

**A STUDY ON INVESTMENT STRATEGY SELECTION FOR BIG BRANDS
OF PHARMACEUTICAL ENTERPRISES**

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ABSTRACT

With the rapid development of national economy, intensified opening up of the pharmaceutical industry, and deepening reform of the medical system, the business environment faced by Chinese pharmaceutical companies is undergoing tremendous changes. As a vital industry to the national economy and people's livelihood, it is of critical significance for pharmaceutical industry and even the health industry that the pharmaceutical industry can correctly assess its own competitive advantages in the face of increasingly fierce competition at home and abroad, and integrate resources to cultivate and enhance its core competitiveness, thus gaining the upper hand in domestic and international competition.

Product is the life-blood of corporate survival. The development of big brand with an annual sales exceeding RMB 1 billion has increasingly become a hot spot for pharmaceutical companies. This study analyzes the strategies and approaches for pharmaceutical companies to select competitive big brands from the perspective of core competitive products of the pharmaceutical companies. Firstly, it analyzes the main elements of core competitiveness of big brands and constructs a big brand evaluation index system through the investigation and screening of specific factors and principal component analysis. The evaluation indicators include factor 1: influence of the pharmaceutical company and sales of the product, including the market acceptance of the drug, the production and supply capacity of the drug, the sales scope of the drug (the domestic sales scope), the market share of the drug, the market growth potential of the drug, the annual sales of the drug over RMB 1 billion, the production scale of the drug manufacturer, and the reputation of the drug manufacturer (including visibility and recognition); factor 2: scale and influence of drug exports, and influence of the domestic drug list, including the drug list, whether the drug is included in the basic drug list or the basic medical insurance list, the sales scope of drug exports, and the annual sales of drug exports; factor 3: R&D value of the drug, including the unit price of the drug, whether the drug has independent intellectual property rights, and the added value of the drug (such as production technology, and appearance, etc.); factor 4: effect of the drug, including the efficacy of the drug (such as effective rate, and cure rate, etc.), and the incidence and harm of

the adverse reaction of the drug; factor 5: special effects of the drug, including whether the drug is for treating difficult diseases, and substitutability of the drug (whether there are similar products with same indications). Levoamlodipine Maleate Tablets (Xuan Ning) produced by CSPC Ouyi Pharmaceutical Co., Ltd., Compound Danshen Dripping Pills produced by Talsly Holding Group, Houltuynia Cordata Injection produced by Shineway Pharmaceutical Group Ltd., and NBP Soft Capsules produced by CSPC Pharmaceutical Limited, which are four big brands certified by the Ministry of Science and Technology, are chosen as the test objects to verify the feasibility and validity of the model.

In view of the increasingly strict safety control over clinical big brands, the incidence of adverse reactions of the big brands has become an important factor in considering and selecting big brands. In this study, a standard game theory model is used to determine the optimized incidence of adverse reaction of big brands, and a game theory equilibrium model of optimized incidence of adverse reactions is constructed.

This study plans to analyze the strategies of pharmaceutical companies for big brand development from four aspects: product, price, distribution and promotion based on the Marketing Theory of 4Ps.

DEDICATION

This dissertation stands as a testament to many years of relentless effort - late nights, crossed time zones, and countless moments where perseverance triumphed over exhaustion. To my colleagues: your trust in our shared vision fueled my resolve. To my family: your sacrifices were the invisible foundation of this achievement.

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CHAPTER 1 PURPOSES AND SIGNIFICANCE

As a college student who graduated in 1987, I was initially assigned to work in a state-owned enterprise. I had a stable job that everyone envied, however was too comfortable to be challenging. Seven years later, I was courageous enough to leave the state-owned enterprise and became a pharmaceutical sales representative. Another six years later, I entered a new battlefield – I founded the Haisco Pharmaceutical Group (with a Chinese name of ‘Hai Si Ke’) with my partners. In the Chinese interpretation, ‘Hai ’ means the ocean, "Si" means the thought, and "Ke" means the science. Taken together, ‘Hai Si Ke ’ represented the company has the mindset like the ocean, and the scientific thoughts always come first. I believed that with the three key elements bearing in the company name, this company can fight against the obstacles along the way and become one of the top pharmaceutical companies in the industry.

As of today, Haisco Pharmaceutical Group has been a public listed company for almost ten years. Compared with other industries, the pharmaceutical industry is highly relevant to the health of the people, as well as the national economy and people's well-being. Therefore, the government regulation to the pharmaceutical industry is relatively strict, and a pharmaceutical enterprise must be in compliance with the national policies and regulations.

The ability to innovate novel drugs is the key to the survival of pharmaceutical companies, especially to develop innovative drugs with promising efficacy and clinical value. ‘Big Brand ’ product often refers to those pharmaceutical products with good efficacy, large market share or growth potential, high added value or pharmaceutical products that has annual sales greater than RMB 1 billion. In order to meet the needs for prevention and treatment of major diseases in China, as well as the development of the pharmaceutical industry, improving the quality of the big brands and selecting the right product to invest became very essential and with great meanings.

On July 20, 2011, the Ministry of Science and Technology issued the “Twelfth Five-Year Plan for Development of Science and Technology” , which made an overall plan for the development of science and technology in China in the next five years. The Plan stated that the implementation of major national science and technology projects will be the top priority of science and technology development. In terms of innovation of major new drugs, the Plan proposed to breakthrough a number of key technologies and production techniques for drug innovation, develop 30 innovative drugs and transform about 200 big brands to form a national drug innovation system with Chinese characteristics, in order to meet people ’s basic drug needs and cultivate and develop the pharmaceutical industry. In addition, 10 big brands should be transformed to meet the basic medical needs for safeguarding life security. In June 2017, the Ministry of Science and Technology issued the “Thirteenth Five-Year Plan for Scientific and Technological Innovation of Traditional Chinese Medicine” , which pointed out the direction for the scientific and technological innovation of traditional Chinese medicine in the next five years. The Plan focused on the secondary development of big brand traditional Chinese medicine. This is also the first development plan for scientific and technological innovation of traditional Chinese medicine in China. In February 2017, at the Special Press Conference on National Major Science and Technology Projects and Innovation of Major New Drugs, the technological transformation of big brands is also listed as a major science and technology project in the “Innovation of Major New Drugs” formulated by the Ministry of Science and Technology. Big brand development not only can bring huge profits to a company, but also can create tax and employment for local government. However, at present, there are less than 200 drugs with annual sales over RMB 1 billion. Lack of big brands and new drugs has become an important factor restricting the construction of China’s drug innovation system.

This study intends to provide a technical indicator system and basic models for the selection of targets for big brand research and development and singling out big brands with large clinical demand, large potential market and reasonable price. Using the Marketing Theory of 4Ps, this study analyzes the basis for investment on big

brands from four aspects which are product strategy, price strategy, distribution strategy and promotion strategy. A quantitative selection model is constructed to provide a scientific basis for selecting high quality, low price, safe and effective big brands for prevention and control of major diseases in China and for enterprises to improve their market competitiveness and the size of related industries.

CHAPTER 2 RESEARCH RESULTS

China's drug consumption and demand will increase significantly due to an aging population, increase in per capita income and enhancement of health awareness. The pharmaceutical industry has good prospects for development and is supported by national policies and finances. According to the National Bureau of Statistics, as of December 31, 2014, China's elderly population over the age of 60 was about 212 million, accounting for 15.5% of the total population, and showed an upward trend. According to the predictions in the "Report on the Development of Aging Industry in China (2014)", by 2050, China's aging population will reach 480 million people. Moreover, China is actively promoting the development of the pharmaceutical industry, is introducing medical reform programs, and is increasing fiscal expenditure on health care. The average growth of fiscal expenditure on health care in the past five years reached 21.1%, and more than RMB 1 trillion was spent on health care at the end of 2014. Health care is closely tied with people's livelihood and public will. For this cause, China will certainly support the development of the pharmaceutical industry to improve people's lives and treatment and improve social harmony.

2.1 Study on the development status and trend of big brands

This study involves the construction and demonstration of economic feasibility analysis models for big brands by combining qualitative research with quantitative research, and literature research with empirical research.

2.1.1 Development status

According to the Pharmaceutical Database (PDB) of China National Pharmaceutical Industry Information Center, there were 124 big brands with an annual sale over RMB 100 million and annual growth rate exceeding 10% in sample hospitals in 2015. In 2016, the figure reached 162, an increase of about 30% compared with 2015, which is a quite considerable growth. Except that two of the big brands were newly included in the database, over 30 big brands were included in the database because of their market size and growth rate.

The statistics of PDB show that there were 330 brands in 2015 and 356 brands in 2016 that had an annual sale over RMB 100 million in sample hospitals. Accordingly, the proportion of drugs with a growth rate of more than 10% increased from 37.5% to 45.5% in the big brands with an annual sale over RMB 100 million. In terms of average growth rate, the proportion of high-growth big brands in 2015 was 20.45%, and the figure was 21.20% in 2016.

2.1.2 Problems in development

Firstly, China has tightened the regulation on big brands for clinical use. On February 24, 2017, the whole medical system has been significantly improved in targeted sampling, timeliness of information disclosure, and standardized problem handling in accordance with the requirements of “the strictest standards, the strictest regulation, the strictest penalties, the strictest accountability” . The National Working Conference on Drug Sampling was held in Chengdu. At the conference, Deputy Director Wu Zhen emphasized that the primary task of drug sampling in 2017 is to arrange quality sampling and exploratory research on 138 big brands with large clinical demand and high risk.

Intensive monitoring on big brands with large clinical demand were carried out throughout the country. In 2016, China Food and Drug Administration (CFDA) issued 586 “Drug Quality Prompts” to 471 drug producers to guide the enterprises to check quality risks, eliminate hidden dangers, and continuously improve product quality. On December 30, 2016, Qinghai Provincial Health and Family Planning Commission issued the “Circular on Printing and Distributing the List of Key Monitored Drugs to Some Class III Medical Institutions in 2016”, which summarized the list of key monitored drugs for some Class III medical institutions in Qinghai. The use of seven types of drugs was intensively monitored. These seven types of drugs were

antibacterial drugs, cardiovascular and cerebrovascular drugs, drugs for digestive system, antineoplastic drugs, traditional Chinese medicine injections, adjuvant drugs, and hormone drugs. The drugs involved in the list included well-known traditional Chinese medicine injections such as Xiyanping Injection, Shenqi Fuzheng Injection, Xueshuantong Injection and Xuesaitong Injection, as well as Lipitor (Atorvastatin Calcium Tablets), Plavix (Clopidogrel Hydrogen Sulphate Tablets) and other big brands. In terms of enterprises involved, this list included AstraZeneca, Sanofi, Roche and other multinational giants as well as well-known domestic enterprises such as Yangtze River Pharmaceutical Group, Harbin Pharmaceutical Group and CR Double-Crane.

On December 19, 2016, Qinghai Provincial Health and Family Planning Commission announced the results of intensive monitoring on drugs. According to the statistics: from January to August, the expenditure on key monitored drugs decreased by 3.61% compared with the same period in 2015. Among the six hospitals affiliated to the Commission, including Qinghai Provincial People's Hospital, the average decrease was 14.6%, with the maximum decrease being 51.2%.

Secondly, the future of big brand traditional Chinese medicine injections looks daunting. The *Annual Report for National Adverse Drug Reaction Monitoring (2016)* issued by CFDA stated that, top five formulas of Chinese patent medicine in suspected drugs involved in the adverse reactions/incident reports of traditional Chinese medicines (by the number of cases) are drugs for invigorating blood circulation and eliminating stasis in blood-regulating formula (29.7%), heat-clearing and detoxicating drugs in heat-clearing formula (9.7%), Qi supplementing and Yin nourishing drugs in tonic formula (8.5%), cool and refreshing drugs in formula for resuscitation (8.4%), and cold-pungent and diaphoretic drugs in superficial-relieving formula (6.0%). By the distribution of administration routes, the proportion of injections in the traditional Chinese medicine adverse reactions/incidents in 2016 was 53.7%, which was 2.6 percentage points higher than the 51.3% in 2015.

At the same time, regulation has also tightened, which will block the sales of many big brand Chinese patent medicines. In recent years, China has adopted a number of specific measures for medical reform, including reducing the percentage of drug expenditure and strengthening the regulation on adjuvant drugs. In particular, several provinces have introduced the list of monitored adjuvant drugs, many of which are big brand Chinese patent medicine injections.

In addition, the restrictions and regulation on Chinese patent medicine injections have also been fully reflected in the new National Drug Reimbursement List (NDRL) issued in 2017. Compared with the previous NDRL, the traditional Chinese medicine injections indicated with restrictions on clinical drug reimbursement are retained in the new NDRL, and new clinical drug reimbursement restrictions for many traditional Chinese medicine injections have been added. See Table 2 for details.

Table 1 Big brand traditional Chinese medicine injections in 2016 adverse drug reaction monitoring report

| Rank | Product Name | Therapeutic Field | Manufacturer | 2016 Annual Income (RMB 100 million) | Growth |
|------|---|--|--|---|--------|
| 1 | Danhong Injection | Cardiovascular and cerebrovascular diseases | Shandong Danhong Pharmaceutical Co., Ltd | 44.00 | 5.55% |
| 2 | Xiyanping Injection | Respiratory diseases | Qingfeng Pharmaceutical Group | 25.00 | 5.00% |
| 3 | Kang'ai Injection | Neoplastic diseases | Changbaishan Pharmaceutical Co., Ltd | 21.51 | 2.21% |
| 4 | Xingnaojing Injection | Cardiovascular and cerebrovascular diseases | Wuxu Shanhe Group Co., Ltd | 18.00 | 5.00% |
| 5 | Shenqi Fuzheng Injection | Neoplastic diseases | Livzon GroupLimin Pharmaceutical Factory | 16.80 | 9.31% |
| 6 | Kanglaite Injection | Neoplastic diseases | Zhejiang Kanglaite Pharmaceutical Co., Ltd | 15.00 | 10.00% |
| 7 | Tanreqing Injection | Respiratory diseases | Shanghai Kaibao Pharmaceutical Co., Ltd | 14.07 | 8.44% |
| 8 | Xueshuantong for Injection | Cardiovascular and cerebrovascular diseases | Wuzhou Pharmaceutical (Group) Co., Ltd | 13.83 | 33.49% |
| 9 | Reduning Injection | Respiratory diseases | Jiangsu Kanion Pharmaceutical Co., Ltd | 12.33 | 1.54% |
| 10 | Xuebijing Injection | Respiratory diseases | Tianjin Chase Sun Pharmaceutical Co., Ltd | 11.24 | 18.29% |
| 11 | Xueshuantong for Injection (lyophilized) | Cardiovascular and cerebrovascular diseases | Harbin Zhenbao Pharmaceutical Co., Ltd | 10.50 | 11.46% |

Table 2 Restrictions on the use of traditional Chinese medicine injections in the 2017 NDRL

| Drug Name | Restrictions for Reimbursement |
|--------------------------|---|
| Shenqi Fuzheng Injection | Restricted to be used simultaneously with radiotherapy and chemotherapy for lung cancer and gastric cancer |
| Guanxinning Injection | Restricted to Class II or higher rated medical institutions |
| Safflower Injection | Restricted to Class II or higher rated medical institutions and patients with clinical evidence of emergency rescue |
| Kudiezi Injection | Restricted to Class II or higher rated medical institutions and patients with clear coronary heart disease and angina pectoris |
| Kuhuang Injection | Restricted to Class II or higher rated medical institutions |
| Mailuoning Injection | Restricted to Class II or higher rated medical institutions |
| Reduning Injection | Restricted to Class II or higher rated medical institutions and patients with serious diseases |
| Shenkang Injection | Restricted to Class II or higher rated medical institutions and patients with chronic renal failure |
| Shuxuetong Injection | Restricted to Class II or higher rated medical institutions and patients in the acute stage of ischemic cerebrovascular disease |
| Tanreqing Injection | Restricted to Class II or higher rated medical institutions and severely ill patients |
| Xiyanping Injection | Restricted to Class II or higher rated medical institutions and severely ill patients |
| Xiangdan Injection | Restricted to Class II or higher rated medical institutions |

2.1.3 Development trend of big brands

Firstly, adjustment in the new NDRL will stimulate the cultivation of new big brands. Adjustments in the 2009 NDRL have encouraged a number of big brands such as entecavir, mouse nerve growth factor, rosuvastatin, edaravone and butylphthalide. In response to the adjustments in the new NDRL, the promulgation of 2017 NDRL will inevitably drive the emergence of a number of new big brands. According to the data from sample hospitals, 25 drugs newly added in the new NDRL are selected for analysis, involving more than 60 pharmaceutical companies. Domestic enterprises mainly include CSPC, Hengrui Pharma, Hansoh Pharma, Qilu Pharma, CPGJ, Betta Pharma, Chiatai Tianqing Pharma, Guizhou Baiqiang Pharmaceutical and Livzon Group while foreign companies mainly include Novartis, AstraZeneca, and Lilly.

Antineoplastic drugs: main products include pemetrexed, imatinib, gefitinib, doxorubicin, ectinib, compound cantharidate vitamin B6 and decitabine. According to the statistics from sample hospitals, in 2016, the sales of antineoplastic drugs and shares of enterprises among the top were shown in the Table 3.

Main products for digestive system include palonosetron, ilaprazole and dolasetron. According to the statistics from sample hospitals, it is estimated that the sales of palonosetron will be RMB 1.13 billion in 2016 and there are 9 producers, among which, Qilu Pharmaceutical (Hainan) accounts for 44.8%, Chiatai Tianqing Pharma accounts for 22.4%, Jiuyuan Pharma accounts for 17.1%, and the other six producers account for 15.7% in total. The sales of ilaprazole are predicted to be RMB 120 million. Ilaprazole is the exclusive product of Livzon Group. The sales of dolasetron are predicted to be RMB 120 million. Dolasetron is the exclusive product of Liaoning Haisco Pharma.

Main products for nervous system include butylphthalide and pregabalin. Main product for psychotic disorders is dexmedetomidine. According to the statistics from sample hospitals, it is estimated that the sales of butylphthalide in 2016 will be RMB 680 million. Butylphthalide is the exclusive product of CSPC. The sales of capsules will be RMB 440 million, while that of injections will be RMB 240 million. The sales of pregabalin will be RMB 42.67 million yuan. Currently there are only 2 producers of pregabalin in which Pfizer accounts for 87.0%, and Chongqing Succeway Pharma accounts for 13.0%. It is estimated that the sales of dexmedetomidine in 2016 will be RMB 484 million and there are 4 producers, among which the top three producers are Hengrui Pharma which accounts for 90.5%, Guorui Pharma which accounts for 5.6%, and Nhwa Pharma which accounts for 3.7%.

Table 3 Big brand products of anti-neoplastic drugs

| | Sales (RMB 1 billion) | Number of producers | Leading enterprise and proportion |
|--|-----------------------------|------------------------|---|
| Pemetrexed | 11.3 | 12 | Jiangsu Pharma Qilu |
| Imatinib | 11.3 | 4 | Novartis Hansoh (9.9%), Tianqing |
| Gefitinib | 3.2 | 2 | AstraZeneca (89%), and Qilu Pharma (11%) |
| Doxorubicin | 2.82 | 8 | CSPC (52.3%), Shanghai Fudan Zhangjiang Pharma (38.2%),and Changzhou Kinyond Pharma (8.5%) |
| Ectinib | 2.4 | 1 | Betta Pharma (%) |
| Compound cantharidate vitamin B6 | 1.64 | 1 | Guizhou Baiqiang Pharma |
| Decitabine | 0.65 | 6 | Pharmachemie (54. 1%), Chiatai Tianqing (28.7%), and Hansoh (9.4%) |

Main anti-infective drugs include tigecycline, tenofovir and ertapenem. According to the statistics from sample hospitals, it is estimated that the sales of tigecycline in 2016 will be RMB 288 million and there are 7 producers, among the top three producers, Wyeth accounts for 33.6%, Hansoh Pharma accounts for 25.5%, and Hisun Pharma accounts for 19.5%. The sales of tenofovir will be RMB 110 million and there are two producers which are Glaxo and Chengdu Brilliant Pharmaceutical approved in November 2016. The sales of ertapenem will be RMB 44.43 million. Ertapenem is the exclusive product of MSD.

Main products of immunomodulators include recombinant human type II tumor necrosis factor receptor-antibody fusion protein and PEGylated recombinant human granulocyte stimulating factor. According to the statistics from sample hospitals, it is estimated that the sales of recombinant human type II tumor necrosis factor receptor-antibody fusion protein in 2016 will be RMB 288 million and there are 3 producers, in which Shanghai CP Guojian Pharma accounts for 94.1%, Shanghai Celgen Pharma accounts for 5.8% and Hisun Pharma accounts for 0.1%. The sales of PEGylated recombinant human granulocyte stimulating factor are predicted to be RMB 110 million and there are 2 producers, in which GeneLeuk Biopharmaceutical accounts for 72.0% and Qilu Pharma accounts for 28.0%.

Main drugs for cardiovascular system include pitavastatin, olmesartan and levosimendan. According to the statistics from sample hospitals, it is estimated that the sales of pitavastatin in 2016 will be RMB 157 million and there are 5 producers, among which the top three are CR Double-Crane Pharma which accounts for 75.1%, Kowa Pharma which accounts for 16.7%, and Wanbang Pharma which accounts for 5.4%. The sales of Olmesartan are predicted to be RMB 109 million and there are 4 producers, among which the top three are Daiichi Sankyo Pharma which accounts for 78.9%, Beijing Wansheng Pharma which accounts for 15.3% and Shanghai Sine Pharma which accounts for 3.4%. The sales of levosimendan are predicted to be RMB 57.24 million and there are 2 producers, in which Qilu Pharma accounts for 96.6% and Chengdu Shengnuo Pharma accounts for 3.4%.

Main products for blood and hematopoietic system include polysaccharide iron and argatroban. Main product for endocrine and metabolic regulation is terlipressin and main product for bone and muscle drugs is febuxostat. According to the statistics from sample hospitals, it is estimated that the sales of polysaccharide iron in 2016 will be RMB 102 million and there are 2 producers which are UCB that accounts for 55.1% and Qingdao Growful Pharma that accounts for 44.9%. The sales of argatroban will be RMB 57.54 million and argatroban is the exclusive product of TIPR Pharmaceutical Responsible Co., Ltd. Among the drugs for endocrine and metabolic regulation, the sales of terlipressin will be RMB 96.57 million and there are 2 producers which are Shenzhen Hybio Pharma which accounts for 75.0% and Ferring Pharma which accounts for 25%. The sales of bone and muscle medications will be RMB 64.24 million and there are 3 producers which are Jiangsu Wanbang Pharma which accounts for 61.0%, Hengrui Pharma which accounts for 31.6%, and Hangzhou Zhuyangxin Pharma which accounts for 7.3%.

Secondly, big brand first generic drug will become a new hot spot. The list of first generic drugs proposed for priority evaluation issued on July 21, 2017 will benefit 22 drugs of 14 pharmaceutical companies. The dividend of drug evaluation reform is being released. The Center for Drug Evaluation (CDE) issued the “Basic Principles for Priority Evaluation of First Generic Drugs” and the list of 22 “first generic drugs” proposed for priority evaluation and solicited public opinions. This is the further implementation of the “Opinions on Priority Evaluation and Approval for Resolving the Backlog of Drug Registration Applications” issued on February 26.

As of July 22, 2016, CDE has announced a total of 79 acceptance numbers for 7 batches of drugs that have been included in the priority evaluation. According to the statistics, in the list of drugs proposed for priority evaluation, 60 acceptance numbers are granted to local pharmaceutical companies. Among which, Hengrui Pharma has 6 acceptance numbers, which are dexmedetomidine hydrochloride nasal spray, caspofungin acetate, caspofungin acetate for injection, fondaparinux sodium injection, gadobutrol injection, and paricalcitol injection. Qilu Pharma has 5 acceptance

numbers, which are gefitinib, gefitinib tablets, brinzolamide eye drops, lotepredorone tobramycin eye drops and tacrolimus eye drops. Hansoh Pharma has 4 acceptance numbers which are bortezomib, bortezomib for injection, micafungin sodium and micafungin sodium for injection. Chiatai Tianqing Pharma has 4 acceptance numbers which are budesonide formoterol powder inhaler, linezolid injection, ganirelix acetate injection and disodium citrate injection. Most of the above-mentioned enterprises have comprehensive strength and strong research and development strength.

In terms of the drugs of multinational pharmaceutical companies included in the list for priority evaluation, 19 acceptance numbers granted to 11 multinational pharmaceutical companies may enter the “fast lane”, and each enterprise has 1 to 2 acceptance numbers. These include asunaprevir soft capsules and dalavivavir hydrochloride tablets by Bristol-Myers Squibb, oral solution of atomoxetine hydrochloride by Lilly, tocilizumab injection by Roche and afatinib tablets by Boehringer-Ingelheim.

In the therapeutic field, pediatric drugs were first listed for priority evaluation in early 2017. The first batch of drugs for priority evaluation issued by the CDE were mainly pediatric drugs. Five pediatric drugs were included in the list for priority evaluation. At present, 10 acceptance numbers for pediatric drugs have entered the “fast lane” for drug evaluation. Specialized drugs such as antineoplastic, anti-hepatitis C and anti-infective drugs are also hot areas that will be included in the priority evaluation.

22 first generic drugs were included in the list of “first generic drugs” for priority evaluation issued on July 21, 2017, and the first generic drugs of big brand were the latest hotspots. The priority evaluation of first generic drugs provides the pharmaceutical companies with greater market imagination. In terms of the declared category, there are 22 acceptance numbers in the list of first batch of “first generic drugs”, including two products in category 3.1, which are tenofovir disoproxil fumarate capsules by Fujian Cosunter Pharma and dronedarone hydrochloride tablets

by CSPC. There is also one product in category 5, which is rivastigmine sulphate tablets by Jiangsu Wante Pharma. The remaining 19 products are in category 6.

In terms of the declared dosage form, there are 6 injections that have been included in the list of “first generic drugs” for priority evaluation, which are gadobutrol injection, paricalcitol injection, disodium citrate injection, ganidiacetate injection, linezolid injection and fondaparinux sodium injection. The last two injections are big brands in the domestic market. In addition, there are 10 products in external dosage forms such as eye drops, ointments, gel creams and creams, among which fluticasone propionate nasal spray, compound flumetasone ointment and brinzolamide eye drops are big brands in the domestic market.

In terms of declared enterprises, there are four enterprises which have three products that have been included in the list of “first generic drugs” for priority evaluation. These products are fondaparinux sodium injection, gadobutrol injection, paricalcitol injection by Hengrui Pharma, brinzolamide eye drops, loteprednol etabonate and tobramycin eye drops and tacrolimus eye drops by Qilu Pharma, linezolid injection, gadoxetic acid disodium injection, and ganirelix acetate injection by Chiatai Tianqing Pharma, and travoprost eye drops, bimatoprost eye drops and trefotimo eye drops by Hubei Yuanda Everyday Bright Eyes Pharma.

Hengrui Pharma, Qilu Pharma and Chiatai Tianqing Pharma are three companies with strong R&D strengths and have three products included the list of “first generic drugs” for priority evaluation respectively. Linezolid injection, a generic drug of Chiatai Tianqing from Fresenius Kabi, fondaparinux sodium injection, a generic drug of Hengrui Pharma from GlaxoSmithKline, and brinzolamide eye drops, a generic drug of Qilu Pharma from Alcon performed well on the market.

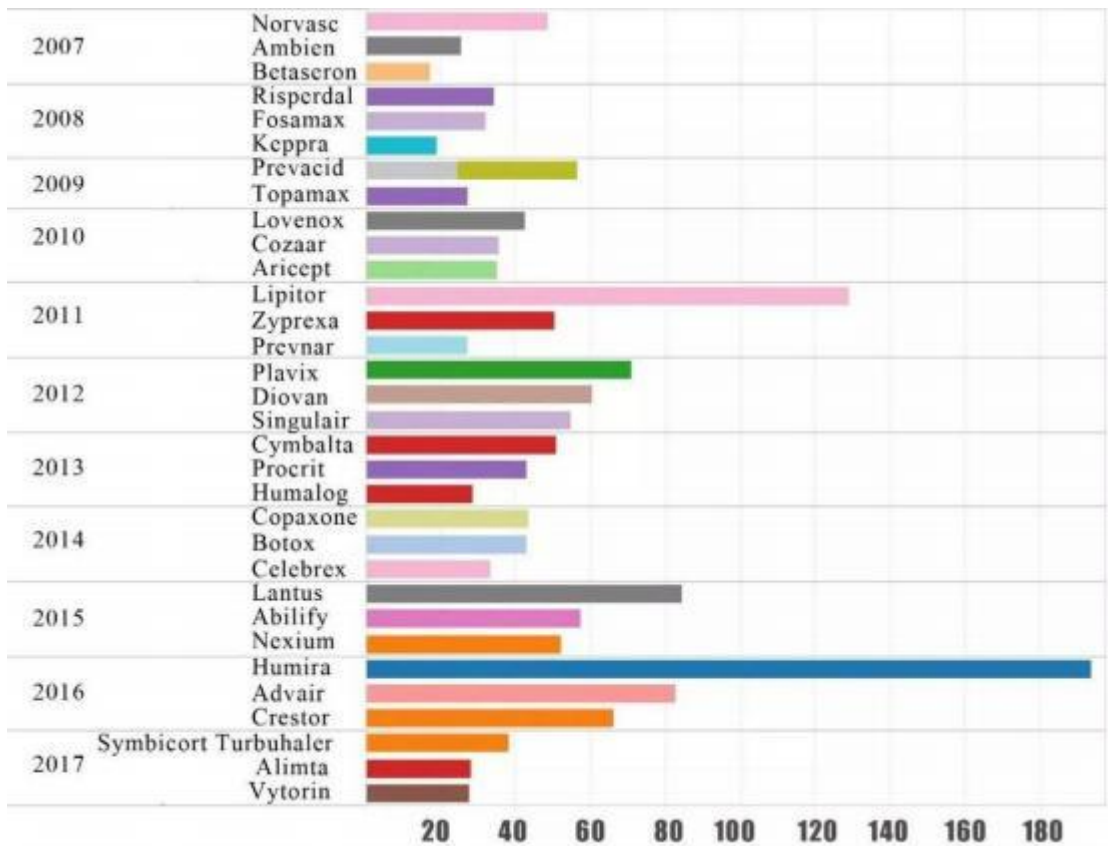
Thirdly, patent expiration of international super blockbuster drugs provides an opportunity for the cultivation of new big brands. In the pharmaceutical field, significant changes may occur in 10 years. During this period, some super “blockbusters” may lose patent protection, which often forces large pharmaceutical

companies to fully cope with the competition brought by low-cost generic drugs. In the past 10 years, there were many global best-selling products that have lost patent protection.

Evaluate, a life sciences business intelligence company, lists the top 10 best-selling drugs that have lost patent protection since 2007 (ranked based on the estimated cumulative sales from the time of launch to 2022). The cumulative sales of these 10 drugs will reach USD 915 billion. Among them, Humira by AbbVie is a patent expired drug with the highest cumulative sales (from the time of launch to 2022) which is USD 179 billion.

Table 4 List of ‘first generic drugs ’ proposed for priority evaluation

| S/N | Acceptance No | Drug Name | Applicant |
|-----|---------------|--|---|
| 1 | CYHS1100050 | Travoprost Eye Drops | Hubei Yuanda Everyday Bright Eyes Pharmaceutical Co., Ltd. |
| 2 | CYHS1001110 | Fluticasone Propionate Nasal Spray | Shandong Jingwei Pharmaceutical Group Co., Ltd. |
| 3 | CYHS1200320 | Linezolid Injection | Chitai Tianqing Pharmaceutical Group Co., Ltd. |
| 4 | CYHS1200814 | Gadobutrol Injection | Jiangsu Hengrui Pharmaceutical Co., Ltd. |
| 5 | CYHS1200320 | Cabalatin Ditartrate Tablets | Jiangsu Wante Pharmaceutical Co., Ltd. |
| 6 | CYHS1200781 | Cetrorelix Acetate Powder for Injection | Shenzhen Hybio Pharmaceutical Co., Ltd. |
| 7 | CYHS1201399 | Bimatoprost Ophthalmic Eye Drops | Hubei Yuanda Everyday Bright Eyes Pharmaceutical Co., Ltd. |
| 8 | CYHS1300223 | Fondaparinux Sodium Injection | Jiangsu Hengrui Pharmaceutical Co., Ltd |
| 9 | CYHS1301372 | Paricalcitol Injection | Jiangsu Hengrui Pharmaceutical Co., Ltd. |
| 10 | CYHS1301560 | Compound Flumetasone Ointment | Chengdu Mingri Pharmaceutical Co., Ltd. |
| 11 | CYHS1301621 | Calcipotriol Betamethasone Ointment | Jiangsu Sempoll Pharmaceutical Co., Ltd. |
| 12 | CYHS1300931 | Brinzolamide Eye Drops | Qilu Pharmaceutical Co., Ltd. |
| 13 | CYHS1301070 | Loteprednol Etabonate and Tobramycin Eye Drops | Qilu Pharmaceutical Co., Ltd. |
| 14 | CYHS1302063 | Tacrolimus Eye Drops | Qilu Pharmaceutical Co., Ltd. |
| 15 | CYHS1400157 | Tenofovir Fumarate Dipifurate Capsules | Fujian Cosunter Pharmaceutical Co., Ltd. |
| 16 | CYHS1400909 | Acetylcysteine Solution for Inhalation | Hunan Warrant Pharmaceutical Co., Ltd. |
| 17 | CYHS1401893 | Clobetasone Butyrate Ointment | Chongqing Huapont Pharmaceutical Co., Ltd. |
| 18 | CYHS1401461 | Trefotimo Eye Drops | Hubei Yuanda Everyday Bright Eyes Pharmaceutical Co., Ltd. |
| 19 | CYHS1500266 | Gadolinium Sebacate Disodium Injection | Chitai tianqing Pharmaceutical Group Co., Ltd. |
| 20 | CYHS1500865 | Gandrake Acetate Injection | Chitai tianqing Pharmaceutical Group Co., Ltd. |
| 21 | CYHS1500143 | Dronedarone Hydrochloride Tablets | CSPC Ouyi Pharmaceutical Co., Ltd.; CSPC Zhongqi Pharmaceutical |
| 22 | CYHS1501213 | Loxolofen Sodium Gelatin Capsule | Hunan Jiudian Pharmaceutical Co., Ltd. |



Peak sales (USD 100 million)



Figure 1 Blockbuster drugs lost patent protection during 2007-2017

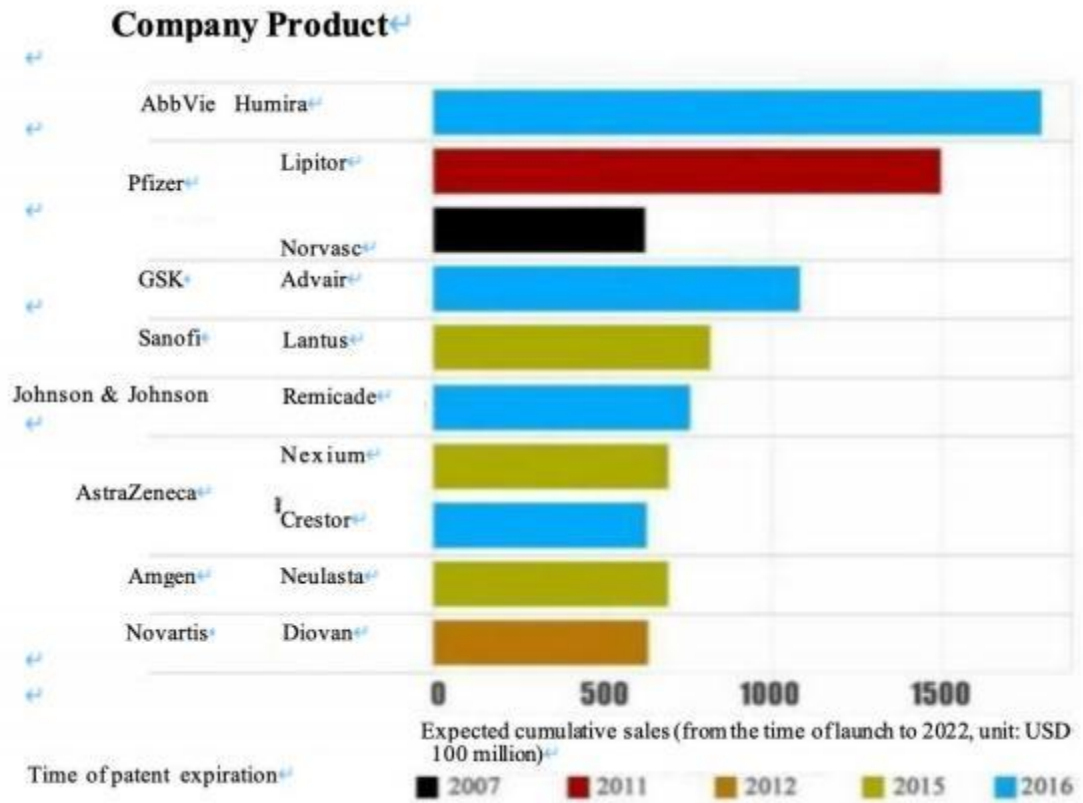


Figure 2 Top 10 best-selling drugs lost patent protection in the last 10 years

2.2 Theoretical basis

For an enterprise, the cultivation process of big brand can be defined as a process that after several years of cultivation, a product with annual sales of RMB 5 million becomes a product with annual sales of RMB 1 billion. For this reason, sales above a certain value become the most direct indicator of a big brand. This process has been experienced by many companies. Many successful cases have been accompanied by the release of a large number of academic achievements and huge national and local support funds. For this reason, some in the industry believe that big brands are cultivated relying on the government or researchers in colleges and universities. So, who should be the subject of big brand cultivation?

Theoretically speaking, an enterprise, as the initiator and goal setter of big brand cultivation should be the subject of big brand cultivation as well as the plan maker and implementer. However, should the enterprise bear all investment risks in the cultivation process? Government or university should also bear key responsibilities in the process of big brand cultivation. In this case, how should the enterprise weigh the division of labor of each subject in order to avoid greater risks? These are the problems that should be addressed.

2.2.1 Introduction to the theory of value investing

The theory of value investing was created by Graham, who believed that securities have intrinsic value and the price fluctuates around the value, and that the intrinsic value can be measured in a certain way. In the long run, the stock price will regress to its “intrinsic value” . When trading securities, one should buy when the market price is lower than the intrinsic value and sell when the price is higher than the intrinsic value. The intrinsic value of a product depends on the future development prospects of the company’s products and the profit generated for shareholders. Although in the

short term, the market price of the stock will deviate from the intrinsic value as price is affected by various external factors, it will regress to its intrinsic value in the long term. Value investing is based on three assumptions: first, the factors affecting the stock price are diversified and unpredictable. The influence of the same factor is not the same at different times and the synergy of these factors forms the market price; second, although the market price is unpredictable, the corresponding object of many securities has stable value; and third, when the market price of the stock is significantly lower than its intrinsic value, there will be a return, that is, there may be return on value and partial premium. The difference between value and price is called “margin of safety” by Graham, which is generally between 1/3 and 1/2 of the intrinsic value.

In this theory, the key is how to measure the intrinsic value. In the measurement of intrinsic value, John B. Williams has made important contributions. In this study, we borrow the theory of value investing to transform the subject from the enterprise into the main product of the enterprise, and assume that the theoretical basis is the same.

2.2.2 Factors of value investing

The “top-down” method is a common method for value analysis of a product. This method first analyzes the macroeconomic environment and the industry environment and at last analyzes the specific product which is the micro subject. Firstly, macro environment is analyzed, which focuses on the analysis of macroeconomic environment and economic growth factors and is background and a premise of industry analysis. Then, based on macro analysis, the industry development direction, product supply and market capacity are analyzed. Based on the above, a complete analysis and judgment of the product itself is carried out, including the financial conditions, business conditions and future prospects.

Firstly, analysis of macroeconomic factors. The macro economy is a systematic factor, and most products will be affected by the macro economy. The operation and

development of the products is closely related to the macro economy, especially in the context of economic globalization. The growth of product value depends on the stable growth of the macro-economy, and the growth of product value also promotes the improvement of the macro environment, forming a bidirectional interaction relation. Improvements in the overall operation of the products are also conducive to promoting macroeconomic growth. Macroeconomic cyclical fluctuations will affect the value of products to a certain extent, resulting in obvious fluctuations in stock price. Macro economy and stock price are positively correlated: as the macro economy improves, the stock price will be more likely to rise, while in the face of economic downturn, if there is insufficient support from business performance, the stock price will be more likely to decline. Changes between the stock market and the macroeconomic cycle may not be synchronized, but the two are still closely related.

Secondly, analysis of industry factors. Industry analysis is the link between the macro environment and the micro product. The industry prosperity is an important factor for judging the investment value of listed products. The weighted average growth rate of each enterprise in the industry is equal to the growth rate of the industry, and the weighted average growth rate of each industry is equal to the growth rate of GDP. Therefore, the industry prosperity can also reflect the external environment of the product, the overall profit margin of the industry, and the growth space and trends of the industry. These are more informative for investors.

Thirdly, analysis of micro factors. According to the theory of value investing, the investor should buy the stock when the market price of a product is lower than its intrinsic value. The key for investors to gain profit and excess returns is to accurately assess the intrinsic value of the company. On this basis, the difference between market price and intrinsic value can be compared to make investment decisions. For microscopic product, there are two important factors that need to be measured: one is the operation and management capabilities of the product, and the other is the future profitability of the product. This requires specific analysis on the product's operating conditions, financial capabilities, core competencies, managers, and so on.

2.2.3 Integration of marketing theory of 4Ps and Theory of Value

In the following section, we'll proceed to explore all the possibilities using the Marketing Theory of 4Ps, the most classical theory in marketing. 4Ps refer to a mix of four elements including product, price, promotion and placement. This theory, coined by Prof. E. Jerome McCarthy from the University of Michigan in 1960, was known as "a simplified set of factors for market planning that is easy to remember and disseminate."

Product includes core product, physical product and augmented product. A product, in the broad sense, can be either a tangible item or intangible service, technology, knowledge or intellect.

There are many pricing methods, including competitive pricing, cost-plus pricing, target-return pricing and market-niche pricing. All these methods are targeted for converting a product into an exchangeable commodity. The primary goal of an enterprise is to make a profit, so a balance between marketing efficiency and business efficiency is important for pricing considerations. Promotion in the conventional sense includes popularization, advertising, public relations and sales promotion. These methods are widely applied in marketing. Placement refers to the marketing path a product goes from the manufacturer to the consumer or end user. General consumer goods typically go through agents and wholesalers before landing at shopping malls or retail stores.

The strategies for pharmaceutical companies to make investment decisions on blockbuster drugs should also be established from the 4Ps standpoint.



Figure 3 Structure of Marketing Theory of 4Ps

(1) Product strategy

A product is more competitive if it creates more values for customers. The customer value of pharmaceuticals lies in clinical efficacy. A company attaching great importance to improving clinical efficacy is doomed to invest heavily and take a high risk. Chemical drugs often have clearly-defined ingredients, but how to identify and synthesize effective compounds will cost much. As to risks, except the uncertainty in identifying and synthesizing compounds, another critical risk is that a used-to-be successful drug might be soon replaced by other alternatives owing to the development of drug discovery. Then, how should a pharmaceutical company scientifically choose target alternatives to be developed?

(2) Price strategy

The public welfare characteristics of pharmaceuticals and relevant medical services make their prices extremely sensitive. Of all the rival products sharing the same generic name, the one sold at a lower price would be more competitive in the market, which could not be better reflected in province-level pharmaceuticals purchase by public bidding. In the field of pharmaceutical circulation, Weikangling Capsule and Calcium Carbonate/ Vitamin D3 Tablet is a typical case of pharmaceuticals that capture market with low price and high quality. Companies in seek of breakthroughs in pricing must always bear in mind that pharmacy is about manufacturing but not

merely pharmaceuticals. Then howThus they should optimize the manufacturing technique, improve the productivity, lower the cost and determine a reasonable price for blockbuster drugs.

An overseas scholar Sairenchill asserted that most members of OECD report an increasing total expenditure on health (ETH) as a share of GDP (%). In America, the spending on treatment of Crohn's disease reaches as much as USD 6.3 billion yearly. Indeed, soaring medical cost is a common issue facing all countries. And drug cost, as an integral part of health expenditures, is trending upward worldwide and is growing faster than GDP. Hence, it is imperative to explore effective ways to control drug cost. Reasonable pricing for pharmaceuticals will not only drive the innovation and sustainable development of the pharmaceutical industry but also lower the drug cost and relieve consumers ' financial burden to some extent. Commodity price is nothing but the monetary expression of value, and the price fluctuates around the value with supply and demand of commodities. So, it is not that a lower price is always better; instead, a reasonable price must be in line with the pharmaceutical's price. After the drug pricing reform came up, most drugs can be priced by manufacturers independently based on production cost and market supply and demand. In fact, cost-based pricing is nothing wrong. But due to an unreasonable cost structure, inadequate supervision over drug price and other problems, drug price cannot truthfully reflect its value in most cases. Therefore, more and more countries try to determine drug prices around their values. Throughout the ages, some sophisticated pricing mechanisms have been developed for drugs at home and abroad, including free pricing, profit-driven pricing, reference pricing, international reference pricing, cost-driven pricing, value-based pricing, etc. Each pricing mechanism played an important role at particular places in a given period. Nowadays, value-based pricing is gradually dominating drug price control in foreign countries.

In the UK, branded drugs and generic drugs have always been priced differently. Specifically, the prices of branded drugs are controlled by the Pharmaceutical Price Regulation Scheme (PPRS), allowing pharmaceutical companies to determine prices for new drugs independently but requiring that the drugs be sold to the National

Health Service (NHS) at a profit margin of 17%-21%. When the real net profit is higher than 40% of the target profit, the manufacturer must lower the price or return the excess profits to the Department of Health; when the real net profit is only 40% or less of the target profit, the manufacturer may increase the price. As it turns out, PPRS, as a voluntary participation-based regime, does to some extent control UK's drug prices, but it also discourages pharmaceutical companies from innovating. Besides, when the Department of Health and pharmaceutical companies were negotiating over PPRS affairs, they mainly considered pharmaceutical companies' cost and profit but ignored drugs' efficacy, giving rise to the risk associated with price-value inconsistency in NHS-covered drugs. Seeing this, the Office of Fair Trading (OFT) proposed in 2007 that the PPRS should shift from the current profit-driven pricing mechanism to a value-based pricing mechanism.

Value-Based Pricing (VBP) is a pricing strategy which sets the price of a drug at the threshold of willingness-to-pay (WTP) for a particular disease according to the drug's clinical treatment value and relevant cost. It is targeted at the drug's efficacy rather than its novelty or features in order to eliminate the room for low efficacy. Under the VBP strategy, maximum prices are set for post-market drugs and new drugs based on the drugs' value, which reflect the efficacy brought by the drugs. The top priority of VBP is to measure the drug value which primarily evaluates the drug's clinical efficacy and cost-effectiveness based on the evaluation methodology in pharmacoeconomics. Clinical efficacy is mainly assessed by the National Institute for Health and Clinical Excellence (NICE) and the Scottish Medical Coalition (SMC) according to Quality Adjusted Life Years (QALYs). The result will have a direct bearing on whether the drug can enter the list of NHS recommended drugs.

In order to maximize the value of NHS Fund, NICE and SMC should set an incremental cost-effectiveness for each drug, typically at £ 20,000-30,000. But for the drugs indicated for serious diseases, a higher threshold may be set to reflect a higher clinical efficacy. The VBP strategy helps to bridge the gap between industrial enterprises and customers and improve enterprises' profitability and value creation. But some scholars argue that VBP is not suitable for assessing the price level

determined by pharmaceutical companies; instead, it must be used as a benchmark for consumers to decide whether a drug is worth to buy.

When a drug's actual price is higher than the value-based pricing, the pharmaceutical company will not volunteer to adjust the price, but sales decline will force the company to lower the price. Researchers have proved that the introduction of VBP may ease consumers' financial burden and in turn release financial resources to meet other medical demands, but there is still a long way to go. When the UK, Germany and other world-leading pharmaceutical markets delayed the introduction of VBP, the optimistic feelings about VBP seem to be fading away. It not only weakens VBP's potential of being established as a universal methodology but is also expected to cause snowball effect in ministates. For these reasons, it is not the right time to introduce VBP.

In Japan, the health expenditure per capita is low and drug cost is placed under strict control, which is mainly attributable to a complete set of drug pricing management system. The Ministry of Health, Labour and Welfare (MHLW) is responsible for centralized control of drug prices, which practices government pricing for all the reimbursed prescriptions and different pricing for new drugs, branded drugs and generic drugs. Among them, new drugs are priced using a strategy combining the efficacy comparative (vs. generic drug) pricing, cost-based pricing and international reference pricing: For a new drug developed out of a generic drug but with a high level of novelty, calculate the generic drug's daily treatment cost first to determine the new drug's unit cost; and then, establish the calculation method and rate for additional cost according to the new drug's novelty, application and marketability; at last, compare the calculated price (inclusive of additional cost) with the international reference price (the USA, UK, Germany and France); if the calculated price is 1.5 times higher than the reference price, then lower the price; if the calculated price is 0.75 times lower than the reference price, then increase the price.

For a new drug developed out of a generic drug but with a low level of novelty, the international reference pricing should apply, which means, the average of the prices fixed by the reference countries is directly used as the benchmark. For a new drug without any generic drug, the cost-based pricing should apply; and then, the price must be adjusted against the international reference pricing as described in paragraph to avoid over-pricing or under-pricing. Overall, value-based pricing is the core of Japan's drug pricing practices. Higher prices are set for the products with a high quality, remarkable efficacy and strong serviceability (and vice versa) in order to achieve optimal cost-effectiveness or high price for high quality and encourage pharmaceutical companies to put more efforts in R&D innovation and effectively curb inefficient reproduction. These are the merits of Japan's drug pricing strategy we should learn from. However, some other scholars claim that although pharmaceutical companies filing a new drug application (NDA) are required to submit the pharmacoeconomic analysis report, it is not so useful as intended. So, pharmaceutical companies need to thoroughly discuss how to make the utmost of the pharmacoeconomic analysis report so as to lay the groundwork for rolling out the trial of pharmacoeconomic analysis in 2016.

Nowadays, most countries in the world tend to include drug value in the considerations for new drug pricing through pharmacoeconomic evaluation. Australia is the first to apply pharmacoeconomic evaluation results in drug pricing control, with satisfactory outcomes. In Australia, all the pharmaceuticals applying to enter the Pharmaceutical Benefits Scheme (PBS) must be examined and approved by the Therapeutic Goods Administration (TGA), Pharmaceutical Benefits Advisory Committee (PBAC), Pharmaceutical Benefits Pricing Authority (PBPA) and other competent authorities. Further, PBAC made it a compulsory obligation effective as of 1993 that pharmaceutical companies present relevant pharmacoeconomic analysis reports. First of all, TGA examines the pharmaceutical's clinical efficacy, safety and quality to determine whether the pharmaceutical can be marketed. Generally speaking, TGA approval is the precondition for filing an application to PBAC. In the next step, PBAC analyzes the pharmaceutical's clinical efficacy, cost-effectiveness and incremental cost-effectiveness according to the submission furnished by the manufacturer to determine whether the pharmaceutical can be included in the PBS.

Finally, PBPA sets a recommended price for the pharmaceutical based on its evaluation results and then negotiates with the manufacturer to finalize the price. For a PBS-included pharmaceutical, when a similar product with a lower price appears on the market, the manufacturer must provide a pharmacoeconomic analysis report to prove its pharmaceutical's value advantages. Ding Jinxi examined the effects of Australia's pricing strategy in controlling drug prices through a case study of Lucentis (An Empirical Study and Enlightenment on the Australian Patent Drug Price Negotiation System, Chinese Health Economics, 2016, 35(12): 116-119), concluding that the price of Lucentis in Australia is only 23.4% of that in America and 37.8% of that in Japan. It not only benefits from the introduction of the efficacy-oriented pharmacoeconomic evaluation policy but also is closely related to a clear division of labor among functional departments involved in the governmental pricing system.

(3) Channel strategy

Channel strategy is especially favored by many manufacturers who produce and supply exclusive medicines. The primary cause is that clinical settings which constitute the main marketing channel of medicines feature a low level of marketization. So, pharmaceutical companies would find themselves more unrivaled once the channel problem is solved. In a word, it is basically a solution good for all the time. By analyzing the exclusive medicines included in the essential medicine list, we can find that the drugs with a high bidding price are almost blockbuster drugs. In such context, how to get their medicines approved for inclusion in the health insurance directory and essential medicine list become the top priority for the pharmaceutical companies seeking to make breakthroughs in marketing channel. In particular, how should they measure the return on investment in applying for inclusion in the above-mentioned directory and list so as to establish the investment orientation and channel layout?

(4) Promotion strategy

Pharmaceutical companies should come up with a particular way to disseminate relevant product or service information to consumers or users so as to arouse their interest and attention and stimulate their aspiration for purchase. It is also of great importance to investing in blockbuster drugs.

Then in practice, how should a pharmaceutical company consider and balance all the critical issues mentioned above? How should they make the most suitable decisions and centralize all the internal resources to get all jobs done perfectly so as to foster unique competitive edge under the ever-changing external environment? These problems must be effectively solved through methodical evaluation.

2.3 Creation and evaluation of indicator system for selection of blockbuster drugs

We've created the Evaluation Indicator System for Blockbuster Drugs in order to help pharmaceutical companies select target blockbuster drugs to develop in a reasonable way. Through literature review, we've identified 20 essential elements underlying blockbuster drugs. I designed a questionnaire (see Attachment 1), and handed out the questionnaires anonymously to experts and scholars in pharmaceutical producing and trading enterprises, pharmaceutical research institutions, colleges and universities, administrative organizations and medical establishments, seeking for their opinions. 70 copies were distributed, 66 of which were collected at a recovery rate of 94%. 65 questionnaire forms are valid.

2.3.1 Respondents characteristic

A majority of the respondents are young and middle-aged clinicians, mostly aged 50 or below. They have rich social experiences and a good mastery of relevant expertise.

They work in large and medium-sized cities like Beijing, Shanghai and Shenyang. They are employed by pharmaceutical producing and trading enterprises, medical establishments, administrative organizations, colleges and universities and research institutions, and they have made extensive and in-depth researches in pharmaceutical-related fields. Most of the respondents hold bachelor or higher degrees, including 9 doctors and 29 masters. 43 of them hold intermediate or higher professional titles. 32 of the respondents have been working for less than 5 years, 15 for 5-10 years, and 18 for 10 or more years.

Table 5 Respondents characteristics

| | N | % |
|------------------------|----|-------|
| Age group | | |
| 20-29 | 29 | 44.6% |
| 30-39 | 23 | 35.4% |
| 40-49 | 13 | 20.0% |
| Region | | |
| Beijing | 17 | 26.2% |
| Haikou | 14 | 21.5% |
| Shanghai | 9 | 13.8% |
| Shenyang | 6 | 9.2% |
| Guiyang | 4 | 6.2% |
| Tianjin | 3 | 4.6% |
| Benxi | 2 | 3.1% |
| Dalian | 2 | 3.1% |
| Occupation | | |
| Pharmaceutical company | 14 | 21.5% |
| Scholar | 14 | 21.5% |
| Drug manufacturer | 13 | 20.0% |
| Research institution | 12 | 18.5% |
| Medical authority | 4 | 6.2% |
| Hospital | 3 | 4.6% |
| Education | | |
| Master | 29 | 44.6% |
| Bachelor | 26 | 40.0% |
| PhD | 9 | 13.8% |
| Professional titles | | |
| Junior | 20 | 30.8% |
| Associate senior | 19 | 29.2% |
| Intermediate | 14 | 21.5% |
| Senior | 10 | 15.4% |
| Working experiences | | |
| Less than 2 years | 19 | 29.2% |
| More than 10 years | 18 | 27.7% |
| 2-5 years | 13 | 20.0% |
| 5-8 years | 11 | 16.9% |
| 8-10 years | 4 | 6.2% |

2.3.2 Indicator system creation and model evaluation

(1) Questionnaire reliability and validity analysis

This questionnaire is designed to survey the respondents' attitudes and opinions by using the Likert Scale. 70 forms were distributed, 66 of which are collected at a recovery rate of 94%. And 65 forms are valid. First of all, the reliability and validity of the questionnaire are evaluated using the SPSS17.0 Statistics software to determine its rationality and reliability, as illustrated in Table 6-9.

Cronbach's Alpha is employed to analyze questionnaire reliability, as shown in Table 5. As can be seen from Table 2, Cronbach's Alpha=0.795. There are 20 items in total. Table 7 presents the results of any detected items that cause significant differences in questionnaire reliability. Table 7 shows there is no item having significant impacts on questionnaire reliability. And Table 8 is a summary of Hotelling's T-Squared Test results, suggesting a heterogeneity of variance in the questionnaire. To sum up, the questionnaire is reliable; and the test results suggest a high reliability (the questionnaire is well designed if Cronbach's Alpha=0.7-0.8).

Table 6 Case processing summary

| | N | % |
|------------|----|-----|
| Case valid | 65 | 100 |
| Excluded | 0 | 0 |
| Total | 65 | 100 |

Table 7 Reliability statistics

| Cronbach's alpha | Cronbach's alpha based on standardized items | Number of items |
|------------------|--|-----------------|
| 0.795 | 0.784 | 20 |

Table 8 Item total statistics

| No | Item | Scale mean if item deleted | Scale variance if item deleted | Corrected item total correlation | Cronbach's alpha if item deleted |
|----|---|----------------------------|--------------------------------|----------------------------------|----------------------------------|
| 1 | Clinical efficacy (efficiency, cure rate, etc.) | 70.6 | 64.400 | 0.065 | 0.799 |
| 2 | Adverse effects rate and hazards | 70.83 | 64.424 | 0.044 | 0.800 |
| 3 | Unit price | 72.00 | 60.437 | 0.267 | 0.792 |
| 4 | Economy (cost-effectiveness ratio) | 71.63 | 60.830 | 0.295 | 0.790 |
| 5 | Incidence (or morbidity) of the indicated diseases | 71.11 | 61.410 | 0.248 | 0.793 |
| 6 | Whether or not a medicine for stubborn disease? | 71.52 | 61.597 | 0.193 | 0.797 |
| 7 | Production and supply capacity | 71.92 | 56.135 | 0.558 | 0.774 |
| 8 | Sales area (in China) | 71.88 | 57.235 | 0.488 | 0.778 |
| 9 | Inclusion in the essential medicine list or health insurance directory? | 71.49 | 61.473 | 0.260 | 0.792 |
| 10 | International popularity | 71.92 | 59.885 | 0.297 | 0.791 |
| 11 | Whether or not supported by proprietary intellectual property rights? | 71.49 | 59.129 | 0.286 | 0.793 |
| 12 | Market share | 71.46 | 57.211 | 0.526 | 0.776 |
| 13 | Market growth potential | 71.32 | 59.691 | 0.372 | 0.786 |
| 14 | Whether or not generating annual sales of at least RMB 1 billion? | 72.09 | 55.023 | 0.607 | 0.770 |
| 15 | Value added | 72.09 | 59.241 | 0.302 | 0.791 |
| 16 | Sustainability | 71.18 | 60.997 | 0.340 | 0.788 |
| 17 | Export sales area | 72.38 | 56.990 | 0.463 | 0.780 |
| 18 | Annual export sales | 72.46 | 57.377 | 0.450 | 0.781 |
| 19 | Manufacturer's annual output | 71.88 | 57.485 | 0.502 | 0.778 |
| 20 | Manufacturer's reputation | 71.32 | 58.222 | 0.444 | 0.781 |

Table 9 Hotelling's T-squared test

| Hotelling's T-squared | F | df1 | df2 | sig |
|-----------------------|--------|-----|-----|--------|
| 376.159 | 14.230 | 19 | 46 | <0.001 |

(2) Component analysis

Component analysis is a method of describing the correlation between original variables or original samples. The so-called component refers to a few comprehensive calculation variables extracted from multiple complex independent variables by effective means, through the multivariate statistical analysis method. The load matrix with higher scores is determined by component scores to replace the original variables (equivalent to dimensional reduction). The starting point is the correlation coefficient matrix of the original variables.

This study used the principal component method to perform value decomposition on the correlation coefficient matrix and sort it according to the size of the value (the variance threshold is not selected here, that is, all of the principal components are retained). The combination of the principal components is obtained by the vector corresponding to each value, which is recorded as Y.

When performing the validity analysis, we employ component analysis to evaluate the validity relevance and consistency of the questionnaire items (questions). The result of KMO and Bartlett's Test shows that KMO=0.898, indicating a suitability for further factor analysis.

Table 10 Descriptive statistics

| No | Item | Mean | Standard deviation | Analysis N |
|----|---|------|--------------------|------------|
| 1 | Clinical efficacy (efficiency, cure rate, etc.) | 4.8 | 0.506 | 65 |
| 2 | Adverse effects rate and hazards | 4.57 | 0.585 | 65 |
| 3 | Unit price | 3.40 | 0.932 | 65 |
| 4 | Economy (cost-effectiveness ratio) | 3.77 | 0.806 | 65 |
| 5 | Incidence (or morbidity) of the indicated diseases | 4.29 | 0.805 | 65 |
| 6 | Whether or not a medicine for stubborn disease? | 3.88 | 0.910 | 65 |
| 7 | Production and supply capacity | 3.48 | 0.970 | 65 |
| 8 | Sales area (in China) | 3.52 | 0.954 | 65 |
| 9 | Inclusion in the essential medicine list or health insurance directory? | 3.91 | 0.765 | 65 |
| 10 | International popularity | 3.48 | 0.954 | 65 |
| 11 | Whether or not supported by proprietary intellectual property rights? | 3.91 | 1.100 | 65 |
| 12 | Market share | 3.94 | 0.899 | 65 |
| 13 | Market growth potential | 4.08 | 0.835 | 65 |
| 14 | Whether or not generating annual sales of at least RMB 1 billion? | 3.31 | 1.014 | 65 |
| 15 | Value added | 3.31 | 1.045 | 65 |
| 16 | Sustainability | 4.22 | 0.696 | 65 |
| 17 | Export sales area | 3.02 | 1.023 | 65 |
| 18 | Annual export sales | 2.94 | 0.998 | 65 |
| 19 | Manufacturer's annual output | 3.52 | 0.903 | 65 |
| 20 | Manufacturer's reputation | 4.08 | 0.907 | 65 |

Table 11 KMO and Barlett's test

| | |
|--|---------|
| Kaiser-Meyer-Olkin Measure of Sampling Adequacy | 0.898 |
| Bartlett's Test of Sphericity Approx. Chi-Square | 450.189 |
| df | 190 |
| sig | <0.001 |

Table 12 Component extraction

| No | Item | Initial | Extraction |
|----|---|---------|------------|
| 1 | Clinical efficacy (efficiency, cure rate, etc.) | 1.000 | 0.614 |
| 2 | Adverse effects rate and hazards | 1.000 | 0.742 |
| 3 | Unit price | 1.000 | 0.672 |
| 4 | Economy (cost- effectiveness ratio) | 1.000 | 0.462 |
| 5 | Incidence (or morbidity) of the indicated diseases | 1.000 | 0.814 |
| 6 | Whether or not a medicine for stubborn disease? | 1.000 | 0.692 |
| 7 | Production and supply capacity | 1.000 | 0.720 |
| 8 | Sales area (in China) | 1.000 | 0.705 |
| 9 | Inclusion in the essential medicine list or health insurance directory? | 1.000 | 0.541 |
| 10 | International popularity | 1.000 | 0.663 |
| 11 | Whether or not supported by proprietary intellectual property rights? | 1.000 | 0.519 |
| 12 | Market share | 1.000 | 0.703 |
| 13 | Market growth potential | 1.000 | 0.619 |
| 14 | Whether or not generating annual sales of at least RMB 1 billion? | 1.000 | 0.674 |
| 15 | Value added | 1.000 | 0.719 |
| 16 | Sustainability | 1.000 | 0.659 |
| 17 | Export sales area | 1.000 | 0.850 |
| 18 | Annual export sales | 1.000 | 0.897 |
| 19 | Manufacturer's annual output | 1.000 | 0.760 |
| 20 | Manufacturer's reputation | 1.000 | 0.562 |

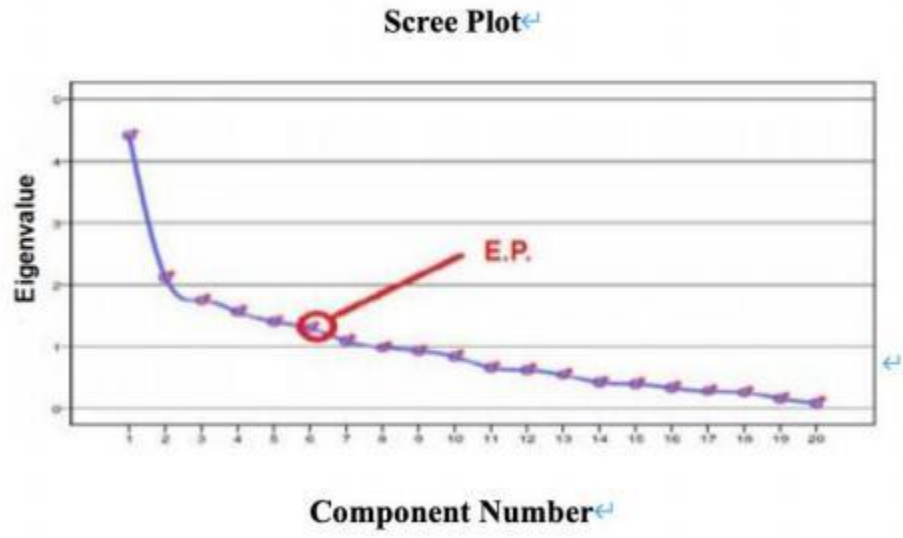


Figure 4 Scree plot of component analysis

Table 13 Component matrix

| No | Item | Component | | | | |
|----|---|-----------|--------|--------|--------|--------|
| | | 1 | 2 | 3 | 4 | 5 |
| 1 | Clinical efficacy (efficiency, cure rate, etc.) | 0.057 | 0.453 | 0.080 | 0.464 | -0.237 |
| 2 | Adverse effects rate and hazards | 0.024 | 0.191 | -0.111 | 0.693 | -0.407 |
| 3 | Unit price | 0.401 | 0.233 | -0.445 | -0.244 | 0.183 |
| 4 | Economy (cost- effectiveness ratio) | 0.383 | -0.115 | -0.331 | 0.355 | 0.033 |
| 5 | Incidence (or morbidity) of the indicated diseases | 0.335 | 0.036 | 0.060 | 0.180 | 0.317 |
| 6 | Whether or not a medicine for stubborn disease? | 0.226 | 0.155 | 0.138 | 0.370 | 0.583 |
| 7 | Production and supply capacity | 0.674 | 0.036 | -0.271 | 0.152 | 0.014 |
| 8 | Sales area (in China) | 0.638 | -0.427 | -0.180 | -0.103 | -0.121 |
| 9 | Inclusion in the essential medicine list or health insurance directory? | 0.346 | -0.565 | -0.067 | 0.186 | 0.111 |
| 10 | International popularity | 0.395 | 0.060 | 0.104 | -0.261 | -0.250 |
| 11 | Whether or not supported by proprietary intellectual property rights? | 0.364 | 0.037 | 0.492 | -0.088 | -0.357 |
| 12 | Market share | 0.625 | -0.286 | 0.316 | -0.011 | -0.321 |
| 13 | Market growth potential | 0.425 | -0.191 | 0.417 | 0.382 | 0.000 |
| 14 | Whether or not generating annual sales of at least RMB 1 billion? | 0.717 | -0.202 | 0.021 | -0.264 | -0.002 |
| 15 | Value added | 0.379 | -0.018 | 0.676 | -0.058 | 0.038 |
| 16 | Sustainability | 0.402 | -0.206 | 0.153 | 0.196 | 0.495 |
| 17 | Export sales area | 0.538 | 0.692 | 0.074 | -0.213 | 0.114 |
| 18 | Annual export sales | 0.530 | 0.679 | 0.066 | -0.235 | 0.196 |
| 19 | Manufacturer's annual output | 0.628 | 0.350 | -0.364 | 0.023 | -0.122 |
| 20 | Manufacturer's reputation | 0.554 | 0.066 | -0.363 | 0.021 | -0.256 |

Table 10 summarizes the basic statistics of the component analysis, in which 20 items are included, with a satisfactory data integrity. Table 11 shows the preliminary results of relevance evaluation. The result of KMO and Bartlett's Test shows that $KMO=0.898$, implying a strong relevance and suitability for further component analysis. The result of Bartlett's Test shows that $P<0.001$, again suggesting a strong relevance. In summary, the component analysis is necessary and valid. Table 12 shows the analysis result of correlation between variances, suggesting a strong correlation and also a high validity.

Following a preliminary evaluation, we may proceed to component analysis. Table 12 presents the relevance of items expressed by correlation factor. Then, a scree plot analysis is conducted to further demonstrate the reliability of retained components. As illustrated in Fig. 4, an elbow point (E.P.) appears at the 6th component, suggesting that its preceding components are the main components or indicators to be analyzed. And the reliability of the analysis results is thus established. As can be seen from Table 13, Component 1 is highly correlated with items 7, 8, 12, 13, 14, 19 and 20, Component 2 with items 9, 17 and 18, Component 3 with items 3, 11 and 15, Component 4 with items 1 and 2, and Component 5 with items 6 and 16. Table 14 presents direct statistics of item-item correlation.

Component 1: manufacturer's influence and market size

Component 2: influences of export sales and China's essential medicine list

Component 3: pharmaceutical's scientific research value

Component 4: pharmaceutical's efficacy

Component 5: pharmaceutical's specificity

In brief, the questionnaire designed has a satisfactory item validity and data consistency. It can be used for further statistical analysis and provide a scientific basis for evaluating the reliability of the statistical results.

Table 14 Component correlation test

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|------------|----|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| sig | 1 | .003 | .063 | .381 | .476 | .457 | .420 | .379 | .153 | .480 | .482 | .312 | .279 | .315 | .320 | .264 | .068 | .100 | .057 | .394 |
| (1-tailed) | 2 | | .342 | .116 | .158 | .144 | .232 | .229 | .348 | .358 | .198 | .474 | .146 | .091 | .187 | .275 | .453 | .439 | .268 | .074 |
| | 3 | | | .068 | .137 | .224 | .030 | .002 | .022 | .359 | .424 | .164 | .500 | .000 | .352 | .078 | .196 | .100 | .023 | .038 |
| | 4 | | | | .259 | .242 | .011 | .076 | .025 | .203 | .423 | .112 | .045 | .026 | .260 | .083 | .263 | .265 | .013 | .082 |
| | 5 | | | | | .026 | .000 | .127 | .225 | .440 | .300 | .080 | .257 | .217 | .182 | .095 | .071 | .313 | .150 | .024 |
| | 6 | | | | | | .107 | .246 | .481 | .454 | .368 | .410 | .018 | .128 | .281 | .027 | .112 | .043 | .429 | .463 |
| | 7 | | | | | | | .000 | .094 | .203 | .083 | .001 | .121 | .009 | .293 | .062 | .009 | .027 | .000 | .001 |
| | 8 | | | | | | | | .001 | .039 | .272 | .000 | .052 | .000 | .045 | .008 | .426 | .393 | .001 | .001 |
| | 9 | | | | | | | | | .256 | .136 | .084 | .012 | .008 | .491 | .003 | .268 | .239 | .439 | .213 |
| | 10 | | | | | | | | | | .245 | .010 | .089 | .004 | .211 | .450 | .006 | .025 | .399 | .008 |
| | 11 | | | | | | | | | | | .000 | .192 | .005 | .002 | .297 | .037 | .114 | .444 | .177 |
| | 12 | | | | | | | | | | | | .000 | .000 | .003 | .122 | .207 | .256 | .021 | .041 |
| | 13 | | | | | | | | | | | | | .016 | .001 | .102 | .238 | .261 | .188 | .396 |
| | 14 | | | | | | | | | | | | | | .040 | .043 | .022 | .004 | .005 | .004 |
| | 15 | | | | | | | | | | | | | | | .005 | .087 | .044 | .161 | .476 |
| | 16 | | | | | | | | | | | | | | | | .203 | .110 | .371 | .167 |
| | 17 | | | | | | | | | | | | | | | | | .000 | .000 | .022 |
| | 18 | | | | | | | | | | | | | | | | | | .000 | .100 |
| | 19 | | | | | | | | | | | | | | | | | | | .000 |

(3) Multivariate linear regression analysis and decision modeling

At first, P-P Plot and Q-Q Plot are employed to conduct a Normality test of the data, the results of which indicate that all the data follow the Normal distribution and are thus suitable for linear regression analysis.

Table 15 Model summary

| | |
|--------------------------------|---------|
| Model | 1 |
| R | 0.987 |
| R square | 0.974 |
| Adjusted R square | 0.972 |
| Standard error of the estimate | 0.06783 |

Table 16 ANOVA

| Model | Sum of squares | df | Mean square | F | sig |
|----------------|----------------|----|-------------|---------|--------|
| Regression | 10.158 | 5 | 2.032 | | |
| Residual Total | 0.271 | 59 | 0.005 | 441.492 | <0.001 |
| | 10.429 | 64 | | | |

Table 17 Regression coefficient test

| Model | Un-standardized | | Standardize | t | sig | Correlations | | |
|---|-----------------|-----------|-------------|--------|--------|--------------|---------|-------|
| | Beta | Std error | Beta | | | Zero-order | Partial | Part |
| 1 (constant) | 0.347 | 0.112 | | 3.106 | 0.003 | | | |
| X 1 - manufacturer's influence and market size | 0.416 | 0.017 | 0.628 | 24.826 | <0.001 | 0.890 | 0.955 | 0.521 |
| X2 - influences of export sales and China's drug list | 0.172 | 0.172 | 0.290 | 12.072 | <0.001 | 0.679 | 0.844 | 0.254 |
| X3 - pharmaceutical's scientific value | 0.123 | 0.123 | 0.199 | 8.102 | <0.001 | 0.630 | 0.726 | 0.170 |
| X4 - efficacy | 0.091 | 0.091 | 0.101 | 4.750 | <0.001 | 0.148 | 0.526 | 0.100 |
| X5- specificity | 0.112 | 0.112 | 0.177 | 7.006 | <0.001 | 0.442 | 0.722 | 0.168 |

Normal P-P Plot of Regression Standardized Residual

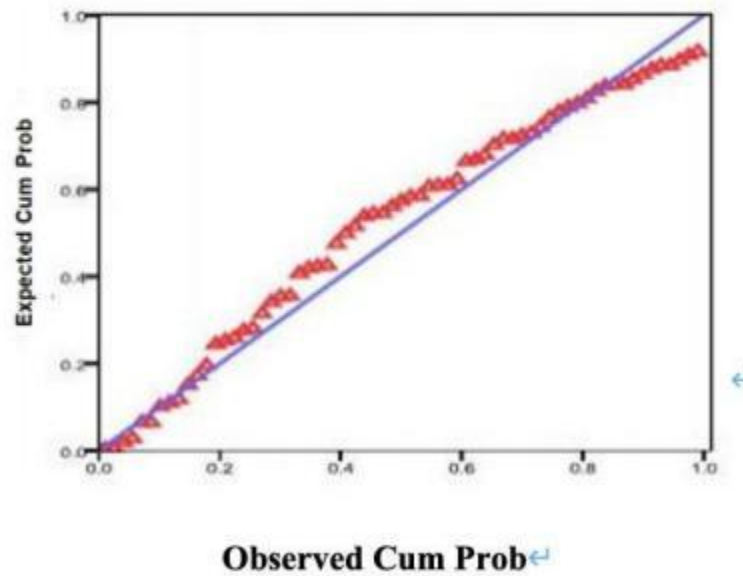


Figure 5 Normal P-P plot of regression standardized residual

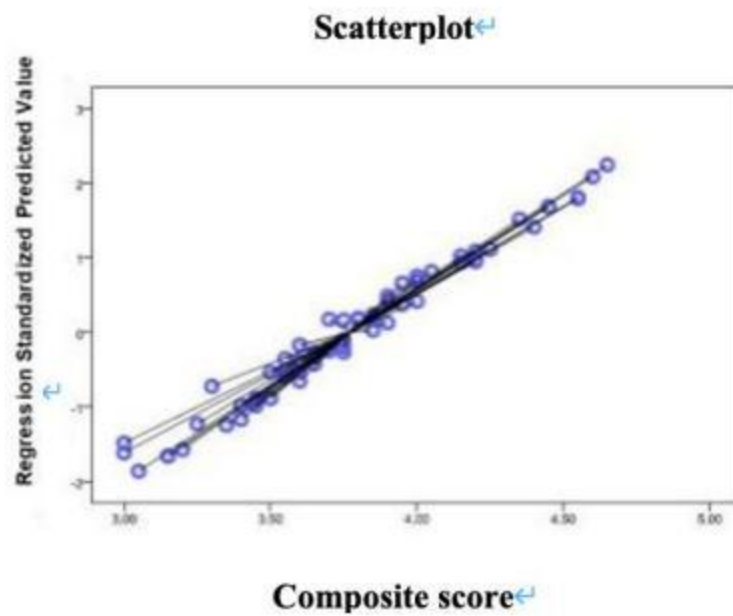


Figure 6 Comparison of regression standardized predicted value and composite score

As shown in Table 15, the five components are significantly correlated ($R^2=0.987$, adjusted $R^2=0.974$) with the composite value, suggesting that the data can be used for multivariate linear regression analysis. The results of regression and variance analysis as shown in Table 17 indicate that the multivariate linear regression equation is valid, with a high significance level ($P < 0.001$). Table 17 shows the relations among all the variables, where the regression equation can be expressed as:

The residual analysis of regression equation, as illustrated in Fig. 5, demonstrates that the P-P Plot produces a good result, with almost all the residuals distribute on the diagonal line. The predicated value of the maximum value somewhat deviates from its actual value. As revealed by Fig.6 - Comparison of Regression Standardized Predicated Value and Composite Value, the maximum value is higher than 4.7. This composite score can be rarely acquired in practice. Therefore, the regression equation displays a high level of robustness and predictability and thus can be used for reasonable evaluation and analysis of blockbuster drugs.

As revealed by the above equation, the manufacturer's influence and market size has a decisive effect on the composite score, the pharmaceutical's international market presence, scientific research value and specificity exert significant influences on the composite score, and the pharmaceutical's efficacy has a minor effect on the composite score. Most pharmaceuticals can achieve therapeutic equivalence, so this factor is less discussed. But users are much concerned about the efficacy (as shown in Table 17, the coefficient of variation $Beta=0.101$, implying a high level of stability). To conclude, the evaluation of blockbuster drugs has little direct connection with the efficacy but depends highly on the manufacturer's influence and market size, further suggesting that the development of pharmaceuticals cannot do without brand effect and commercial effect.

As can be seen from the above multivariate linear regression analysis, a blockbuster drug should be specially evaluated using five indicators whose standard values can be determined through One-tailed T Test. As shown in Table 18, the second column from the right lists the standard values of all the five indicators.

A pharmaceutical might be determined as a blockbuster drug only if all its five indicators exceed the established standard values. The first column from the right lists the floor levels of all the five indicators. And a pharmaceutical will be disqualified from being recognized as a blockbuster drug if any of its five indicators is below the established floor value.

Table 18 One-tailed test

| | Test value = 0 | | | | |
|---|---|----|-------------------|--------------------|--------|
| | 95% confidence interval of the difference | | | | |
| | t | df | Sig (1-tailed) | Mean difference | Lower |
| Composite score | 75.295 | 64 | <0.001 | 3.77000 | 3.6864 |
| x1 - manufacturer's influence and market size | 48.994 | 64 | <0.001 | 3.70330 | 3.5771 |
| x2 - influences of export sales and China's drug list | 39.017 | 64 | <0.001 | 3.28718 | 3.1466 |
| x3 - pharmaceutical's scientific value | 43.708 | 64 | <0.001 | 3.53846 | 3.4033 |
| x4 - efficacy | 84.504 | 64 | <0.001 | 4.68462 | 4.5921 |
| x5- specificity | 51.317 | 64 | <0.001 | 4.04615 | 3.9146 |

Conclusions of statistical analysis:

1. The questionnaire is well designed and collected, without any loss of data. The statistical analysis results show that the questionnaire has a high level of reliability and validity, with significant item and consistency validity. And the items are suitable for further statistical analysis.
2. A high level of correlation is established for the questionnaire through component analysis. Then, 5 components are extracted for further analysis. These 5 components have practical significance and are analyzed scientifically. So, the data can be used for regression analysis and prediction.
3. The composite score obtained is then combined with the 5 components for regression analysis, the results of which demonstrate that they exhibit a significant linear regression relationship, all the 5 components show a significant regression effect, and the regression equation is reliable. The variance analysis results show that the equation displays a high level of robustness and thus can be used for reasonable evaluation and analysis.
4. Based on the results of regression analysis, we depict the relation between correlation coefficient and the components to set a standard score for each component. In this way, we finally establish the criterion for determining a blockbuster drug, i.e., any pharmaceutical with its composite score lower than 3.6864 will not be established as a blockbuster drug.
5. The questionnaire design and data collected have ruled out the pharmaceutical grade factor, making it impossible to determine blockbuster drug grades. Hence, further questionnaire design and analysis is required for establishing criteria of blockbuster drug grades.

(4) Empirical test of models

Based on the dose type and annual sales volume, four types of blockbuster drug recognized by the Ministry of Science and Technology of the People's Republic of China, which are CSPC Ouyi Pharma levoamlodipine maleate tablets, Tasly compound red sage root dripping pill, Shineway houttuynia injection and CSPC butylphthalide soft capsule, are used as the subjects. Dose types of the four drugs include tablet, dripping pill, injection and soft capsule. Sales volume of each of the four types of blockbuster drug is the highest among drugs of the same dose type. Literatures and materials were collected and distributed to 10 experts selected randomly. And the experts were invited to score five factors (impact on pharmaceutical enterprise and market scale (x1), impact on drug export and domestic drug directory (x2), scientific and technological value of drug R&D (x3), drug effect (x4) and special effect of drug (x5)) based on basic information about each of the blockbuster drugs. The lowest score for the "poorest one" is "1" and the highest score for the "best one" is "5". Average value is used in the discriminative model to determine whether the drug should be cultivated into a blockbuster drug. List of average scores given by the 10 experts is shown in Table 19.

Table 19 Average scores of five factors rated by experts

| | Levoamlodipine maleate tablet | Compound red sage root dripping pill | Houttuyia injection | Butylphthalide soft capsule |
|----|----------------------------------|---|------------------------|--------------------------------|
| x1 | 4.6 | 4.8 | 4.2 | 4.2 |
| x2 | 2.8 | 4.8 | 3.4 | 3.6 |
| x3 | 4.8 | 3.8 | 3.8 | 3.4 |
| x4 | 4.6 | 5 | 2.6 | 3.6 |
| x5 | 3.4 | 3.4 | 3 | 4.8 |
| y | 4.132 | 4.4726 | 3.719 | 3.9968 |

According to Y values in the model shown in Table 19, Tasly compound red sage root dripping pill has the highest score, 4.4726, which is followed by levoamlodipine maleate tablet with the score of 4.132 and butylphthalide soft capsule with the score of 3.9968. Scores of the three types of drug are higher than 3.77, which means that the three types of drugs have passed the model test and may be cultivated into blockbuster drugs. However, the value of houttuynia injection is 3.719, which means that houttuynia injection may or may not be cultivated into a blockbuster drug. Scores of drug effect and adverse reaction rate (X4) are low, which is directly relevant to the unstable clinical property and adverse reactions of the Chinese medicine injection. Therefore, if the factor of houttuynia injection is improved significantly, houttuynia injection may be cultivated into a blockbuster drug. However, if the existing situation is not improved, it is not recommended to cultivate the drug into a blockbuster drug. Correspondingly, this problem may be a general one among all Chinese medicine injections.

Cultivation of blockbuster drugs is an important content of the “new drug research and development project” under the national medium and long-term scientific and technological development planning. Guiding ideology and major task of the “new drug research and development project” is to develop a batch of scientific drugs and biological drugs with high innovation value to provide safe, effective and cheap new drug for the public and shift the situation of new drug industry from imitation to innovation.

Evaluation standards for blockbuster drugs is an important orientation for leading the new drug development. In this study, key factors for whether the drug may be developed into a blockbuster drug are determined through the analysis of principal constituent factor based on consultation of experts and questionnaire, and the multiple regression model is built as the discriminative model for blockbuster drugs. Afterwards, four types of blockbuster drug recognized by the Ministry of Science and Technology of the People’s Republic of China, which are CSPC Ouyi Pharma levoamlodipine maleate tablet, Tasly compound red sage root dripping pill, Shineway houttuynia injection and CSPC butylphthalide soft capsule, are used as the subjects to

test the rationality of the model. According to the test result, only houttuynia injection failed to pass the verification. Among the four types of drugs, the score of houttuynia injection falls in the interval between the interval suitable for cultivation and the interval not suitable for cultivation, which is consistent with the actual situation. The result indicates that the mode is scientific and rational.

2.4 Building of blockbuster drugs selection gaming model based on adverse reactions

Clinical supervision of blockbuster drug is increasingly stricter mainly because of safety problems of the clinical administration, particularly in relation to Chinese medicine injection. Owing to the driving force of benefits, drugs creating high profit rate are more likely to be used, and both the clinical administration institutions and pharmaceutical enterprises will be benefited. Safety problems of clinical administration include two aspects: Some safety problems are caused by mistaken administration and some are caused by adverse drug reactions. The two aspects of problems need to be managed with different supervision measures. According to rules of the WHO Collaborating Center for International Drug Monitoring, adverse drug reactions (ADR) refer to hazardous reactions or reactions irrelevant to the purpose of administration which appear when a drug of normal dose is administered to prevent, diagnose or treat diseases or adjust physiological functions. The definition excludes the reactions caused by intentional or accidental overdose. In other words, ADR is not completely avoidable, and it is a part of the drug property. ADR is irrelevant to the purpose of administration to patients, and appears due to the function of the drug or interaction between drugs occurring in the process of disease prevention or diagnosis with normal dose of drug. ADR is a common cause of disease incidence and mortality. ADR rate of hospitalized patients in each country is about 10%-20%, and about 5% of the patients die of serious ADR. In the USA, serious and fatal ADR incidents of hospitalized patients account for 0.32%-6.7% of total hospitalized patients. Mortality caused by ADR takes up 1/2,200 of the population of the society. Average mortality caused by ADR ranks only behind mortality caused by heart disease, cancer and apoplexy. In Europe, 15% of hospitalized patients are in hospital because of ADR. In

UK, ADR occurs to about 11% of medical patients. In China, 2.5 million people are in hospital because of ADR in each year and about 192,000 people die of ADR.

In 2016, the number of Adverse Drug Reaction/Incident Report Sheet received by the national adverse drug reaction monitoring network was up to 1.43 million, which was increased by 2.3% compared with the figure of 2015. The number of new and serious adverse drug reaction/incident reports was over 423,000, which was increased by 7.4% compared with the figure of 2015. New and serious reports accounted for 29.6% of total reports of the same period, which was increased by 1.4 percentage points compared with the figure of 2015. According to the statistics based on suspected drug types, pharmaceutical chemicals accounted for 81.5%, Chinese medicine accounted for 16.9% and biological products (excluding vaccine) accounted for 1.6%, which were basically consistent with figures of 2015. According to statistics based on administration channels in 2016, as for the drugs and administration channels mentioned in the adverse drug reaction/incident reports,

ADRs caused by drugs administered via intravenous injection accounted for 59.7%, ADRs caused by drugs injected in other ways (such as intramuscular injection and hypodermic infection) accounted for 3.4%, ADRs caused by drugs administered orally accounted for 33.7%, and ADRs caused by drugs administered in other channels (such as external application and patching) accounted for 3.2%.

ADR not only causes heavy disease burden but also imposes heavy economic burden on the society. Evaluating ADR in the perspective of pharmaceutical economics and reducing ADR incidents will significantly reduce the number of days of hospitalization, lower medical cost and avoid disputes, thus providing a guarantee for people's safety in drug administration and protecting the health of people.

Among the 4, 108 cases investigated by Bates et al. (Bates DW, Spell N, Cullen DJ, Burdick E, Laird N, Petersen LA, Small SD, Sweitzer BJ, Leape LL: The costs of

adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. 1997, JAMA, 277 (4): 307-11), 190 cases were in hospital because of ADRs. Average hospitalization time of each ADR case is 2.2 days longer than normal case. Results of another two similar studies show that extra hospitalization time caused by ADR is 1.91 days and 3.5 days respectively. In UK, for example, Nonsteroidal Anti-inflammatory Drugs (NSAIDs) used for treating RA cost over 35 million pounds while the cost for preventing and treating gastrointestinal tract ADR caused by these drugs is up to 58 million pounds.

Drugs are produced for the purpose of preventing and treating specific diseases. ADR is concomitant with the course of drug treatment. From the perspective of economics, we need to avoid ADRs as far as possible. In this way, the loss of social resources caused by ADR treatment may be reduced. However, from the perspective of avoiding the ADR incidence, measures for reducing ADRs include reducing drug administration, strengthening regulation, establishing drug information evaluation system and so on. These measures are also consumers of social resources. Therefore, we need to think in other way. That is to admit the existence of ADRs instead of attempting to avoid all ADR incidents as it is objectively impossible. We need to consider to save social resources. In other words, while enhancing the evaluation and research on social burden created by ADR in the perspective of pharmaceutical economics, we need to measure the relation among social burden caused by ADR, treatment effectiveness of drugs and the social cost for avoiding ADR from the perspective of economics by admitting the objective existence of ADR. In other words, when the sum of the cost for avoiding ADR and cost of treating ADR is cut down to the lower limit, the ADR incidence rate is not at the lowest point but at the premium point.

Currently, some scholars have adjusted the thought of economic evaluation of ADR. However, systematic research and empirical analysis has not yet conducted for the premium point of ADR incidence rate in the industry. In addition, China was late in ADR monitoring and management. Policies and measures implemented in China for avoiding ADR lag behind developed countries. Therefore, it is necessary to conduct

systematic and in-depth exploration of this field to provide reference for the formulation of relevant policies.

In this part of study, we will try to build an optimized economic model of ADR, which is a model for determining the optimum point of ADR when total social cost is maintained at lowest point. While providing a basis for clinical decision-making and based on the relation between input of medical resources for controlling ADR and total social cost, the model will provide a reference for the formulation of ADR drug management policies and facilitate the optimized configuration of rare medical resources.

Two opposite restricting factors are involved in the determination of ADR rate. For the first factor, ADR rate may be lowered down as far as possible, even to zero (it is technically not realizable but an ultimate target) to guarantee the safety of patients taking medicine and reduce the risk borne by patients. The second factor is based on the perspective of drug R&D and drug selectiveness. When ADR incidence rate is reduced, expense of drug R&D will be increased and the drug selectiveness will be lowered down respectively.

2.4.1 Cause and influential factors of ADR

Drug is a special commodity which has double-sided properties. It may be used to treat diseases and may also cause hazardous reactions. According to the Management Measures of Adverse Drug Reaction Report and Monitoring promulgated by the China Food and Drug Administration (CFDA) on March 4, 2004.

ADRs refers to the reactions irrelevant to the purpose of drug administration or accidental hazardous reactions of drug when qualified drugs are used in normal dosage and in the right method. ADRs exclude reactions caused by unintentional or intentional overdose or reactions caused by improper administration. ADRs include

side effect, toxic reaction, allergic reaction, after effect, withdrawal symptom, carcinogenicity, teratogenicity, mutagenicity, idiosyncratic reaction, drug dependence and so on. Causes of ADRs are complicated and vary from one another. The causes may be classified into two aspects: drug aspect and human body aspect. Factors in connection with the causes include pharmacological actions, impurities and dose of drug, race, gender, age, individual difference and pathological state of patients. In daily life, irrational application of drug is common, which leads to occurrence of ADRs. The causes may be summarized into following aspects:

I. Factors in connection with drugs

(I) Physicochemical property and chemical structure of drug

Oral drug with higher liposolubility is easier to absorb by the alimentary tract, thus being more likely to cause ADRs. Some drugs are very similar in chemical structures. For example, penicillin may cause allergic reactions; and penicillin G, ampicillin and p-hydroxy-ampicillin may cause allergic nephritis or interstitial nephritis. Some drugs with similar chemical structures have distinctive ADRs. For example, ketoprofen and flurbiprofen have similar chemical structure but the ADR rate of the former is 1.612% while that of the latter is 5.215%.

(II) Dose, dose type and administration channel of drugs

Generally speaking, higher dose is more likely to cause ADRs. For instance, normal dose of aspirin is 1-2 pills. When 2 pills are administered, the discomfort rate of gastrointestinal tract is increased significantly. In addition, different administration channels will lead to significant difference in drug absorption and distribution and cause ADRs. According to some literatures, intervenous drop infusion is the first-place cause (accounting for 62.147%) of ADRs. Therefore, it is advocated to administer oral drugs and control the administration via injection. Currently, WHO has listed the per capita time of injection administration as one of the important standards of rational administration. However, some drugs may have great impact if

the drugs are taken orally. For example, orally taken chloromycetin will harm more to the hemopoietic system. If it is administered through other channels except for the stomach and intestines, the harm to the hemopoietic system will be reduced. On the contrary, if chloromycetin is applied externally, more allergic reactions may occur. In addition, the longer the drug is taken, the more the drug will accumulate in the body and the possibility of ADR will be increased.

According to instructions of some medicine, if the patient use the drug constantly for a long time, ADR incidence rate will be increased. Interaction between drugs may also have direct impact on ADRs. In clinical practice, two or more drugs are often administered at the same time or successively for the purpose of enhancing the curative effect and relieving the effect of adverse reaction by taking advantage of the beneficial interaction between drugs or their functions on different parts. In most cases, however, application of two or more drugs at the same time may cause adverse interaction, and the ADR incidence rate will be increased with the increase of number of types of drugs taken at the same time.

II. Factors in connection with drug production

(I) Drug impurity

Drug production is a complicated process which should be executed in strict accordance with GMP standards. According to relevant quality standards, impurity of certain quantity is allowed for drugs. However, the impurity may lead to ADRs. For example, dyes of capsule often cause fixed eruption. Penicillin causes allergic reactions due to the slight trace of penicillin olefinic acid, benzylpenicilloic acid and penicillin polymer.

(II) Drug contamination

If drugs are contaminated by microorganism or other drugs, the drug may cause serious ADRs. Cross contamination may occur if the site is not cleaned thoroughly.

(III) Drug quality problem

ADR incidence rate of the same group of drugs may be different due to the difference in manufacturers, preparation processes and impurity removal rates. For example, impurity in clofibrate/p-chlorophenol 0 are major causes of dermatitis. Protein in ampicillin is the cause of drug eruption. In addition, dose types adopted by production enterprises also have direct impact on the degree of ADRs. For example, incidence rate of ADRs, except for malleolus dropsy and constipation, caused by nifedipine delayde-release tablets is lower than that of ordinary preparations.

III. Factors in connection with drug-circulating enterprises

Drug-circulating enterprises include drug wholesalers, retail drugstores, hospital pharmacies and so on, which are bridges for connecting drug producers and consumers. Therefore, drug-circulating enterprises also have certain impact on ADRs.

A drug wholesaler often has one or more warehouses. During the storage and maintenance of drugs, drugs may become crystalized, deposited, discolored or go bad before the expiration of life circle because of changes in storage conditions (temperature, humidity, light and ventilation degree), thus increasing the incidence rate of ADRs. In addition, insulation or refrigeration measures should be adopted for some drugs, such as serum, vaccine, insulin and other biological products. If specified conditions are not available, the drugs may lose effect or go bad, thus causing ADRs.

There are many kinds of retail drugstores. In China, prescribed drugs and OTC drugs are available in retail drugstores. A consumer of prescribed drugs needs to show the

prescription issued by a practicing doctor (pharmacist). Professional quality of the pharmacist has direct impact on the ADRs caused by relevant drugs.

Furthermore, some chain drugstores promote drugs to seek for personal benefits without considering the individualized difference of patients.

IV. Factors in connection with doctors (pharmacists)

Clinical medication safety has something to do with the whole administration process covering diagnosis, prescription, dispensation, monitoring and evaluation. Therefore, clinical medication safety is closely related to doctors, pharmacists, nurses and other personnel. Any mistake of any person may do harm to patients.

(1) Doctor: A doctor is a person who is mainly responsible for disease diagnosis and treatment and often held liable for drug-induced harms. Drug-induced harms are mainly caused by the lack of knowledge on drugs, especially new drugs, lack of sense of responsibility, and failure in effective clinical medication control.

(2) Pharmacist: A pharmacist is a person who provides drugs and monitors drug safety. A pharmacist may do harm to patients because of mistakes in prescription review and drug distribution, failure in giving particular instructions on drugs to patients, insufficient cooperation and communication with medical personnel, and failure in conducting drug safety monitoring.

(3) Nurse: Administration is the last link of the medication process, which is important for safe medication. A nurse may do harm to patient because of failure in following medical advice in a right way, mistake in administration operation and failure in conducting effective clinical observation and reporting.

V. Factors in connection with patients

(I) Patient's attitude

Most ADRs are predictable and preventable. Generally speaking, reasons for ADRs caused by abuse and misuse are that patients increase the dose arbitrarily to demand instant success or have themselves treated by several doctors at the same time and use drugs provided by different doctors or listen to non-professional personnel's advice and use large dose of drugs for serious diseases or buy drugs by themselves. These behaviors of non-scientific medication also increase the ADR incidence rate.

(II) Race difference of patients

The white and colored races have different reactions to drugs. The incidence rate of hemolytic anemia caused by methyldopa differs among different races. In the direct antiglobulin test, for example, the result for about 15% of Caucasian taking the medicine is positive but none of the results for the American Indians, Africans and Chinese is positive. Perofen, a prescription for reducing fever and relieve inflammation, causes damage to the English but seldom causes damage to the Japanese.

(III) Gender of patients

Gender has certain impact on the ADR incidence rate. In the drug eruption test, male is more likely to suffer from drug erupt than female. The ratio of incidence is 3:2. Cimetidine may cause mammary development of male. As for the agranulemia caused by phenylbutazone and chloromycetin, the incidence on female is 3 times higher than the incidence on male. The incidence of aplastic anemia caused by chloromycetin on female is twice of that on male. According to Hurtwity's report, the ADR incidence rate among male is up to 7.13% (50/682) while that among female is 14.12% (68/478).

(IV) Age of patients

Aged people, juvenile and children differ in their reactions to drugs. For example, the half decay time of penicillin taken by an adult is 0.155h while the time for an aged person is 1h. Plasma protein concentration of aged people is reduced, and the ability of plasma protein in binding drug is also weakened. For example, the binding rate of dilantin sodium and plasma protein of an aged person is 26% lower than that of a person younger than 45. Children are more sensitive to central depressants and drugs affecting water-electrolyte metabolism and acid-base balance. Generally speaking, children are more likely to suffer from ADRs because of the lower drug metabolism ability than adults, poor renal excretion ability, higher sensitivity to drug action and drug's likelihood of entering brain. According to statistics, the ADR incidence rate of people younger than 60 is 6.13% (42/667) and that of people older than 60 is 15.14% (76/493). Therefore, special attention should be paid when an aged person takes digitalis, reserpoid and other similar drugs.

(V) Individual difference of patients

Individuals have different reactions to the same drug, which is a normal biological difference. For example, ADRs to sodium salicylate vary from one another. Among 300 male patients treated with sodium salicylate, about 2/3 suffer from ADRs when the total dose reaches up to 615-1,310g. However, ADR has occurred to some patients when total dose is 3,125g and to individual patients when total dose reached about 3,010g. Among different individuals, difference in doses causing ADR may reach up to 10 times. Individual difference also affects the nature of drug action. For example, barbiturates in general hypnotic dose will have hypnotic action on most people. However, it is not useful for some individuals. Instead, it may cause anxiety, discomfort and insomnia. Morphine has similar actions. It does not function as a depressant but an excitant for some individuals.

(VI) Nutritional state of patients

Imbalanced diet may also affect the action of drugs on human body. For example, nerve damage caused by isoniazid is more serious when the human body lacks vitamin B6. The action of pentothal in anaesthetizing animals not fed with nicotinic acid is enhanced.

(VII) Drink and food

As for the impact of ADRs, alcohol is an inducer of metabolic enzyme for many drugs and may accelerate the metabolism of some drugs and weaken the curative effect. On the other hand, merely a little drink will lead to expansion of blood vessels in the alimentary tract, thus enhancing drug absorption and inducing ADRs. Liver function may be damaged by long-term drinking, causing changes in drug metabolism and increasing ADRs.

2.4.2 Study on decisive factors of ADR incidence rate

According to results of the analysis on the above, ADR incidence rate is relevant to many subjects, including patient, doctor, pharmaceutical enterprise, circulation enterprises and so on. To further define the subjects having key impact on ADR incidence rate, we conducted face-to-face interviews with experts based on the questionnaire I designed. There are 9 questions in the questionnaire. Experts invited to participate in the survey include 4 clinicians from Grade III Level A medical institutions, 2 clinicians from medical institutions of basic level, 12 managerial personnel from drug administration departments and 2 scholars in drug policies. The research group distributed 20 copies of questionnaire and collected all of the questionnaires. The recovery rate is favorable.

Questions and answers:

Question 1: In your opinion, what are the factors that affect ADR incidence rate?

Most experts considered that the seriousness degree of ADR incidents is a factor that affects the ADR incidence rate. Correspondingly, pharmaceutical enterprises are motivated by the seriousness degree of ADR incidents to control the ADR incidence rate. If any drug is involved in a serious ADR incident, the pharmaceutical enterprise concerned will be seriously punished and the market prospect of such enterprise will be affected correspondingly.

Question 2: Among the government, pharmaceutical enterprise, medical institution and patient, which one concerns the most about ADR incidence rate?

Most experts considered that pharmaceutical enterprises are concerned the most about ADR incidence rate, and that pharmaceutical enterprises may control the ADR incidence rate. In other words, pharmaceutical enterprises may take effective measures to reduce ADR incidence rate. Compared with pharmaceutical enterprises, government and medical institution would shoulder less responsibility when ADR incidents occur.

Question 3: What is the highest cost for a pharmaceutical enterprise to lower the ADR incidence rate?

Most experts considered that the R&D and test in primary period cost the most when a pharmaceutical enterprise tries to lower the ADR incidence rate. Therefore, the willingness of a pharmaceutical enterprise to lower ADR incidence rate mainly depends on the increase in cost of R&D and test for lowering ADR incidence rate. If the cost is too high, the activeness of the pharmaceutical enterprise in lowering ADR incidence rate will be reduced.

Question 4: In your opinion, what are the costs to be borne by patients for ADR incidence rate?

Most experts considered that patients bear the opportunity cost incurred by the patients' reluctance in purchasing drug with ADR, for the purpose of avoiding ADRs, which causes loss of opportunity of receiving the best treatment; 35% of the experts considered that patients need to bear the pain caused by the avoidance of ADRs while

another 35% of the experts held that patients need to bear other treatment cost when serious ADR occurs. Therefore, the reason for a patient to choose a drug causing certain ADRs and bear certain risks is that there are few or no other alternative drugs or treatment schemes.

Question 5: In your opinion, what are the factors to be considered by a patient when he chooses a drug?

Most experts held that a patient need to consider the curative effect and seriousness degree of ADRs when he chooses a drug. Among the experts interviewed, 20% considered that patients need to take ADR incidence rate into consideration. From the perspective of experts, patients attach great importance to the curative effect and seriousness degree of ADRs of a drug, which is relevant to the drug availability in China. As many regions in China lack drugs with good curative effect, patients would rather take the risk of suffering from ADRs than caring about ADR incidence rate when they use the drug because they think ADR will not necessarily occur to them.

Question 6: In your opinion, what are effective measures to be taken by the government to lower ADR incidents?

Most experts considered that the government needs to strengthen market regulation, establish an information feedback mechanism for medical institutions, perfect the legislation, punishment and compensation systems for drug safety.

Question 7: What are the motivations for pharmaceutical enterprises to control ADR incidence rate?

Most experts considered that the government needs to strengthen the regulation. Some experts held that pharmaceutical enterprises try to control ADR incidence rate for the purpose of avoiding compensation and punishment. Some other experts believed that ADR incident would impact the sales volume of the drug concerned and therefore affect the profit created by the drug.

Question 8: In your opinion, what are the response of patients when they know any serious ADR?

Experts considered that patients aware of serious ADRs will reject to buy or buy less drug concerned. Some experts held that patients will not have any response.

Question 9: In your opinion, what are the reasons for patients to accept drugs causing ADRs?

Experts considered that ADR incidence rate of certain level is acceptable for patients. In other words, patients would accept drug with certain risk in safety as long as such risk is not too high.

2.4.3 Building optimum ADR decision-making model

A target function model will be built with pharmaceutical enterprises, medical institutions and patients as interest subjects and with the realization of optimum social welfare (optimum interests for the three parties) on condition of compliance with relevant laws and regulations of the country as the target. R&D costs of enterprises (mainly for safety test), ADR regulation cost of medical institutions and patients ' ADR treatment cost will be used as variables, and constitution and relation of such variables will be analyzed for the purpose of building an optimum economic model.

Gaming between pharmaceutical enterprises and patients based on cost condition

Pharmaceutical enterprises may lower ADR incidence rate by strengthening quality control, improving technological level, increasing R&D input and taking other measures. Of course, these measures will lead to increase in R&D cost. A doctor will consider the drug safety when he chooses a drug. However, drug safety is not a

decisive factor for the doctor to decide whether to treat the patient with the drug. If patients are asked to make a decision independently, patients with higher income will choose expensive drug to avoid the risk in drug safety based on their economic condition, knowledge level and administration experience. Therefore, the three parties will seek for dynamic game balance in ADR incidence rate when they make decisions.

According to the analysis on the above, the selected ADR level is the result of balanced decisions of pharmaceutical enterprises, doctors and patients. In other words, pharmaceutical enterprises will consider the cost for and sales volume after lowering ADR incidence rate, and will not lower ADR incidence rate blindly. Doctors will consider to use a rational drug instead of a drug causing least ADR to maximum their own benefit. Patients will choose drugs with rational ADR incidence rate under the restriction by purchasing power, knowledge level and risk awareness. Therefore, the channel for balancing ADR will be discussed in the cost perspective.

Case 1: Decision made by both patients and enterprises at the same time

(1) Patients and enterprises play the game at the same time

At first, a simple decision-making model is built without taking the decision of the doctor into consideration or by considering that the doctor may make a decision on behalf of the patient. The formation of balance is the result of gaming between the pharmaceutical enterprise and patient. If we assumed that r is the ADR rate, the cost function for patients will be $C^C = C(r, P, Q)$, (P represents price, and Q represents quantity). Administration cost of patients is relevant to ADR rate, drug price and drug sales volume. $C_r > 0$ indicates that patients will cost less when ADR rate is lower. $C_Q < 0$ indicates that patients will cost more when the used dose is higher. We assume that enterprise cost function is $C^G = C(r, Q)$. In other words, enterprise cost is relevant to sales volume. Higher sales volume needs more cost, higher ADR rate will cost less, and $C_r < 0$.

In fact, price and and ADR rate do not have a defined relation while drug sales volume is always relevant to ADR rate. If a drug causes ADR, especially serious ADR, sales volume of the drug will be affected. In other words, there is a function relation between ADR rate and drug sales volume: $Q=Q(r)$ and $Q_r < 0$, which means that lower ADR rate is relevant to higher sales volume. If we assume that patients and enterprises make decisions at the same time, the optimum decision of patients will be as follows if they want to minimize the cost:

$$\frac{\partial C^C}{\partial r} = C_r^C(r, P, Q) + C_Q^C(r, P, Q)Q_r = 0$$

$$C_r^C(r, P, Q) = - C_Q^C(r, P, Q)Q_r$$

Profit function of enterprises: $\Pi = PQ(r) - C^g(r, Q)$

The optimum decision will be: $\frac{\partial \Pi}{\partial r} = PQ(r) - C_r^g(r, Q) - C^g(r, Q)Q_r = 0$, in other words: $PQ(r) = C_r^g(r, Q) + C^g(r, Q)Q_r$

After establishing an equation set for equation (1) and (2), we can obtain the optimum ADR incidence rate.

(2) Gaming model design and realization of balance gaming

We assume that consumer cost function is $C^C = C(r, P, Q) + PQ + ar^2$, where a is the ADR cost factor. The larger the factor is, the higher of ADR cost will be, vice versa. Drug sales volume is inversely proportional to ADR incidence rate, thus forming the function of $Q = Q(r) = b - cr$, where c is the ADR-sales volume factor. The higher the factor is, the sales volume will be lower because of ADR, which is consistent with $Q_r < 0$. Therefore, $C^C = P(b - cr) + ar^2$, $\frac{\partial C^C}{\partial r} = -Pc + 2ar = 0$, which means $r = \frac{Pc}{2a}$ (7).

Drug cost function is $C_g = C(r, Q) = \varepsilon - dr^2 + eQ$, where d is the ADR-cost factor.

The higher the factor is, the lower drug cost will be; e is the marginal sales cost of drug. If we assume that the marginal cost of drug is a fixed value, the marginal cost is irrelevant to ADR.

$$\pi = PQ(r) - (\varepsilon - dr^2 + eQ) = (P - e)(b - cr) + dr^2 - \varepsilon,$$

$$\frac{\partial \pi}{\partial r} = -c(P - e) + 2dr = 0, r = \frac{c(P - e)}{2d}, P > e(8).$$

Based on the simultaneous equations (7) and (8), we can find that $r = \frac{ce}{2(a-d)} > 0, a > d$. This condition indicates that increase in ADR incidence rate will push social cost up from the perspective of ADR incidence rate and social cost. Therefore, ADR incidence rate is relevant to cost factor and marginal cost.

Case 2: Decision made by both doctors and enterprises

(1) Doctors and enterprises play the game at the same time

If a doctor makes a decision based on the principle of minimizing patient's cost, the decision-making behavior of the doctor is equivalent to the behavior of the patient. On the contrary, if a doctor needs to consider both the patient's cost and his own benefit, the decision-making behavior of the doctor will be changed to certain extent. Assume that the revenue of the doctor is relevant to drug sales volume. In other words, the doctor will receive revenue from some drug. Revenue function of the doctor will be $W = W(P, Q)$ and $Q = Q(r)$. The doctor will bear certain risks (cost) because of ADR incident, such as revenge from patients, censure from the society, administrative punishment and reduction in income. These risk costs may be classified into two parts: cost for revenge of patients against doctors because of excessive ADRs and enterprises' drug cost increased due to the chase of doctors for excessively low ADR incidence rate. The cost may affect the income of doctors, thus creating an opportunity cost on doctors. If these costs are relevant to r , doctors' cost function will be $C^D = C^D(r)$ and doctors' net revenue function will be $R = W(P, Q) -$

$C^D(r)$. The optimum decision of doctors is: $\frac{\partial \Pi}{\partial r} = W_Q(P, Q)Q_r - C_r^D(r) = 0$. Therefore, $W_Q(P, Q)Q_r = C_r^D(r)$ (3). At this time, profit function of pharmaceutical enterprises will be changed as doctors' income should be deducted: $\Pi = P(r, Q)Q - C^g(r, Q) - W(P, Q)$, and the optimized equation is $\frac{\partial \Pi}{\partial r} = Q_r(r, Q)P - C_r^g(r, Q) - W_Q Q_r = 0$

Therefore, $Q_r(r, Q)P - W_Q Q_r = C_r^g(r, Q)$ (4).

If the patient has no right of speech, the selection of ADR incidence rate is just the result of gaming between pharmaceutical enterprises and doctors. Therefore, (3) and (4) may be formed into a system of inequalities, and we can obtain the optimum ADR incidence rate and drug sales volume. If hospitals need to meet requirements of medication safety, other conditions may be added. For example, ADR incidence rate shall not exceed a value (\bar{r}), which means $r \leq \bar{r}$ (5).

Therefore, (3), (4) and (5) may be formed into a system of inequalities, and we can obtain the optimum ADR incidence rate and drug sales volume.

(2) Doctors and enterprise gaming model design and the balance

As $W = W(P, Q)$ and the revenue of doctors always comes from drugs, if f represents drug sales revenue, then $W = fPQ$. Doctors' cost function is $C^D = C^D(r) = kr^2 - jr + l$. If sales volume function is $Q(r) = b - cr$, doctors' net revenue function will be $R = W(P, Q) - C^D(r) = fP(b - cr) - kr^2 + jr - l$. When the interest of doctors is maximized, $\frac{\partial R}{\partial r} = -cfP - 2kr + j = 0$, and the optimum ADR incidence rate will be $r = \frac{j - cfP}{2k}$.

Gaming between pharmaceutical enterprises and patients based on interest (or patients' preference)

According to the report of UK media in 2012, Roche was investigated by European drug supervision departments as it concealed the fact that its products resulted in mortality of 15,000 cases and 65,000 ADR reports. The incident was in connection

with 8 types of drug. Sales volume of these drugs in some fields, especially for cancer treatment, was very high. For example, the global sales revenue of Rituxan was up to 6 billion Swiss Francs in last year. The incident may have certain impact on the market, and doctors will be cautious when they make out a prescription with drugs of Roche.

In 2009, Hefei Academy of Forensic Science drew a conclusion that Li Lili died of multiple organ failure caused by extensive rhabdomyolysis based on muscle damage due to the administration of “telbivudine” . Before the incident, there have been 5 ADR cases caused by the drug in Zhejiang Ningbo, Jinhua and other places. Two patients died of the ADR. On some patient forums in China, some people indicated that “telbivudine” causes heart palpitation, faintness, vomit, shock and other symptoms. However, no warning about side effects of the drug was provided in the instructions.

Based on the analysis of the above-mentioned two ADR cases, we can see that international famous pharmaceutical enterprises are not willing to publish ADR problems which were true and may result in more panic to the public because the enterprises worried about that the sales volume might be affected. Pharmaceutical enterprises may have two choices: The first choice is to publish the real ADR incidence rate to the market, which may affect the sales volume of the drug concerned. The second choice is to conceal the truth, which may increase the sales volume as well as the risk faced by patients. Pharmaceutical enterprises would choose the sales volume or the sales profit which is higher than the compensation for patients faced higher risk. If the compensation may be covered, pharmaceutical enterprises would conceal the ADR incidence rate. In fact, the compensation for ADR to be paid by pharmaceutical enterprises is minor compared with the high sales revenue and profit of the drug concerned or the compensation for ADR to be paid by pharmaceutical enterprises is far less than the profit gained by these enterprises through concealing the ADR incidence rate. However, loss may be fatal to patients who are harmed by ADRs. Pharmaceutical enterprises and patients are different in the choice about ADR incidence rate. Cause and route of generation of such difference are major content of this study.

(1) Assumption of patients' preference for ADR incidence rate

We assume that the ADR incidence rate is r , which is relevant to drug safety. For convenience in understanding, we assume that s is the drug safety coefficient, and the relation between the safety coefficient and ADR incidence rate is $S = \frac{1}{r}$. When patients buy prescription drugs or OTC drugs, doctors would have more decision-making power. Regardless of ethical risk faced by doctors, we assumed that doctors represent the benefit of patients, which is rational to a certain extent. If any serious ADR incident occurs, doctors need to bear high risks, such as being subject to administrative punishment or revenge from patients. Therefore, the study is conducted in the perspective of patients without considering benefit of doctors for the purpose of studying the development law of things in a direct and simple way. We assume that the preference of patients are as follows: $u = \{\theta s - p\}$, where θ is a parameter representing drug safety preference of patients. When the price is fixed, patients prefer drugs with higher safety level. By comparison, higher θ indicates that patients are willing to pay more for drugs with higher safety level. We assume that θ complies with a cumulative probability distribution function $F(\theta)$, an increasing function, that falls in the interval of $[0, +\infty]$, where parameter lower than θ . In the market, market demand is $D(p) = N[1 - F(p/s)]$, where N is the number of patients purchasing certain drug.

(2) Choices of patients and pharmaceutical enterprises about drug safety Case 1:

Patients' choice about drug safety

If pharmaceutical enterprises care about drug price p and drug safety s , $p = P(q, s)$ represents the inverse demand curve, which is the price of drug with demanded quantity of q and safety of s . Drugs with higher safety level will be more expensive. We assume that drug cost is $C = C(q, s)$, which indicates the cost of drug with demanded quantity of q and safety of s . The cost will increase with the rise in safety level. In other words, a great amount of fund should be invested if safer drugs are needed.

From the perspective of social welfare, drug with demanded quantity of q and safety of s and which will minimize the difference between patients' surplus and drug cost will be selected: $W(q, s) = \int_0^q P(x, s)dx - C(q, s)$. The optimum conditions are as follows:

$$P(q, s) = C_q(q, s) \quad (1), \quad \int_0^q P(x, s)dx = C_s(q, s) \quad (2)$$

(1) and (2) indicates the choice about the drug safety. Partial derivative of total patients' surplus for safety equals to marginal cost of the drug for safety. As $P(x, s)$ is the price paid by patients for drug safety, we can consider it as the price which will be paid by patient x for the increase of each unit of safety s . $R(x, s)$ is the marginal value of the drug safety chosen by marginal patients, is the marginal value of drug safety chosen by patients, and is the marginal value of average drug safety chosen by patients.

Case 2: Pharmaceutical enterprises' choice about drug safety

Pharmaceutical enterprises may only care about their own profit without considering patients' surplus. The profit function is as follow: $\pi(q, s) = qP(q, s) - C(q, s)$. Optimum conditions are as follows:

$$P(q, s) + qP_q(q, s) = C_q(q, s) \quad (3), \quad qP_s(q, s) = C_s(q, s) \quad (4)$$

According to equation (4), it is optimum for pharmaceutical enterprises when marginal value of drug safety chosen by patients equals to marginal cost of drug safety.

With respect to the choice about drug safety, we can see from the result of comparison between optimum choice of patients and optimum choice of pharmaceutical enterprises that patients attach the greatest importance to the impact of improvement in drug safety on all patients, which is the marginal value of drug safety chosen by marginal patients, and pharmaceutical enterprises focus on the impact of improvement

in drug safety on marginal patients, which is the extra revenue created by the improvement of each unit of safety. Therefore, optimum target of patients may be different from optimum target of pharmaceutical enterprises as patients focus on the impact of increase of each unit of drug safety on the value of all patients while pharmaceutical enterprises focus on the revenue created by the increase of each unit drug safety.

Based on the foresaid assumptions, when N is 1 and the formula are standardized, market demand will be $D(p) = 1 - F(p/s)$, the inverse function of which is $p = P(q, s) = sF^{-1}(1 - q)$, and average safety evaluation by patients is

$$\frac{1}{q} \int_0^q P_s(x, s) dx = \frac{1}{q} \int_0^q F^{-1}(1 - x) dx$$

It is optimum for pharmaceutical enterprises to care about marginal evaluation of marginal consumers: $P_s(q, s) = F^{-1}(1 - q)$. As $F^{-1}(1 - q)$ is an increasing function, $x \leq q$, $F^{-1}(1 - x) \geq F^{-1}(1 - q)$

To illustrate the difference in quality levels which are respectively optimum for patients and pharmaceutical enterprises, we assume that the safety preference coefficient θ is evenly distributed in the interval of $[0, 1]$, and $D(p) = q = 1 - F(p/s) = 1 - p/s$. Therefore, $p = s(1 - q)$. We can find that optimum safety choice of patients is:

$$\frac{1}{q} \int_0^q P_s(x, s) dx = \frac{1}{q} \int_0^q (1 - x) dx = 1 - \frac{1}{2}q$$

while that of pharmaceutical enterprises is $R(q, s) = 1 - q$. Therefore, $\frac{1}{q} \int_0^q P_s(x, s) dx > P_s(q, s)$ In other words, when the drug supply is fixed, pharmaceutical enterprises' safety supply does not reach the required level. We can say that the ADR incidence rate offered by pharmaceutical enterprises is lower than the rate required by patients (optimum rate) when the market-balanced sales volume remains unchanged.

If the drug safety cost is taken into consideration, drug supply and quality level for the optimum choice of patients and drug supply and quality level for optimum choice of pharmaceutical enterprises may be compared. We assume that there is a simple cost model which is consistent with the aforesaid assumptions. If the cost of a kind of drug is relevant to the supply and drug safety, which means $C(q, s) = c \frac{s^2}{2} q$, then we can find that $q = 2/3$ and $q = 2/3c$. Therefore, when drug safety level remains unchanged, the drug supply will be lower than the quantity demanded by patients (optimum).

2.5 Selection of pricing strategy for blockbuster drugs

Drugs are a special kind of commodities closely related to human life and health. How to provide safe, effective and accessible drugs has always been an important topic in global health. In July 2016, CFDA issued the Measures for the Administration of Drug Registration (Amendment) (hereinafter referred to as “the Amendment”). The Amendment focuses more on the essence of drug registration administration, that is, lead drug registration applicants and food and drug administrations by law to attach more importance to drug safety, efficacy and quality control in the process of drug registration from the perspective of drug functions. Drug innovation should return to clinical value and all innovative drugs should have clear clinical value. Similarly, modified new drugs should have a clear clinical advantage over original ones. Later, the Ministry of Human Resources and Social Security of the People’s Republic of China published a Notice on Requesting

Public Comments on the Work Plan for the Adjustment of the National Drug Catalog for Basic Medical Insurance, Work-Related Injury Insurance and Maternity Insurance 2016 (Draft for Comments) (hereinafter referred to as “the Notice”). The Notice specifies the revision principles, methods and ideas and the deadline for comments on the revision of the National Drug Catalog. The core work of this adjustment is to appropriately expand the scope of the Catalog, consider more about the clinical value

and replace the drugs without obvious clinical effects in the Catalog with similar ones which are clinically effective. According to the Notice, the following drugs will be given priority in selection of the drugs to be included in the Catalog: new drugs with high clinical value, drugs added in many local Class B drug adjustments, drugs for treatment of serious diseases, drugs for children, drugs for emergency treatment and special drugs for occupational diseases. It can be seen that the clinical value of a drug has become a key factor in determining whether the drug can be marketed and included in the Catalog. In consequence, the influence factors and evaluation indicators of the clinical value of drugs should be systematically studied and analyzed.

2.5.1 Selection of pricing strategy for blockbuster drugs

According to the definition of drugs, drugs are special substances ingested or otherwise introduced into the body by a specified method and in a particular dosage for prevention, treatment and/or diagnosis of diseases, and their use value is derived from clinical use. Clinical value is the core value of a drug and also the basis for determining its market value and social value. It can be said that without clinical value, other values are out of the question.

In many countries (e.g., Germany and France), the clinical value of drugs has been given much attention and regarded as an important basis for drug-related decisions, such as drug pricing, selection of the drugs in the National Drug Catalog and formulation of the guidelines for clinical medication.

Among put into effect in Germany in 2011 divides innovative drugs into six categories by their added benefits: “Major”, “Considerable”, “Minor”, “Non-quantifiable”, “No added benefits” and “Less benefits (than the appropriate comparative therapy)”. It can be seen that the first three categories of drugs have added benefits and the rest have no added benefits. Among specifies that the medical insurance payment price of a drug, of which the added benefits are unaccepted, should be subject to the price of the price reference group, and that of a drug with added

benefits should be jointly determined by the pharmaceutical company and the drug foundation, which may always be much higher than the price of the price reference group. The basis for determining added benefits is clinical value, and the evaluation indicators of added benefits include all-cause mortality, incidence rate, health-related quality of life and adverse effects [1]. In determining the price of a new drug, files should be submitted by the drug manufacturer and evaluated by IQWiG based on the four indicators to determine the added value of the drug relative to the appropriate comparative therapy.

In France, a drug should go through three processes before launched, that is, marketing approval, value assessment and price negotiation. Once a drug is approved for marketing, it will be assessed by HAS and the Transparency Commission for its therapeutic value and rated by its therapeutic progress (ASMR rating). On the basis of the assessment of the Transparency Commission, CEPS will negotiate with the manufacturer about the drug price (including retail price and hospital price) [2]. ASMR rating is also a process of determining the clinical value and the indicators for measuring the clinical value include safety, efficacy, quality controllability, compliance, innovativeness, meeting social needs or not and other social properties. ASMR rating directly determines the ex-factory price of drugs. In general, innovative drugs should reach ASMRI-ASMRIII and conventional drugs should be ASMRIV or ASMRV. The price difference between each two neighboring level is 30%. The drugs to be covered by medical insurance should reach ASMRIV at least. In order to be covered by medical insurance, the drugs at ASMRV should be cheaper than similar ones.

2.5.2 Preliminary construction of indicator system for clinical classification of drugs

China's indicator system for clinical value classification of drugs was preliminarily established based on the drug value evaluation standards in Germany and France and relevant researches in China [3]. Later, the research group held the first expert forum, carried out the first expert questionnaire, and modified the system according to

experts' opinions. The modified system is comprised of 2 Grade I indicators and 15 Grade II indicators under the two criteria of use value and innovation value, as shown in Table 20.

Table 20 Grade I and II indicators for clinical value classification of drugs

| Grade I | Grade II |
|------------------|---|
| Use value | Cure rate or efficiency Duration of efficacy All-cause mortality Severe adverse effects rate Non-severe adverse effects rate Compliance Convenience |
| Innovation value | Improvement of the health-related quality of life Included in China Pharmaceutical Reference or not Improved method for disease or injury treatment Modified preparation more practical in medical treatment Highly effective or highly safe Have any new main indication and efficacy-related pharmacological action Have any new main indication and efficacy for children Have any new main indication and efficacy for rare diseases |

2.5.3 Weights in indicator system for clinical value classification of drugs

The research group determines the weights in the indicator system by the Delphi method which is an important method of expert investigation. This method was first used for prediction by RAND Corporation in 1964 [4]. It is a quantitative and qualitative forecasting and evaluation method used to evaluate an object based on experts' consensus by anonymously collecting a wide range of experts' opinions and gradually making them accordant by repeated information exchanges, feedback and corrections.

(1) Expert questionnaire

To get the first-hand data and thereby make the investigation results more targeted and accurate, the research group repeatedly modified and improved the questionnaire design at three group meetings and then distributed the questionnaires to the experts present at the meetings and specially invited experts in the fields of clinical medicine, pharmacy and pharmacy management. Finally, 143 questionnaires were received, including 139 valid.

The statistics of expert information in the table above show that most of the interviewees in this survey are highly educated experts with high title and rich clinical experience, thus providing a professional and reliable guarantee for the survey.

Table 21 Expert information

| Item | Distribution | Number | Proportion (%) |
|----------|----------------------------------|--------|----------------|
| Work | Medical institutions | 111 | 79.9 |
| | Administrative departments | 2 | 1.4 |
| | Colleges and universities | 22 | 15.8 |
| | Scientific research institutions | 2 | 1.4 |
| | Pharmaceutical enterprises | 2 | 1.4 |
| | Doctor's degree or above | 53 | 38.1 |
| Diplomas | Master's degree | 58 | 41.7 |
| | Bachelor's degree or below | 28 | 20.1 |
| | Senior or above | 76 | 54.7 |
| Title | Deputy senior | 18 | 12.9 |
| | Intermediate or below | 45 | 32.3 |
| Total | | 139 | |

(2) Statistical analysis of data

Authority coefficient (CR) is calculated in this study, A high CR value represents a high authority coefficient. In this survey, experts ' familiarity with the indicators is 0.65 on average, 1.0 at maximum and 0.2 at minimum; the criterion of experts 'judgments is 0.78 on average, 0.8 at maximum and 0.2 at minimum; the authority coefficient calculated according to the above formula is 0.715 on average, 0.9 at maximum and 0.2 at minimum. In general, $CR \geq 0.7$ is deemed to be acceptable. It can be seen that the experts in this survey meet the requirements of authority, thus they can provide data support to the further study.

The enthusiasm coefficient is an important link in Delphi quality control. It shows the concerns of the selected experts on the issue in question, and indirectly reflects whether the selection of the experts is proper. Researches show that expert enthusiasm can be measured by the response rate of questionnaires, which can be calculated as per the formula below: response rate = (number of collected questionnaires/ number of distributed questionnaires) $\times 100\%$ = $(139/143) \times 100\%$ = 97.2%.

The expert opinion concentration is expressed as the mean value and full mark rate. Their results are shown in Table 22.

Expert opinion coordination is usually expressed as the coefficient of variation and the coordination coefficient. The coefficient of variation is an important indicator that represents the fluctuations in assessments, that is, the fluctuations of expert opinions. The lower the coefficient of variation is, the higher the expert opinion coordination will be. The calculation results of the coefficient of variation are shown in Table 22. It is 0.2342 at maximum and 0.0551 at minimum, indicating that each indicator has a good coordination.

By studying the coordination coefficient, we can understand experts' coordination towards all indicators. The coordination coefficient, i.e., Kendall coefficient, usually ranges from 0 to 1. A high coordination coefficient represents good expert opinion coordination; on the contrary, a low coordination coefficient represents poor expert opinion coordination. The results of the coordination coefficient calculated are shown in Table 23. The coordination coefficient: $W=0.771$, which is statistically significant.

Table 22 Mean, full mark rate and coefficient of variation of indicators

| Grade I | Grade II | Mean | Full mark rate | Standard deviation | Coefficient of variation |
|------------------|--|--------|----------------|--------------------|--------------------------|
| | Cure rate or efficiency | 4.9209 | 0.9209 | 0.2709 | 0.0551 |
| | Duration of efficacy | 4.219 | 0.6277 | 0.7348 | 0.1742 |
| | All-cause mortality | 4.4706 | 0.5588 | 0.677 | 0.1514 |
| | Severe adverse effects rate | 4.7482 | 0.7986 | 0.5529 | 0.1164 |
| Use value | Non-severe adverse effects rate | 3.7554 | 0.2302 | 0.9235 | 0.2459 |
| | Compliance | 4 | 0.2101 | 0.7249 | 0.1812 |
| | Convenience | 3.8905 | 0.1898 | 0.7734 | 0.1988 |
| | Improvement of the health-related quality of life | 4.413 | 0.4565 | 0.6362 | 0.1441 |
| | Included in China Pharmaceutical Reference or not | 4.0584 | 0.365 | 0.9056 | 0.2231 |
| | Improved method for disease or injury treatment | 4.2518 | 0.3525 | 0.6381 | 0.1501 |
| | Modified preparation more practical in medical treatment | 4.0217 | 0.2536 | 0.7396 | 0.1839 |
| | Highly effective or highly safe | 4.8175 | 0.8467 | 0.5032 | 0.1045 |
| Innovation value | Have any new main indication and efficacy-related pharmacological action | 4.0432 | 0.3022 | 0.8242 | 0.2038 |
| | Have any new main indication and efficacy for children | 4.0073 | 0.2774 | 0.7998 | 0.1999 |
| | Have any new main indication and efficacy for rare diseases | 3.7971 | 0.1971 | 0.8892 | 0.2342 |

Table 23 Kendall W test statistics

| N | Kendall W | Chi-square | df | sig |
|-----|-----------|------------|----|--------|
| 138 | 0.771 | 522.902 | 14 | <0.001 |

(3) Calculation of indicator weights

The weight of an indicator is the quotient calculated by dividing the score of this indicator by the total score of all indicators. It is usually expressed in decimal form.

The weight in percentage of each indicator can be calculated as per the formula:

$S_j = \sum W_i N_i$, where S_j is the score of the j^{th} indicator, j is the evaluated indicator; i is the evaluation rating. W_i is the score at the i^{th} level (weight coefficient), and N_i is the frequency of a specific indicator at the i^{th} level. Formula of the weight in percentage is $K_j = S_j / \sum W_i N_i$

Based on the statistical analysis of all indicators, the weight of the Grade I indicators under “Clinical Value” is calculated to be 0.606737 and that of the Grade II indicators under “Innovation Value” is calculated to be 0.393263. The initial weight and combination weight of each Grade II indicator and their rankings are shown in Table 24.

Based on the statistical analysis of all indicators, the weight of the Grade I indicators under “Use Value” is calculated to be 0.606737 and that of the Grade II indicators under “Innovation Value” is calculated to be 0.393263. Among the indicators, “cure rate or efficiency”, “Highly effective or highly safe”, “severe adverse effects rate”, “all-cause mortality”, “improvement of the health-related quality of life” and “improved method for disease or injury treatment” ranking in the first six places have a significant impact on the building of the indicator system for clinical value classification of drugs; hence, they should be given more attentions. Besides, “convenience”, “have any new main indication and efficacy for rare diseases” and “non-severe adverse effects rate” rank in the last three places, indicating that they have no prominent impact on the indicator system, compared with others.

Table 24 Initial weight and combination weight of all indicators and their rankings

| Grade I | Grade II | Initial weight | Combination weight | Ranking |
|------------------|--|----------------|--------------------|---------|
| | Cure rate or efficiency | 0.127895 | 0.077599 | 1 |
| | Duration of efficacy | 0.109653 | 0.06653 | 7 |
| | All-cause mortality | 0.116192 | 0.070498 | 4 |
| | Severe adverse effects rate | 0.123407 | 0.074876 | 3 |
| Use value | Non-severe adverse effects rate | 0.097604 | 0.05922 | 15 |
| | Compliance | 0.103961 | 0.063077 | 12 |
| | Convenience | 0.101115 | 0.06135 | 13 |
| | Improvement of the health-related quality of life | 0.114695 | 0.06959 | 5 |
| | Included in China Pharmaceutical Reference or not | 0.105479 | 0.063998 | 8 |
| | Improved method for disease or injury treatment | 0.170491 | 0.067048 | 6 |
| | Modified preparation more practical in medical treatment | 0.161264 | 0.063419 | 10 |
| Innovation value | Highly effective or highly safe | 0.193174 | 0.075968 | 2 |
| | Have any new main indication and efficacy-related pharmacological action | 0.162126 | 0.063758 | 9 |
| | Have any new main indication and efficacy for children | 0.160687 | 0.063192 | 11 |
| | Have any new main indication and efficacy for rare diseases | 0.152258 | 0.059877 | 14 |

(4) Application of the indicator system for clinical value classification of drugs based on the case study of statins

After getting the weight of each Grade I indicator and Grade II indicator, the research group studied the application of clinical value classification by taking statins as samples. According to the background information related to each indicator, the research group invited 6 senior experts with rich cardiovascular clinical experience from Fuwai Hospital, Beijing Hospital and Peking University First Hospital to score the 7 generic statins and then summarized the experts' scores and determined the ranking. The sources of the background information are shown in the Figure.7.

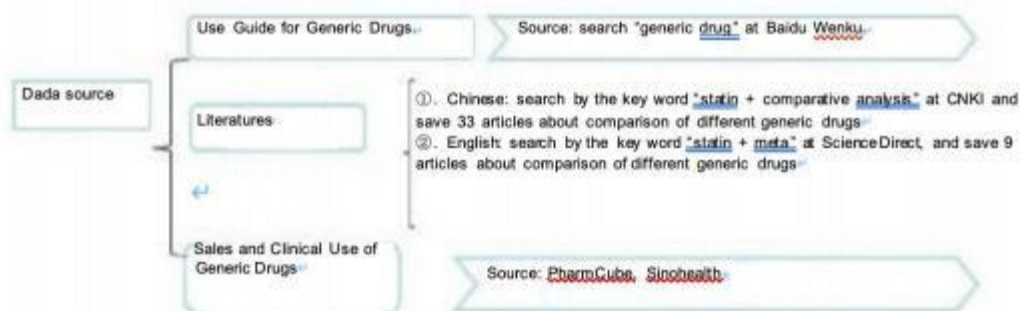


Figure 7 Source of the related data statins

The calculation process in Delphi statistical analysis is the same as the process of determining the weight of each indicator in the indicator system for clinical value classification of drugs in part 2 above; hence, no more detailed description here.

Based on the analysis of the collected questionnaires, the research group conducted a comparative analysis on atorvastatin and the other six statins (e.g., fluvastatin), calculated their weights by Delphi method and ranked them. Under the circumstance that atorvastatin is taken as the benchmark drug, the seven statins can be ranked by the total weight as follows: rosuvastatin, atorvastatin, pitavastatin, fluvastatin, pravastatin, simvastatin and lovastatin. After comparing this ranking with the ranking of DDD drug costs calculated at the bid price in Beijing in 2015, we found that the ranking of the bid prices of all drugs completely corresponds to that of their clinical value, except atorvastatin and pitavastatin. It can be seen that the bid prices of statins in China are mostly reasonable.

Table 25 Comparison of the weights of Atorvastatin and other generic statins and their bid price ranking

| Drug name | Total weight | Score ranking | Bid price ranking |
|--------------|--------------|---------------|-------------------|
| Atorvastatin | 1 | 2 | 3(4.38)10mg |
| Fluvastatin | 0.996925 | 4 | 4(3.29)40mg |
| Lovastatin | 0.988755 | 7 | 7(0.72)20mg |
| Rosuvastatin | 1.001979 | 1 | 1(5.66)10mg |
| Simvastatin | 0.9942 | 6 | 6(2.22)20mg |
| Pitavastatin | 0.997192 | 3 | 2(4.87)1mg |
| Pravastatin | 0.994986 | 5 | 5(2.98)10mg |

We further compared the consistency in the rankings of the price and clinical value of statins at home and abroad, including Germany, France, UK, US, Japan, South Korea, Chinese Mainland and Taiwan, China, by comparing the DDD costs of Lipitor (atorvastatin 10mg), Zocor (simvastatin 20mg) and Crestor (rosuvastatin 5mg) that are sold in all said countries and regions. Under the circumstance that atorvastatin is taken as the benchmark drug, the clinical value of the three drugs can be ranked as follows according to their total weights: rosuvastatin, atorvastatin and simvastatin. After comparing the DDD costs of the three drugs in different countries and regions, we found that the DDD cost of the same drug differs greatly in different countries and regions. In Germany, France, Chinese Mainland and Taiwan, China, the ranking of the DDD costs of the three drugs completely corresponds to that of their clinical value; however, simvastatin price ranks first in the UK, Japan and South Korea and atorvastatin price ranks first in the US. Besides, the prices of these three drugs are nearly the same in France and the South Korea; the DDD costs of Lipitor and Zocor in Chinese Mainland are much higher than those in other countries except the US. On the whole, the sales prices of the three drugs are low (less than € 1) in Germany, France, UK, South Korea and Taiwan, China. These differences may be related to such factors as the pricing strategy, medical insurance payment and market demand.

Table 26 Comparison of the weights of Rosuvastatin, Simvastatin and Atorvastatin and their price ranking in different countries and regions

| Drug name | Clinical value (ranking) | Commodity name | Specification | Germany | France | UK | US | Japan | South Korea | Mainland China | Taiwan China |
|--------------|--------------------------|----------------|---------------|----------|----------|----------|----------|----------|-------------|----------------|--------------|
| Atorvastatin | 1 (2) | Lipitor | 10mg | 0.59 (2) | 0.42 (2) | 0.46 (3) | 12.3 (1) | 0.87 (3) | 0.53 (2) | 6.20 (2) | 0.52 (2) |
| Simvastatin | 0.9942 (3) | Zocor | 20mg | 0.35 (3) | 0.41 (3) | 1.06 (1) | 8.19 (3) | 3.64 (2) | 0.54 (1) | 0.47 (3) | 0.18 (3) |
| Rosuvastatin | 1.001979 (1) | Crestor | 5mg | 1.09 (1) | 0.55 (1) | 0.64 (2) | 8.91 (2) | 1.08 (1) | 0.50 (3) | 7.83 (1) | 0.58 (1) |

2.5.4 Conclusions

The clinical value of a drug is an internationally accepted standard used to determine its reasonable price; it is feasible to determine the rationality of the price ranking of similar products based on the clinical value classification for drugs; among a large variety of statins, the price rankings of most generic statins are consistent with their clinical value ranking, that is, their bid prices can basically reflect their clinical value. The completeness and authenticity of the background information directly determines the clinical value classification, and further classifications entail more detailed information and data provided by manufacturers, medical insurance providers and other related parties. This study can judge whether the price of a drug is reasonable by comparing its clinical value ranking and price ranking; however, the specific price needs to be determined by pharmacoeconomic evaluation methods.

CHAPTER 3 RESEARCH PLAN

Our study has determined the basis for selection and indicator system of blockbuster drug R&D, and verified the feasibility and rationality of the selection model. As the regulatory policies of blockbuster drugs get increasingly stringent, safety has also become an important consideration for blockbuster drug R&D. At present, we have studied the optimal adverse effects rate of blockbuster drugs by building a game model, and determined the equilibrium game model. In the next sections, we will further study the rest three strategies in the Theory of 4Ps, namely, price, place and promotion, and develop the development strategies and paths of blockbuster drugs and determine the investment objectives and specific procedures of blockbuster drug R&D by drawing lessons from the international experience in blockbuster drug development and based on the current medical reform policies in China. The specific framework of the research plan is shown in Figure 8.

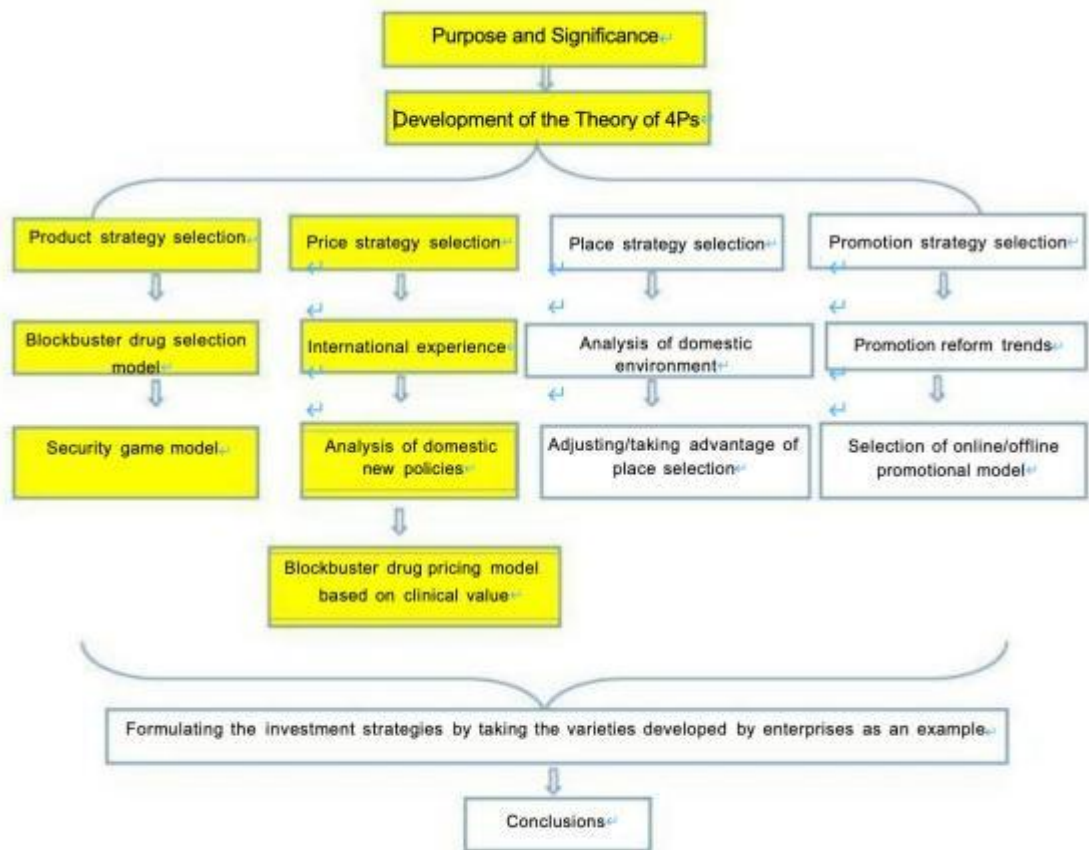


Figure 8 Research plan

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APPENDIX

Questionnaire of blockbuster drug evaluation indicator system

I. Basic Information

Please check the corresponding options or properly fill in the blanks.
(Note: the duration covered in the Questionnaire is nearly 5 years).

1. Age: _____; Gender: _____; Living city: _____

2. Work in: drug manufacturer pharmaceutical trading enterprise medical institution

administrative organ college/university medical research institution others

3. Academic degree: below technical secondary school technical secondary school college degree bachelor's degree master's degree doctor's degree

4. Title: none primary intermediate deputy senior senior

4. Work experience in this field: <2 years 2-5 years 5-8 years 8-10 years > 10 years

II. Evaluation Indicator Scoring

Please score the following twenty “factors influencing whether or not a specific drug produced by a specific enterprise is a blockbuster drug” on a five- point scale (1-not important; 5-very important) based on your experience by putting a tick in right blanks. If you have any question, please write it down in the “Remark” column.

III. Suggestions and Opinions

Please provide constructive opinions and suggestions on the following two questions.

1. Is there any other factor that should be considered in selection and evaluation of blockbuster drugs?

2. What are the key constraints in developing blockbuster drugs?

***The Questionnaire is over. Please check if all questions have been completed.
Thanks again for your cooperation! ***

| No | Item | Very important | Important | Moderate | Less important | Not important |
|--------|---|----------------|-----------|----------|----------------|---------------|
| 1 | Clinical efficacy (efficiency, cure rate, etc.) | | | | | |
| 2 | Adverse effects rate and hazards | | | | | |
| 3 | Unit price | | | | | |
| 4 | Economy (cost-effectiveness ratio) | | | | | |
| 5 | Incidence (or morbidity) of the indicated diseases | | | | | |
| 6 | Whether or not a medicine for stubborn disease? | | | | | |
| 7 | Production and supply capacity | | | | | |
| 8 | Sales area (in China) | | | | | |
| 9 | Inclusion in the essential medicine list or health insurance directory? | | | | | |
| 10 | International popularity | | | | | |
| 11 | Whether or not supported by proprietary intellectual property rights? | | | | | |
| 12 | Market share | | | | | |
| 13 | Market growth potential | | | | | |
| 14 | Whether or not generating annual sales of at least RMB 1 billion? | | | | | |
| 15 | Value added | | | | | |
| 16 | Sustainability | | | | | |
| 17 | Export sales area | | | | | |
| 18 | Annual export sales | | | | | |
| 19 | Manufacturer's annual output | | | | | |
| 20 | Manufacturer's reputation | | | | | |
| REMARK | | | | | | |