Exploring the Inheritance and Innovation of Traditional Chinese Medicine from the Perspective of Registration

Zhu Juncheng, Wang Shuling*

(School of Business Administration, Shenyang Pharmaceutical University, Shenyang 110016, China)

Abstract

Objective To study the inheritance and innovation of traditional Chinese medicine, and to offer an insight for the public. **Methods** Literature review, data retrieval and systematic analysis were used to elaborate and summarize the influence of changes in related classification and policy reform of traditional Chinese medicine (TCM) registration on its inheritance and innovation. The study was carried out in the context of the TCM registration related classification and policy reform and evolution on TCM inheritance and innovation. **Results and Conclusion** TCM registration plays an important role in the inheritance and innovation of TCM, which greatly influences on its inheritance and innovation. The reform of new registration classification respects the law of TCM research and development, reflecting the establishment of the review and approval system in line with the characteristics of TCM inheritance, which promotes the research and development of new drugs. The establishment of the review and approval system also accelerates the marketing transformation of new traditional Chinese medicine. TCM innovation should attach importance to clinical value orientation and improve the scientific connotation of TCM. Meanwhile, the advantage of China's accession to ICH, PIC/S and other international drug certification organizations should be taken to speed up the construction of international mutual recognition of TCM standardization system, which can provide a broader path for the inheritance and innovation of TCM in the new era.

Keywords: traditional Chinese medicine registration; traditional Chinese medicine innovation; internationalization of Chinese medicine

The "Outline of Strategic Plan for the Development of Traditional Chinese Medicine (2016−2030)" points out that there is an urgent need to inherit and make good use of traditional Chinese medicine (TCM) and give full play to the role of TCM in deepening the reform of the medical and health system. However, at present there are some problems such as lack of high-level talents, insufficient inheritance and innovation in traditional Chinese medicine. As a special commodity to cure diseases and save lives, medicine has a dual role of "positive and negative". Therefore, in the drug development and innovation, registration applications, review and approval, it needs scientific supervision. In the above context, traditional Chinese medicine industry gradually gets rid of the previous rough model and becomes refined. Besides, the standardization of TCM research and technology has also been significantly developed [1, 2]. As one of the elements to promote

* Corresponding author: Wang Shuling, professor. Major research area: Pharmacy management regulations and human resources research. Tel: 13998302138, E-mail: lingyi50@163.com.

the high-quality development of traditional Chinese medicine industry and to practice the concept of "cultural confidence" in the new era, this paper explores the inheritance and innovation of traditional Chinese medicine based on the perspective of TCM registration in order to make some contribution to the new drug innovation.

1 The meaning of TCM registration and the changes of regulations and policies

1.1 TCM registration classification

China's 2020 version of the "Provisions for Drug Registration" (hereinafter referred to as "Provisions") clearly defined drug registration. The drug registration applicants should be in accordance with the statutory procedures and related requirements to submit drug clinical trials, drug marketing licenses, re-registration and other supplemental applications. Drug regulatory authorities, based on laws and regulations and existing scientific knowledge of safety, efficacy and quality control and other reviews, can decide whether to agree to their applications [3]. The essence of drug registration is also an administrative approval behavior, not only to consider the safety and efficacy of drugs, but also to comply with and promote the government's policy [4]. Therefore, drug registration is the start of drug regulation, which has significance for drug innovation, listing and people's medication safety.

1.2 Regulations and policies of TCM registration

The core focus of the TCM registration management system lies in the registration classification, and the management of registration classification has a direct role in leading the innovative development of TCM [5]. Therefore, promoting TCM registration reform is one of the paths of its inheritance and innovation. The government has also issued a series of policies on TCM registration-related classification reform (Table 1) to gradually promote the inheritance and innovation of TCM.

Table 1 Policy changes of TCM registration and classification reform

Regulatory document	Publisher	Release time	Driving innovative content
New Drug Approval Scheme	Former Ministry of Health	1985	The first to manage the classification of Chinese medicine
New Drug Approval Scheme	Former Ministry of Health	1999	Chinese medicine "compound" for the first time in the registration of classification; Emphasis on the application of herbal resources in the classification; "Indications" changed to "primary medical conditions"
Provisions for Drug Registration (Trial Implementation)	National Medical Products Administration (NMPA)	2002	The first clear concept of drug registration; From 5 categories to 11 categories
Provisions for Drug Registration (Board Order No. 17)	State Food and Drug Administration (SFDA)	2005	Classification from 11 categories to 9 categories; There are national standards for Chinese pharmaceutical preparations as long as they meet national standards can be reduced or exempted from relevant research
Provisions for Drug Registration (Board Order No. 28)	SFDA	2007	Natural drugs that have been standardized to generics

(to be continued)

Continued Table 1

Regulatory document	Publisher	Release time	Driving innovative content
Notice on the Issuance of Supplementary Provisions on the Administration of Registration of Traditional Chinese Medicine	SFDA	2008	The development of new Chinese medicine should be consistent with the theory of Chinese medicine, focusing on the basis of clinical practice, with clinical application value
Opinions on Deepening Drug Review and Approval Reform to Further Encourage Drug Innovation	SFDA	2013	Encourage clinical value-oriented drug innovation and further accelerate the review of innovative drugs
Opinions on Deepening the Reform of the Review and Approval System to Encourage Innovation in Pharmaceuticals and Medical Devices	General Office of the Central Committee of the Communist Party of China Office of the State Council	2017	Establish and improve the registration management system and technical evaluation system in line with the characteristics of Chinese medicine; Chinese medicine should emphasize new therapeutic effects
Provisions for Drug Registration (Bureau Order No. 27)	State Administration for Market Regulation	2020	Cancel the restrictions and concepts such as "not marketed in China" and "active ingredients and parts"; The classification conforms to the characteristics of traditional Chinese medicine and is managed in four categories
The Classification of Chinese Medicine Registration and Reporting Information Requirements	NMPA	2020	3.2 class development, in addition to pharmacological and non-clinical safety studies, should also assess the clinical value of drugs
Notice of the National Medical Products Administration on the Implementation of the Second Batch of Key Projects of the China Pharmaceutical Regulatory Science Action Plan	NMPA	2021	Development of new tools, standards and methods for review and approval in line with the characteristics of Chinese medicine
Several Measures to Further Strengthen the Scientific Supervision of Traditional Chinese Medicine to Promote the Inheritance and Innovative Development of Traditional Chinese Medicine	NMPA	2023	Continuously promote the research and innovation of Chinese medicine evaluation system; Improve the emergency review and approval mechanism of Chinese medicine

2 Dilemma of the inheritance and innovation of TCM from the perspective of registration

2.1 Sluggish application and lagging transformation of new Chinese medicine drugs before policy reform

In this paper, we search the acceptance and approval of new applications for TCMs from 2014–2021 from the official documents of the NMPA and Center for Drug Evaluation, NMPA taking investigational new drug (IND) and new drug application (NDA) as examples, and the results are shown in Fig. 1 and Fig. 2. The overall trend of new clinical trial and marketing applications for new Chinese medicines in the period of 2014–2020 is decreasing. The number of approved new drug clinical trial applications during 2014–2020 is at a relatively high level, but the approved new drug

marketing applications are no more than ten, indicating the overall enthusiasm for new drug applications in traditional Chinese medicine is not high during the period before the implementation of the new version of the "Provisions". Besides, the transformation of the results of new Chinese medicines also has a certain lag.

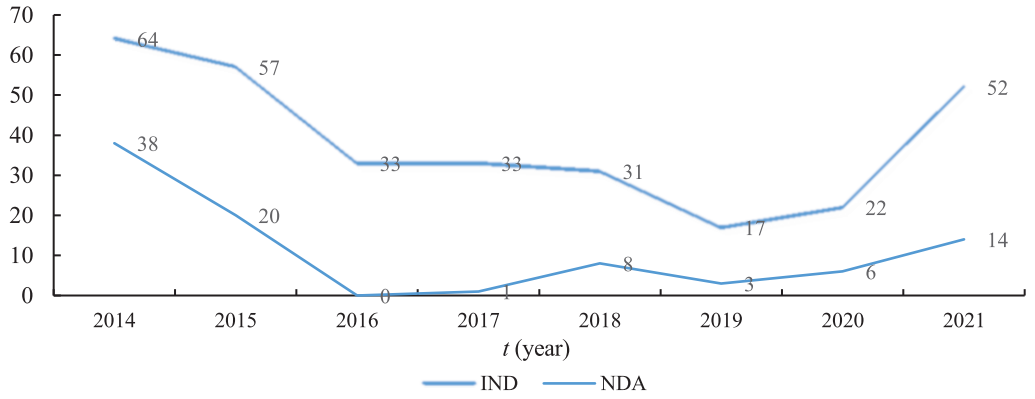

Fig. 1 Number of investigational new drug (IND) applications and new drug applications (NDAs) in traditional Chinese medicine from 2014 to 2021

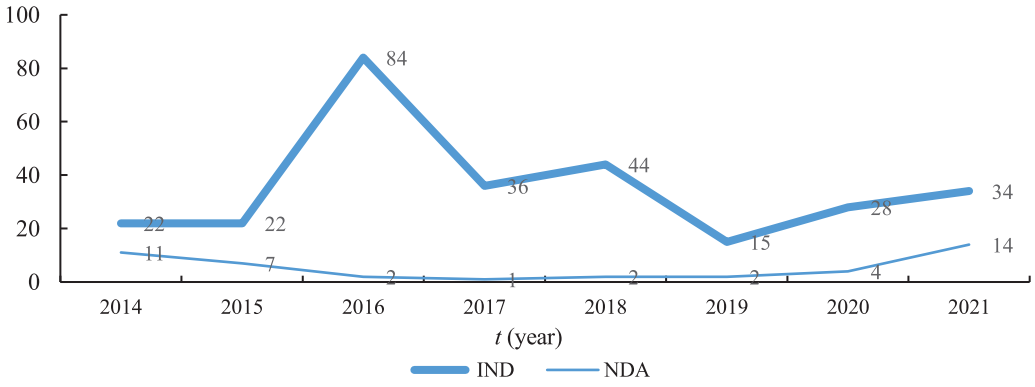

Fig. 2 Number of IND applications and NDA approvals in traditional Chinese medicine from 2014 to 2021

2.2 Narrow path of international registration

Due to the geographical proximity and cultural similarities between Asia and China, Asian countries become the main import regions for Chinese medicine products. Meanwhile, in the international mainstream pharmaceutical market in Europe and the United States, Chinese medicine products mainly enter [6] in the form of botanical medicines and nutritional supplements. Take Australia as an example, Australian GMP is a relatively early implementation of drug production standards worldwide after the U.S. FDA and the World Health Organization (WHO). Australia released the "Regulatory Overview of Registered Medicines and Registered Supplementary Medicines 1.1" in 2021 [7], which classified plant or herbal materials (or synthetic substitutes for such materials) as supplementary medicines. It also classified supplementary drugs, over-the-counter drugs and prescription drugs as listed drugs and registered drugs TCMs (Fig. 3). occupy a small percentage of its registered listings in Australia. However, TCM is one of the three major legal categories for drug registration in China (Fig. 4).

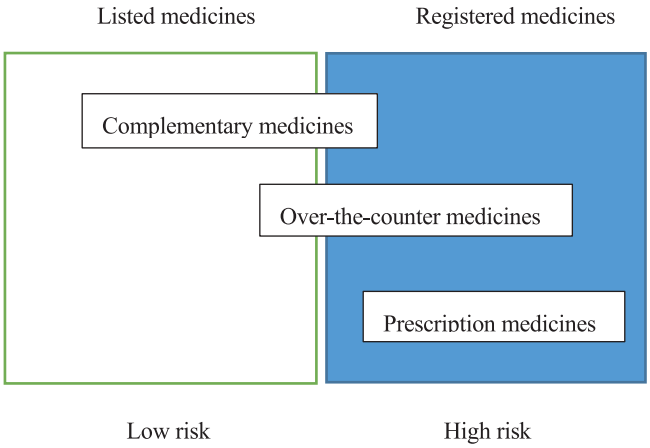

Fig. 3 Chinese herbal medicine as complementary medicine in Australia

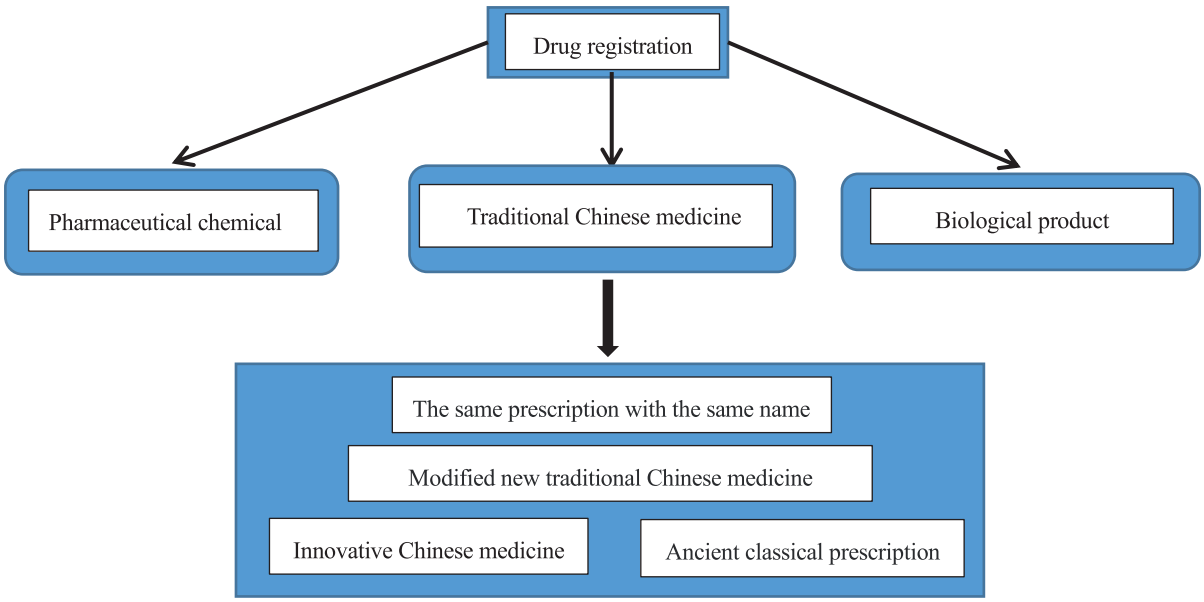

Fig. 4 Classification of TCM registration in China

3 Analysis of promoting the inheritance and innovation of TCM from the perspective of registration

3.1 Strengthening ancient classical prescriptions combing to promote the inheritance of TCM

The rapid rise in new drug applications from 2020 (Fig. 1) may be due to the General Secretary's clear request to strengthen the collation and development of classical prescriptions and medical books, improve the review and approval mechanism of TCM, and accelerate the R&D of new TCMs and the progress of related industries [8], it pointed out the direction for previous documents and policy reform. In this context, in 2020, the "Traditional Chinese Medicine Registration Classification and Reporting Requirements" [9] was released to subdivide the "ancient classical Chinese medicine compound preparations" into 2 cases: 3.1 means that Chinese

medicine compound preparations should be managed according to the ancient classical prescriptions catalog" and 3.2 refers to "other Chinese medicine compound preparations from ancient classical prescriptions", it provided for the two types of ancient classical Chinese medicine compound preparations in the case of functional subjects to use a special expression in Chinese medicine, both in accordance with the traditional process of preparation and the use of traditional routes of administration, they all respect for the unique laws, characteristics and advantages of TCM research and development. For example, in March 2021, the NMPA urgently approved the listing of Clear Lung Detox Granules, Dampness Defeating Granules and Xuan Fei Defeating Granules (all of the above are from ancient classical recipes) through a special approval process, which is the first time after the reform of the registration classification of TCM in accordance with the "Traditional Chinese Medicine Registration Classification and Reporting Requirements" for approval of the varieties within category 3.2 [10].

3.2 Improving the review and approval system to speed up the listing of new TCM

The 2017 "Opinions on Deepening the Reform of the Review and Approval System to Encourage Innovation in Pharmaceuticals and Medical Devices" requires the construction of a registration and management system that meets the characteristics of traditional Chinese medicine. In recent years, China has promoted the reform of the review and approval system for traditional Chinese medicine continuously, establishing a review and approval evidence system that combines theories of traditional Chinese medicine, human experience and clinical trials (the "three combined" review system). Besides, the new version of the "Provisions" also added breakthrough therapeutic drugs and conditional approval procedures, increasing the ways to speed up the listing of new traditional Chinese medicines [11, 12]. For the approval of classical Chinese medicines and compounded Chinese medicines derived from ancient classical prescriptions, the process should be optimized and reduced, and the latter is also classified as a separate "clinical exemption" [13, 14]. It can be seen that China's policy on the approval of traditional Chinese medicine has changed a lot.

With the implementation of the 2020 version of the "Provisions", a registration and approval model in line with the theoretical characteristics of TCM was gradually formed on the premise of respecting the law of TCM development [15]. Then, the approval volume of TCM started to rise rapidly (Fig. 2). In 2021, the State Drug Administration approved the registration and marketing of five innovative TCMs, namely Xuanqi Jianbone Tablets, Astragalus Beneficial Kidney Capsules, Kunxin Ning Granules, Huzhen Qingfeng Capsules, and Xiejiao Dejian Capsules. In 2022 In 2022, the innovative Chinese medicine Guang Qian Cao Total Flavonoid Capsules that belonged to 1.2 class was approved to be marketed. Among them, 2021 witnessed the largest number of approved new Chinese medicines in the past five years (Fig. 2), which shows that some achievements have been made in the reform and improvement of traditional Chinese medicine review and approval system.

3.3 Encouraging innovation in TCM

The 2020 version of the "Provisions" classified four categories of drug management for traditional Chinese medicine according to innovative traditional Chinese medicine, improved traditional Chinese medicine, ancient classical prescriptions of traditional Chinese medicine compound preparations, and TCM with the same name and prescription. The classification of ancient classical prescriptions and homonymous prescriptions highlights the inheritance characteristics of TCM, and the classification of innovative Chinese medicine and improved new drugs highlights the innovation orientation. The new version of the "Provisions" abolished the old model of TCM registration, which had been used for nearly 20 years and it defined "drugs that have not been marketed and

sold in China" or "drugs that have not been produced in China" as new TCM. Therefore, it greatly raised the threshold for new Chinese medicines and guided R&D personnel to focus on the originality of traditional Chinese medicines. In addition, the new version of the "Provisions" has many significant changes compared to previous versions, such as breakthrough therapy, conditional approval, special review, 60-day clinical trial implied permission, and safety update report during research and development, reflecting the attitude of the regulator to encourage new drug innovation [16].

3.4 Cultivating talents of TCM registration for innovation transformation

Talents are the backup force for TCM inheritance and innovation, and TCM enterprises are the main force [17]. The purpose of new drug development in enterprises is to be marketed, and the system is the guarantee. Drug registration connects the regulatory agencies and the market, which plays an important role in the transformation of innovation of TCM. Therefore, enterprises should pay attention to the training of registration-related talents, establish a team of related professional talents to transform the innovation results. Wang Qingbai, et al. [18] pointed out that drug registrars should be good gatekeepers of drug management in the whole life cycle and focus on the process from drug development to post-marketing. Guo Jianfei, et al. [19] developed a method of competency evaluation index system for drug registrars, which had certain theoretical value for enriching competency research in drug development. Liu Yuting [20] concluded that the establishment of a competency evaluation system for drug registrars was conducive to improving registrars' comprehensive competence as well as strengthening the construction of drug registration professionals. The evaluation system of drug registration specialists is relevant to the development of China's drug registration, which is conducive to the overall improvement of China's drug registration level and the success rate of drug registration and marketing.

4 Suggestions for the inheritance and innovation of TCM from the perspective of registration

4.1 Focusing on clinical efficacy

After the implementation of the "Provisions" in 2020, the approved marketing of innovative Chinese medicines all have obvious clinical efficacy. For example, Xuanqi strengthener bone tablets can be clinically used for the treatment of mild to moderate knee osteoarthritis (Chinese medicine evidence of stagnation of tendons and veins), and Kunxinning granules can be clinically used for the treatment of female menopausal syndrome (Chinese medicine evidence of deficiency of both kidney yin and yang). For the innovative Chinese medicine, the adjustment of the new drug registration classification of TCM mainly lies in two aspects. Firstly, it is no longer only based on the content of ingredients and the basic category of substances for classification. Secondly, it emphasizes the clinical value orientation to encourage the innovative development of TCM [21].

The purpose of drug development is to treat or alleviate patients' diseases and protect their physical and mental health. Therefore, the quality and clinical efficacy of a good drug must be maintained at a high level. The innovation of traditional Chinese medicine comes from clinical experience, and traditional Chinese medical theory is the foundation of new traditional Chinese medicine. So, clinical evidence is very critical in the development of new Chinese medicine [22]. To ensure the safety of people's medication and meet patients' needs, the 2020 version of the "Provisions" emphasizes the importance of clinical efficacy and clinical value orientation [23, 24]. The "patient-centered" value orientation is conducive to improving patient satisfaction and better clinical services [25].

4.2 Improving the scientific evidence content and provide data interpretation

The use of TCM is guided by the theory of

TCM, and the experience of various medications is summarized through a large number of cases. Facing the cultural differences between China and Western countries, the lagging of relevant regulations and standards, and being in the environment of modern scientific system, it is challenging to register and market TCM in foreign countries in the form of drugs. For the domestic market, we need to improve the modern scientific connotation of TCM. In the case of Chinese medicine injections, most of them contain some unknown ingredients and it is difficult to clarify them, so they are mainly used in China and rarely exported to other countries TCM [26], as one of the China's excellent traditional cultures, must have its "merits". Adhering to and promoting traditional culture is the key to keeping the innovation of traditional Chinese medicine. Based on "cultural confidence", the modern scientific connotation of TCM should be improved by integrating TCM with modern science and technology, which can provide data interpretation under modern scientific system.

4.3 Promoting international registration of TCM and mutual recognition of standards

For the registration of TCM outside China, we should pay attention to the data of human use. The significance of simplifying registration is not to reduce the process but to reduce the materials required for registration. Therefore, we should categorize the degree of scientific proof of the application evidence for registration and management, reflecting the regulatory concept of combining inheritance and innovation [27, 28]. China joined the ICH (International Coordination Committee for the Registration of Pharmaceutical Products for Human Use) as the eighth regulatory body member in 2017, and the China Food and Drug Administration was re-elected to the ICH Management Committee in June 2021. It also applied to join the International Pharmaceutical Inspection Co-operation Scheme (Pharmaceutical Inspection Co-operation Scheme, or PIC/S) in the same year, fully demonstrating the international community's recognition of China's capabilities in drug innovation and scientific regulation. However, as mentioned above, the path to market registration of traditional Chinese medicine in Western countries, represented by Australia, is very narrow. Therefore, it is difficult for traditional Chinese medicine to enter the Western mainstream pharmaceutical market in the form of drugs.

5 Conclusion

We compare the policy reform of TCM registration, pointing out the dilemma of inheritance and innovation TCM from the perspective of registration. Then, we summarize the unique role and influence of TCM registration reform in promoting its inheritance and innovation and give some suggestions. In the new era, TCM inheritance and innovation should always take people's health as the center, follow the clinical value orientation, and focus on clinical efficacy. Besides, it should also focus on the training of talents for TCM registration to transform the biggest pharmaceutical market into "the most powerful pharmaceutical production". We should improve the scientific connotation of TCM to promote the sales of TCM in western market, thus contributing to the inheritance and innovation of TCM.

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