a Qingkailing injection solution combined with Ertongqingfei or Kechuanling oral solution was >90% after 10 days of treatment, while the efficacy rate of the ribavirin control group was 81%. The experimental group also showed superior results in terms of drug onset time and improvement in symptoms such as fever, cough, and phlegm [Yang Y].

2.7 Influenza

Influenza is a common acute respiratory infectious disease caused by influenza viruses. Type A and B influenza viruses are the most common causes of respiratory disease. However, only pathogens of the type A cause high-mortality pandemics. Since the 20th century, the type A influenza virus has caused a number of global influenza pandemics.

2.7.1 Influenza prevention

A safe and effective influenza vaccine has always been the basis of influenza prevention. The high mutation rate and frequent genetic recombination of the influenza viruses promote a variety of changes in its hemagglutinin (HA) and neuraminidase (NA) antigens. Therefore new influenza virus strains must be continuously isolated to update the vaccine immunogens to match the viruses that are currently spreading and/or that may cause next pandemic.

The currently available influenza vaccines include the inactivated whole virus vaccine, split-virus vaccine, and subunit vaccines. However, in most countries, the whole-virus vaccines have gradually been replaced by the split-virus vaccines and subunit vaccines. The most commonly used regular flu vaccines are the 3-valent split-virus vaccines, which include two Type A viruses (hemagglutinin 1 neuraminidase 1 (H1N1) and H3N2), and one B virus. The sub-unit vaccine, the newest of the influenza vaccines, is further purified after the virus is split. Only the HA and NA antigens are retained in the vaccine.

Currently, there are more than ten manufacturers of influenza vaccines in China. Most of these companies can manufacture both the seasonal and H1N1 influenza vaccines, and the majority of these vaccines are split-virus vaccines. **Table 28 summarizes the major manufacturers of**

influenza vaccines in China.

Tianjin Tasly Pharma has developed a 3-valent seasonal subunit influenza vaccine that has been approved for marketing by the SFDA approval in 2010. This vaccine was the first domestically produced subunit influenza vaccine.

Table 28 Major manufacturers of influenza vaccines in China.

Category	Company name	Total
Seasonal (whole virus)	Beijing Wantai Biopharma	2
Seasonal (split-virus)	Zhejiang Tianyuan Bio-Pharma, Changchun Changsheng Life, China National Biotec Group, JiangSu Ealong Biotech, Hualan Biological, Beijing Tiantan Biological, Beijing Sinovac Biotech	7
Seasonal (subunit)	Tianjin Tasly Pharma	1
H1N1 (split-virus)	Zhejiang Tianyuan Bio-Pharma, Changchun Changsheng Life, China National Biotec Group, JiangSu Ealong Biotech, Hualan Biological, Dalian Aleph Biomedical, Beijing Tiantan Biological, Beijing Sinovac Biotech	8

A number of academic institutes and companies in China are currently conducting research and development on new influenza vaccines, including sub-unit vaccines, DNA vaccines, oral or nasal delivery vaccines, and new adjuvant vaccines. Some of the significant achievements are listed as follows:

Subunit influenza vaccines

Professor Ze Chen's group at Hunan Normal University is committed to research and development of novel subunit influenza vaccines. The group has studied whether the application of influenza matrix proteins M1 and M2 and ribosomal nucleoprotein (RNP) can prevent influenza in mice. The results have shown that these protein antigens, together with specific immune adjuvants, such as chitosan, provide good cross-protection against multiple subtypes of influenza viruses, including H1N1, H5N1, and H9N2 [Sui ZW]. This study is currently in the laboratory research stage.

New adjuvant influenza vaccines:

Professor Ze Chen's group at Hunan Normal University is also researching and developing novel adjuvant influenza vaccines. They has studied the application of several natural or synthetic chemical compounds, such as chitosan, pachymaran, and $(WAF)^3$, as new immune adjuvants for the influenza subunit vaccines. Among these compounds, chitosan is the easiest to obtain because its raw materials are plentiful in nature. Chitosan is also non-toxic, can be degraded *in vivo*, and has good biocompatibility. Pachyman comes from the traditional Chinese medicine tuckahoe and is easy to extract and purify. Studies using pachyman as an immune adjuvant of a new influenza split-virus vaccine have shown that the effect of pachyman is comparable to that of aluminum hydroxide. Pachyman can significantly increase serum antibody levels in mice and improve their ability to fight against a lethal dose of the influenza virus [Xie GX].

Vaccines with new delivery method

Yunnan Watson Biotech is currently developing a nasal spray version of the split-virus influenza vaccine that contains the CpG/ODN and polyI:C adjuvants. The influenza virus is isolated from chicken embryo cultures and then split to obtain the influenza vaccine stock solution. The vaccine is then made by combining the stock solution and CpG/ODN and polyI:C adjuvants in particular ratios. Animal studies have shown that after domestic rabbits were immunized with this vaccine, the titers of specific H1N1, H3N2, and Type B influenza virus antibodies were all significantly higher than those of rabbits immunized with the split-virus influenza vaccine and the nasal spray vaccine currently on the market (the geometric mean titer [GMT] was 6.96-21.11 vs. 4.59-6.96) [Patent No. CN201010103470.2]. This vaccine is expected to enter phase I clinical trials soon.

2.7.2 Influenza diagnosis

Influenza diagnosis requires a comprehensive analysis of the clinical symptoms and the laboratory test results. Influenza virus laboratory test methods mainly include the following: (1) virus isolation and culture: this method requires virus specimen collection, transport, and storage and takes a long time. (2) Serological detection: two serum samples are used for the hemagglutination inhibition test or complement fixation test to detect a patient's serum antibody levels. (3) Immunological detection: the commonly used techniques include IFA, EIA, ICG, etc. (4) Molecular biology detection: the commonly used techniques include PCR and NASBA.

Currently, there are more than 10 companies that have obtained SFDA approval to manufacture influenza diagnostic reagents in China. The products can detect various Type A and Type B influenza viruses, with the typical techniques including Dot-ELISA, EIA, fluorescent PCR, and ICG. **Table 29 summarizes the major manufacturers of influenza diagnostic reagents in China.**

Table 29 Major manufacturers of influenza diagnostic reagents in China

Method	Company name	Total
Dot-ELISA	Beijing Wantai Biopharma	1
EIA	Beijing Wantai Biopharma, Guangzhou Huayin Pharma, Shanghai Kehua Bio-engineering	3
Fluorescent PCR	Guangzhou Huayin Pharma, Beijing KingHawk Pharma, Daan Gene, Shanghai Zj Bio-Tech, Beijing BGI-GBI Biotech, Beijing ASCLE Bioengineering, Beijing Sino-MDgene, Shanghai Clone Biotech	8
ICG	Guangzhou Wondofo Biomedical, Hangzhou Genesis Biodetect, ABON Biopharm, Beijing Zhuangdi Biomedicine	4

2.7.3 Influenza therapy

Currently, there are hundreds of manufacturers to produce chemical anti-influenza virus drugs in China, and most of these drugs are generic. For example, more than 100 companies can produce adamantine or adamantanee ethane, and three companies can produce abidor. In addition, Roche has authorized Shanghai Zhongxi Pharma to manufacture oseltamivir, and GlaxoSmithKline has authorized Nanjing Simcere Pharma to manufacture zanamivir.

In addition, the SFDA has approved a number of traditional Chinese medicine preparations

or combinations of both traditional Chinese medicine and Western medicine for the treatment of influenza. For example, more than 100 manufacturers in China can produce a combination of paracetamol and amantadine hydrochloride in tablet form.

The research and development of new anti-influenza drugs in China is mainly focused on synthesis of chemical compounds, isolation of natural compounds, and traditional Chinese medicine compounds with antiviral activity.

The Academy of Military Medical Sciences is currently developing a novel anti-influenza drug peramivir hydrate. In vitro experiments have shown that the half inhibitory concentration of this compound on the neuraminidase of Type A and Type B influenza viruses is 1,600 times that of Tamiflu. The compound has also been shown to have a good inhibitory effect on the majority of influenza virus strains. This project has been transferred to Hunan Nonferrous Metals for further product development. The results of phase I clinical trials have shown that the drug has a good safety and tolerability characteristics. This drug is currently in phase II clinical trials.

Professor Zhanqiu Yang's group at the Institute of Medical Virology of Wuhan University has developed an anti-influenza compound that is an arbidol analogue. The group has used entirely new chemical raw materials and reaction routes for compound synthesis [Patent No.: CN200510018613.9]. Animal studies have shown that this drug has a strong inhibitory effect on multiple respiratory viruses, including Type A influenza viruses [Shi L].

Chapter 3 Challenge and Opportunities for Global Health R&D in China

3.1 Potential opportunities for Global Health R&D in China

3.1.1 Diagnostics

(1) A hepatitis C virus antigen-antibody joint detection kit has been developed by the Hunan Jynda Bioengineering. The kit utilizes EIA technology can simultaneously detect HCV core antigens and antibodies with high sensitivity, and shortens the "window" for detecting HCV infections from ten weeks to two weeks.

(2) A hepatitis and HIV combined detection kit has been developed by the Shanghai Kehua Bio-engineering. The kit utilizes an immunomagnetic separation instrument to enable the specific, synchronized acquisition of viral nucleic acids, which are subsequently detected using immunofluorescence PCR. The method employs a high degree of automation and is suitable for large-scale blood screening and clinical testing.

(3) A real-time PCR kist has been developed for rapid detection of multidrug-resistant MTB by Professor Qian Gao at Fudan University. Specificity and sensitivity levels of up to 100% can be achieved when using this technology for the detection of drug-resistant MTB in China. Furthermore, the technology can be used in single-channel PCR instruments.

(4) A rapid diagnosis kit for MTB (LAMP) has been developed by Professor Lei Shi at South China University of Technology. The kit is easy to use, highly specific and highly sensitive.

(5) The 4^{th}-generation HIV test kits (EIA) have been independently developed by the Beijing Kewei Clinical, Beijing Chemclin Biotech and Beijing Wantai Biological. These products are currently on the market and have continuously exhibited high degrees of quality, stability, detection sensitivity, and accuracy.

(6) A saliva HIV test kit (Dot-ELISA) method has been jointly developed by Xiamen University and the Beijing Wantai Biological. The product is currently on the market and exhibits both a rapid detection time and high accuracy.

(7) A CD4 cell diagnostic kit has been developed by the Central Hospital of Shanghai Xuhui District and the Shanghai SemiBio. The product is on the market and is characterized by accurate results, easy operation, room temperature storage, and the potential to permanently archive specimens.

(8) A group A rotavirus diagnostic kit (ICG) has been developed by the Beijing Wantai Biological. The product is on the market and utilizes a double-antibody sandwich technique that enables high sensitivity and specificity and rapid detection time.

(9) A *Plasmodium falciparum* malaria diagnostic kit (ICG) has been developed by the Guangzhou Wondofo Biomedical. The product is currently on the market and uses a double-antibody sandwich technique to detect the panLDH levels. The kit is easy to use and has a rapid detection time.

(10) A rapid diagnostic kit for malaria (ICG) has been developed by the Beijing Jin Wofu Biological. The kit can be used to identify whether subjects are infected with *falciparum* or *vivax* malarial

strains and is highly accurate with a rapid detection time.

3.1.2 Prevention:

(1) A genetically engineered recombinant hepatitis E vaccine has been developed by Professor Ningshao Xia at Xiamen University. The vaccine is currently produced by the Beijing Wantai Biological. Phase III clinical trials have shown that the vaccine exhibits protective effects against hepatitis E. The vaccine was approved for marketing by the SFDA in 2011 and was the first hepatitis E vaccine on the market worldwide.

(2) A variety of new tuberculosis vaccines have been developed by Professor Honghai Wang at Fudan University. These include a recombinant BCG vaccine (composed of polyvalent MTB antigens and cytokines), a subunit vaccine (consisting of polyvalent MTB antigen proteins), and a DNA vaccine (composed of T-cell epitopes of polyvalent MTB antigens). Animal experiments have shown that these vaccines all exhibit immunoprotective effects. Preclinical studies are currently underway.

(3) A new type of DNA tuberculosis vaccine that is composed of multivalent MTB antigens has been developed by Professor Hong Cai at Peking University. Animal experiments have shown that the vaccine has a stronger immunoprotective effect than either univalent DNA or BCG vaccines. Preclinical studies are currently underway.

(4) A combination HIV vaccine has been developed by Professor Wei Kong at Jilin University and is currently produced by the Changchun BCHT Biotech. The combination vaccine contains both a DNA vaccine for primary immunization and a poxviral vector vaccine for booster immunization. Phase I clinical trials results have shown that the combination vaccine induces high levels of HIV-specific antibody production in volunteers. Phase II clinical trials are currently underway.

(5) A trivalent rotavirus vaccine has been developed by the Lanzhou Institute of Biological Products. Animal experiments have shown that the vaccine exerts protective effects against rotavirus serotypes G1-G4. Phase I clinical trial results have shown that the vaccine exhibits positive safety characteristics, and phase II clinical trials of the vaccine are currently underway.

(6) A hexavalent rotavirus vaccine has been developed by Wuhan Institute of Biological Products. Research on virus production and the formulation preparation processes has been completed, and pre-clinical studies are currently in progress.

(7) An oral rotavirus vaccine has been developed by Professor Rongxiang Fang at the Institute of Microbiology, CAS. The vaccine is produced using transgenic tobacco and contains multiple rotavirus antigen proteins. Animal experiments have shown that this vaccine has protective effects that are similar to live attenuated rotavirus vaccines. Pre-clinical studies are currently underway.

(8) A malaria subunit vaccine has been developed by Professor Weiqing Pan at the Second Military Medical University. The vaccine contains a fusion protein of MSPI, AMAI and P28. The results of phase II clinical trials have shown that the vaccine induces the production of high levels of protective antibodies in volunteers.

(9) New 13-valent PCV vaccines have been independently developed by Beijing Sinovac Biotech,

Yunnan Watson Biotech. Both are are suitable for use in children under age two, and have been approved by the SFDA approval to enter phase I clinical trials.

(10) A group A/C meningococcus/Hib polysaccharide conjugate vaccine has been developed by the Beijing Luzhu Biopharma. The results of phase II clinical trials have shown that the vaccine can simultaneously induce high levels of protective antibodies against group A/C meningococcus and Hib while resulting in a lower rate of severe adverse reactions than a single-dose control vaccine.

(11) A new adjuvant influenza subunit vaccine has been developed by Professor Ze Chen at Hunan Normal University. Animal experiments have shown that the effects of chitosan and pachyman are comparable to those of aluminum hydroxide when they are used as immune adjuvant influenza subunit vaccines. Pre-clinical studies are currently underway.

3.1.3 Treatment:

(1) A hepatitis B antigen-antibody complex therapeutic vaccine has been developed by Professor Yumei Wen at Fudan University. The vaccine is currently produced by the Beijing Institute of Biological Products and is the first Chinese hepatitis B therapeutic vaccine to enter clinical trials. Phase III clinical trials of the vaccine are currently underway in China.

(2) A new anti-MTB lead compound, I2906, has been developed by Professor Honghai Wang at Fudan University. Animal experiments have shown that the drug exhibits both strong antimicrobial activity and low toxicity. Furthermore, the treatment of tuberculosis was more effective when the drug was coupled with isoniazid. Pre-clinical studies of the drug are currently underway.

(3) A new anti-AIDS drug, Nifeviroc, has been developed by Professor Dawei Ma at the Shanghai Institute of Organic Chemistry, CAS. The drug is now jointly developed by Shanghai Targetdrug and the Australian company Avexa. Phase II clinical trials are currently underway in China.

(4) A new anti-AIDS drug, polymannuroguluronate, has been developed by Professor Huashi Guan at Ocean University of China. The drug has been shown to interfere with the adsorption of viruses by cells and inhibit reverse transcriptase activity. It is currently manufactured by the Lantai Pharma. Phase II clinical trials of the drug are currently underway in China. The drug has been shown to significantly improve the therapeutic effects of HAART when used intermittently during therapy.

(5) A new anti-AIDS drug, asymmetric 6-hydroxy-biphenyl derivative, has been developed by Professor Junbiao Chang at Zhengzhou University. Animal experiments have shown that the compound exhibits strong anti-HIV and anti-hepatitis virus activities and few side effects. The drug is currently manufactured by Xingyu Zhongke Co., and applications have been submitted to the SFDA to enter clinical trials.

(6) A traditional Chinese herbal compound preparation for AIDS therapy, Tang herb tablets, has been developed by the Shanghai Hundreds' Ace Herbal. The compound has been approved for marketing. Phase III clinical trial results have shown that the drug exerts positive therapeutic effects in the treatment of AIDS when used alone or together with HAART.

(7) An artemisinin-based anti-malarial compound has been developed by the Guilin Pharma. This artesunate and amodiaquine compound has been shown to exhibit positive therapeutic effects

against multiple types of malaria.

(8) A traditional Chinese herbal compound, Lianfan Zhixie Jiaonang, has been developed by Professor Baotian Chen at Southern Medical University for diarrhea therapy. The preparation has been approved for marketing. The results of phase III clinical trials have shown that the drug exhibits positive therapeutic effects in the treatment of pediatric diarrhea caused by rotavirus and norovirus when used alone or in combination with montmorillonite powder.

(9) A traditional Chinese medicinal compound, Qinbai Qingfei concentrated pellets, has been developed by Weiming Wang at Heilongjiang Academy of Traditional Chinese Medicine for the treatment of pneumonia in children. Phase III clinical trials of the drug were completed in 2012 and the results have shown that that the overall effectiveness of this drug in the treatment of *Mycoplasma pneumonia* in children is comparable to that of azithromycin, and the drug is superior to azithromycin for improving the symptoms of pneumonia.

3.2 Challenges for Global Health R&D in China

Pharmaceutical firm sizes are relatively small and investments in R&D are insufficient.

Over 6,000 pharmaceutical enterprises existed in China in 2011. The products of these companies are primarily bulk pharmaceuticals, generic drugs, and traditional Chinese medicines, with fewer patented drugs with independent intellectual property rights. The market concentration of the Chinese pharmaceutical industry is relatively low. The average annual sales of the top ten domestic pharmaceutical companies are only $500 million. The R&D investments of large and medium-sized pharmaceutical enterprises are consistently low, currently representing approximately two to five percent of their budgets, which is far below the average R&D investment of international pharmaceutical companies.

Innovation for independent intellectual property rights requires long-term support.

The provisions of the World Trade Organization (WTO) for the protection of intellectual property rights will change the Chinese government’s long-term excessive administrative protection of Chinese pharmaceutical companies. More stringent protection of intellectual property rights will enable pharmaceutical companies to invest more resources in scientific research and technological innovation and will enable them to focus their R&D efforts on independent research and the development of new drugs, the production of generic drugs with expired patents, and technological transformations of existing drugs.

The new drug approval policy needs further reform.

The excessively long processing time of investigational new drug (IND) applications in China has been historically criticized by the pharmaceutical sector. The SFDA stipulates that the IND time for new drugs should be approximately two to three months, but the process often requires six months to one year. The Center for Drug Evaluation of the SFDA is gradually implementing internal institutional reforms, including evaluating innovative and generic drugs within different departments and providing a 'green channel' (i.e., a fast path) for the evaluation of innovative drugs that are supported by various forms of government funding. These reform measures make the promotion of innovative drug research and development a high priority in the SFDA drug-approval

process.

The scientific and technological achievement transformation policy requires further reform.

The difficulty in transforming research findings from scientific and technological innovations obtained by state-established institutions of higher learning and scientific research institutions into practice has historically hindered the development of science and technology in China. In 2007, the Chinese Government established the “Law of the People's Republic of China on Promoting the Transformation of Scientific and Technological Achievements”, which clearly stipulates that the government will employ various measures to promote the transformation of scientific and technological achievements made by persons holding positions in institutions of higher learning and scientific research into business opportunities. Furthermore, these businesses will be bolstered by preferential policies in terms of financial subsidies, taxes, and loans to allow for the establishment of multiple industrial drug development bases, industry-university-research institute alliances, and high-tech parks.

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Appendix

1. Chinese/English bilingual names for companies and enterprises

Company name in Chinese	Company name in English	Abbreviaion
艾康生物技术（杭州）有限公司	Acon Biotechnology (hangzhou) Co., Ltd.	Hangzhou Acon Biotech
厦门艾德生物医药科技有限公司	Amoy Diagnostics Co.,Ltd.	Amoy Diagnostics
安徽大千生物工程有限公司	Anhui Daqian Bio-Engineering Limited Company	Anhui Daqian Bio-Engineering
英科新创（厦门）科技有限公司	ASIATEC(Xiamen) CO,.LTD.	Xiamen Asiatec
郑州安图绿科生物工程有限公司	Autobio Diagnostics Co., Ltd.	Autobio Diagnostics
北京中检安泰诊断科技有限公司	Beijing Antai Diagnostic Science and Technology Co., Ltd.	Beijing Antai Diagnostic
北京奥博星生物技术有限责任公司	Beijing Aoboxing Bio-tech Co., Ltd.	Beijing Aoboxing Biotech
北京阿斯可来生物工程有限公司	Beijing ASCLE Bioengineering Co., Ltd.	Beijing ASCLE Bioengineering
北京贝尔生物工程有限公司	Beijing Beier Bioengineering Co.,Ltd	Beijing Beier Bioengineering
北京华大吉比爱生物技术有限公司	Beijing BGI-GBI Biotech Co., Ltd.	Beijing BGI-GBI Biotech
北京新兴四寰生物技术有限公司	Beijing Bioneovan Biotech Co., Ltd.	Beijing Bioneovan Biotech
创新光电技术有限股份有限公司	Beijing Bohui Innovation Technology Co., Ltd.	Beijing Bohui Innovation
北京科美东雅生物技术有限公司	Beijing Chemclin Dongya Biotech Co., Ltd.	Beijing Chemclin Biotech
北京易斯威特生物医学科技有限公司	Beijing Easyweet Biomedical Science and Technology Co., Ltd.	Beijing Easyweet Biomedical
北京健乃喜生物技术有限公司	Beijing Genesee Biotech,Inc.	Beijing Genesee Biotech
北京海康基因芯片开发有限公司	Beijing Haikang DNA Chips Co., Ltd.	Beijing Haikang DNA Chips
北京海瑞祥天生物科技有限公司	Beijing Health & Our Biotechnology Biotech Group	Beijing HOB Biotech
北京希波生物医学技术有限责任公司	Beijing Hepo Biomedical Technology Co., LTD.	Beijing Hepo Biomedical
北京华尔盾生物技术有限公司	Beijing Huaerdu Biotechnology Co., Ltd.	Beijing Huaerdu Biotech
北京爱普益生物科技有限公司	Beijing IPE Biotechnology Co., Ltd.	Beijing IPE Biotech
北京金沃夫生物工程科技有限公司	Beijing Jin Wofu Biological Engineering Technology Co., Ltd.	Beijing Jin Wofu Biological
北京金伟凯医学生物技术有限公司	Beijing Jingweikai Medical Biotechnology Co., Ltd.	Beijing Jingweikai Med-Biotech
北京君禾药业有限公司	Beijing Junhe Pharmaceutical Co., Ltd.	Beijing Junhe Pharma
北京科卫临床诊断试剂有限公司	Beijing KeWei Clinical Diagnostic Reagents Co., Ltd.	Beijing KeWei Diagnostic
北京金豪制药股份有限公司	Beijing KingHawk Pharmaceutical Co., Ltd.	Beijing KingHawk Pharma
北京绿竹生物技术有限责任公司	Beijing LuZhu Biotechnology Co.,Ltd	Beijing LuZhu Biotech
北京玛诺生物制药有限公司	Beijing Manuo Biology Pharmacy Co., Ltd.	Beijing Manuo Biopharma
北京民海生物科技有限公司	Beijing Minhai Biotechnology Co., Ltd.	Beijing Minhai Biotech
北京现代高达生物技术有限责任公司	Beijing Modern Gaoda Biotechnology Co., Ltd.	Beijing Modern Gaoda Biotech
北京鑫诺美迪基因检测技术有限公司	Beijing Sino-MDgene Technology Co., Ltd.	Beijing Sino-MDgene
北京科兴生物制品有限公司	Beijing Sinovac Biotech CO.,LTD.	Beijing Sinovac Biotech
北京天坛生物制品股份有限公司	Beijing Tiantan Biological Products Co., Ltd.	Beijing Tiantan Biological
北京优耐特生物医学有限公司	Beijing United Biomedical Co., Ltd.	Beijing United Biomedical
北京万泰生物药业股份有限公司	Beijing Wantai Biopharmaceuticals Co., Ltd.	Beijing Wantai Biopharma
北京祥瑞生物制品有限公司	Beijing Xiangrui Biological Products Co., Ltd.	Beijing Xiangrui Biological
北京耀华生物技术有限公司	Beijing Yaohua Biotechnology Co., Ltd.	Beijing Yaohua Biotech
北京源德生物医学工程有限公司	Beijing Yuande Bio-Medical Engineering Co., Ltd.	Beijing Yuande Bio
北京庄笛浩禾生物医学科技有限公司	Beijing Zhuangdi Haohe Biomedicine Technology Co., Ltd.	Beijing Zhuangdi Biomedicine
贝瑞特生物技术(郑州)有限责任公司	Beiruite Bio-technology (zhengzhou) Co., Ltd.	Zhengzhou Beiruite Bio-tech

博阳生物科技(上海)有限公司	Beyond Biotechnology (Shanghai) Co., Ltd.	Shanghai Beyond Biotech
生物梅里埃(上海)公司（外资）	Biology Myla (Shanghai) company	Shanghai Biology Myla
蓝十字生物药业（北京）有限公司	Blue Cross Bio-Medical (BeiJing) Co.,Ltd	Beijing Blue Cross
三明博峰生物科技有限公司	Bofeng Biolongical Science Teghnology Co., Ltd.	Bofeng Biolongical
厦门市波生生物技术有限公司	Boson Biotech Co., Ltd.	Boson Biotech
博奥生物有限公司	CapitalBio Corporation Co., Ltd.	CapitalBio Corp
长春百克生物科技股份公司	Changchun BCHT Biotechnology Co.,Ltd.	Changchun BCHT Biotech
长春长生生物科技股份有限公司	Changchun Changsheng Life Sciences Limited	Changchun Changsheng Life
成都永安制药有限公司	ChenDu Yongan Pharmaceutical Co.,Ltd.	ChenDu Yongan Pharmaceutical
成都康华生物制品有限公司	Chengdu Kanghua Biological Products Co.,Ltd.	Chengdu Kanghua Biological
上海海规生物科技有限公司	China Cuslink Company, Ltd.	China Cuslink
中国生物技术集团公司	China National Biotec Group	China National Biotec Group
北京北大未名生物工程集团有限公司	China PKU Weiming Biotech Group Co., Ltd	PKU Weiming Biotech
重庆埃夫朗生物技术有限责任公司	Chongqing Aifulang Biotechnology Co.,Ltd	Chongqing Aifulang Biotech
重庆啤酒集团有限责任公司	Chongqing Beer Group	Chongqing Beer Group
重庆华立药业股份有限公司	Chongqing Huali Pharmaceutical Co., Ltd.	Chongqing Huali Pharma
重庆庞通医疗器械有限公司	Chongqing Pang Tong Medical Devices Co.,Ltd.	Chongqing Pang Tong Medical
重庆通和制药有限公司	Chongqing Tonghe Pharmaceutical Co., Ltd.	Chonngqing Tonghe Pharma
中山大学达安基因股份有限公司	Daan Gene Co.，Ltd. Of Sun Yat-Sen University	Daan Gene
大连雅立峰生物制药有限公司	Dalian Aleph Biomedical Co., Ltd.	Dalian Aleph Biomedical
上海迪赛诺药业有限公司	Desano Pharma Co., Ltd.	Desano Pharma
上东健康药业有限公司	East Health Pharmaceutical Co., Ltd.	East Health Pharma
中国香港 E-Y 公司	E-Y Laboratories(H.K) Ltd.	E-Y Laboratories
福建省明溪海天蓝波生物技术有限公司	Fujian Haitian Lanbo Biological technology Co., Ltd.	Fujian Haitian Lanbo Biological
福建省洪诚生物药业有限公司	Fujian Hongcheng Biological Medicine Industry Co., Ltd.	Fujian Hongcheng Biogical
福建泰普生物科学有限公司	Fujian Triplex Biosciences Co., Ltd.	Fujian Triplex Biosciences
天津扶素生物技术公司	Fusogen Pharmaceutical Co., Ltd.	Fusogen Pharma
广州拜迪生物医药有限公司	Guangzhou BaiDi Bio-Technology CO., Ltd.	Guangzhou BaiDi Bio-Tech
兰州（广州）标佳科技有限公司	Guangzhou BGH Biomecial Co.,Ltd.	Guangzhou BGH Biomedical
广州迪澳生物科技有限公司	Guangzhou DeAou Biological technology Co., Ltd.	Guangzhou DeAou Biological
广州市丰华生物工程有限公司	Guangzhou Fenghua BioEngineering Co., Ltd.	Guangzhou Fenghua BioEngineering
广州华银医药科技有限公司	Guangzhou Huayin Pharmaceutical Technology Co., Ltd.	Guangzhou Huayin Pharma
广东凯普生物科技股份有限公司	Guangzhou HybriBio Biological technology Limited	Guangzhou HybriBio Biological
广州新南方集团	Guangzhou New Southern Group Co., Ltd	Guangzhou New Southern
广州瑞达医疗机械有限公司	Guangzhou Ruida Medical Devices Co., Ltd.	Guangzhou Ruida Medical
广州万孚生物技术有限公司	Guangzhou Wondofo Biomedical Co., Ltd.	Guangzhou Wondofo Biomedical
桂林南药股份有限公司	Guilin Pharma Co., Ltd.	Guilin Pharma
杭州艾力康医药科技有限公司	HangZhou Alicon Pharm Sci&TED Co.,Ltd.	HangZhou Alicon Pharma
杭州澳亚生物技术有限公司	Hangzhou Ausia Biological Technology Co., Ltd.	Hangzhou Ausia Biological
杭州创新生物检控技术有限公司	Hangzhou Genesis Biodetection & Biocontrol Ltd.	Hangzhou Genesis Biodetect
杭州威晟生物科技有限公司	Hangzhou Weimao Biological Technology Co., Ltd.	Hangzhou Weimao Biological
河南赛诺特生物技术有限公司	Henan Cellnovo Biotechnology Co.,Ltd	Henan Cellnovo Biotech
河南理利生物工程有限公司	Henan Lili Biology Engineering Co., Ltd.	Henan Lili Biology
河南华美生物工程有限公司	Henan Sino-American Biotechnology Co.,Ltd.	Henan Sino-American Biotech

河南天方药业股份有限公司	Henan Topfond Pharmacuetical Co., Ltd.	Henan Topfond Pharma
广州华峰生物科技有限公司	Huafeng Biotechnology (Guangzhou) Ltd.	Guangzhou Huafeng Biotech
浙江华海药业股份有限公司	Huahai Pharmaceutical Co., Ltd.	Huahai Pharma
华兰生物股份有限公司	Hualan Biological Engineering Inc.	Hualan Biological
华美伦祥和医疗用品（上海）有限公司	Huamei Lunxianghe Medical Products (Shanghai) Co., Ltd.	Huamei Lunxianghe Medical
惠州市阳光生物科技有限公司	HuiZhou Sunshine Biological Corporation	HuiZhou Sunshine Biological
葫芦岛爱克生物工程有限公司	Huludao Eyck Biological Engineering Co., Ltd.,	Huludao Eyck Biologica
湖南长沙天地人生物科技有限公司	Hunan Changsha Tiandiren Biotechnology Co., Ltd.	Hunan Tiandiren Biotech
湖南景达生物工程有限公司	Hunan Jingda Bioengineering Co., Ltd.	Hunan Jingda Bioengineering
湖南有色金属控股有限公司	Hunan Nonferrous Metals Holdings Co., Ltd	Hunan Nonferrous Metals
江苏延申生物科技股份有限公司	JiangSu Ealong Biotech Co., LTD.	JiangSu Ealong Biotech
江苏默乐生物科技有限公司	JiangSu Mole BioScience Co., LTD.	JiangSu Mole BioScience
江中制药（集团）有限责任公司	Jiangxi Jiangzhong Pharmaceutical Co., Ltd.	Jiangzhong Pharma
济南百博生物技术有限责任公司	Jinan Baibo Biotechnology Co., Ltd.	Jinan Baibo Biotech
济南杏恩生物科技有限公司	Jinan Jei Daniel Biotech Co., Ltd.	Jinan Jei Daniel Biotech
兰太药业有限责任公司	Lantai Pharmacy Co., Ltd.	Lantai Pharmacy
兰州雅华生物技术有限公司	Lanzhou Yahua Biotech Co., ltd.	Lanzhou Yahua Biotech
南京普朗医用设备有限公司	Nanjing Periong Medical Equipment Co., Ltd.	Nanjing Periong Medical
南京大渊生物技术工程有限责任公司	Nanjing Potomac Bio-Technology Co., Ltd.	Nanjing Potomac Bio-Tech
南京神州英诺华医疗科技有限公司	Nanjing Sinnova Medical Science & Technology Co., LTD.	Nanjing Sinnova Medical
南通市伊士生物技术有限责任公司	Nantong Egens Biotechnology Co., LTD.	Nantong Egens Biotech
天津中新科炬生物制药有限公司	NewScen Coast Bio-Pharmaceutical Co., Ltd	NewScen Coast Bio-Pharma
宁波瑞源生物科技有限公司	Ningbo Rui Bio-technology Co., Ltd.	Ningbo Rui Biotech
宁波四明恩康生物科技有限公司	Ningbo Simingenkang Bio-technology Co., Ltd.	Ningbo Simingenkang Biotech
宁波天润生物药业有限公司	Ningbo Tianrun Bio-Pharmaceutical Co., Ltd.	Ningbo Tianrun Biopharma
华北制药集团有限责任公司	North China Pharmaceutical Group Corp.	North China Pharma
普生（天津）科技有限公司	Pusheng(Tianjin) technology Co., Ltd.	Tianjing Pusheng Tech
凯杰生物工程（深圳）有限公司	Qiagen Biotech (Shenzhen) Co., Ltd.	Shenzhen Qiagen Biotech
其昌达生物高科技（上海）有限公司	Quick Dabiology High-Tech (Shanghai) Co., Ltd	Quick Dabiology
瑞莱生物工程（深圳）有限公司	Relia Biotech (Shenzhen) Co., Ltd.	Shenzhen Relia Biotech
润和生物医药科技（汕头）有限公司	Runbio Biotech (Shantou) Co., Ltd.	Shantou Runbio Biotech
湖南圣湘生物科技有限公司	Sansure Biotech Inc.	Sansure Biotech
陕西瑞凯生物科技有限责任公司	Shaanxi Ruikai Biological Technology Co., Ltd.	Shaanxi Ruikai Biological
山东博科生物产业有限公司	Shandong Biobase Biology Co., Ltd.	Shandong Biobase Biology
山东莱博生物科技有限公司	Shandong LaiBo Biotechnology Co., Ltd.	Shandong LaiBo Biotech
上海阿尔法生物技术有限公司	Shanghai Alpha Biotechnology Co.,Ltd.	Shanghai Alpha Biotech
上海克隆生物高技术有限公司	Shanghai Clone Biotech Co. ltd.	Shanghai Clone Biotech
上海中信国健药业股份有限公司	Shanghai CP Guojian Pharmaceutical Co., Ltd.	CP Guojian Pharma
上海恩康生物科技有限公司	Shanghai Enkang Biology Technology Co., Ltd.	Shanghai Enkang Biology
上海复星佰珞生物技术有限公司	Shanghai Fosun Biolog Biotech Co., Ltd.	Shanghai Fosun Biolog
上海复星医药(集团)股份有限公司	Shanghai Fosun Pharmaceutical (Group) Co., Ltd.	Shanghai Fosun Pharma
上海复旦张江生物医药股份有限公司	Shanghai Fudan-zhangjiang Bio-Pharmaceutical Co.,Ltd.	Fudan-zhangjiang Bio-Pharma
上海浩源生物科技有限公司	Shanghai Haoyuan Biotech Co., Ltd.	Shanghai Haoyuan Biotech
上海华泰医院有限公司	Shanghai Huatai hospital Co., Ltd.	Shanghai Huatai Hospital

上海百岁行药业有限公司	Shanghai Hundreds' Ace Herbal Pharmaceutical Co., Ltd.	Shanghai Hundreds' Ace Herbal
上海科华生物工程股份有限公司	Shanghai Kehua Bio-engineering Co., Ltd.	Shanghai Kehua Bio-engineering
上海科玛嘉微生物技术有限公司	Shanghai Kemajia Biotechnology Co., Ltd.	Shanghai Kemajia Biotech
上海铭源数康生物芯片有限公司	Shanghai Mingyuan Health-digit Biochips Co., Ltd.	Shanghai Mingyuan Health
上海仁度生物科技有限公司	Shanghai Rendu Biotechnology Co., Ltd.	Shanghai Rendu Biotech
上海荣盛生物技术有限公司介绍	Shanghai Rongsheng Bio-Tech Co., Ltd.	Shanghai Rongsheng Biotech
上海汇中细胞生物科技有限公司	Shanghai SemiBio Techonology Co., Ltd.	Shanghai SemiBio Tech
上海申友生物技术有限责任公司	Shanghai Shenyou Bio Technolgy Co.,Ltd.	Shanghai Shenyou Biotech
上海靶点药物有限公司	Shanghai Targetdrug Ltd.	Shanghai Targetdrug
上海联合赛尔生物工程有限公司	Shanghai United Cell Biotechnology Co., Ltd.	Shanghai United Cell
上海奥普生物医药有限公司	Shanghai Upper Bio-Tech Pharma Co.,Ltd.	Shanghai Upper Bio-Pharma
上海万兴生物制药有限公司	Shanghai Wanxing Biological Pharmacy Co., Ltd.	Shanghai Wanxing Biopharma
上海伊华临床医学科技公司	Shanghai Yi-Hua Clinical Medicine Technology Co., Ltd.	Shanghai Yi-Hua Clinical
上海英旻泰生物技术有限公司	Shanghai Yingmintai Biolog Tec Co., Ltd	Shanghai Yingmintai Biolog
上海永华细胞和基因高技术有限公司	Shanghai Yonghua Cell & Gene High Technology Co., Ltd.	Shanghai Yonghua Cell & Gene
上海裕隆生物科技有限公司	Shanghai Yulong Biotech Co.,Ltd.	Shanghai Yulong Biotech
上海锃嘉生物工程有限公司	Shanghai Zenka Biotechnology Co., Ltd.	Shanghai Zenka Biotech
上海泽润生物科技有限公司	Shanghai Zerun Biotechnology	Shanghai Zerun Biotech
上海中西三维药业有限公司	Shanghai Zhongxi Sunve Pharmaceutical Co., Ltd.	Shanghai Zhongxi Pharma
上海之江生物科技股份有限公司	Shanghai Zj Bio-Tech Co.,Ltd.	Shanghai Zj Bio-Tech
上海凯创生物技术有限公司	Shanghaih Chemtron Co., Ltd.	Shanghaih Chemtron
陕西百盛园生物科技信息有限公司	Shanxi Cnbios Teghnology and information Co., Ltd.	Shanxi Cnbios Teghnology
沈阳惠民生物工程有限公司	Shenyang Huimin Biological Engineering Co., Ltd.	Shenyang Huimin Biological
深圳市安群生物工程有限公司	Shenzhen Anqun Biotech Co., Ltd.	Shenzhen Anqun Biotech
深圳市奥克生物技术有限公司	Shenzhen Aokoo Biotechnologies, Ltd.	Shenzhen Aokoo Biotech
深圳华康生物医学工程有限公司	Shenzhen Huakang Biological Medical Engineering Co.,Ltd.	Shenzhen Huakang Biolical
深圳市华美圣科生物工程有限公司	Shenzhen Huamei Shengke Biological Engineering Co., Ltd.	Shenzhen Huamei Shengke
深圳市惠安生物科技有限公司	Shenzhen Huian Bio-Technology Co., Ltd.	Shenzhen Huian Bio-Tech
深圳康生保生物技术有限公司	Shenzhen Kang Sheng Bao Bio-Technology Co., Ltd.	Shenzhen Kang Sheng Bao
深圳康泰生物制品股份有限公司	Shenzhen Kangtai Biological Products Co., Ltd.	Shenzhen Kangtai Biological
深圳市生科源技术有限公司	Shenzhen Mabsky Technology Co., Ltd.	Shenzhen Mabsky Tech
深圳迈瑞生物医疗电子股份有限公司	Shenzhen Mindray Bio-Medical Electronics Co., Ltd.	Shenzhen Mindray Bio-Medical
深圳匹基生物技术开发有限公司	Shenzhen Piji Bioengineering Stock Co.,Ltd.	Shenzhen Piji Bioengineering
深圳市亚辉龙生物科技有限公司	Shenzhen Yhlo Biotech Co.,Ltd.	Shenzhen Yhlo Biotech
深圳市怡百世生物技术有限公司	Shenzhen Yibaishi Biotechnology Co., Ltd.	Shenzhen Yibaishi Biotech
四川迈克生物科技股份有限公司	Sichuan Maker Biotechnology Co., Ltd.	Sichuan Maker Biotech
四川协力制药有限公司	Sichuan Xieli Pharmaceutical Co., Ltd.	Sichuan Xieli Pharma
苏州新波生物技术有限公司	Sym-Bio Life Science Co.,Ltd.	Sym-Bio Life
天津生物芯片技术有限责任公司	Tianjin Biochip Corporation	Tianjin Biochip Co
天津瑞爱金生物科技有限公司	Tianjin Ruiaijin Bio-Tech Co., Ltd.	Tianjin Ruiaijin Bio-Tech
天士力制药集团股份有限公司	Tianjin Tasly Pharmaceutical Co., Ltd.	Tianjin Tasly Pharma
天水市福音医疗电器厂	Tianshui Fuyin Medical Treatment Electrical Appliance Factory	Tianshui Fuyin Medical
潍坊三维生物工程集团有限公司	Weifang 3V Bioengineering Group Co., Ltd.	Weifang 3V Bioengineering
潍坊汉唐生物工程有限公司	Weifang Hightop Biotech Co.,Ltd.	Weifang Hightop Biotech

潍坊市康华生物技术有限公司	Weifang Kanghua Biotech Co., Ltd.	Weifang Kanghua Biotech
威海威高生物科技有限公司	Weihai Weigao Biotechnology Co., Ltd.	Weihai Weigao Biotech
温州市康泰生物科技有限公司	Wenzhou Kangtai Biotechnology Co., Ltd.	Wenzhou Kangtai Biotech
武汉市爱恩地生物技术有限公司	Wuhan Aiengdi Biotechnology Co., Ltd.	Wuhan Aiengdi Biotech
武汉菁华时间科技有限公司	Wuhan Showtime Science and Technology ltd,co	Wuhan Showtime Science
无锡百进生物技术有限公司	Wuxi Baijin Biotechnology Co., Ltd.	Wuxi Baijin Biotech
厦门安普利生物工程有限公司	Xiamen Amplly Bioteh Co.,Ltd.	Xiamen Amplly Bioteh
厦门万泰沧海生物技术有限公司	Xiamen Innovax Biotech Co., Ltd.	Xiamen Innovax Biotech
亚能生物技术（深圳）有限公司	Yaneng Bioscience（Shenzhen）Co.,Ltd.	Shenzhen Yaneng Bioscience
云南司艾特药业有限公司	Yunnan Sh-idea Pharmaceutical Co., Ltd.	Yunnan Sh-idea Pharma
云南沃森生物技术有限公司	Yunnan Walvax Biotech Co., Ltd.	Yunnan Walvax Biotech
浙江夸克生物科技有限公司	Zhejiang Kuake Bioscience Co., Ltd.	Zhejiang Kuake Bioscience
浙江普康生物技术股份有限公司	Zhejiang Pukang Biotechnology Co..Ltd.	Zhejiang Pukang Biotech
浙江天元生物药业有限公司	Zhejiang Tianyuan Bio-Pharmaceutical Co., Ltd.	Zhejiang Tianyuan Bio-Pharma
郑州兰森生物技术有限公司	Zhenghzhou Labscience Co. Ltd	Zhenghzhou Labscience
郑州贝达生物技术有限公司	Zhengzhou Beida Biotechnology Co., Ltd.	Zhengzhou Beida Biotech
郑州博赛生物技术股份有限公司	Zhengzhou Biocell Biotechnology Co.,Ltd	Zhengzhou Biocell Biotech
郑州浪峰生物技术有限责任公司	Zhengzhou Langfeng Biotech Co., Ltd.	Zhengzhou Langfeng Biotech
郑州威可瑞生物科技有限公司	Zhengzhou Vigorous Biotech Co., Ltd.	Zhengzhou Vigorous Biotech
郑州万泰生物科技有限公司	Zhengzhou Wantai Bio-Science & Technology Ltd.	Zhengzhou Wantai Bio-Science
中山生物工程有限公司	Zhongshan Bio-Tech Co., Ltd.	Zhongshan Bio-Tech
珠海市银科医学工程有限公司	Zhuhai Encode Medical Engineering Co., Ltd.	Zhuhai Encode Medical
珠海丽珠试剂股份有限公司	Zhuhai Livzon Diagnostics Inc.	Zhuhai Livzon Diagnostics
珠海美华医疗科技有限公司	Zhuhai Meihua Bio-Medical Technology Co.,Ltd.	Zhuhai Meihua Bio-Medical
珠海赛乐奇生物技术有限公司	Zhuhai Sinochips Biotech Co.,Ltd.	Zhuhai Sinochips Biotech

2. Chinese/English bilingual names for academic or government institutions

Institution name in Chinese	Institution name in English	Abbreviation
中国人民解放军第三零二医院	302 Hospital of the Chinese People's Liberation Army	PLA 302 Hospital
中国人民解放军第四五八医院	458 Hospital of the Chinese People's Liberation Army	PLA 458 Hospital
军事医学科学院	Academy of Military Medical Sciences	
首都医科大学	Capital Medical University	
中南大学	Central South University	
中国农业大学	China Agricultural University	
中国医科大学	China Medical University	
中国医学科学院	Chinese Academy of Medical Sciences	CAMS
中国科学院(简称中科院)	Chinese Academy of Sciences	CAS
中国疾病预防控制中心	Chinese Center for Disease Control and Prevention	China CDC
重庆医科大学	Chongqing Medical University	
大理学院	Dali University	
华东理工大学	East China University of Science and Technology	
复旦大学	Fudan University	
中国人民解放军总医院	General Hospital of the Chinese People's Liberation Army	PLA General Hospital
广西壮族自治区疾病预防控制中心	GuangXi Center for Disease Prevention and Control	Guangxi CDC
广州生物医药与健康研究院(中科院)	Guangzhou Institute of Biomedicine and Health	
广州中医药大学	Guangzhou University of Chinese Medicine	
华中农业大学	Huazhong Agricultural University	
华中科技大学	Huazhong University of Science & Technology	
湖南师范大学	Hunan Normal University	
传染病预防控制所	Institute for Infectious Disease Control and Prevention	ICDC
生物医学研究所(中科院)	Institute of Biological Medicine	
北京生物物理所(中科院)	Institute of Biophysics, CAS	
微生物所(中科院)	Institute of Microbiology	
北京微生物研究所(中科院)	Institute of Microbiology, CAS	
上海巴斯德研究所	Institute Pasteur of Shanghai	
江苏大学	Jiangsu University	
吉林大学	Jilin Univerisity	
昆明植物研究所(中科院）	Kunming Institute of Botany	
昆明动物研究所(中科院)	Kunming Institute of Zoology	
中国卫生部	Ministry of Health of the People’s Republic of China	
中国工业与信息化部	Ministry of Industry and Information Technology of the People’s Republic of China	
南昌大学	Nanchang University	
南京大学	Nanjing University	
南开大学	Nankai University	
中国海洋大学	Ocean University of China	
北京大学	Peking University	
中国人民解放军军需大学	Quartermaster University of the Chinese People's Liberation Army	PLA Quartermaster University

山东大学	Shandong University	
上海药物研究所(中科院)	Shanghai Institute of Materia Medica	
上海有机所(中科院)	Shanghai Institute of Organic Chemistry	
上海交通大学	Shanghai Jiao Tong University	
沈阳药科大学	Shenyang Pharmaceutical University	
四川大学	Sichuan University	
华南植物园(中科院)	South China Botanical Garden	
华南理工大学	South China University of Technology	
东南大学	Southeast University	
南方医科大学 （原第一军医大学）	Southern Medical University (former First Military Medical University)	
中山大学	SUN YAT-SEM University	
香港中文大学	The Chinese University of Hong Kong	
第四军医大学	The Fourth Military Medical University	
第二军医大学	The Second Military Medical University	
第三军医大学	The Third Military Medical University	
香港大学	The University of Hong Kong	
清华大学	Tsinghua University	
中国科学技术大学	University of Science and Technology of China	
武汉病毒研究所(中科院)	Wuhan Institute of Virology	
武汉大学	Wuhan University	
厦门大学	Xiamen University	
浙江大学	Zhejiang University	
郑州大学	Zhengzhou University	

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