Evolution of the registration regulations for proprietary Chinese medicines in China

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[ABSTRACT] In this review, we provide a comprehensive overview on the registration of proprietary Chinese medicines (PCMs) in China over the past century by examining published literature and historical data. We will examine this evolving administrative practice for PCMs registration in China, which is divided into the following five stages: (1) initial measures (1915–1948); (2) early development (1949–1965); (3) provincial approval and trial implementation of the “approval number” system (1966–1984); (4) legislation and cleanup (1985–1999); and (5) centralized national approval (2000 until now), offering a panoramic view on the characteristics of PCMs registration management in China.

[KEY WORDS] Registration; Proprietary Chinese Medicine; China


Introduction

The use of proprietary Chinese medicines (PCMs) in China was first recorded in Prescriptions for Fifty-two Diseases (52 Bingfang in Chinese), which dates back to 3000 years ago [1]. There were many dosage forms recorded in this ancient medical book, including medicine pills, tablets, yeasts, liquors, oils/ointments, decoctions and powders. Through the end of the Qing Dynasty, PCMs were usually prescribed by doctors according to the patient’s conditions and used in the form of decoctions or self-made proprietary medicines. Large-scale pharmaceutical preparations mostly occurred during epidemic outbreaks. Governmental regulation of preparations of proprietary medicines rarely appeared in any of the past dynasties. At the beginning of the twentieth century, with the introduction of western industrial technology, western medicine, and vaccines into China, modern techniques of PCM preparation began to be adopted across China, while the government of the day started to strengthen the regulation of various preparations, including PCMs. Today, PCMs enjoy the same equal status as chemical drugs and biological products in China, where systematic and refined regulatory practices have been adopted for such medicines. This review summarizes the design of PCMs regulatory systems and the basic situations of PCMs in different historical periods, focusing on the administrative practices of PCMs registration.

Evolution of the administrative practice for PCMs registration in China

Initial measures (1915–1948)

Regulations on Management of Pharmacists [2], issued by the Beiyang Government in 1915, stated that “When the pharmacists prepare medicines in the forms of pills, powders, ointments, boluses and tablets, etc. They must submit and report the medicines along with their prescriptions to the governing police agency for review and approval, if the medicines have not been prepared as per established formulae”. In 1929, the government of the day had explicitly stated in the Rules on Management of Pharmacists [3] that “any newly invented medicine not recorded in Chinese and foreign pharmacopeias shall not be manufactured, sold, or introduced before a general description of its properties, quality, and preparation method, along with samples, has been reviewed and approved by the Health Department”. The Amendment to Rules on Management of Proprietary Medicines [4] issued in 1936 stated that “any newly invented medicine not recorded in Chinese and foreign pharmacopeias shall not be manufactured, sold, or introduced before a general description of its properties, quality, and preparation method, along with samples, has been reviewed and approved by the Health Department”. The Amendment to Rules on Management of Proprietary Medicines [4] issued in 1936 stated that “Those who apply for the preparation or introduction of proprietary medicines shall fill out the Request for Inspection on Proprietary Medicines and submit the samples and instructions for use to the health agency for review and approval. Such Proprietary Medicines can only be
sold when their licenses are granted”. It can be seen from these regulations that the governments of the day had already realized the importance of regulating PCMs through marketing registration. At that time, PCMs were mostly manufactured in a workshop owned by the pharmacy that sold them; and the workshop was usually built behind the pharmacy. Besides, all these pharmacies compiled the formulae of their self-manufactured PCMs into what was called “pei ben”, which literally means “formula books.” These pei ben recorded the prescription, formula, and preparation method of various PCMs made by each pharmacy-trade secrets that would never be disclosed to others. Therefore, PCMs sold to the patients might bear the same name, but their composition and efficacy could be completely different.

Later, the government of the day published documents such as Rules on Management of Proprietary Medicines [3], Provisional Rules on Ban of Proprietary Chinese Medicines in Ancient Prescriptions issued by Health Bureau of Peiping Municipal Government [6] and By-laws of Implementation issued by Peiping Municipal Government [7]. It also established the Proprietary Medicines Review Board and implemented regulatory measures on proprietary medicines regarding their registration, licensing, provisional licenses, etc. While standardizing the regulation of PCMs, the governments of the day acted against the use of these medicines. For instance, shortly before the People’s Republic of China was founded in 1949, the government ordered a ban of traditional Chinese medicine (TCM) [1], and only had to cancel it after strong opposition from the pharmaceutical industry.

**Early development (1949–1965)**

After the People’s Republic of China (PRC) was founded in 1949, commercially available PCMs came from two main sources: proprietary medicines made and sold by big pharmacies according to their own pei ben; and proprietary medicines prepared by small and medium pharmacies following the licenses granted by regulating agencies of the previous government. Since proprietary medicines manufactured according to pei ben were treated as “trade secrets never disclosed to the public”, it was impossible for the regulatory authorities to carry out effective supervision without the knowledge about the composition of these medicines, as described by the proverb “it is difficult even for the gods to distinguish between all those pills, powders, ointment, and pellets”. In order to standardize pei ben and assess the safety and efficacy of PCMs manufactured, some local governments established supervisory organizations such as the “Proprietary Chinese Medicines Review Board” in Tianjin, while others, like the municipal government of Beijing, convened medical experts to undertake such tasks. During this period, it was the responsibility of each province to regulate PCMs [8-11]. In 1954, the Health Department proposed the Interim Procedures on Management of Proprietary Medicines (First Draft Version) which was circulated internally to elicit opinions from health administrative departments of all provinces and cities. There were no records of its promulgation and enforcement, but some experts and available information indicated that some of the local governments were already following these rules.

In 1963, the Ministry of Health of PRC issued Notice on Strengthening the Work of Management on Drug Administration and Medical Device Manufacture [12]. In October of the same year, Rules Concerning Drug Administration was enacted after years of preparation, which has been known in the medical community as “the first law on drug regulation in PRC”. The Rules were put into trial implementation in its draft form upon the No. 63 joint notification made by Ministry of Health, Ministry of Chemical Industry and Ministry of Commerce of PRC on October 15, 1963, in the name of No. 642 Cynanchum paniculatum for drugs approved by health department, No. 202 Tetradium ruticarpum for chemical drugs and No.486 for drugs presented by doctors and manufacturers, respectively. In 1965, the Ministry of Health and the Ministry of Chemical Industry jointly developed the Temporary Provisions on Management of New Drugs, which spelled out more detailed requirements on new drug approval. This was the first piece of regulation on new drug regulation formulated by the Chinese Government, but it was not implemented due to the subsequent ten years of the Cultural Revolution (1966–1976).

The above rules and regulations showed that the national and local governments were aware of the importance of the standardization and regulation of medicines during the early years of PRC. However, due to a number of limiting factors, including comprehensive national power, level of industrialization, and overall distribution of businesses, the approval and regulation of PCMs mainly happened at provincial level with less strict requirements, despite government considerations on national review and approval of new drugs.

**Provincial approval and trial implementation of the “approval number” system (1966–1984)**

The Great Cultural Revolution that occurred between 1966 and 1976 severely impacted China’s drug regulation. Many effective rules and regulations, systems, and measures were abolished. Numerous unqualified pharmaceutical factories were established without permission. The quality of the drugs brought into the market was not properly controlled, resulting in bitter lessons from serious drug safety accidents. The subsequent period of “Setting Wrong Things Right,” where mistakes in the Cultural Revolution were corrected, saw the issuance of Regulations on Drug Administration (Trial) [13] by the Ministry of Health in 1978 with the endorsement of the State Council, which elaborated on the “clinical trial, identification, and approval of a new drug” in a separate chapter and proposed general principles for the submission

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1. TCM is a general concept, which may include PCMs, crude Chinese medicines and prepared slices of Chinese medicines.
of clinical and manufacturing information. The 1978 Regulations specified no special requirements for the review and approval of PCMs other than a chapter dedicated to general guidelines on “the gathering and planting of medicinal herbs and the preparation and use of Chinese herbal medicines”. Furthermore, the national government clarified for the first time in this document that approval numbers should be marked on the packaging of medicines. Based on the 1978 Regulations, the Ministry of Health issued the Regulations on New Drug (Trial) in 1979, which defined “new drugs” as any traditional Chinese or Western medicine that was developed or imitated in China (including radiopharmaceuticals and synthetic TCM products), classified into four categories according to whether they are novel products, manufactured domestically, and recorded in standards. Most PCMs were assigned to Category I and Category IV. The 1979 Regulations were the first regulations in China truly dedicated to the regulation of new drug registration. However, since China had still a planned economy back then, research and development of all new drugs had to be proposed first by R&D organizations based on the needs for disease prevention and treatment, before being planned by the governing authorities. The 1979 Regulations further stated that “all major drug products created in China, as well as radiopharmaceuticals, narcotics, synthetic TCM products, and contraceptives never manufactured in China previously shall be reviewed by the governing Health Bureau and approved by the Ministry of Health.” All other new drugs were to be reviewed and approved at the provincial level, and there were no special requirements for generic drugs, which would also be subject to provincial regulation as appropriate.

In order to achieve further standardization of regulation, the State Council and the Ministry of Health issued the Decision on Strengthening Medicines Management and Notification on Concerned Pharmaceutical Products Packaging Issues during Implementation of “Decision on Strengthening Medicines Management”, which emphasized the importance of “approval and issuance of drug approval numbers”. During this period, the national government clearly defined the review and approval authority of the health administrative departments of each province, which prevented the “phenomenon of drugs having to be approved by different departments simultaneously”. In the subsequent period, where the authority to review and approve proprietary medicines for marketing was largely held by provincial level governments, some of the provinces and cities cleaned up their market and even eliminated some products, while others approved many new products or expressly agreed on the replication of products from other provinces. It was also during this stage that the approval number system was first proposed by the national government as a way to regulate marketed products. In response, each province reissued or reapproved their “drug approval numbers”. However, the national government made no standardizing requirements for the format of approval numbers, so the provinces devised their own formats, causing serious inconsistencies nationwide.


In 1984, the first Drug Administration Law of PRC emerged as the times required, opening a new chapter of legislative progress for drug registration. The 1984 Law stipulated that the review and approval of the drugs shall be organized into a two-tiered system, i.e., new drugs shall be approved at the national level, while drugs produced in accordance with established national or provincial standards shall be approved at the provincial level; approval numbers shall be issued to drugs approved at both levels.

At this point, the mandates for review and approval became clearly divided between the national and local governments, while the legal status of approval numbers issued at the national and local level were explicitly defined in the national law. 1985 saw the implementation of Provisions for New Drug Approval, which for the first time separated TCMs from Western medicines in the new drug category. This document classified TCMs into five categories: Category I included processed products of TCM materials, newly discovered medicinal materials, and parts of TCM medicinal materials newly employed for remedy; Category II included new preparations with new administration routes, and effective parts extracted from natural medicinal materials and preparations made with such parts; Category III included new TCM preparations (including ancient, secret, and proven formulae, as well as traditional formulae with changed compositions); Category IV included PCMs with a new dosage form and the same administration route; and Category V included PCMs with new and additional indications. This classification system indicated that the medical community had acquired an in-depth understanding of TCMs, not merely relying on experiences passed on from earlier generations. After that, the 1985 Provisions underwent various revisions, with its requirements on review and approval changed significantly, but the general classification was never subjected to any substantive change. Also proposed in the 1985 Provisions was the concept of pilot production, which has lasted for more than 20 years and greatly influenced China’s pharmaceutical regulation.

The 1985 Provisions created “Wei Yao Shi Zi Hao” as the prefix for approval numbers given to drugs approved for pilot production, and “Wei Yao Zhun Zi Hao” as the prefix for PCMs’ approval numbers. In the meantime, the former Bureau of Drug Administration of the Ministry of Health ordered all provinces to report their existing drug approval numbers for a general review, and later released the Notice on Review and Release of Directory of Drug Approval Numbers in September, 1985. The Directory annexed to that document showed the serious inconsistencies in the formatting of drug approval numbers across China, with a
top priorities. In 1999, the Administration issued Provisions for New Drug Approval \cite{Provisions} as its No. 2 Order, which basically adopted the same definitions of new drugs as the 1985 Provisions for New Drug Approval. As for the classification of PCMs, “TCM injection” has been added to Category II at a time when there were already more than 100 kinds of such injections in the market. The 1999 Provisions again emphasized that any “new drug” shall be reviewed and approved by the national regulating authorities prior to its marketing. On the same day, Provisions on Review and Evaluation of Generic Drugs was issued as the No. 5 Order, specifying that generic drugs shall also be subject to the final review and approval of the national regulators. At this point, from the regulations perspective, national regulating agencies regained the authority to review and approve nearly all drugs before they are marketed (excluding some excipients and bioequivalence tests, which are still subject to the review and approval of provincial authorities). Besides, the 1999 Provisions also clarified that the responsibility for specific reviews and approvals would be transferred from the Ministry of Health to the newly established SDA.

In 2001, the first revision of the Drug Administration Law also included clear legal statements granting national regulators the mandate to manage the review, approval, registration, and regulation of drugs, which is in line with the basic rules of drug circulation in a market-based economy.

The development and refining of these laws and regulations reflected the overall philosophy of the national government for regulating drug registration. Meanwhile, the SDA initiated the cleanup of TCM healthcare products and PCMs approved by local governments, and started the renewal of approval numbers for all PCMs.


The Ministry of Health implemented Administrative Provisions on Traditional Chinese Health Care Medicines \cite{Provisions} in October, 1987, which specified that “the review and approval of clinical trials and manufacturing of TCM healthcare products shall be entrusted to provincial regulators who shall file all their approvals with the Ministry of Health at the time of such approvals, using approval numbers in the format of “No. X Wei Yao Jian ( ) Z–XX”, e.g., “No. Ji Wei Yao Jian (87) Z–01”, in which the first letter stands for Hebei Province. What followed was chaotic management of these products across China, prompting the national government to order a pause of the review and approval of TCM healthcare products in 1996. During this period, some regions approved products using provincial drug approval number starting with “Lei”, “L” and “Zhun L”. The Ministry of Health issued the Notice on Strengthening Supervision and Management of Drug Approval Number \cite{Notice} in 1995, stating that “by September 30th, 1995, production of all drugs with approval numbers starting with “Similar”, “L” and “Quasi-L” shall be halted, and such approval numbers shall be revoked”.

Immediately after its creation, the SDA included the cleanup of TCM healthcare products into its agenda and
issued a document in 2000 announcing the formal launch of the cleanup initiative [42]. The effort was led by the Drug Registration Department, while the Center for Drug Evaluation was responsible for reviewing specific products against technical criteria and decide whether to approve a product and allow its approval number prefix to be changed from “Jian” to “Zhun”. Before the cleanup, there were a total of 4,627 TCM healthcare products approved in China, and more than 2,100 manufacturers producing these products in over 20 dosage forms. Only 1,064 products were approved by the SDA during the cleanup and had their approval number prefix changed to “Guo Yao Zhun Zi B”. 3,211 products were revoked by the SDA or by the provincial bureaus after a primary review, and others were treated as PCMs in line with local standards [43-47].


Strictly speaking, the provinces had no authorities or responsibilities to review and approve new drugs after 1985 (including changes in preparation, addition of new indications, and changes in administration route), meaning that new drugs can only obtain their approval for marketing from the national regulators. The 20 volumes of the ministerial standards of PCMs were a collection of standards for drugs approved by all provinces before 1985. In the meantime, the Ministry of Health also documented the drugs approved by all provinces according to these ministerial standards. However, due to a variety of reasons, many products were still being approved for marketing before the SDA was established. In order to address this problem, the SDA issued the Emergency Notice on Firmly Stopping the Illegal Approval on Drugs [48] in 2000, ordering all provinces to revoke the approval numbers granted to new drugs that had been approved locally for manufacturing after 1985, as well as generic drugs approved locally for manufacturing after 1996, and to ask the manufacturers to stop their production, otherwise the products would be treated as counterfeits.

In 2001, after issuing the Notice on Strengthening Management of National Standards on Proprietary Chinese Medicines [49], the SDA established the “Work Office for Management of Local Standards on Proprietary Chinese Medicines,” initiating the rationalization and management of local PCMs standards. During this period, the SDA looked at a total of 5,915 PCMs that had been granted approval numbers based on local standards, involving 1,666 manufacturers. After reviewing all these cases submitted by local authorities, the SDA eventually approved and released 1,518 new drug standards, granting 3,020 PCM approval numbers, which were all collected in the Corpus of National Standards on Proprietary Chinese Medicines (upgrading the local standards to national standards) [50, 51].

Standardized renewal of drug approval numbers

In 2001, the SDA issued the Notice on Implementation of No. 23 Order–Standardization of Drug Approval Numbers [52], followed by the Notice on Implementation of Unified Renewal of Drug Approval Number [53], launching the standardized renewal of drug approval numbers for all marketed drugs in China. This initiative appeared to be a survey of all the marketed drugs, but its underlying purpose was to further rationalize and standardize the registration of certain drugs, and resolve various legacy issues. To this end, a number of normative documents were issued before the renewal initiative was launched, including Administrative Provisions on Drug Packaging, Labels and Package Inserts (Interim) [54], Detailed Rules on Drug Package Insert (Interim) and Detailed Rules on Package Inserts of Traditional Chinese Medicine [55], which specified detailed requirements on the contents, writing style, and basic formats for the inserts of PCMs. The SDA also organized expert reviews of the submission standards and inserts for specific PCMs, based on which the standardized renewal of approval numbers was conducted. The renewal effort had not finished until 2005.

After the renewal, all marketed PCMs were granted a standardized approval number prefix as “Guo Yao Zhun Zi B’” or “Guo Yao Zhun Zi B”. Local PCMs standards and their approval numbers were no longer in existence.

Laws and regulations on the registration of PCMs (2002 until now)

Since the promulgation of Provisions for New Drug Approval and Provisions for Generic Drug Approval in 1999, the SDA developed and issued three editions of Drug Registration Regulations [56-58] in 2002, 2005, and 2007, respectively, which integrated the marketing approval of all new and generic drugs, including TCMs, chemical drugs, and biological products into one regulatory document, while proposing different technical requirements for each product category. At a time when pharmaceutical marketing authorization has been completely centralized, it may be said the Drug Registration Regulations—the most frequently revised drug regulatory document with its three recent editions—is the product of a long history of regulatory evolution that provided rich experiences.

The Drug Registration Regulations issued in 2002 divided the registration of TCMs into 11 categories, which showed the medical community’s new thinking and guidance on the research and development of TCMs during that period of time. This edition also made “natural medicines” a category parallel to TCMs for the first time. The specific classifications, nevertheless, were still ambiguous or even improper to some extent, which was why the 2005 Regulations changed the classification into a nine-category system, which remains in use today. In addition, the 2002 Regulations proposed the concept of new drug monitoring period and abolished the administrative protection measures for new drugs that were implemented for 15 years.

The Drug Registration Regulations issued in 2005 adjusted the contents regarding TCMs, especially their classifications. Definitions of “traditional Chinese medicines” and “natural medicines” were explained, which was never seen in any previous regulatory document. Apart from that, this edition adopted basically the same ideas for regulating drug registration as the 2002 edition (e.g. the product categories.
granted with new drug certificates include drugs with changed dosage form and shall be subject to the tentative standards).

Proposing the idea of regulation that promotes “innovation, improvement, consistency, and soundness (referring to innovative new drugs, real improvements to existing drugs, generics consistent with the originators, and sound clinical trial data),” the Drug Registration Regulations issued in 2007 made some dramatic changes based on the 2005 edition. For instance, it stated that “the registration for drugs with changes in dosage forms, changes in administration routes, and addition of new indications shall be subject to the NDA applications,” but these drugs would no longer be regulated as new drugs, meaning that they would not be granted new drug certificates any more, and that further emphasis was given to encouraging and supporting real new drugs. Furthermore, products with changed dosage forms must not only reflect new clinical value, but also demonstrate real improvements in efficacy. As for generic drugs, the previous principle of “imitation of standards” was changed into “imitation of products.” Starting from 2007, the review and approval for the PCMs have strictly followed these requirements, resulting in a significant reduction in the annual number of applications for drugs with changed dosage forms or generic drugs, which fell to fewer than 10 or even 0. Additionally, the “trial standards” system that had been implemented for 22 years in China was abolished. The practice of converting trial standards into formal ones was discontinued at the end of 2012.

Following release of the 2007 Drug Registration Regulations, the State Food and Drug Administration (SFDA) published the Supplementary Provisions for Registration Management on traditional Chinese Medicines [59] in 2008, which provided important additional guidelines on encouraging TCM innovation and allowing the unique features of TCM to be fully leveraged, based on the characteristics and theories of traditional Chinese medicines. For instance, the 2008 Supplementary Provisions added that, for “new drugs that may provide remedy for diseases or symptoms not recorded in the nationally approved indications of PCMs,” applicants may request an application for special review and approval; preparations based on classic ancient formulae may apply for a manufacturing approval as long as their non-clinical safety evaluation data is provided. In addition, the Supplementary Provisions also supported the research, development, and marketing of compound TCM preparations targeting TCM syndrome types.

In February, 2013, the SFDA issued the Technical Requirements on Research of New Natural Medicines [60], which was developed over three years. Since the definition “natural medicines” was proposed in 1985 and its explanation in 2005, no drugs have been actually approved to be marketed as a natural medicine in China, and the 2013 Technical Requirements seeks to create new opportunities for TCM innovation by providing important guidelines on the research and development of “natural medicines”.

Conclusion
Supported by many years of development and rich historical heritage, China has achieved great progresses in the production scale, preparation technology, and clinical application of PCMs. By the end of June, 2016, there have been a total of 58,115 approval numbers for TCMs in China, including 987 approval numbers for TCM healthcare products re-designated as medicines and 81 approval numbers for imported TCMs, representing 9,913 different products and 76 dosage forms (calculated based on the name suffix, including some sub-dosage forms), wherein 90% are oral preparations and 145 are injections (with 1,243 approval numbers).

In recent years, an unprecedented level of sophistication has been achieved in the production process and quality control of PCMs, thanks to China’s progress in industrialization, expanded access to information technology, and advances in science and technology. Yet the R & D, application, and understanding of TCMs in this country remain at a rudimentary stage, due to the complexity of source materials and the emphasis on highly individualized diagnosis and treatment. TCMs, after all, are the embodiment of traditional Chinese medical theories. As China reforms its system for drug review and approval, it is imperative that the healthy development of PCMs be sustained with proper technical review strategies and a suitable administrative approval system, which should be designed with full consideration of the unique source materials, production process, quality control, and standards of PCMs, as well as the advantages of these medicines in clinical practice.

References

2 State Drug Administration (SDA) was renamed State Food and Drug Administration (SFDA) in 2003.


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Mr. YUAN Lin was assigned as Director-General of the Department of International Cooperation and Hong Kong, Macao and Taiwan Affairs Office in CFDA in 2013. Mr. Yuan is fully committed to advancing the international regulatory capacity building of CFDA in the regulation of food, drug, medical devices and cosmetics. He has been making great contribution to the CFDA’s bilateral and multi-lateral cooperation with other countries and international organizations. He and his team have accomplished a series of strategy research which better serves the regulatory work of CFDA.

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