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**Speeding up the Launch of Generic Drugs Under China’s Current Regulatory System**­­

THE THESIS OF PROJECT-BASED ACADEMIC ENGLISH

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| **Date** | **Dec 28th, 2019** |

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### Speeding up the Launch of Generic Drugs Under China’s Current Regulatory System

**Abstract:** Patented drugs, as the first initiative drugs, have an excellent effect on the treatment of diseases. But the price of patented drugs are unaffordable for many families. How to ìmprove accessibility and affordability becomes a critical issue needed stressing. Therefore, as an alternative of patented drugs, generic drugs has emerged rapidly. However, with a problem of whether generic drugs can replace patented drugs has long been questioned in their efficacy and quality. Having studied on comparing patented drugs and the generics and readed a lot of literature, we found that it is possible to substitute patented drugs in common disease. Besides, under the existing legal and regulatory system, bioequivalence standards are inadequate and the CFDA’s drug approval process was marked by decades of lags and slow processes. So, we summarized efforts the government had done and also put forward useful suggestions in this paper. （张少英，李娅）

**Key words：**Generic drugs; Patented drugs; Bioequivalence; Generic substitution; Patent Law; Approval Process

#### 1 Introduction（张少英）

The definition of Patented drugs, comes from the National Medical Products Administration of China, is the first one in the world to apply for and receive patent protection generally. Because patented drugs have a 20 years protection period, during these years, other companies are not allowed to copy them. The advantages of patented drugs are as follows: encourage innovation, meet the needs of patients and protect the intellectual property. Therefore, owing to patented medicine has advantages for its pioneering treatment of diseases and patent protection, so it occupies a huge market in medicine[1].

Although patented drugs have such a large advantages of its properties, due to the long development cycle, high research costs, and the expense of a series of clinical trials, the price of patented drugs is dramatically expensive[2]. And for 20 years of patent protection, patented drugs have caused monopolies during this period and have benefited tremendously. Higher prices have caused many ordinary families to be unable to afford treatment costs, therefore, in this situation, generic drugs have emerged[3]. A pharmaceutical product, usually intended to be interchangeable with an innovator product, that is manufactured without a license from the innovator company and marketed after the expiry date of the patent or other exclusive rights.

The generic drug is similar to a patented drug in terms of efficacy but has a significantly lower price than a patented ones. Cost reduction, Time saving and Sale at low price are advantages of gengric drugs. According to the survey, generic drugs accounted for 90 % of the total pharmaceutical market in China at the end of 2017. Generic prescribing already accounts for 83 % of prescriptions in the United Kingdom[4]. Moreover, generic drugs accounted for 88 % of all dispensed retail prescriptions in the U.S in 2014, while consuming only 28 % of total drug spending. The use of generics, where available, is estimated to have saved the U.S.healthcare system $1.68 trillion between 2005 and 2014, with $254 billion saved in 2014 alone[5]. It can be seen that the advent of generic drugs has greatly reduced the cost of medicines, so that more people have access to treatment.

The use of generic drugs products typically yields lower costs to insurers and patients than use of branded products. According to the survey, In 2017, the United States' net drug expenditures reached US $ 324 billion, and it is expected to increase 2 % to 5 % annually over the next 5 years[30]. In the United States, per capita drug expenditure is 54 % to 209 % higher than in other high-income countries. This trend persists despite an increase in the proportion of generic drugs prescribed, which has lowered spending when generic drugs are available[31], and is associated with the high and growing costs of brand-name drugs granted government-protected market exclusivity.

While in some cases patented drugs represent the best treatment option for an individual patient, in many cases when a patented drug is used, a lower-cost generic could have been directly substituted (i.e., a pstented drug replaced with a generic of the same drug) or therapeutically substituted (i.e., a patented drug replaced with a generic of a different but therapeutically similar drug). However, due to the low price of generic drugs and the different appearance, shape, and odor et.al compared with patented drugs, people have doubts about the efficacy of them. Some people said that generics altered the efficacy of patented drugs, and some even said they had side effects.

Those factors have eventually resulted in some patients and providers are resistant to generic substitution. For example, a 2016 national consumer survey found that 13 % of respondents believed that patented drugs are more effective than generic drugs, and 20 % of respondents believed that generic drugs have different side effects than patented drugs[6]. In a parallel survey of physicians, 11 % of physicians expressed negative perceptions about the efficacy of generic drugs and 27 % believed they caused more adverse effects. Further, an estimated 5 % of prescription drugs are dispensed“as written”with patented product due to the active requests of patients and physicians, contributing annually almost $1.2 billion in excess drug costs[7].

In terms of drug composition, the formulations of innovative brand medicines and generic medicines may differ. The "inactive" ingredients in the generic version must be the same as those in the innovative agent, which is not a regulatory requirement. However, minor changes or impurities in the excipients used in the formulation can alter the properties of the drug and cause unexpected adverse effects on drug absorption, bioavailability, efficacy, and safety. Certain excipients are not tolerated by some patients, including lactose and gluten and certain dyes[32].

In addition, the approval process for generic drugs is also complex and takes a long time, which has led to the delay in marketing of many already developed generic drugs[8].

Therefore, in view of the above phenomenon, we want to explore two questions, that is, whether the generic drugs really can replace the patent drugs in terms of efficacy? How can we speed up the time to market of generic drugs when generics can replace patented ones?

#### 2 Methodology（张少英，张广华）

**A literature search of peer-reviewed articles published in** English between 1995 and 2019, was conducted using PubMed, Springer and Heinonline, with the purpose of identifying all relevant original research articles on generic and patented drugs. The search terms used were a combination of words related to “patented drug,” “generic drug,” “brand drugs,” “brand to generic switching,” “generic substitution,” “bioequivalence” “Regulation System” based on title and abstract, articles were identified for further analysis. In addition, a manual screen of the reference lists of any identified articles was conducted. Many relevant articles were screened based on our search terms, among which 8 articles discussed the therapeutic equivalence of generic medications. （张少英）

Apart from literature review, comparison study were used for introducing relevant laws and regulations in China and the US. We attempt to learn excellent experience from Americans’ system and practice and reveal the relationship between patented drugs and generic drugs which hid in the legal system. （张广华）

#### 3 Results and Discussion （李娅，张广华）

About the relationship between the generic drugs and patented drugs,we divided it into the following two aspects.

3.1 Biomedical Field （李娅）

These generic products includes multifaceted and dynamic interaction of scientific, regulatory, and economic factors. The financial advantages for patients and consumers seem to be because of the numerous interactions of academic scientists, generic product developers, regulators, healthcare providers. Because of the widespread use of generic drugs, it is critical that the accuracy of decisions about generic drug substitution that this system is responsible for is supported by solid scientific foundations. In this issue, multiple articles explore the complexit of generic drug development, regulation, and use and identify key impact points for the clinical pharmacology community.

### 3.1.1 The Patient’s Clinical Efficacy

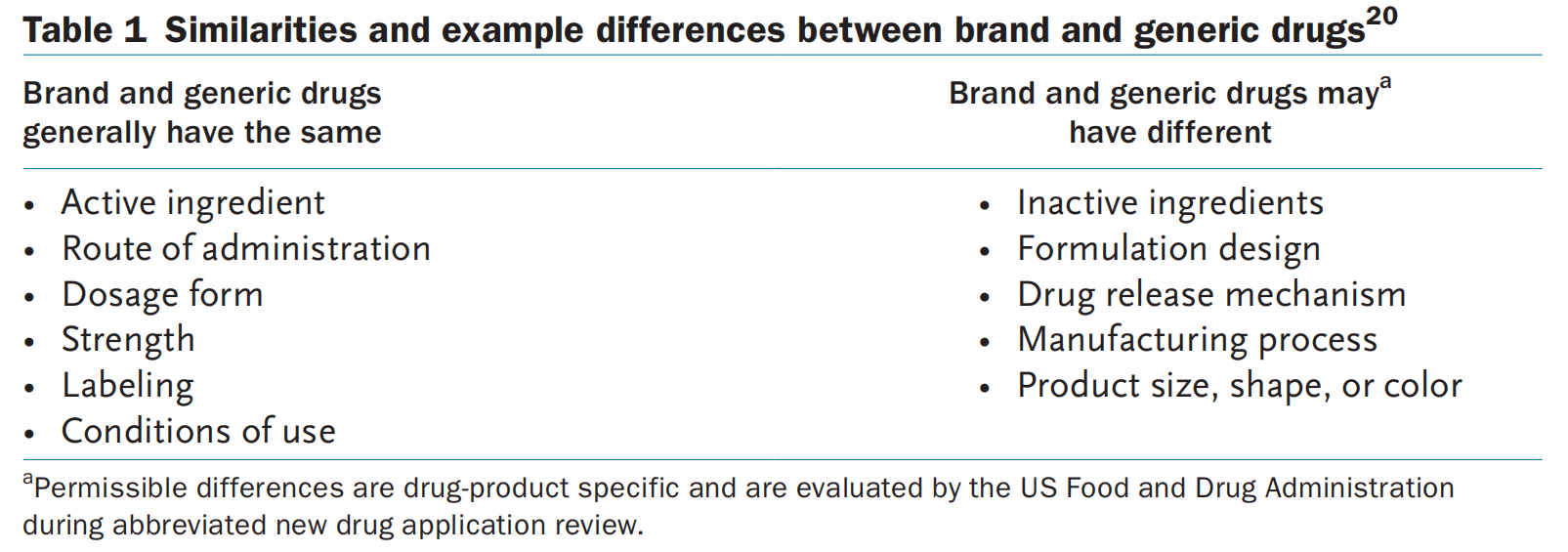
Mentioned in the previous literature,a 2016 national patient survey found that 13% of respondents believed that patented drugs are more effective than generic drugs, and 20% of respondents believed that generic drugs have different side effects than patented drugs.The same case show in a parallel survey of physicians, 11% of physicians expressed negative perceptions about the efficacy of generic drugs and 27% believed they caused more adverse effects[6].

But we deem that the behavior and perception of doctors and patients may affect the feasibility of patented drugs to replace generic drugs.Thus,it is not reliable to use subjective reasons, such as patients and doctors, to argue that generic drugs are inferior to patented drugs.

We will find the relationship between patent and generic drugs from the research of biomedical experts.

### 3.1.2 Research by Biomedical Experts

The Drug Price Competition and Patent Term Restoration Act (Public Law 98-417), informally known as the Hatch-Waxman Amendments, established the approval pathway for generic drug products in the United States through the submission of abbreviated new drug applications (ANDA). Compared with the patented product (also referred to as the reference listed drug), a generic drug must contain the same active pharmaceutical ingredient, strength, dosage form, route of administration, and labeling and be bioequivalent and meet the US Food and Drug Administration (FDA)’s high standards for drug product quality.Robert and Kathleen compared their differences in Table 1[9].The contrast is obvious,and the main aspect of them is active ingredient and inactive ingredients.



There are some evidence in minor ailments such as allergies, colds and flu, 78% preferred generic drugs, but for major problems such as heart disease, asthma and diabetes, 59% preferred patented drugs[10].

On the other hand, patented drugs use tends to be higher among products such as sterile injectables, specialty drugs, atypical antipsychotics, biologics, and NTI drugs such as antiepileptics, thyroid drugs, and immunosuppressant drugs[11].

Therefore,generics are less effective and safe than patented drugs, depending on the severity of the disease.we will discuss both common and complex diseases in bioequivalence and safety.

### 3.1.2.1 Common Disease

Several studies including clinical trials have provided evidence that patented drugs and generics are equivalent in terms of safety and efficacy[12][13]. Patients using generics vs. patented drugs were similar in terms of outpatient visits, urgent care visits, hospitalizations, and medication discontinuation. These data suggest that generics were clinically no worse than their proxy brand comparators[14].

Data from another study showed that it is possible that inactive ingredients used by the generic companies have a better safety profile than those used by the patented drugs[15].This is a reassuring indicator that generic drugs are generally tolerable.

We can infer that generic drugs can substitute patented drugs in common disease.

### 3.1.2.2 Complex Diseases

Some drug safety experts have argued that the FDA's bioequivalence standards are inadequate, especially for drugs with an NTI(Narrow Therapeutic Index)[16].So, for some rare diseases, experts can't guarantee that the standard of bioequivalence is reasonable. Adverse effects of generic drugs have been reported in epilepsy and psychiatric disorders,such as increased frequency of epileptic seizure, reduced clinical efficacy and other problems，the reappearance or deterioration of symptoms of psychosis[9].

Through above data,we summarized that common disease patients can use generic drugs.However, the generic drugs about clinical efficacy of complex and serious diseases remains to be considered.

### 3.1.3 Advice from Biomedical Experts

There are profound scientific complexities in assessing generic sameness, bioequivalence, and substitution in patient populations, which interact with complex regulatory and economic environments. For example, the FDA's generic drug program receives about 1,000 new ANDA applications and more than 3,000 controlled letters (written questions about drug development prior to filing), as well as more than 1,600 product-specific development guidelines for specific patented products, each year. Each of these events has a scientific basis, potential regulatory and economic impact on the developers of patented and generic products, and determines when patients have access to generic products[9]. Clinical pharmacologists working in this field ensure timely access to generic drugs through the most effective, sensitive and accurate bioequivalence studies and provide a scientific basis for correct decisions about generic drug substitution, with a lasting impact on public health.

Clinical pharmacologists believe that, generic drugs can replace patented drugs to some extent, especially for common diseases. On the other hand, there are many opportunities for developers to expand the use of these tools, which are identical, equivalent and alternative, and to refine them for further application in the generic domain, as well as in other aspects of drug and biological product development.According to the advice of clinical experts,we propose the following three points：

1.Improve more effective bioequivalence testing standards, and produce a large number of safe and effective generic drugs to meet the needs of patients;

2.The government should vigorously promotes the development and innovation of new drugs and includes orphan drugs in medical insurance;

3.Educate patients and health-care providers to reduce cognitive biases against generic drugs and encourage their use first.

3.2 Legal Perspective （张广华）

While focusing on regulatory aspects between patented drugs and generic drugs from legal perspective, it is notable that exclusive rights of patented drugs’ owners granted by Patent laws exclude others from commercially making, using and selling the patent owner’s invention. We cannot fully understand regulatory situation of generic drugs without mentioning patent laws. Besides, studying relevant situation in the US in contrast with China’s system can provide us with useful experience and help to better reflect China’s reality.

### 3.2.1 Relevant Laws and Regulations in China

### 3.2.1.1 Patent Laws

China’s Patent Law was first enacted in 1984 (effective April 1, 1985) and amended three times in 1992, 2000 and 2008. The issues of whether to grant patent protection for pharmaceutical products, the extent of protection, and exceptions to patent infringement have always been important.

China’s patent law experienced changes in the historical legislative process, from denying to recognizing patent protection for pharmaceutical products, from experimental use exception to Bolar exception etc.[21]What’s more, China followed the Patent Cooperation Treaty, joined the WTO in 2001 and became a member of TRIPS Agreement.

Recent years’ series reform shows the tendency that Government intend to strengthen intellectual property protection. For example, in the draft of amended patent law (2018), establishing the patent term compensation system for innovative pharmaceutical inventions were proposed. We will not mention more details about it as recognizing the trend is enough to understand the relationship between patented drugs and generic drugs under patent laws.

### 3.2.1.2 Regulations on Approval Process

National Medical Products Administration, which took the place of China Food and Drug Administration (CFDA), is the administrative body responsible for the regulation of medical devices and pharmaceuticals on the Chinese mainland.

Regulations on drugs are rather complicated in China, including registration, pricing, marketing regulations and so on. The access to pharmaceutical market reflects the regulatory requirements of the pharmaceutical industry, particularly for new drug products, which mainly include the registration and administrative approval of new drugs and technical review requirements.

The “Provisions for Drug Registration” (PDR) issued by CFDA in 2007, defines the regulatory framework for registration in China.[22]

Drug registration refers to the process of review and approval on which the administrative authorities, in accordance with the official procedures, evaluates the safety, efficacy and quality of the drugs applied for marketing, and decides whether or not to approve such an application.

The market entry for new drugs start from the initial research stage and goes through seven phases in total. Overall, it takes at least 3 years for new drugs to be listed in China. Even if the new drug is listed, it also has to face market access problems and must go through the provincial access (drug bidding) and hospital access. The average bidding period of 31 provinces and autonomous regions in China is 14 months.[18]

The process of approving generic drugs in China is similar to that of new drugs. There is a significant backlog of reviews by CDE (Center for Drug Evaluation) in China, leading to surprisingly long review waiting periods. According to statistics, Generic drug’s approval time in China may exceed six years.[19]

The lengthy and repeating approval process made it difficult for drugs to be listed in the market in time, resulting adverse impact on innovation and reducing accessibility of drugs.

### 3.2.2 Relevant Laws and Regulations in the US

### 3.2.2.1 Patent Laws

US patent law is authorized and protected by Article 1 of the US Constitution, and gives the holder the right to prevent others from making, selling, and using the invention during the patent term.[18]

In order to gain exclusive patent rights, the inventor or owner must file an application with the government’s patent office ——United States Patent and Trademark Office. The term typically lasts for twenty years from the time of filing the patent application.[27]

However, it is impossible to understand the role of intellectual property rights, as they exist in the United States today, without understanding the current regulatory environment.[20]

### 3.2.2.2 Regulations on Approval Process

The regulation of generic drugs in the US has paralleled that of brand-name drugs.[24]

The Federal Food, Drug and Cosmetic Act of 1938 required proof of safety prior to marketing. Experimental therapies are required to undergo phased testing for safety and efficacy prior to being marketed.[25]The 1962 Drug Amendments to the Food, Drug and Cosmetic Act, which formally created the modern system of drug regulation in the USA, added requirement for proof of drug’s efficacy.[26]

According to statistics, average total drug development time went from 8.1 years in the 1960s, to 11.6 years in the 1970s, to ~14.2 years in the 1980s and 1990s. Since 1980, the average number of clinical trials conducted prior to fi ling a new drug application (NDA) has more than doubled, and the number of patients in clinical trials has tripled.[20]

As was shown by data, stricter Federal controls increased approval time and effective patent term for patented drugs decreased from 17 years to 9 years).[21]On the one hand, the increase of clinical time and stricter approval access would use up some of the patent term, On the other hand, the amendment contained no exception to generic drugs, which means generic drugs are also required to undergo repeated procedures.

To address these concerns, Congress carefully crafted the Hatch-Waxman Act in 1984 to address two competing goals: to spur new pharmaceutical development and to encourage greater public access to generic drugs.[17]Generic drug firms gained greater access to the market for prescription drugs, and innovator drug firms gained certain increased periods of market protection through special patent extensions, and award of periods of market exclusivity.

The Hatch-Waxman Act extended the abbreviated new drug application (ANDA) process to generic drugs first approved and marketed after 1962. This allowed generic versions of brand name drugs to enter the market when any patent or period of exclusivity expired.

The Act streamlined the approval process by eliminating the need to repeat duplicate, unnecessary, expensive and ethically questionable clinical and animal research to demonstrate the safety and efficacy of the drug product as it was recognized that pioneer drug manufacturers had done ample and well controlled studies.[25]What the ANDA applicant has to demonstrate is that the drug product is the same in active ingredient, route of administration, dosage form, and strength as the product in the full NDA and is bioequivalent to the NDA product.[26]

Though straightforward in principle, the Hatch-Waxman Act operates through a series of regulatory tradeoffs that can seem complex.[20]It sought to regulate and encourage the manufacturing of generic drugs; brought about significant changes to patent laws, specifically pharmaceutical patents.The Act would help establish a modern system for generic drug manufacturing that would not only protect intellectual property rights, but also provide a gateway that encourages the production of generics in the pharmaceutical industry.[27]

In the aftermath of the Hatch-Waxman Act, the generic drug industry experienced considerable “growing pains”: a bribery scandal, disenfranchisement by FDA regulatory reform , persistence of barriers to generic entry, continuing problems with establishing equivalence to pioneer drugs etc.[24]

### 3.2.3 Findings

By comparison study, the relationship between patented drugs and generic drugs has emerged. On the one hand, exclusive protection enjoyed by patented drugs prevent preventing generic drugs entering into the market within a certain period of time. On the other hand, encouraging generic drugs’ development will inevitably injure the innovator’s benefit and thus suppress innovation. It would be unwise to promote patented or generic drugs’ development unilaterally as it will reduce affordability and accessibility of drug products and ultimately do harm to public health. Therefore, efforts need to be made to strike a good balance between them.

Although great differences can be found between the US and China’s laws and regulations governing drugs. However, common problem is faced by two countries: complex and lengthy approval process reduced the effective patent term for patented drugs and also prevent generic drugs enter into market, which result in adverse impact on public welfare.

### 3.2.4 Solutions and Suggestions

Back to China’s reality, since scientific research has proven generic drugs’substitutability in common disease, which greatly removed misunderstanding towards generic drugs’ safety and efficacy and laid foundation for accelerating approval process in China.

In recent years, China’s government has taken a series of measures aimed at speeding drugs approval. NMPA, as the result of regulatory authority reforms aimed at streamlining administration and delegate power, is responsible for reducing the number of items requiring specific administrative review and approval and innovate regulatory model.[25]

First of all, it implemented a priority review process to fast-track approval for drugs targeting unmet medical needs. Secondly, it allowed for the Phase I trials of generic products to be conducted on sites that have not been formally vetted by the government. Thirdly, it increased the reviewer workforce eleven-fold over two years, from 70 to 800, with more hiring planned for future years.[29]

In addition, the National Health and Fitness commission, the National Development and Reform Commission and other 12 departments jointly issued the work plan on accelerating the implementation of policies on the supply and use of generic drugs. In December 2018, the first batch of drug catalogs was issued so as to guide pharmaceutical enterprises in R&D, registration and production. Among them, 34 drugs were listed, including a variety of cancer drugs, infectious drugs, drugs for rare diseases and drugs that had previously been in short supply.[30]

In 2018, the average drug approval took just over three years. Drugs that received priority status, meaning they meet an unfulfilled medical need, took an astonishingly short 16 months for approval.

Having seen efforts done by Government, we put forward following suggestions based on our literature and reflection.Firstly, enhancing Information disclosure. A common reason that the application or materials were rejected was lack of required information, data or evidence. By disclosing the required information that the applicant should submit helps to avoid multiple rounds of approval and thus save time.Secondly, Promulgating Procedural Manual in order to regulate reviews’ assessment practice and improve the efficiency of evaluation process. While enterprises take responsible for their application materials, reviewers also have to improve their work efficiency. Thus, promulgating such norm is necessary.Finally, Speeding up the establishment of patent linkage system and patent term compensation system.[28]

#### 4 Conclusion（张少英，李娅，张广华）

Although patented drugs are known for their initiation and efficacy, the price of it is expensive. So as an alternative of patented drugs, generic drugs has emerged rapidly. In spite of the generics has the similar efficacy compared with patented ones in many cases, owing to the low price different appearance, shape, and odor et.al, it is being questioned. Some people said that generics altered the efficacy of patented drugs, and some even said they had side effects. Resulting in some patients and providers are resistant to generic substitution. Otherwise, some disease are complex and intractable, such as orphan diseases and rare diseases, that need to take the generic substitution more into account.

Since biomedical research has proved generic drugs’ substitutability in common disease, what we have to find out is that whether it is feasible to replace patented drugs from legal perspective. By introducing and summarizing main contents of patent laws and approval regulations in China and the US, two conclusions can be drawn from our research. Firstly, the relationship between patented drugs and generic drugs is rather complicated, thus any policy or decision to be made shall strike a good balance between them so as to improve public welfare. Secondly, lengthy approval process of generic drugs was a common problem faced by China and the US, efforts should be made to streamline approval process. （张广华）

Speeding up the launch of Generic Drugs Under China’s Current Regulatory system is a long-term project. we noticed huge efforts had been done by Government accompanied by deepen reforms. Other suggestions were put forward based on our research. In view of the complexity of relationship between generic and patented drugs, how to provide more streamlined ways for generic drugs to enter into the market needs well knitted designs. （张广华）

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