

# A Study on the System of Marketing Authorization Holder in China

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**Keywords:** marketing authorization holder system, drug registration system.

**Abstract.** This paper analyzes the characteristics of the current drug registration permit system in China and its shortcomings in the face of new drug development. It points out the necessity and positive significance of the system of marketing authorization holder (MAH) in China. Through interpretation of the “Pilot Scheme for MAH system Program”, this paper puts forward the need to pay attention to the pilot program and the corresponding recommendations.

## 1. Introduction

China's current drug market uses the administrative licensing system which includes the drug manufacturing certification, “*Good Manufacture Practice*” (GMP) certification, pharmaceutical production and operating license, and the drug approval number. The drug approval number is the only “identity card” listed on the drug.[1] The characteristics of the administrative licensing system are: First, the main body is limited to pharmaceutical production enterprises and related research institutions; Second, drug registration and drug production enterprises are closely linked. Each drug approval number corresponds to a GMP certified enterprise. So, China's drug registration system is a “bundled” system. The GMP certification is required in order to get the drug manufacturing certification. Once the manufacturing certification is in place, then application can be made for the drug approval number.

Implementation of this system helped to organize the disorganization of the drug registration system, has played a positive role in the protection of drug quality, safety and the regulation of the pharmaceutical market. However, the improvement of the level of medical science and technological innovation, especially in the face of the international trend of the pharmaceutical market, the current “bundled” drug registration system defects have been exposed.

a) Drug research institutions, research and development (R&D) enterprises, because they do not have the GMP standard pharmaceutical manufacturers, cannot obtain a drug approval number. Foreign drug research enterprises of new drugs that want to be listed in China, should be established in line with GMP certified production enterprises, to achieve local production. The current “bundled” drug registration system, means a lot of significant foreign drugs cannot be simultaneously listed in the foreign and domestic markets. We currently have to wait for drugs to be listed on foreign markets using Chinese drug import channels or after the expiration of patents, to set up domestic generic channels. New varieties and special drugs listed have a serious lag despite the domestic medical needs of patients.

b) China's current drug registration system relies on the pharmaceutical manufacturers for the reliability, stability and ability to assure the quality of drugs listed, in cases of security incidents. However, the security of drug quality and safety should take place throughout the whole process of development, production and listing. The current system does not stipulate the safety responsibility of drug developers for listed drugs. This leads to a lack of legal responsibility for drug quality and safety by the developer.

c) Under the current drug registration system, on the one hand, drug developers want to maximize the benefits of research results, so they choose to sell drug research results to multiple end users or sell the partial results several times. On the other hand, pharmaceutical manufacturers want to use their idle equipment to expand production, and will produce the same drug by changing the name, packaging or minor changes in chemical makeup, then file a new drug listing registration, that results in a variety of similar drugs on the market. For example, there are 756 aspirin drug approval numbers, acetaminophen has 1502 drug approval numbers, radix isatidis has 1371, etc.[2] This repeated use of the same results of research and development has led to low levels of domestic pharmaceutical production, resulting in extremely large waste of resources and disorderly competition in the pharmaceutical market.

In the face of the shortcomings of the current drug registration system in China, by drawing lessons from the experience of the license holder system of European, American and the Japanese, the Standing Committee of the National People's Congress decided to authorize the State Council to carry out a pilot work of marketing authorization holder (MAH), in Beijing, Tianjin, Hebei, Shanghai and ten other provinces and municipalities, on January 4, 2015. The MAH system tried to separate drug listing license and production license. Under the MAH, the drug R&D institutions or individuals could apply for the drug listing from the drug administration directly and get a drug approval number. Under this system, the licensee is responsible for the quality and safety of the entire life cycle of the drug. The MAH and the product license holder can be the same subject or a separate one.[3] As a result, on May 26, 2016, the State Council issued the "*Pilot Scheme for MAH system Program*" (hereinafter referred to as the "Program"), which opened a major reform of China's drug registration system.[4]

## **2. Establishment of China 's marketing authorization holder system (trial implementation)**

### **2.1 The "Program" interpretation**

China's "*Pilot Scheme for MAH System Program*" includes within its scope, the applicant and the holder of the conditions, the conditions of the production enterprises entrusted, the applicant and the owner's obligations and responsibilities, entrusted production enterprises obligations and responsibilities, and other aspects of the institutional arrangements made.[5] Three of the more important aspects of the program are:

First, subject area. Article 1 of the "regulations" stipulates that "the drug research and development institutions or scientific research personnel in the pilot administrative areas may serve as applicants for drug registration." The provisions stipulate that the licensees of drug listing may be either a research institution or a natural person. The establishment of the organization should be for the purpose of drug research and development, must be established in accordance with the law, with legal personality, can independently bear the legal responsibility of economic entities. Natural persons must be researchers who are citizens of the People's Republic of China, and work in the pilot administrative area.

Second, the obligations and responsibilities of the applicant, the holder and the entrusted enterprise. Article 5 and Article 6 of the "Regulations" respectively stipulate the principles and obligations of the applicant, the holder and the entrusted enterprise of the drug registration.

a) the applicant, the license holder, has comprehensive monitoring obligations and responsibilities for the entire life cycle of the drug quality and safety. The license holder is the primarily responsible party for the drug licensing system. The license holder is responsible for the quality and safety of all aspects of drug research and development, production, circulation, clinical trial and evaluation. It is regulated by the "*Good Clinical Practice*" (GCP), GMP, "*Good Supply Practice*" (GSP) and related laws in the pharmaceutical clinical trials, production and business activities of the drug clinical trial institutions, pharmaceutical production enterprises and pharmaceutical enterprises. The license holder also has legal responsibility for reporting related data and information on registration of drugs

in testing, production, sales, adverse reactions, re-evaluation, etc., to the drug regulatory authority. It also is responsible for public license approval information through the Internet, truthful publication of the public drug brochures, reasonable use of the true information, and bears the legal responsibility of misleading information to the public.

b) The entrusted pharmaceutical manufacturer is responsible for fulfilling its obligations under the “*Pharmaceutical Administration Law*”. Production should be in accordance with the standards of the GMP and the requirements of the contract in order to ensure the quality of pharmaceutical production, and bears legal responsibility.

c) The program sets “fault liability” principle as the universal principle of responsibility. License holders, entrusted production enterprises, and business sales enterprises have joint and several liability to the injured party or parties.

Third, the responsibility of the license holder. Article 2 of the “regulations” stipulates that the applicant for the drug listing license must have the capacity to insure the quality and safety of the drug. The content of the commercial drug insurance should be stipulated, in order to guarantee the license holder's ability to deal with the drug safety risk.

## **2.2 Benefits of the “Program”**

The “Program” points out that, to carry out the pilot drug MAH system is an important part of drug review and approval system reform. It has great significance in the encouragement of drug innovation and enhancement of the quality of drugs.

a) It promotes drug innovation. The “Program” provides that drug researchers can obtain the drug approval number independently. It completely reverses the problem of research institutions and personnel not being able to get the drug approval number and potential losses to the final market interests situation. It may also solve the problem, that the primary responsibility is not clear which causes confusion. Because the license holders (researchers) best understand the whole process of drug research and technical requirements, they may have more impetus to continued drug innovation.

b) It maximizes the quality of drugs. The “Program” clarifies that the license holder of the drug is responsible for the quality and safety of the whole life cycle of the drug. This prompts the holder to take the initiative to monitor the entrusted pharmaceutical production enterprises strictly, in accordance with the GMP and GSP requirements. License holders must pay attention to the monitoring of the safety and effectiveness of drugs listed, use their research and development advantages to improve the quality of drugs, and can effectively prevent and control drug security risks.

c) It optimizes the allocation of resources. The drug listing license and production license are independent, and can enable developers to focus on research and increase R&D investment. Pharmaceutical production enterprises can also promote the improvement of the production industry technology to improve production quality. This reduces duplication of investment and construction and makes the production of drugs in line with international requirements.

## **3. The important problems and suggestions on the development of the MAH system in China**

In order to ensure the good operation of the MAH system, the author puts forward the following questions and suggestions on the system design of the pilot scheme.

### **3.1 Establish the principle of attribution in the MAH system**

To implement the MAH system, the first need is to address the liability of the license holder, entrusted production enterprises, sales enterprises and other parties in drug security incidents. Establishment of the principle of drug safety scientific risk has a positive effect on the good operation of the MAH system. It could balance the interests of the main parties in the system, and could also maximize the protection of the legitimate rights and interests of the injured party.

Developed countries that have the drug injury accident tort liability principle have experienced a “fault liability” to “no-fault liability” (strict liability) change. However, in recent years, the rapid development of biological science and technology, the widespread use of biological products increased the risk of drug quality and safety uncertainty, which has led to drug companies overwhelmed by the principle of “strict liability”. For example, in 2001, the Merck company produced Vioxx (rofecoxib) drugs, the use of the drug caused serious adverse reactions to patients with heart disease. Patients resorted to the law and in the Angleton, Texas courts, sued Merck for \$253 million. In 2007 the company announced that it had paid nearly \$5,850 million for nearly 50,000 litigation cases in the United States.[6] There also was a lawsuit regarding cerivastatin serious injury by the German Bayer Drug company. Bayer will face billions of euros in litigation compensation.[7] Because of huge settlements, a number of pharmaceutical research institutions and pharmaceutical manufacturers have gradually lost the motivation to be the driving force of innovation which has effected the development of pharmaceutical technology innovation and the pharmaceutical industry. As a result, Europe, the United States and other countries are starting to review the principle of “no-fault liability”, to set the necessary restrictions.

China's MAH system design needs to consider the promotion of innovative drug research, development and production, prevention and control of drug safety risks, protection of the legitimate rights and interests of patients. Therefore, design of the principle of the responsibility of the MAH system, should consider all parties in the whole life cycle of drugs, which have different behavioral characteristics, and also should pay attention to the balance of rights and obligations, and to consider different principles of responsibility.

a) Due to the monitoring and attention obligations of the drug registration applicants and listed license holders, during the whole life process of drug quality and safety, the principle of responsibility should adopt a “fault presumption” as main, with “no-fault liability” as a supplement.

The main purpose of the “fault presumption liability” is to consider the serious asymmetry of the information available to the injured party. It is difficult for the injured party to find the fault evidence from the drug development for use in legal recourse. Therefore, they should be specially protected by legislative inversion which would require the developer to produce relevant evidence.

Application of the principle of “no-fault liability”, the system needs to be explicit and restrictive in only one case. That is, the design of drugs which due to the restrictions of the current level of scientific and technological understanding, cannot predict and control the resulting injury. This provision must be refined and determined, not only in line with the law of scientific understanding, protection of scientific and technological innovation; but also to prevent using the restriction of understanding to cover an actual existing fault just to escape liability.

In determining the “responsibility of the burden”, the “principle of attribution” should be differentiated from the system design “damage indemnification” and “damage compensation”. Damage indemnification to the premise of “fault” is the injured person's personal injury indemnification, including payment of medical expenses, disability compensation, death compensation and other economic compensation. Damage compensation to the premise of “no-fault liability” is based on the principle of balance of rights and obligations. It is the responsibility of drug registration applicants and licensing holders in drug damage considerations to give economic compensation. These two systems should not be separated. We cannot say that “no-fault liability” can be the only applied compensation mechanism and cannot be indemnified. It requires careful screening of the system design and scientific definition to determine which principle applies.

b) The principle of attribution of trustees in the MAH system of listed companies, including entrusted manufacturers, sales enterprises, experimental researchers and clinical users (medical personnel). The principle of “fault presumption liability” should be adopted. The trustees of each of these systems should have to show evidence to prove their “no-fault” in the drug damage incident in each of their individual roles. If they cannot prove “no-fault”, they should bear “fault liability”.

c) Applicants, license holders, entrusted enterprises, sales enterprises, medical institutions and other institutional entities bear joint and several liability, in the drug research, production, sales, and

clinical use of all aspects of the quality and safety issues. The injured party may claim damages from all or some of the institutions or persons. After implementation of tort liability, “no-fault”, one can have the “fault” entity repair the loss.

### **3.2 Determination of the responsibility of the license holder of the drug market**

The “Program” has no more definite restrictions on the listing of applicants and license holders for pharmaceutical listing, except for the basic conditions and requirements. The general purpose is to encourage drug research and development institutions and researchers to actively innovate. The “Program” Article 2 provides that “applicants should have the responsibility of drug quality and safety.” It is a threshold of the license holder, which is both a difficulty of system design and a difficulty of implementation in China. At present, there are three factors that should be considered.

First, as a license holder, the research institutions or researchers should have a certain economic capacity, and can bear security responsibility.

Second, as a license holder of the research institutions or researchers, the license holder is no longer considered a purely medical science research institution or researcher. They need to be considered managers, operators in consciousness and ability. Only with these three capabilities, can the holder ensure the quality, stability and safety of the listed drugs. This is the nature of the responsibility of the license holder.

It is suggested to establish an operating organization of the license holder in the system design. This can be learned from the European standards of quality and safety system. On the safety responsibility of the listed drug, the license holder bears all the security responsibility for the listed drug, producers and sellers are only responsible to the license holder.[8] This can also be learned from Japan's “three manager” system. The Japanese regulations require listing license holders must be equipped with three qualified full-time managers. They are executives, quality managers and safety managers, responsible to the license holder. To ensure the quality and safety of listed drugs, they monitor all stages of the drug's life, from clinical trials, through drug production to clinical application.[9]

Third, currently, China's pharmaceutical research institutions are mainly the university institute and the all levels of national research institutions. They are funded by the state and are committed to national and government research projects. Such researchers may not enter the drug market, apply for drug licensing in these institutions, and need follow-up systems to regulate them.

### **3.3 Establish a thorough relief system**

The establishment of a relief system for adverse drug reactions and drug injury accidents is a guarantee for the good operation of the MAH system. The huge safety risk of drugs is the key consideration that each country must consider in formulating a pharmaceutical-related system. The social contradictions and property losses that occur during any serious drug disaster, cannot be borne by each individual pharmaceutical company. The state should design systems to deal with pharmaceutical accidents.

a) The “Program” has been implemented for commercial drug insurance to solve the insufficient capacity of license holders in drug safety risks. The supporting insurance laws should be adjusted as soon as possible. Compulsory drug insurance should be one of the conditions for approving a drug licensing permit.

b) Because of the occurrence of a large range of “drug misadventures”, a national drug safety risk fund should be established. Sources of funds can be: investment by the government, pharmaceutical company fees, drug sales and other sources. The drug market license holders should also pay a certain amount of funds. The payment of the drug safety risk fund should be the condition for approval of the drug license. This fund system has successful precedent in Taiwan, Japan and Germany.[10]

#### 4. Conclusion

The “Pilot Scheme for MAH system Program” is a major reform of China's drug registration system. The implementation of the MAH system, is not a simple form of drug registration and procedural change, but an important basic reform of China's pharmaceutical system. The essence of reform is the improved distribution of medical and health resources and benefits in the country. It is not only in the interest of the medical system, but also the interests of the whole society and people's health. In order to ensure the good operation of the MAH system, it is necessary to establish the principle of attribution in the system, to determine the responsibility of the license holder, and to perfect the drug injury accident relief system. This will help to clarify the rights, obligations, responsibilities of the drug industry throughout the development and life cycle of medical drugs. It will also help to promote drug research and innovation, optimize the industry's resource allocation, improve the drug regulatory system, and protect national public health.

#### Acknowledgement

This research was financially supported by the Humanwell Healthcare Group Co., Ltd (Grant NO. 0231403070).

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