Editorial

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Tailored to fit: China optimizes policies and regulations regarding drug registration and review to promote innovation in traditional Chinese medicine

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SUMMARY The classification system for drug registration and the review and approval process influence the innovation and development of pharmaceuticals. China's previous classification standards for registration of traditional Chinese medicines (TCMs) overly emphasized the material basis while neglecting the clinical value of TCM. Moreover, the review and approval system did not fully consider the characteristics of new TCM drugs, such as the clinical experience already available for many TCM formulations guided by TCM theories. This resulted in suboptimal quality and quantity in the development of new TCM drugs. Since 2019, China has introduced a series of policies and regulations aimed at reforming the classification system for registration of TCMs and establishing a review system tailored to TCM characteristics. The new classification system for registration of TCMs emphasizes that the development of new TCM drugs should be oriented towards clinical value, focusing on meeting unmet clinical needs. The policies and regulations promote the conversion of prescriptions in ancient classics into new drugs and encourages the conversion of preparations from medical facilities into new TCM drugs. Secondary development of already marketed TCM products is encouraged to enhance the advantages of their clinical use. The new review system places importance on the role of TCM theories and clinical experience in supporting the registration of new TCM drugs. These reform measures have paved a path for registration and review of the characteristics of TCMs and will positively promote the development of new TCMs.

Keywords traditional Chinese medicine, registration, classification, policy, regulations

Traditional Chinese medicine (TCM) is a treasure of the Chinese nation, having made enormous contributions to the health and well-being of the Chinese people over thousands of years. Compared to modern medicine, TCM has a unique theoretical system and plays a distinct role in maintaining and promoting people's health. It has particularly notable advantages in the treatment of specific conditions and specialties such as orthopedics, proctology, pediatrics, dermatology, gynecology, cardiovascular diseases, kidney diseases, and peripheral vascular diseases. During the fight against the COVID-19 pandemic, TCM gained significant attention for its ability to effectively alleviate symptoms, reduce the progression of mild cases to severe cases, increase cure rates, and promote the recovery of individuals in the convalescent phase (*1*). Despite this, the development of innovative TCM drugs faces several challenges and issues. As an example, the classification of TCMs for registration is not sufficiently rational, leading to an overemphasis on the material basis while undervaluing their clinical significance. In addition, the policies and regulations related to the review and approval process are incomplete, causing suboptimal quality and quantity in the development of new TCMs.

In October 2019, the government issued the Opinions on Promoting the Passing Down, Innovation, and Development of Traditional Chinese Medicine (*2*). Addressing various issues and deficiencies in the development of TCM, such as an incomplete TCM care system, inadequate supply of quality TCMs, the shortage of skilled personnel, an imperfect innovation system, and lack of prominent development characteristics, the document proposed comprehensive requirements for reform. In promoting quality drug development, the document emphasized optimizing

the management of TCM evaluation and approval and refining the management of TCM classification and registration. Revised Measures for the Administration of Drug Registration in China were promulgated in January 2020, introducing a new, more rational classifications for TCM registration (*3*). In September 2020, detailed classifications for TCM registration and corresponding application requirements were issued by the National Medical Products Administration (NMPA) (*4*). In February 2023, the NMPA issued the Special Provisions for Registration of Traditional Chinese Medicines, which further refined the requirements for TCM research and development based on the general provisions of drug registration management (*5*). This enhanced the management of the development and registration of new TCMs.

After the reform, the system to manage drug classification categorizes TCM registration into four types: innovative TCMs, improved TCMs, TCMs in ancient classics, and drugs with the same name and formula (*4*). The first three categories fall under the scope of new TCMs. Innovative TCMs include preparations of Chinese herbal medicines, extracts, and preparations obtained from single plants, animals, minerals, *etc*., as well as new herbal materials and their preparations (*4*). Improved TCMs modify the administration route or dosage form of existing marketed TCMs, with advantages and characteristics in terms of clinical use such as enhanced therapeutic functions or new indications (*4*). TCMs in ancient classics refer to formulas recorded in ancient TCM classics that are still currently widely used with proven efficacy, distinctive features, and advantages (*4*). Unlike the previous classification system for registration of TCMs that emphasized the material basis for innovation in TCM, the revised system underscores that the development of new TCM should be guided by clinical value (*5*). It emphasizes assessing clinical benefits and risks, capitalizing on the unique advantages of TCM in disease prevention and treatment, and addressing unmet clinical needs. The strategy for developing novel TCMs focuses on promoting research and development of preparations based on TCM formulas in ancient classics and encouraging the conversion of preparations from medical facilities into new TCMs (*5*). Secondary development of existing marketed TCMs is encouraged to enhance the advantages of their clinical use (*5*).

Another highlight of the reform is the emphasis on the support role of TCM theories and clinical experience in the registration of new TCMs. Unlike chemical drugs, Chinese herbal medicines are often clinically used to treat related diseases before registration. Therefore, the policies and regulations emphasize the supporting role of clinical experience in the safety and effectiveness of TCMs. During the registration and approval process, an integrated system for evaluating evidence that combines TCM theories, clinical experience, and clinical trials is used to comprehensively assess the safety, effectiveness, and quality controllability of TCMs (*5*). A point worth noting is that preparations based on TCMs in ancient classics generally do not require clinical trials (*5*). The approval of these new TCMs mainly relies on the opinions of experts (*5*). This reform reflects respect for the clinical use of TCM formulas from ancient classics in TCM practice and highlights the academic inheritance and clinical characteristics of TCM. For other new TCMs used in clinical practice, if clinical experience can provide supporting evidence in terms of clinical positioning, patient selection, consideration of the duration of treatment and dosage, *etc*., such medicines may skip Phase II clinical trials but generally require Phase III clinical trials to confirm the safety and efficacy (*5*). In contrast, if the development of a new TCM is based on studies involving pharmacological screening rather than TCM theories and clinical experience, necessary Phase I clinical trials should be conducted, followed sequentially by Phase II and Phase III clinical trials (*5*). These reform measures open up a registration and evaluation pathway that considers the characteristics of TCM.

Compared to modern medicine, TCM has its own characteristics regarding indicators of efficacy and methods of assessment. The effectiveness of TCM is not only reflected in the improvement of indicators of disease pathology but also in the improvement of TCM syndromes. Therefore, assessment of the efficacy of TCM can now involve a combination of diseases and syndromes (*5*). TCMs can be classified into three specific categories based on their therapeutic indications (*5*): (*i*) Syndrome-based TCMs: These are formulations guided by TCM theories to specifically treat TCM syndromes. Their therapeutic functions and indications are described using TCM terminology. (*ii*) Combined disease-syndrome-based TCMs: These address both modern medical diseases and TCM syndromes. Their indications are described in terms that combine modern medical diseases and TCM syndromes. (*iii*) Disease-based TCMs: These are medications for specific modern medical diseases formulated in accordance with TCM theories. Their therapeutic functions are described using TCM terminology, while their indications are based on modern medical diseases. In clinical trials, the assessment of efficacy should be based on corresponding indicators of disease pathology or TCM syndromes, fully reflecting the unique characteristics of the efficacy of TCMs. Establishing methods of evaluating safety and efficacy and technical standards that align with the characteristics of TCM is a goal of the reform.

In response to specific situations in clinical use of TCM, recent policy reforms have clarified the criteria for implementing priority review and approval, conditional approval, and special approval. (*i*) Priority review and approval: TCMs that have clear clinical positioning and

significant clinical value and that are used to treat major diseases, rare diseases, clinical emergencies as a result of market shortages, or for pediatric use are eligible for priority review and approval (*5*). (*ii*) Conditional approval: TCMs to treat diseases that are life-threatening and for which no effective treatment is available may be conditionally approved if clinical trial data or quality clinical experience with the TCM indicates its efficacy and predicts its clinical value (*5*). (*iii*) Special approval: TCMs already on the market that require additional indications to address urgent needs during sudden major public health emergencies may undergo special approval to expand their therapeutic indications (*5*). These reforms aim to streamline the regulatory processes for TCMs, ensuring timely access to effective treatments for critical medical conditions and public health emergencies.

In order to fully capitalize on the advantages of the healthcare security system and support the innovation and development of TCM, the National Healthcare Security Administration and the National Administration of Traditional Chinese Medicine jointly issued the Guiding Opinions on Medical Insurance Supporting the Passing down, Innovation, and Development of Traditional Chinese Medicine in December 2021 (*6*). This guidance includes coverage of suitable TCMs by health insurance payments. In order to enhance the full lifecycle management of TCMs and promote continuous improvement in their quality, the NMPA drafted the Regulations on Protection of Traditional Chinese Medicine Varieties (Draft for Public Comments) in December 2022 and solicited public opinions (*7*). These policies and regulations comprehensively and systematically create a TCM management system in order to positively promote the development of new TCMs.

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References

1. Huang M, Liu YY, Xiong K, Yang FW, Jin XY, Wang ZQ, Zhang JH, Zhang BL. The role and advantage of traditional Chinese medicine in the prevention and treatment of COVID-19. J Integr Med. 2023; 21:407-412.
2. Central Committee of the Communist Party of China and the State Council. Opinions on Promoting the Passing Down, Innovation, and Development of Traditional Chinese Medicine. *https://www.gov.cn/zhengce/2019-10/26/content_5445336.htm* (in Chinese).
3. State Administration for Market Regulation. Measures for the Administration of Drug Registration in China. *https://www.gov.cn/zhengce/zhengceku/2020-04/01/content_5498012.htm* (in Chinese).
4. National Medical Products Administration. Classification and Application Requirements for the Registration of Traditional Chinese Medicines. *https://www.nmpa.gov.cn/directory/web/nmpa/xxgk/ggtg/ypggtg/ypqtggtg/20200928164311143.html* (in Chinese).
5. National Medical Products Administration. Special Provisions for Registration of Traditional Chinese Medicines. *https://www.nmpa.gov.cn/xxgk/ggtg/ypggtg/ypqtggtg/20230210173401120.html* (in Chinese).
6. National Healthcare Security Administration and the National Administration of Traditional Chinese Medicine. Guiding Opinions on Medical Insurance Supporting the Passing Down, Innovation, and Development of Traditional Chinese Medicine. *https://www.gov.cn/zhengce/zhengceku/2022-01/01/content_5665996.htm* (in Chinese).
7. National Medical Products Administration. Regulations on Protection of Traditional Chinese Medicine Varieties (Draft for Public Comments). *https://www.nmpa.gov.cn/xxgk/zhqyj/zhqyjyp/20221223171015116.html?type=pc&m=* (in Chinese).

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