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Review and Prospective on Biomedical Development

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Abstract

This paper reviewed the progress of global biomedical development in 2017, as well as perspectives. First of all, there were many new drugs developed globally in 2017. In addition, scientific regulation has been paied more attention, by setting up review modes for both innovative and generic drugs, aiming to promote novel drug development, and restore balance between innovation drugs and generic drugs. Thirdly, it is expected that in 2018, the new pattern of drug development will become stable, the number of listed companies will increase, the key position of the global antidrug tumor and research and development for rare disease will remain unchanged. The development of generic drugs will also remain as the mainstream worldwide. Biotech drug research and development is expected to be rapidly developed, and immunotherapy becomes a new "hopspot" as well. Consequently, the original goal of Chinese medicine should not be left behind.. To develop Chinese biological medicine in order to increase the drug supply to meet the increasing demand of society is the mission and responsibility.

Key words: biomedicine; Innovative development; Innovative drugs; Generic drugs; Regulatory science; National drug safety

Introduction

Focusing on some hot issues of biomedicine development we published a commentary on the development of in China science daily for four consecutive weeks in the spring of 2018[1-4]. In In this article we will review global biomedical development at following four aspects: (1) global biomedicine research and development pattern has become more and more popular; (2) special consideration of the development of worldwide medical innovation and regulatory reform; (3) the development pattern of new drugs in the world is seeking progress in stability; and (4) in China development of biomedicine by remembering original, absorbing foreign, facing the future. Consequently, the original goal of Chinese medicine should not be left behind.. To develop Chinese biological medicine in order to increase the drug supply to meet the increasing demand of society is the mission and responsibility.

1. Global biomedicine research and development pattern has become more and more popular

From technological innovation, research and development pipeline to clinical examination, approval, and listed sales, 2017 is the year that global new drug research and development has come to blossom. In 2017, the FDA approved 46 new drugs, of which 35 were the first to be approved globally. The EMA recommended 92 drugs. Of the 92 listed, 51 are new indications, and four are the first to be approved globally. Japan is the third largest market for new drugs after the United States and the EU. In 2017, the PMDA approved 23 new drugs, three of them are new to the world.

1.1 *Global biomedicine research and development in* 2017

2017 is the year when the world's new drug research and development is in full bloom, and it offers higher expectations for the new drug market. In 2017, the FDA approved 46 new drugs, of which 35 were approved for the first time globally[5]. In 2017, 46 new drugs were approved by FDA in the US, hitting the highest number over 20 years, including 34 new small drug molecule and 12 biological products.

The US has approved new drugs to be against tumors and rare diseases, including 18 new drugs classified as orphan drugs, which accounts for 39 percent of new drug approvals. The EU approved 19 drugs for rare diseases treatment , accounting for 38% of the approval of new drugs. If the US determines a drug that has the potential to make substantial push on health care, it will receive priority

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review. In the field of treatment, anti-tumor drugs are still the majority in 2017, accounting for about 26%. In addition, anti-infective drugs have also made great progress, including 4 new antibacterial and 3 antivirals drugs. Breakthroughs were also made in areas such as glaucoma, hepatitis c, psoriasis, and diabetes. Of the new drugs approved in 2017, 20 were given priority reviews, accounting for 43.5% of the approved new drugs. The United States also applied a variety of regulatory approaches to speed up the development and approval of new drugs, including fast-track and breakthrough treatments. Accelerated reviews and new drug approvals for rare diseases have also been linked to a bumper harvest of new drugs last year.

The European Union (EMA) recommended 92 drugs, did not recommend 6 drugs, and 14 applications for approval were withdrawn. In those 92 recommended drugs, 51 were given new indications, 4 were firstly approved globally, 35 are never in EMA to approve new active substances before (the new active substance, NAS), and 2 are advanced treatment products (advanced therapy medicinal products, ATMPs). By speeding up the review of 19 orphan drugs, seven were speeded up in evaluation (accelerated assessments), three listed conditions permission (conditional marketing authorization), two were approved by special circumstances (approval under exceptional circumstances).

EMA, for the first time, listed four new drug approvals in the world. Eli Lilly's JAK inhibitor baricitinib was approved for the treatment of rheumatoid arthritis. Baricitinib is the first head butt beat adalimumab, a JAK inhibitor with resistance. The Pfizer's Besponsa (inotuzumab ozogamicin) is approved to treat acute lymphoblastic leukemia (ALL) in adult patients with recurrent or refractory b-cell precursors. In addition, the full genotype hepatitis C cocktail (Mavyret), which is composed of the NS3/4A protease inhibitor glecaprevir (100mg) and the NS5A inhibitor pibrentasvir (40mg), and padeliporfin for prostate cancer treatment that marks the birth of another new treatment for prostate cancer were given approval for marketing.

Japan has a large number of pharmaceutical companies; many pharmaceutical enterprises have strong new drug research and development capabilities. In 2017, Japan's PMDA approved 23 new drugs,among which 20 have been approved either in US or EU, and only three are PMDA's first global approval. The first is the Mundi-Pharm's Forodesine, which is used for the treatment of recurrent or refractory peripheral t-cell lymphoma (PTCL). The Second is Kowa Pharm's Pemafibrate, a PPAR α agonists for the treatment of hyperglycemia; The third is Maruho's Amenamevir for treatment of herpes zoster (Amenamevir initially developed by Astelas Co. then authorized to Maruho company).The product is a new type of resistance to banded virus drugs, helicase-primers combined enzyme inhibitors, through the influence DNA synthesis and exhibits antiviral effect.

The first FDA approved drug in 2017 is Synergy Pharmaceuticals' new drug, Trulance, which is used to treat chronic constipation. Another four for treatments of diseases of the central nervous system, are Ocrevus for multiple sclerosis, Radicava for amyotrophic lateral sclerosis (ALS), Xadago to control of Parkinson's disease, and Austedo to alleviate the symptoms of huntington's disease respectively. Of the new drugs approved by the FDA, 35 new drugs are among the first in the world. On December 11, 2017, the FDA approved the listing of Ozenoxacin of Medimetriks Co., a new antibiotic that is used to treat children with pustules for more than two months.

A total of 120 new drugs have been approved worldwide. In 2018, there are currenly 40-50 large clinical trials of investigated new drugs (IND), including the review of new drugs and filing of new drugs on the first half of this year. From the point of clinical safety and effectiveness, developed countries have different opinions on speeding up the review approval. For example, the American medical association (JAMA, 2016) comment pointed out that use of the end points for drug approval often lacks formal empirical verification of the strength of the surrogate-survival association after analysis on 83 new anti-cancer drugs (2009 − 2014)[6]. Of the 222 listed new drugs published in 2017, two-thirds have safety concerns, of which 71 have safety problems and 61 need to use black boxes to warn them of their safety[7]. Therefore, new drug users (medical practioners and patients) must pay great attention to safety, availability and accessibility.

1.2 *New drug discovery and development record.*

In 2017, the world's new drug research and development has achieved three milestones.

First, on May 23, 2017, MSD Keytruda was approved by FDA for carrying high instability or mismatch repair defects treatment of solid tumor patients. It became the first for treatment not based on tumor location, but based on tumor markers of cancer treatment, making significance in history.

Second, on August 30, 2017, the FDA approved the listing of Novartis's Kymriah for treatment of refractory or recurrent acute lymphatic leukemia in children under 25 years of age. Kymriah became the world's first CAR-T therapy[8,9]. Kymriah is used a genetically modified auto cell immunotherapy, which is a customized treatment produced by the patient's own T cells, and its safety and efficacy has been confirmed in clinical trials. Within three months treatment, although the response rate has high curative effect, the treatment still has potentially serious side effects: it may produce cytokine release syndrome (CRS) risk warning, which may result in life-threatening events. Other serious side effects include severe infection, hypotension, acute kidney injury, fever and lack of oxygen, disturbance of the normal B cells to produce antibodies, which further increase the risk of infection.

Third, on December 19, 2017, FDA approved Luxturna, a gene therapy by Spark Therapeutics, for the treatment of hereditary retinopathy. Luxturna corrects the gene directly in the patient, which marks the formal arrival of the era of gene therapy[10,11]. The ability of patients in the experimental group to avoid obstacles in dark light was significantly improved after an injection of Luxturna. However, it has the most common adverse reactions, such as conjunctival congestion, cataracts, high intraocular pressure, and retinal tears, which should not be ignored.

In addition, the problem of the development of Chimeric Anti-

gen Receptor T-cell Immunotherapy (CAR-T) are further discussed. Since this is a new type of cell therapy that has been investigated for years, but was improved only recently.

CAR-T treatment process is complicated, a typical car-t treatment process is divided into the following five steps: (1) separation: isolate immune T cells from cancer patients. (2) modification: using genetic engineering technology, T cells can be added to a cell that can recognize tumor cells and activate T cells at the same time to produce CAR-T cells. (3) amplification: in vitro culture, amplification of CAR-T cells. (4) quality control: closely monitor the patient, especially the violent reaction of the body during the first few days. (5) return: the amplified CAR-T cells return to the patient. The duration of the treatment is longer, lasting about three weeks, and the cell "extract-modification-amplification" takes about two weeks.

Patients with refractory or recurrent chronic lymphocytic leukemia (CLL) have poor prognosis. The sustained remission of b-cell malignancies with the targeted CD19 chimera antigen receptor (CAR) T cells has the potential to improve the low remission rate of conventional therapy. Preliminary results of 3 cases of intractable CLL treatment have been reported. The treatment of acute leukemia and non-hodgkin's lymphoma has a significant curative effect and is considered to be one of the most promising approaches to tumor treatment. As with all technologies, CAR-T technology has undergone a long evolutionary process, and it is in this series of evolution that CAR-T technology is gradually maturing.

The successful approval of CAR-T therapy is inseparable from the innovation and development efforts of the troika (Novartis, Kite, Juno), and the participation and promotion of large pharmaceutical companies such as Pfizer, GSK and Eli Lilly. China's representative enterprises have also made great contributions to the development of technology and application in the field of global cell therapy. Based on the broad market prospect of CAR-T drugs, China is also seeking a breakthrough in the industrialization of cell immunotherapy represented by CAR-T therapy. Released on December 22, 2017, the China FDA (CFDA) published the cell therapy product research and evaluation of technical guidelines (Draft), as the standardization of the drug properties for cell therapy products in our country industrialization production. In the field of CAR-T, China has launched more than a hundred exploratory clinical research projects, such as global immune cells in clinical treatment.

CAR-T is no doubt a promising therapy, but issues remians. At present, the key problem of CAR-T is how to improve its medical availability, memorize T cells and maintain persistence, reduce side effects and costs, and automation of equipment. Industrializing autologous adoptive immunotherapies are manufacturing advances and challenges for manufacturing process changes. Newer manufacturing technologies and platforms will have their greatest impact on early stage clinical products, where they can be designed and validated in IND submissions for Chemistry, Manufacturing and Control (CMC) documentation[9].

1.3 *China's new drug examination and approval policy has led to a surge in new drug approvals.*

2017 is China's "New Year of new drugs": the clinical and public approval policies for new drugs have been released, the Chinese food and drug administration (CFDA) has developed on a speedway, and a large number of new drugs have been approved for clinical trials. In 2017, clinical trials are approved for nine new drugs, the number reached the top in recent years. According to the China medical industry information center, the number of clinical trial applications of class 1 drugs by CDE has reached 199 by the end of 2017, increased rapidly from 2016. The number of drugs approved for listing in 2017 reached 48. The number of anti-tumor drugs is on the top of the list and the anti-infective drugs and nervous system drugs are ranked second and third place.

China's intrinsic innovations are obviously deficient. According to the application of new drugs, domestic innovative drugs are at the early stage of development and relatively few of them have been approved. 16 domestic chemical new drugs are approved in 2017, and nine enterprises have applied to cover the active ingredients of five drugs. Currently, more than 300 domestic new drugs are filed each year, and these products are expected to be approved gradually in three to five years. On biotech drugs, only one domestic product was approved in 2017. Ebola virus vaccine jointly developed by institute of biological engineering, the military academy of medical sciences, and Tianjin Kang-Xi-Nuo Biological co., LTD has been approved by CFDA in October 2017.

To speed up the marketing of new products, we can better meet the clinical needs of the patients. From the recent outbreak of "health deficit" public opinion, innovative drugs of the future market prospects may not be optimistic, health hope to meet clinical needs and restore the balance between medical insurance funds as a whole. Over the next five to ten years, a large number of drug post-marketing curative effect similar to that of innovation will likely face the situation of price fight, if continue to use the drug bidding method, the predicament of bidding in the new drugs and generic drugs will remain unchanged.

As the "priority review" system officially launched in China, the speed of "assimilation of forgein technology" is accelerated, and imported drugs start to pile into the Chinese market. According to incomplete statistics, in 2017 there were approximately 20 foreign drug approved, including Bayer, Novartis, Sanofi, Johnson & Johnson, multinationals such as Astrazeneca products, covering hepatitis C, diabetes, Parkinson's disease, AIDS, hypertension, depression and others. Among these new drugs, oncology drugs holds 35%, hepatitis C about 20 %, and diabetes drugs about 10 %, respectively. Of HCV drugs, in addition to two new drug approvals by Bristol-Myers Squibb (China) investment and Sofosbuvir Tablets by Jiliya, are also listed entered the CDE "priority review product list". The result is confirmed in Europe and the curative effect is distinct, HCV drugs battle is unfolding.

1.4 *domestic drugs have achieved good results abroad.*

In 2017, a total of five drugs for monoclonal antibodies were announced successful in the United States. During the research and development of biosimilars, it is mainly foucused on those products

such asadalimumab, trastuzumab, bevacizumab and rituximab. The production costs and prices of biosimilars have been reduced, so the patient access to drugs can be expanded. Furthermore, Chinese medicine products from six domestic companies are now at the stage of clinical trials in the United States.

Domestic enterprises Hengrui Pharma, Zhengda Tianqing, He-Huang Pharma have heavily invested on those innovative small molecule targeted drugs. Although the mechanisms of action and indications are different, all belong to me-too class of drug.The registration applications of ilaprazole Sodium for Injection and raw material production have completed the evaluation and approval.

So far, Huahai pharmaceutical has holding 17 independent research and development of prescription drugs on market in the United States, In addition, over 20 ANDA generic drugs approved by FDA, and 30 products on the waiting list for FDA approval. It becomes China's first large-scale preparation export pharmaceutical companies in the United States. Qilu pharmaceutical also exports the preparations to the US, covering areas such as anti-tumor, anti-infection, and the growth is increasing at high speed. The transformation and development of preparation export by Hengrui, Shijiezhuang medicine Ouyi, Luye Pharma, Hua-an Pharmaceutical, Xinhua Pharmaceutical, Shenzhen Zhijun, Shenzhen Lijian also made them outstanding achievements in high-end markets, for instance EU and US.

2. Special consideration of the development of worldwide medical innovation and regulatory reform.

Driven by heavy weight product, the rapid development of biotechnology, pharmaceutical consumption structure changed. Drug safety issues, Status of chemical medicine in market is now under serious challenge, and biomedicine has become a hotspot in drug development. At the same time, new technology will be applied to the germplasm improvement of natural medicine, and natural medicine will develop rapidly.

High investment, high risk and low return are still a great challenge faced by the world's pharmaceutical industries. In 2017, the rate of return is only 3.1%, far below the value of 10.7% in 2010, also less than 3.7% in 2016. In particular, multinational pharmaceutical companies entering the Chinese market are faced with problems such as how to promote sales in hospitals, medical insurance, opening channels and seize the market.

In 2017, the authorities in United States have realized the importance of scientific supervision to promote the development of innovative new drugs, and establish an innovative drug and generic drug review pattern to achieve a win-win mode to restore balance between innovative drugs and generic drugs. China has also introduced a number of new policies to encourage innovation and speed up the review and approval process, but there is still a long way to go for drug regulatory reform.

2.1 *The United States great importance to the development of regulatory science.*

The FDA commissioner is nominated by the President of the United States and approved by the senate. Dr Scott Gottlieb, who has been appointed director of the US Food and Drug Administration, has demonstrated the breadth and depth of management that he has shown at the helm since 2016. In various aspects of management activities, such as dealing with opioid epidemic, improving the approval efficiency of generic drugs and speeding up the review of new drugs. He has also started a process to promote new equipment development in response to changing medical plans. 2017 is the year of achievements: the number of new drugs approved by FDA hutted new high record, the CAR-T treatment has became a milestone, the first prescription for dealing with opioid addiction APP applications was also put forward.

The FDA's reform of drug review systems, such as the inclusion of patients' opinions and recommendations in drug review decisions is believed that patients can understand more of the pain of illness, and that patients are more qualified to weigh the risks and benefits of a drug. Therefore, the patient's opinions and suggestions should be taken into full consideration in the process of drug review. It is encouraged to speed up the development of antimicrobials, allowing certain antimicrobials to be approved only in small clinical trials; allow the inclusion of major innovative medical device products in the FDA's accelerated review channel. The exclusive period of new indications for rare diseases is now extended by 6 months.

The United States has seen great changes in the development of new drugs for innovation in regulatory science[12-14]. The first is the promotion of drug development through the CDER (human medicinal center, USA) and CBER (biological products review and research center) communication activities. The progress in the process of drug development and clinical trial sponsors have enhanced communication. There is promotion in the application of biomarkers and pharmacogenomics, promotion in the development of patient reporting outcomes (PROs) and other end-point evaluation tools, and promotion in the development of drugs for rare diseases. Second, the risk benefit evaluation tool was used in the evaluation of new drugs, and the patient centered drug development project (PFDD) meeting was held in the PFDD to publish the summary report. Third, the FDA's drug safety system is modernized, including evaluation of risk assessment and the implementation of the reduction strategy (REMS) effect, promoting the standardization of REMS into the health care system, and promoting the modernization of pharmacovigilance. Fourth, they will continue to enforce eCTD and improve the efficiency of drug evaluation by using the generic technology document (eCTD). Fifth, the review of new drugs is accelerated. The prescription drug user fee method (pdumsf) has proposed to "promoting the transparency and communication exchange program of NME and original BLA" in order to promote the approval of innovative drug reviews.

The generic drug review office (OGD) has als proposed a priority area for generic drugs, which have been approved for about 600 generic drugs a year since 2008. In the study of the replacement of generic drugs with the patients' needs, the patients' opinions were

more integrated into the evaluation of the generic drugs. The aim is to develop a consistent evaluation method of complex dosage forms and slow-release drugs to promote the listing of generic drugs of various types of products, and to develop the bioequivalence (BE) method of inhalation, ophthalmic or gastrointestinal drugs, etc. Treatment equivalent (TE) evaluation and standard is established; advanced computing and analytical tools are also established to promote the development of the modern ANDA review process. In recent years, by contrast, the number of generic drugs that have been approved in China are increasing in double digits. The consistency of generic drugs has been evaluated since the beginning of 2013 to early 2017, and the coming year is the decisive year to achieve the target.

2.2 *Drug test "patient-centered" 4P model.*

The change of clinical research and development pattern of new drug is presented in many aspects. Speeding up the approval process is one of them. The FDA has made four major changes: fast-track, breakthrough therapy, accelerated approval and priority review. Fast track is for treatment of serious diseases and clinical medication vacancies; breakthrough therapy was aimed creating new drugs that are better than existing therapies; acceleration is for the approval for the clinical medication vacancies now, based on the surrogate endpoints and approval of new drugs; priority review refers to the acceptance within 6 months after completion of application for review of new drugs.

With respect to today's new 4P medical model (prevention, prediction, individualization and patient participation), the FDA's CDER attaches great importance to the external participation. The key features are attaching great importance to the patient, systematically considering a patient's experience, views and requirements, prioritizing the patient's condition and treatment options.

Working to strengthen the supervision of making patients the center of drug development and decision making, CDER realized that it is necessary to adopt a scientific and rational way to collect patients, in order to provide information to regulatory decision making. It can be said that patient involvement has become an integral part of the drug development process. But the regulatory work extends to many scientific, clinical and technical fields, and still fails to meet all the patients' requirements.

Under the new 4P medical model, the clinical trial mode is also developing. In the clinical evaluation of targeted drugs for cancer treatment, how to improve the efficiency of research and development is conducive to curative effect of the individual treatment, the research believes basket R&D model will change to the traditional clinical trials to "disease" as the center of the umbrella model (Figure 1).Accurate model of the future of the medical treatment may be an umbrella (the same kind of disease) according to different target design way of thinking, different treatment mode (to have the same molecular targets) or basket of several different types of cancer. The short-term goal of precision medicine is to use targeted drugs based on individual differences, use combination therapy, and understand the resistance of different individuals to achieve accurate treatment. Therefore, the clinical study of the "basket + umbrella" mode (Figure 1) will be benefitical to more patients from precision medicine.

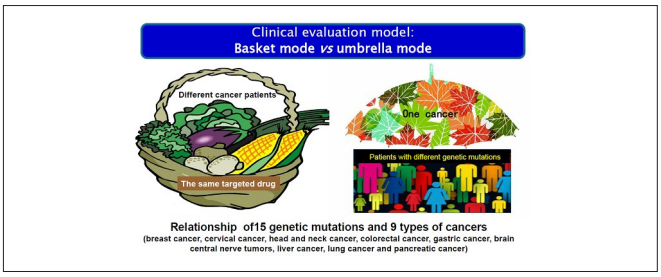

Figure 1. Basket mode and umbrella mode.

2.3 *The regulation of clinical trials of new drugs in India is becoming increasingly strict*

Over the years, India has developed many multinational pharmaceutical companies. As "so called humanitarian" western pharmaceutical companies transfer clinical trials to India, many medical organization in India including international humanitarian organizations have criticized the movement. Yet when multinational pharmaceutical companies are making good returns, the Indians in the trials may pay a heavy price. In 2013, Indian minister of health Ghulam Nabi Azad testified in the Indian parliament that the number of people who have died in clinical trials or suffer severe damage is still not clear; The government has to testify in between 2005 and 2012, about 2644 people died in the new drug clinical trials, with 80 deaths having direct relationship to clinical trials, and another 500 from the serious adverse reactions. The Indian government has attempted to improve management by ruling that all clinical trials must be approved by an independent ethics committee as previously done by pharmaceutical companies. The new regulations also require that companies undertaking trials bear full responsibility for any injury or death that is directly attributed to the test. As a result, many foreign pharmaceutical companies are likely to be more concerned about the long-term health of the participants.

India's regulator has taken a big step forward in its national interest, has become increasingly concerned with the use of human trials, and has been strongly opposed to unsafe new drug trials. Since the new approach was announced, the national institutes of health (NIH) has suspended more than 40 clinical trials in India, and several U.S. and Canadian companies have followed the requirement. Clinical trials are still under discussion, and the possibility of a weaker position is not ruled out by the Indian parliament at the end of this year.

Due to the technical capabilities, cost effective and convenient degree of various factors such as business on pharmacovigilance, health economics and outcomes research, clinical data management, and biostatistics, the number of clinical trials are decreased in India. Under the bat clinical trials, to reduce the approval time and strengthen the coordinated clinical trials, India had done many regulations revision. Through these measures, India will once again be

in the future friendly clinical trial. However, it is still very difficult to continuously monitor, develop and maintain the interests of the subjects and conduct clinical trial management through uniform standards and global standards.

2.4 *Achievements and challenges of China's drug regulatory reform*

In 2016-2017, the state food and drug administration and relevant regulatory authorities have formulated a regulatory system in the pharmaceutical industry. Especially under official document issued on March 5, 2016, by the state council general office on the evaluation opinions of generic drug quality and curative effect of consistency, put forward to carry out the quality of generic drugs and curative effect evaluation of consistency, to improve the overall level of China's pharmaceutical industry, ensuring drug is safe and effective, and further promote industrial upgrading and structural adjustment, strengthen international competitiveness.

China still faces problems and challenges in accelerating drug regulatory reform. First, the policy formulation is directly applicable to clinical medication needs. Second, the policy formulation of the pharmaceutical industry needs to cross a certain enterprise and specific products; Third, the aim of innovation is not only the success of enterprises, but also the availability and accessibility of social development and clinical medication. Therefore, reform must fulfill the demand of social development.

All these measures provide policy guarantee and guarantee of national drug safety for supply-side reform and healthy development. The examination and approval policy need to be improved for the urgent need of clinical products. For the listed clinical urgent drugs, there should be corresponding policies and preferential policies, through the entry into the medical insurance varieties and the bidding of the standard varieties of measures, to improve the return of the drug products.

To encourage research and development of China's drug innovation, the state introduced a lot of new policies to encourage innovation, such as encouraging global multicenter synchronization clinical trials through generics consistency evaluation prior to purchasing drugs, and others. To strengthen the research and development and industrialization of medicinal materials, slow-release for production, and using intelligent agents to provide high-end accessories are still the development goals. Currently, a few enterprises' development pattern and the development environment are not optimistic: domestic clinical trial capacity is insufficient, institutional integrity quality does not reach the designated position (new drug application projects back 80% out of 2016 clinical problems), and lacks scientific evaluation (a large number of medical papers are checked). The national innovation program is too long (long time cost), and the real R&D time is limited. A considerable number of enterprise research institutes are in less good standing, and the level of the contract laboratory is far from each other.

3. The development pattern of new drugs in the world is seeking progress in stability.

The development of new drugs has steadily increased the number of listed companies, and the development of the world's tumor and rare diseases has remained unchanged. In the meanwhile, the development of generic drugs in the world has not been shaken. The research and development of biotechnology drugs continues to expand the therapies for treatment, and the immunotherapy with CAR-T becomes popular. Due to the increasingly fierce competition in the industry development in 2018, a new development pattern has emerged in the global bio-pharmaceutical mergers and acquisitions.

3.1 *The number of new drug development pattern steadily increases.*

To predict the development of new drugs in 2018, it is worth paying attention to the changes in policy regulation. US President Trump and the new administration of the FDA are in charge, and the approval of the FDA in the life of innovation and biosimilars/generic drugs continues to be relaxed. In addition, whether the external migration of Britain's brexit process affects the adjustment of EU approval policy was unknown. More breakthrough drugs or immunotherapies will be hot spots, such as CAR-T therapy, where more products are expected to be available.

Based on the research and analysis of their clinical and development stage, the following monoclonal antibody drugs are expected to be approved in 2018.TMB-355, a target of human immunodeficiency virus (HIV) antibodies to fight against AIDS, has been listed in the review stage. Once approved, the drug will help patients overcome resistance to traditional antiviral drugs. It is believed that in 2018, the field of migraine will leap from "no effective treatment" to "giant competition". There are three drugs for migraine, namely Erenumab, Galcanezumab and tiva's Fremanezumab. Caplacizumab of Ablynx is used to treat acquired thrombotic thrombocytopenic purpura. Once approved, it would be the first approved nano-antibody drug. Abbevi's Rovalpituzumab tesirine, or ADC drug targeted at DLL4, is expected to be used to treat small cell lung cancer. Again, once approved, it will be the world's fifth approved ADC drug. EvaluatePhama, a consultancy, predicts sales of $239 million in 2022. In addition, li's Sirukumab, concord and Burosumab of the kirin are also very promising.

3.2 *The key status of drug research and development of the world tumor and rare diseases is unchanged.*

Cancer has been the main cause of human illness and death. According to the published data, from the comparison between the incidence and death, some tumors not only have low morbidity, but also high mortality due to the lack of effective treatment methods. If the incidence is high, but death rate is not high, it generally indicates that there are better treatment measures.

The lancet, a leading British medical journal, published a report

on the number of young people aged between 20 and 39 who are diagnosed with cancer every year, including 360,000 deaths and 20% are breast cancer. The trend of cancer developing in the younger generation should raise concern. In 2017, 1,688,780 new cancer cases and 600,920 cancer deaths are projected to occur in the United States. For all sites combined, the cancer incidence rate is 20% higher in men than in women, while the cancer death rate is 40% higher. However, sex disparities vary by cancer types. For example, thyroid cancer incidence rates are 3-fold higher in women than in men (21 vs 7 per 100,000 population), despite equivalent death rates (0.5 per 100,000 population), largely reflecting sex differences in the epidemic of diagnosis. Prostate, lung and bronchus, and colorectal cancers account for 42% of all cases in men, with prostate cancer alone accounting for almost 1 in 5 new diagnoses. For women, the 3 most commonly diagnosed cancers are breast, lung and bronchus, and colorectum, which collectively represent one-half of all cases; breast cancer alone is expected to account for 30% of all new cancer diagnoses in women. From 1991 to 2014, the overall cancer death rate dropped 25% , translating to approximately 2,143,200 fewer cancer deaths than would have been expected if death rates had remained at their peak.

Although the cancer death rate was 15% higher in blacks than in whites in 2014, increasing access to care as a result of the Patient Protection and Affordable Care Act may expedite the narrowing of racial gap; from 2010 to 2015, the proportion of blacks who were uninsured halved, from 21% to 11%, as it did for Hispanics (31% to 16%). Gains in coverage for traditionally underserved Americans will facilitate the broader application of existing cancer control knowledge across every segment of the population.

In 2017, Cancer Statistics (2017) published by the American Cancer society points out that over the past two decades, as a number of innovative drugs and treatments have been used in clinical trials, the level of Cancer treatment has gradually increased in 2017. Overall cancer mortality in the United States has dropped by 25%. In contrast, China's latest cancer data published shows that cancer mortality in China is still rising. According to the data, the mortality rate of China's 122.2 per 100,000 people is significantly higher than that of the world average of 102.4/100,000, ranking the 29th in the world[15].

The reasons for the higher mortality are related to the Chinese cancer pedigree and the level of consciousness of screening and the level of diagnosis and treatment.

According to Cortellis data, in 2017, a total of 617 antitumnor drugs were given approval or at least allowed to enter into phase II clinical trials on the mainstream market (refers to the United States, the European Union, Britain, Japan and China) accounts for nearly half of all therapeutic areas[16](Figure 2). Of all drugs at Phase II clinical trials, 225 new drugs within 15 targets are expected to recently approved in 2017.

With the progressing development of molecular oncology research and gene sequencing of precision medical improvement, anti-tumor research of breakthrough progress has been made in recent years, a series of tumor immune escape, signal pathway, the innovation of the targets, such as cell cycle dependent protein drugs are

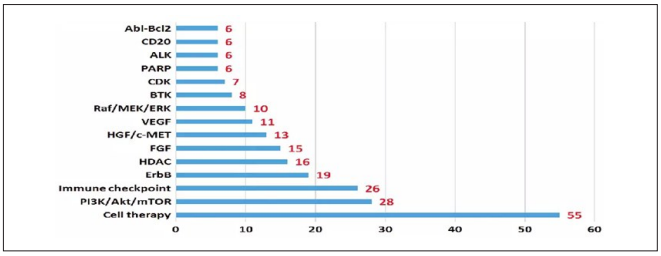

Figure 2. The 15 targets of the world's hottest cancer drugs are 255 varieties in 2017[16]

listed or entered into the middle and later stage of clinical study. Tumor immune is in recent years and the future for a long time the hottest anti-cancer research field, including CAR-T cells immunotherapy and PD-1/L1 immune checkpoint.

Targeted drugs and the use of personalized medicine for new immunotherapy bring practical benefits. Because the urgent need for cancer treatment is still unmet, investment in and outside the industry continues to grow. Fifty percent of the products in cancer drugs are concentrated in non-small cell lung cancer and breast cancer. In 2011-2016, 68 new drugs for 22 indications worldwide were approved. Of all those new drugs approved by FDA in 2017, there were 12 novel anti-cancer drugs, including 5 for blood cancer, 4 are used to treat breast and ovarian cancer, and for urothelial carcinoma, lung cancer, and Angela Merkel cell carcinoma. In 2017, the global tumor market will reach $130 billion, with an average annual growth rate of about 9% over the past five years. Growth is expected to be above 10% this year.

In IMS's latest "Global Oncology Trends 2017"[16], the overall drugs approved in the period of 2011-2016 were 42 anticancer drugs, only four are approved in China. In contrast, the United States and other countries such as Germany, Britain, Sweden, Italy, Canada, France, Japan and Australia approved more than 20, with the United States having the most 37 new drugs. The approved 10-19 drugs by 7countries (Spain 19, Poland 18, South Korea 17, Mexico 17, Russia 16, the Philippines 10, Brazil 10) . The approved drugs are between 1-7 by 7 countries (Turkey 7, India 4, China 4, Indonesia 4, Kazakhstan 4, South Africa 3 and Vietnam 1) [16] .

3.3 *The development of biotechnology is the basis for the development of treatment.*

The basic research of life science is to accelerate the innovation of biological medicine, master the core key technology and intellectual property, and improve the foundation of original ability. We will vigorously develop new products and new formats, occupy the commanding heights of industrial development, enhance the core competitiveness of the industry, and foster a high value-added industrial chain. Basic research of life science is also helping to promote enterprise innovation, maintain the status of enterprise innovation, guide the innovative factors to the enterprise to gather momentum, enhance biological industry and the generic technology's ability to support new forms, new industries, and build a competitive advantage of industry chain, characteristic industrial clusters. Grasping

the development opportunities in the world and new business development and financial innovation, actively exploring new mode of international cooperation, promoting optimizing the allocation of global resources, biological technology, talent and capital, all together promote a mutually beneficial win-win cooperation.

In the 21st century, biotechnology develops faster and faster. Overall, biological technology and comprehensive penetration on science, technology and method innovation appears especially important, such as genomics, bioinformatics, antibody engineering, tissue engineering, and ecology. The development of modern biological science is more and more obvious between biological science and mathematics, physics, chemistry and other sciences. Many are in the use of advanced technology and approaches, such as recombinant DNA, DNA sequencing, DNA synthesis, fast protein synthetic, determination of protein sequences, restriction enzyme technology, antisense RNA, PCR amplification, monoclonal antibodies, pulse electrophoresis, magnetic resonance and atomic force microscopy, scanning tunnel, synchrotron radiation industry electronic technology as the basis for biomedical research. Computers laid a solid foundation for advancement in genetic engineering, cell engineering, enzyme engineering representing the rapid development of modern biological technology.

From the perspective of technological innovation, more than 2, 200 kinds of biotechnology drugs have been developed in the world, with over 1,700 of them entering clinical trials. In the 21st century, when the global pharmaceutical industrialization enters the harvest period, China's innovation ability should not be underestimated[17]. There are six basic research results, (1) the multiplexed automated genome engineering (MAGE) technique can be done in every organism for which viruses are a problem — microorganisms used in the dairy industry and agriculturally important plants and animals; (2) the Codon heavy coding technique is the window of gene editing tool, CRISPR. this new Codon heavy coding (Codon recoding) is a completely generic, which can make all kinds of organisms produce resistance to most or all of the virus; it can accurately change thousands of sites in each cell gene editing techniques. This technique, in the development of biomedicine, is expected to improve the vaccine strain of Salmonella typhimurium; (3) multiple resistance error correction of fluorescence in situ hybridization (MERFISH) in large-scale complex way tags and serial imaging to detect the barcode, and the spatial resolution of RNA analysis data will provide us with the physical picture of human cell mapping plan. Also with other imaging techniques, we can obtain the cell morphology and function of datatotreat diseases, which is helpful to design effective treatment methods; (4) in the field of cancer immunogenomics, mutant proteins encoded by the cancer genome elicit an immune response in a given individual. A new antigen technique (CyTOF) is used to identify the mass cell count method of cells expressing specific proteins. Compared with typical flow cell technology, CyTOF uses mass spectrometry to change the cancer immunogenomics, which can be used to create a personalized "vaccine" against cancer. When the vaccine is combined with a new type of cancer drug that switches on the immune system, cancer patients rely on their own immunity to beat cancer; (5) genotype expression technology will calculate and be formed by the combination of sequential window acquisition of all theoretical mass spectra (SWATH-MS) quantitative proteomic techniques. This method is enough to show mutations that alter protein composition, topology, structure and function;and (6) the improvement of focused ion beam etching technology will help to design targeted drugs to eliminate, inactivate or activate related target proteins[-17] The development of the global monoclonal antibody in 2018 will follow the trend of 2017. On the other hand, indications of diseases other than cancer and immune diseases will continue to develop, and the application of monoclonal antibody drugs is promising. The double specificity antibodies, drug coupling (ADC) and miniaturization of antibodies and other major engineering technology will be continuously developing and application of many new molecular designs will be tried in clinical trials. Monoclonal antibody drugs, targeting immunodeficiency virus (HIV) of anti-HIV antibody have been listed in the review to be approved in 2018. The drugs that treat migraines, the Erenumab of Amgen, Galcanezumab of ELi Lilly, and Fremanezumab of Teva will cross to the competition in 2018. An ADC drug targeted at DLL4 is expected to be used in the treatment of small cell lung cancer, abbevi's Rovalpituzumab tesirine. And the Sirukumab consonant and fermented Burosumab are also promising.

3.4 *The status of generic medicines supply for people's livelihood remains globally unchanged*

Generic drugs are the fundermental of the people's livelihood. The medical expenses of all countries are stubbornly high. The government and medical institutions encourage the use of generic drugs to replace brand drug through legislation, law, government subsidies, patent litigation, forced brand drug price reduction and other means. WHO publishes the generics guide, used to guide each member of the generic drug evaluation through comparative studies in quality, non-clinical and clinical efficacy and clinical safety aspects. The immunity principle guide is helpful to reduce the cost of research and development of generic drug side. The United States, for example, Hatch-Waxman Law of the United States on the drug price competition and patent phase compensation act provisions (1984) [-18] was the first to simplify FDA applications of the enterprise, and awarded the 180 days after approval the market monopoly. During the period of market exclusivity, the company can recover costs and establish its position before the market is flooded with other generic drugs.

In the 2010 American health care bill, it asked drug makers increased subsidies; in recent years it encourages the first generic application, especially the development of biosimilars, to overcome the monopoly of the drug. This legislation will have a great impact on strategies of pharmaceutical companies and further promote the development of generic drugs in the United States and the world. In response to the patent medicine expires, many multinational companies are in huge generics market by adjusting the company structure, adjust drug development strategy and business model into the field of generic drugs.

In many countries, most pharmaceutical companies are mainly engaged in the development and production of generic drugs. There are more than 3,000 pharmaceutical companies in the United States, of which less than 100 have the ability to make innovative drugs; more than 95% of pharmaceutical companies are engaged in generic drug production. In the past five years, less than a tenth of America's generic drugs have been approved each year. 95% of domestic medical use is also generic and non-prescription drugs ($200 billion a year in medical expenses). Like Japan's 1, 600 pharmaceutical companies, only the top 50 companies can make innovative drugs, and more than 90% of them make generic drugs to reduce expenses and meet the needs of the people. The development of the pharmaceutical industry in Japan is far-reaching and the government encourages the development of small and medium-sized enterprises. There are over 4,700 pharmaceutical companies in China. Due to the restriction of China's national conditions, as well as drug research and development goal, China cannot pursue the "blockbuster" of developed countries, but must support the development of the medicine and meet the demand of the people – "could afford, use well, with little risk".

The world's generic drugs have been the essential medicines for the medical needs of countries around the world, and are an important part of national strategies of countries and the main body of people's livelihood. Medicines to meet the needs of different diseases are special commodities, especially the status of national reserve drugs, combat readiness drugs and epidemic drugs. The pattern of drug demand worldwide should include innovative drugs (ID), generic drugs (GD), non-prescription drugs (OTC) and special drugs (SD) to ensure adequate supply of varieties and stability of the national drug safety system. The current global drug demand structure is presented as a "elliptical" (Figure 3): products in the high risk in both ends account for less than 5%; the middle are generic and over-the-counter drugs (more than 95%).Innovative drugs are not the main body of the world's drug supply structure as well. More than 95% of clinical application subjects are GDs, even in the United States.

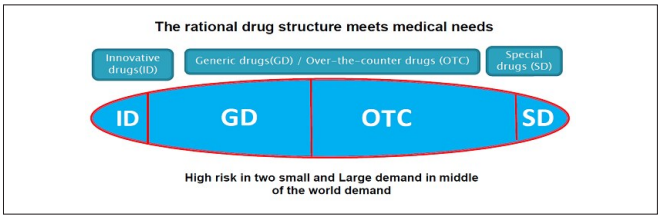

Figure 3. Drug demand worldwide

The journal of the American medical association published the statistics of the top 10 types of drugs (simvastatin, lisinopril, levothyrocine, metoprolol, metformin, hydrochlorothiazide, omeprazole, amlodipine and atorvastatin, salbutamol)[19]. Drug safety issue in China is a national strategy; the comprehensive development strategy is helpful to restore international confidence as soon as possible, make China produce safe products in good quality. Medicine is a special commodity that meets the needs of people's livelihood. So its regulatory authorities should pay special attention to the development of (1) the different diseases with different drugs, different time with different preparations (tablet VS injection), different groups (children, adults, the elderly) shall not use the same drug; (2) national reserve drugs, combat readiness drugs and epidemic drugs are more specific; (3) long production cycle, large investment, high risk and unexpected unmeasurable factors; (4) there are many factors affecting drug demand, and the demand for different drugs varies greatly; and (5) production should not be monopolized, and it is the most unfavorable industry to promote exclusive production and the scientific basis for industrial layout.

From 2008 to 2017, the U.S. food and drug administration approved an annual average of roughly 30 innovative drugs to be listed. However, more than 95% of the drugs approved for marketing are generic drugs, with an average annual approval of about 600 generic drugs. In 2017, the number of generic drugs approved by the United States office of generic drugs was 1027(843, which formally pre-approved 184). 80 are first generic drugs of brand drug, which is beneficial to stimulate the market competition, further reduce the cost of prescription drugs to benefit the people. Chinese companies for instance, Huahai pharmaceutical and other manufacturers have made contributions. The FDA has received priority reviews from the first three applications and strongly supports the company's first copy. It will continue to provide a clear scientific guide to the development of generic drugs to ensure the safety and effectiveness of generic drugs.

3.5 *Mergers and acquisitions of enterprises, the industry development competition is increasingly fierce*

In many countries, biomedicine is the strategic industry of priority development in the 21st century, and the development plan is set up to increase policy support and capital input. For example, in the United States, biomedicine will be used as a new economic growth point to implement the "biotechnology industry incentive policy", and Japan will formulate the strategy of "bio-industrial development". The sixth framework of EU science and technology development will take measures to promote investment in biotechnology development research by industry, universities and research institutions. Singapore also has a five-year plan to be among the best in biotechnology. India has set up a biotechnology division to invest $60 million a year in research and development. Cuba implements the biotechnology investment program to promote the Cuban medicine economy.

The total number of biotechnology companies in the world has reached 4,300, mainly in the US and Europe, accounting for nearly 80% of the global total. The US is now leading in biomedical industry. The developed countries have formed the biological industry cluster and the relatively complete biological medicine industry chain and industrial cluster. Reorganization and annexation are very active. Multinational companies dominate the world patent medicine market, and the global pharmaceutical market monopoly is increasing.

Many developed countries have gradually formed the accumula-

tion area of biological industry in the area of technology, talent and capital, thus forming a relatively complete industrial chain of biological medicine and industrial cluster. The US, Europe and Japan have more than 80 percent share of the market. The concentration of the single product of European and American products in the world market shows an increasing trend. Large multinational corporations dominate the world patent medicine market, and transnational corporations are becoming more and more important in the global pharmaceutical market. The US has formed five biotechnology industry areas in San Diego, San Francisco, Boston, Washington, and North Carolina,-, including professionals in silicon valley. In addition to the United States, several biological parks in the UK, France, Germany and India have gathered a large number of technology transfer centers, investment service institutions and employment opportunities. And almost all the pharmaceutical companies and biotechnology companies form strategic alliances. By the strong technical force of technocrat small biotechnology companies, and development through cooperation for biological medicine production, this model successfully promoted the benign development of biological medicine industry. Some of the US’s policies support horizontal integration between large pharmaceutical companies. There are also lot of overseas capital flow, most likely to appear in 2018 super mergers and acquisitions. In 2017 the takeover rumors of Bristol - Myers - Squibb, its potential buyers could be Pfizer, Amgen, giant Novartis, Roche, etc. Earlier this year, Celgene /Juno announced that Celgene agreed to buy Juno for $9 billion, and sanofi announced an agreement with Bioverativ to buy all of Bioverativ's shares for $11.6 billion. The new group bought Impact on biomedicines for $7 billion, and Bluebird, a partner, developed immunotherapy drugs. The strategic alliance of pharmaceutical and biotechnology companies enables small biotech companies to cooperate in innovation, technology or property rights to promote the development of large companies. Contracted research organization (CRO) has been used in the pharmaceutical industry chain, and the operation of low cost, specialization and high efficiency is valued by big companies.

It is widely believed that 2018 will be the year of global bio-pharmaceutical mergers and acquisitions. The "American first" policy, which supports horizontal integration of large companies and repatriation of overseas funds, will benefit US mega-mergers. New base buys Impact Biomedicines. Note that many Chinese pharmaceutical companies have entered the global bio-pharmaceutical M&A. As China Tricell group purchases Dendreon Pharmaceuticals, China five institutions joint acquisition SciClone Pharmaceuticals, Fosun medicine purchases Gland Pharma 74% stake, Shanghai Pharma acquisition Cardinal Health China business entities, and embodies the Chinese medicine enterprise strength enhanced gradually, which is expected to be more Chinese companies joining the global pharmaceutical market competition.

4. Development of biomedicine in China: not forgetting original, absorbing foreign, facing the future

"Accelerating the construction of an innovation-oriented country, innovation is the primary productive force leading to development and a strategic support for the construction of a modern economic system," said in the 19th congress report of communist party of China (CPC). After the implementation of new drug application, review and approval of new policies in 2017, an estimated number of new drugs will be increasing, and improved innovation will be achieved in the promotion and generic drug market. We should adhere to the direction of socialism with Chinese characteristics and build a moderately prosperous society in all respects to realize the Chinese dream of the great renewal of the Chinese nation. Of China's biological medicine "Industry-Academic- R&D-Administration-Management", must be "Never forget the beginning of the mind and keep in mind the mission", and need to "Never forget the original responsibility, absorbing the foreign, facing the future" spirit in our country, we need to ensure product supply, ensure the urgent clinical needs and the introduction of new drug innovation, scientific and medical supply system for the future construction.

4.1 *never forget the original: promote the development of people's livelihood*

“Don't forget your beginner's mind and keep your mission in mind. Since the 18th national congress of the CPC, general secretary Xi Jinping has attached great importance to food issues and stressed that "the rice bowl of the Chinese people should be firmly in their hands at all times." Our rice bowl should be mainly Chinese food. "Ensuring food security in the country is an eternal topic that cannot be loosened at any time." Guarantee food national security is an important strategic issue, and it is also important for people's livelihood to ensure the national security of drugs as food national security does. To achieve the original goal of providing national security "to meet the growing social needs", it is the mission and responsibility of the Chinese medical people that the Chinese medicine must be firmly held in their hands at all times.

In 2018, the great spirit of 19th congress of CPC is implemented, central deepen reform leading group of CPC on January 23 this year launched a series of policies on reform and enhance the generic drug supply security.

For the development of innovative drugs, it is estimated that several of the innovative drugs that have entered the phase III clinical trials have declared production or marketing this year. The domestic single antibody drug innovation and development situation in 2018 is obvious, and its target will continue to focus on "me-too" and "me-better" in the field of tumor immunity, and other classic targets will continue to receive attention. Overall, the domestic new drug research and development in "me-too" and "me-better" as the main target of evolutionary innovation, some emerging drug firms will try to expand technology innovation, and have differentiation requirements of new products.

CAR-T therapy was approved by the US-FDA for use in cancer treatment in 2017.To expand the application range of the CAR-T therapy and improve its effectiveness, many of the world's research

and development enterprise and university hospital team are actively solving the problem. China's CAR-T craze is already the fastest way for Chinese companies to catch up and even compete with the United States. In the clinical trial website, the number of clinical trials (130 products) found in "CAR-T" in China surpassed that of the US (100 products). In addition to the clinical variety of domestic applications, a number of joint ventures, such as Fosun Sheng-Kaite, JW Biotech and the pharmaceuticals giant, are preparing to take the latest US industrial achievement to China.

Although this new treatment will not cure all tumors, it will be a promising mono-therapy and can be used in combination with other therapies. The effectiveness and safety of any treatment for cancer, due to its progression, deterioration, diffusion, metastasis, and tolerance should be fully investigate in clinical trials.

From the perspective of the special commodity status of the development of drugs, both innovation and imitation, is mainly determined by the following five aspects: (1) the different diseases with different drugs, different time with different agents (tablet VS injection), different groups (children, the elderly) shall not be the same drug dosage forms as adults; (2) national reserve drugs, combat readiness drugs and epidemic drugs are more specific; (3) long production cycle, large investment, high risk and unexpected un-measurable factors; (4) there are many factors affecting drug demand, and the demand for different drugs varies greatly; and (5) production should not be monopolized, and it is the most unfavorable industry to promote exclusive production and the scientific basis for industrial layout. As a result, the clinical curative effect is necessary, and supply shortages, prevention and control major communicable diseases and rare diseases and treatment of emergent public health event, children etc.

In 2018, the implementation will be approved according to the prescribed time limit, and after the backlog of registration application is solved, the challenge of the approval of innovative drug examination and approval will be highlighted. In combination with the national conditions, it is difficult to meet the challenge of innovative drug review, which is of low professional level, heavy duty and rather difficult to be qualified for. There is a large gap between the lack of medical resources, the burden of enterprise, the choice of reference preparation and the evaluation/exemption of bioequivalence (BE). As early as in the 1980s, before the application of foreign enterprise generic drugs, the biological evaluation was the business of the enterprise, and it was very difficult to release the evaluation in China. Domestic generic drugs research and development level and the ability to fulfill the gap with the United States. United States last year approved over 1000 generic drugs, and only approximately 100 generic drugs were approved at home (2 in 2016, 3 in 2017). According to press, large market share can also be found in the United States asthe most successful countries using generic drugswith a 91% share of generic drugs, and 82% in Germany. Unfortunately, China has only 64%, and sales of patented drugs have reached nearly 36%, about the same level as Italy, France, Spain and Japan. According to the public statistics, China's generic drug market in 2016 is ￥928 billion , and the patent medicine is ￥515.6 billion. Therefore, from the perspective of sales, China, Italy, France, Spain and Japan are all big consumers of patent medicine. In as word,, the more stronger new drug innovation ability, the higher number of use of generic drug, vice versa.

Aimed at ensuring people's well-being and satisfying the increasing social demand, we need to reflect on the current situation of the four basic: (1) priority and special consideration should be given to those Chinese medicine generic drug or chemical generic drug companies, , to seek breakthrough in dosage form, give full play to its resources and products advantage, overcome the disadvantages and change the status of previous extensive uncertaintiy, as well as characteristic development pattern, and further establish good complete industrial chain; (2) to achieve reform of supply side in the medicinal industry, for instance thoroughly solve the serious homogeneity and excess capacity and the problem of unfair competition, the number of pharmaceutical production and management enterprises should reduce to reasonable level reduce; (3) a market-oriented industry and business reform grim, related to the consolidation of policy implementation and implementation (in generics consistency evaluation, relationship between price and value, shortage of products, medical treatment, regulation of the three sectors, the implementation of the national negotiation system of imported drugs); and (4) the domestic medicine will soon experience reshuffle in industrial sector, including domestic generics, imported varieties of generics and branded drugs.

Generic drug quality consistency evaluation (evaluation) is a world problem, not unique to China. How to develop consistency evaluation? How to embody and improve the quality management system based on pharmacopoeia standards? What is the safe and effective difference of generic drugs today? With 50 percent of China's API exporting to the world, will the quality of the world be applied? What is the difficulty of making high-end preparations?

In 2018, there are four aspects in the strategy of the generic evaluation: (1) attention should be paid by the US FDA to report of generic drugs on the basis of bioequivalence, guidance of bioequivalence test should be developed for each drug . Strict supervision guarantees the quality stability of multiple batches of products after the drug is approved, and there is an exemption mechanism for the study of bioequivalence. The results were announced at the FDA's Orange Book; (2) for the EU countries, if they can prove that the pharmaceutical products listed in EU member states have been approved less than 8 years, generally there is no need to provide before the clinical experiment and the results of clinical trials; (3) the guiding principles of the bioequivalence test of generic drugs was launched in 1997. Since 1998, the "drug quality reassessment" has been adopted in the quality review of pharmaceutical products. Japan did not adopt the system of the United States directly, dynamic supervision, by in vitro dissolution test for drug quality evaluation, also do not restrict repeated applications, for instance, there are over 20 ANDA application of Clopidogrel; (4) during the past years from 1998 to 2011, Japan evaluated 706 chemical generics, 1362 formulations and approved more than 4000 products. Japan's ministry of health wished not to give exclusive variety of generic drugs. The results were published in the "medical quality intelligence collection" (Orange Book released by the FDA).

4.2 *Absorb outside: encourage "Introducing domestic" and "Going to the world"*

China CFDA joined the ICH in 2017.The international drug development effectiveness (E), safety (S), quality control (Q) and manage files (M), these four aspects with the international synchronization or requirements specification could lead to new drugs into the country of the world, also support export of domestic drug to the rest of world.

The challenge of transnational foreign enterprises is becoming more and more obvious in developing our pharmaceutical industry. In 2017, GSK central nervous system research and development center, Eli Lilly R&D center out of China, Roche, redundancy of Novartis R&D team's staff attracted attention of the world. 5 to 10 years after entry of foreign companies in China, it has led to the trend of foreign companies to build in China. However, many foreign companies are not satisfied with the "acclimatization" or the cancellation of R&D center, or the reduction of R&D team. By analyzing the possible reasons, one is to adapt to the global scope to optimize the operation of the enterprise research and development needs; Second, the need to reduce the cost; Third, the strength and performance of China research and development; Fourth, due to intellectual property rights, sensitive new drugs are not developed in China; Fifth, domestic innovation capacity is improved, and non-high-end pharmaceutical products are also difficult to profit in local market. Sixth, the maturity of domestic cooperation conditions; Seventh, imported drugs require clinical needs and quality control research, and development threshold is raised.

In the meanwhile, complexity of circulation is restricted by the dealer, coupled with lower drug prices and negotiating system to launch for many times. In the fierce competition, equity is urgently required by local enterprises; independent pricing offered to foreign company, , market access, regulatory verification and import registration such as super national treatment is changed or reduced.

How to "go to the world"? According to Chinese customs data, China's import and export of pharmaceuticals in 2016 were chemical API (47.9%), agents (5.6%), traditional Chinese medicine (1.8%), extract 3.8%, proprietary Chinese medicine accounted for 0.4%, Chinese medicine health care products 0.5%. The gap between the preparation and raw material exports was too large, and the contribution of chemical drugs (preparation) to international trade was limited. In 2015, the values of chemical drugs, preparations and biological drugs were 256.98, 31.08 and $2.615 billion respectively, totaling $314.21 billion, accounting for 89% of the total, and the traditional Chinese medicine was only $384.2 billion, accounting for 11% of the total. Western medicine (chemical raw material + preparation + biological medicine) was basically unchanged in 2016, and the contribution of Chinese medicine in world trade was roughly 5%.

Domestic enterprises with innovative, cooperative and financing capacity are accelerating to the world. The existing 10 companies (such as Huahai and others) and 21 companies produced active pharmaceutical ingredients (such as Haizheng and other enterprises) are certified by the world health organization WHO-PQ, on the way to the internationalization, domestic medicine made the great progress to expand the share on the international market. Others also attempted to brace the opportunity of global market, for example, Hefei Tianmai Biotech invested over 200 million yuan to introduce oral insulin project originally from Israel, currently the product has completed phase II clinical trial, which actively promote the transfer of technology and domestic raw materials/preparation.

4.3 *Face to the future: enterprise - industrial structure transformation and construction of medical power*

Back to 1978, China's economy accounted for only 1.8% of the world's total. After 40 years of transformation, China is now the second largest economy in the world, accounting for 14.8% of the global economy. It has increased nine times in the last forty years. Great changes have taken place in China. However, since China is a populous country, accounting for nearly 20% of the world's population, its economic aggregate has not reached the world average, so it is still a developing country.

4.3.1 The reform and opening up has given impetus to the development of medicine

In China, pharmaceutical development also can induce the four major driving force of the development of the medicine: (1) the system innovation of China's reform and opening-up make related policies and regulations, with the development of pharmaceutical industry; (2) the uneven development in China, makes a few medical individuals. These people have made a positive contribution to the development of China's pharmaceutical industry and to meet domestic demand and go to the world market; (3) power effect, appeared in the early years of the reform and opening up "to study of workers, peasants and soldiers" to do pharmaceutical factory, in recent years, there is now such a large pharmaceutical economic volume and market share; (4) technological innovation and technology revolution will become irreversible. It is undeniable that new propulsion development, technology innovation has become the inevitable choice of the enterprise.

Development strategy on adjustable structure can be pressure costs, inventory, and short board, increasing benefits relies on the pharmaceutical companies - an important part of the strategy of the construction of the industrial structure transformation. Recently, the main body of the enterprise needs to combine its own situation, (1) the problem of specific adjustment of industrial structure and variety structure; (2) the problem of oversupply of low-end raw materials, high market and high management cost, cost, excessive repetition, etc.; (3) problems in innovation, preparation technology, biotechnology, manufacturing process and scientific management; and (4) in terms of industrial efficiency and international market increase. More importantly, the combination of "made in China 2025" is the outline requirement for the future development, and the three major transformation and development are the fundamental way out for the construction of medical power.

4.3.2 The three major transformation development is the fundamental way out for the construction of medical power

at the initial stage of reform and opening up, the number of Chinese pharmaceutical companies has expanded, and the situation of product duplication, small scale and low technical content must be faced. For the future, from low-end imitation to innovation, the transformation from the raw material (active pharmaceutical ingredients and medicinal chemicals) to high-end preparation of transition and transformation from domestic demand to global demand of three big development is the fundamental way out for construction of medical power transformation. Traditional Chinese medicine and drug generalization should give full play to the advantages of the "craftsman spirit" and establish a good and complete industrial chain. We need to encourage the ability of innovation and generics companies at home and overseas development, overcome the extensive focus, characteristic development pattern, in order to promote the reform of the pharmaceutical industry supply side, solve the homogeneity, overcapacity and unfair competition.

4.3.3 "Made in China 2025" is the future development

Under the pattern of internationalization, the world medical innovation is characterized by long cycle, high investment and low successes as well as the input-output ratio, and many factors can affect the demand of the Chinese drug varieties and structure contradiction. The biomedical industry is one of the ten key breakthroughs in the development of "made in China 2025".

Manufacturer to manufacture power of the Chinese dream of "three steps" target: the first step, by 2025, the manufacturing industry's overall quality will be improved, the overall labor productivity will be improved significantly, and the industrialization and information fusion will be brought to a new level. The energy consumption, material consumption and pollutant emission of key industrial units are up to the world's advanced level. A number of transnational corporations and industrial clusters with strong international competitiveness have been formed, and their position in the global industrial division and value chain has improved significantly. In the second step, by 2035, China's manufacturing industry will reach the middle level of the world's manufacturing power. Innovation capacity will be greatly improved, major breakthroughs will be made in key areas, and overall competitiveness will be significantly enhanced. The dominant industry will form a global innovation leading capacity and fully realized industrialization. In the third step, till the People's Republic of China founded one hundred years, the position of manufacturing power will be more consolidated, and the comprehensive strength enters the forefront of world manufacturing power. The main areas of manufacturing industry have be at leading position in innovation, with the obvious competitive advantage, in parituclar the establishment of the world leading technology system and the industrial system.

"Made in China 2025" is a key first step in this "three-step" goal. Intelligent manufacturing for the characteristics of "Made in China 2025" requires that manufacturing is the main part of the state of the real economy, the main scientific and technological innovation's basis, and the source of rejuvenating the country's power (virtual push off). Development pattern in the global manufacturing and China's economic development environment has greatly changed, we must grasp the rare strategic opportunity, highlight the innovation drive and optimize the policy environment, give full play to the advantages of system. "Made in China 2025", adhere to the basic policy "innovation drive, quality first, the green development, structural optimization", adhere to the "market" leading, government guidance, based on the current and long-term perspective, the whole advancement, key breakthrough, independent development, opening up and cooperation" of the basic principles.

4.3.4 Improve the understanding of the short board of medical development and improve the technological innovation system and capability of enterprises

The basic situation of China's pharmaceutical industry and enterprises is classified into five weakness: First, many small, scattered and disorderly medical enterprises are prominent. The degree of specialization is not high and lacks its own brand and characteristics -- small scale, poor condition, outdated technology, low management efficiency, high cost, high consumption and scattered layout. Adjusting the industrial structure, giving play to the advantages, famous brands, large-scale varieties and individualized varieties are the way out. Second, the enterprise - centered technological innovation system has not yet formed. The new drug innovation foundation is poor (state-owned enterprises), medical technology innovation is difficult, the science and technology investments are insufficient, the original innovation is small and lacks the competitiveness. Third, the variety of raw materials is not compatible with the product variety, the pharmaceutical preparation technology is outdated, the product quality is not stable, and it is difficult to enter the international market. Low prices and high pollution are another. Fourth, the medical circulation system is not yet sound. After the basic breakdown of the three-level wholesale pattern, the new medical circulation system has not been formed, and the two-ticket system has not reduced the drug circulation cost and the patient's self-expense burden, and the "medicine maintenance" still exists. Fifth, the import and export structure of pharmaceutical products is unreasonable. The export of raw materials with low added value, heavy pollution, Chinese medicinal materials and the export of Chinese medicine products are relatively low. In particular, we lack awareness and mechanism of international market development, modern R&D and internationalization capabilities.

As for the current large-scale enterprises, the technical innovation system and the ability are insufficient. Intelligent manufacturing needs to seek opportunity to make break through. Manufacturing (especially state-owned pharmaceutical enterprise manufacturing) is the main part of the state of the real economy. Scientific and technological innovation, the formation of end-to-end integration, integration of product the lifeline and the conformity of the production cycle, may help achieve the whole process of production quality control with the characteristics of traceability management,

achieving industrial technology to implement intelligent, digital, the purpose of efficiency, and the industry development.

4.3.5 The government continues to support innovative development

With the rapid rise of biotechnology, the biomedical industry worldwide has become a representative emerging technology industry. Based on its important strategic position and broad prospects, it is highly valued and supported by governments around the world. China's government attaches great importance to promoting the development of medical science and technology. Especially a direct relationship between the human health and special industry can bring huge economic benefits. The government investment and policy support also played an important role in drug innovation. Especially for the biological medicine directly related to human health, and special industry can bring huge economic benefits, in addition to our government in basic research funding mainly used in biology and medicine fields. We will support the development of new drugs in the field of bio-and pharmaceutical industry. Facing the future, the direction will continue to be supported. 15 years of science and technology major projects have supported new drug research and development with promising outcomes, even there are also problems not been fixed, such as output, the less obvious original innovation efficiency, long project, application and lower efficiency in review and implementation of research and development.

4.3.6 Generic drugs should be developed with quality as the center for a long period of time

Governments around the world have responded to the spiraling cost of health care, so reducing drug spending by using generic drugs has become a major government goal. At present, the United States, Britain, France, Japan and many other medium-sized generics firms, even giant companies are focused on chemical generic drugs and biological drugs research and development, mountain Texaco, Ranbaxy, Merck and Teva Pharm. In the future, as countries encourage the use of generic drugs, the development of generic drug markets has become a sensible choice for many companies.

Generics industry internationalization, research and development and manufacturing upgrade will have breakthrough in good company with its advantage of internationalization. Complying with the trend of global production transfer, generic market expansion brought historic opportunity for the export of Chinese industry upgrade. There will be a trend of resistance consolidation in the generics industry. The data shows, every year, the world will have many drug with expiration of patents worthy about $200 billion. It evokes great attention in the pharmaceutical industry, unleashing a wave of biosimilardrug’s growth and a huge market "cake" is expected. For biological medicine field, however, the challenges faced was complicated, because the relevant scientific issues and regulatory uncertainty limits its growth potential. Rapid growing in future global market is also expected.

A large number of patent medicines have lost their patent protection. For Chinese enterprises, it is necessary to do a good job with these non-patent protection varieties and select the varieties of clinical needs for making profits. As competition intensifies, the market for generic drugs is growing, patent medicines may leave a lot of room for generics. As some of the trademark generic drugs or patent protection is about to expire, generic drugs will smoothly carries on its advantages. The huge demand for generic drugs in the domestic market is driving the rapid development of the generic drug industry in China. The development prospective of generic drugs is evident. Currently the development of new drugs is very difficult, and the development of generic drugs and the production of generic drugs are still an important part of the innovation strategy of China's pharmaceutical industry. The policy is good to widen the generic drug market. Today, the world medical is reforming thoroughly, lowered drug price will be a trend of the future world. Not everyone can accept the high price of patent medicine, so the generic drugs will be more and more welcomed by general population. As a result, it is a great opportunity for China's pharmaceutical companies, which are the first makers of generic capacity. Domestically, urban community health care and rural medical care have increasingly laid the foundation for the expansion of China's generic drug market over a long period of time. Its overall goal is to provide "safe, effective, convenient and affordable" medical and health services for the broad masses of people. The policy is positive, and it is a good opportunity for generic drugs. However, in the market-oriented industrial and commercial reform, the pharmaceutical industry will be reshuffled, including home-made generic drugs, imported generic drugs, and the reevaluation of the origin varieties of the original pharmaceutical products. In the current generic consistency evaluation of our former work, the enterprise must complete the own variety strategy, market strategy and design strategy, in order to improve the efficiency of the evaluation.

5 Innovate supervision system and mechanism of the drug regulation

With the reform of drug review and approval system, the pharmaceutical industry encourages innovation. In light of international pattern, the innovative research and development ability, research and development of national innovation drugs research and development of the special power transformation were enhanced, but the challenge still remains, with limited strength. This challenge comes from the higher requirement of regulation, research and development and market environment, as well as the industrial ecological chain, development thinking and globalization. Pharmaceutical companies should improve their patent awareness, protect local enterprises' innovation and development, and seize the opportunity to file patents in innovation and development.

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