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POLICY FORUM

Dual-driven by regulatory science and policy reconstruction: Traditional Chinese medicine (TCM) new drugs accelerate development—A critical review of highlights in registration and regulation of TCM and natural medicine new drugs in China (2021−2025)

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Regulatory science for traditional Chinese medicine

Abstract In recent years, China's new round of institution reform has further optimized the drug regulatory system. Relevant departments and institutions involved in traditional Chinese medicine (TCM) regulation have been strengthened. TCM regulatory science, as an emerging interdisciplinary field, has received high regard and experienced rapid development, significantly enhancing TCM regulatory capabilities. Simultaneously, accelerated progress in emerging technologies and production innovation for TCM drug discovery, coupled with the implementation of the National Major Scientific and Technological Special Project for "Significant New Drugs Development" and its translational achievements, have led to a historic turning point in the development of innovative natural TCM drugs over the past five years. Driven by the dual engines of "regulatory science" and "policy restructuring", the development of new TCM drugs has entered a fast lane. Both the quantity and quality of investigational new drug (IND) and new drug application (NDA) registrations and approvals for new natural TCM drugs have shown rapid growth, effectively meeting the public's health demands for TCM products and unmet clinical needs of patients. This study focuses on the development of new TCM drugs during the significant historical phase from 2021 to 2025. It provides a comprehensive overview of new TCM and natural drug applications and regulatory reviews over the past five years, delves into the implementation of the National Drug Regulatory Science Action Plan, and highlights the importance of TCM regulatory science as an emerging interdisciplinary field in accelerating the creation of new TCM drugs. It systematically summarizes the effects of regulatory policies and regulations, the reform of TCM registration classification, specialized TCM registration provisions, and incentive measures such as the National Major Scientific and Technological Special Project for "Significant New Drugs Development". Based on an international perspective, it provides a focused review of recent highlights in TCM new drug development and regulation. This holds significant importance for promoting breakthroughs in TCM new drugs across more disease areas and advancing the international coordination of TCM regulation. The challenge faced in managing the registration of new TCM drugs lies in resolving the conflict between TCM theory and modern drug attributes, while balancing the rapid advancement of traditional medical theory and emerging technologies with the robustness of the drug regulatory framework. In the future, actively advancing research and translation in TCM regulatory science, innovatively establishing benefit-risk assessment systems and standards for new TCM drugs, and accelerating the development of a globally leading regulatory system with Chinese characteristics that aligns with the unique nature of TCM will be particularly crucial for global coordination of TCM regulatory policies, and the modernization and internationalization of TCM.

1. Introduction

Traditional Chinese medicine (TCM) refers to medicinal substances and their preparations used under the guidance of traditional TCM theory. Natural medicines refer to natural medicinal substances and their preparations used under the guidance of modern medical theory. TCM and natural medicines serve as both the material foundation for the inheritance and innovation of TCM and the key vehicles for leveraging the distinctive advantages of TCM. The promulgation of the Drug Administration Law of the People's Republic of China in 1984 and the Law of the People's Republic of China on TCM in 2016 established key public health mandates for relevant authorities such as the National Medical Products Administration (NMPA) and the National Administration of TCM (NATCM). These mandates encourage the application of modern scientific and technological methods alongside traditional TCM research approaches to advance scientific research and drug development in TCM. They also aim to establish and refine a technical evaluation system tailored to TCM, thereby promoting its inheritance and innovation. The period around 2020 marked a critical turning point in the development of new TCM drugs in China, shifting from a low point to a significant leap forward. Between 2016 and 2020, only 11 new TCM drugs (including 6 innovative drugs) were approved for market release, indicating a stagnant phase in the development of new TCM drugs. On January 1, 2021, the National Medical Products Administration implemented the new "Classification of TCM Registration and Requirements for Application Materials". TCM registration is categorized into innovative TCM drugs, modified TCM drugs, compound preparations based on ancient classical formulas, and drugs with identical names and formulas. The first three categories are classified as new TCM drugs. Natural medicines follow the TCM registration classification. Other scenarios primarily refer to TCM and natural medicine preparations that are marketed

overseas but not yet approved domestically (Table 1)[1]. In stark contrast to the 2016−2020 period, the subsequent five-year span (2021−2025) witnessed the approval of 74 new TCM drugs (including 33 innovative drugs), marking a historic leap in the development of new TCM drugs[2,3]. The core hallmarks of this era were the "establishment of regulatory science" and the "reconstruction of regulatory policies". On one hand, regulatory science for TCM—an emerging interdisciplinary field—has seen unprecedented emphasis on new tools, standards, and methodologies. The implementation of technical guidance principles, such as the

Table 1 Classification of TCM registrations and application documentation requirements (Effective January 1, 2021)[1].

Classification	Definition	Further specification scenarios	Characteristics and requirements
Category 1: Innovative TCM	Refers to new TCM prescription formulations whose prescriptions are not included in national drug standards, drug registration standards, or the "Catalog of ancient classic prescriptions" published by the national TCM regulatory authority, possess clinical value, and have not been marketed overseas.	1.1 Compound TCM preparations: Preparations formulated under TCM theory using multiple herbal slices, extracts, etc. 1.2 Extracts and preparations derived from single plants or other substances. 1.3 New medicinal materials and their preparations refer to materials and preparations not included in national drug standards, drug registration standards, or provincial/autonomous region/municipal drug standards, as well as new medicinal parts of plants or animals from the aforementioned standard materials and their preparations.	This marks the first explicit proposal of the concept and classification of innovative TCMs, representing a significant milestone. Characterized by novel therapeutic efficacy, emphasizing clinical value assessment, and focusing on addressing unmet clinical needs
Category 2: Modified TCM	Refers to formulations that modify the administration route or dosage form of marketed TCM products, offering clinical advantages and characteristics, or expanding their indications and therapeutic functions.	2.1 Preparations altering the administration route of marketed TCMs, *i.e.*, preparations that switch between different administration routes or absorption sites. 2.2 Modifying the formulation of an already marketed TCM preparation, *i.e.*, changing the dosage form while maintaining the same route of administration. 2.3 Addition of new indications or therapeutic functions to TCMs. 2.4 Changes to the production process or excipients of marketed TCM formulations that result in significant alterations to the medicinal substance base or drug absorption/utilization.	The application pathway for "adding new indications to TCMs" has been changed from a supplemental application to a new drug application. Changes to the production process of marketed TCM formulations that result in significant alterations to the medicinal substance base or drug absorption/utilization shall also be managed as modified new drugs. Encourage in-depth research and secondary development of marketed TCM to enhance quality and clinical value.
Category 3: Classical Chinese medicine formulas	Refers to formulas recorded in ancient Chinese medical texts that comply with the provisions of the law of the People's Republic of China on TCM, remain widely used to this day, demonstrate proven efficacy, and possess distinct characteristics and advantages.	3.1 TCM compound preparations managed under the ancient classic formula directory 3.2 Other TCM compound preparations derived from ancient classic formulas. This includes TCM compound preparations based on ancient classic formulas not managed under the ancient classic formula directory and TCM compound preparations modified from ancient classic formulas.	Both categories shall be prepared using traditional processes, administered *via* traditional routes of administration, and their indications and therapeutic effects shall be described using TCM terminology. Category 3.1 requires pharmaceutical and non-clinical safety studies. Category 3.2 formulations must undergo systematic summarization of clinical experience with TCM and evaluation of clinical value, in addition to pharmaceutical and non-clinical safety studies.
Category 4: Identical-name, identical-formula preparations	Refers to preparations with the same generic name, prescription, dosage form, indications, administration method, and daily herbal slice dosage as an already marketed TCM, and whose safety, efficacy, and quality controllability are no less than those of the marketed preparation.		This should not be simplistically interpreted as the concept of generic drugs. The key lies in the comparative study results with the marketed TCM of the same name and formula, rather than merely matching quality standards. For registration applications of drugs with the same name and formula,

Table 1 (*continued*)

Classification	Definition	Further specification scenarios	Characteristics and requirements
			while sharing identical generic names, prescriptions, dosage forms, therapeutic indications, administration methods, and daily herbal decoction quantities with the marketed TCM product, it must be ensured that their safety, efficacy, and quality control are no less than those of the marketed TCM product.

expert consensus on the "three-combination" registration review evidence system integrating TCM theory, human experience, and clinical trials, has provided robust scientific support for TCM drug research and development (R&D) and regulatory oversight[4-6]. On the other hand, the systematic restructuring of regulatory frameworks—including the Special Provisions on TCM Registration Management, Special Provisions on TCM Standard Management, and Classification of TCM Registrations and Requirements for Application Materials—has accelerated the construction of an excellent regulatory system tailored to the characteristics of TCM. Consequently, TCM regulatory capabilities have been significantly enhanced[1,7,8]. Taking 2020 as a reference point, this paper focuses on the development of new TCM drugs during the critical historical phase from 2021 to 2025. It provides a comprehensive overview of new TCM and natural drug applications and their review and approval processes over the past five years. The paper delves into the significance of implementing the National Drug Regulatory Science Action Plan and the role of TCM regulatory science—as an emerging interdisciplinary field—in accelerating the innovation of new TCM drugs. Systematically summarizes the implementation outcomes of the TCM Excellence Regulatory System and incentive measures such as policies and regulations. It also provides a focused review of recent highlights in TCM new drug development and regulation from an international perspective. This holds significant importance for driving breakthroughs in TCM and natural medicine new drugs across more disease areas and advancing the international coordination of TCM regulation.

2. Registration application and review/approval of new TCMs

2.1. Acceptance status of TCM registration applications from 2020 to 2025

2.1.1. Overall situation

As shown in Fig. 1, the number of applications for various types of drugs (including chemical drugs, biological products, and TCM) from 2020 to 2025 (covering both technical review-based registrations and direct administrative approval registrations) were 10,305, 11,596, 12,245, 16,812, 17,187, and 18,434, respectively. Using 2020 as the baseline, the five-year average growth rate (G, geometric mean) for all drug registration applications from 2021 to 2025 is 12.33%, indicating a steady overall growth trend in new drug registration applications in China. Specifically, the number of TCM registration applications from 2020 to 2025 was 471, 1371, 1353, 2762, 2816, and 3516 applications, respectively. The proportion of TCM registration applications to the total number of accepted applications for all types of drugs was 4.57%, 11.82%, 12.67%, 16.43%, 16.38%, and 19.07%[9]. Using 2020 as the baseline, the five-year average growth rate (G, geometric mean) of TCM registration applications from 2021 to 2025 is 49.49%, indicating a phase of rapid expansion. The five-year average growth rate (G, geometric mean) of the proportion of TCM registration applications is 33.07%, falling within the high-growth range. Evidently, China's TCM registration applications have

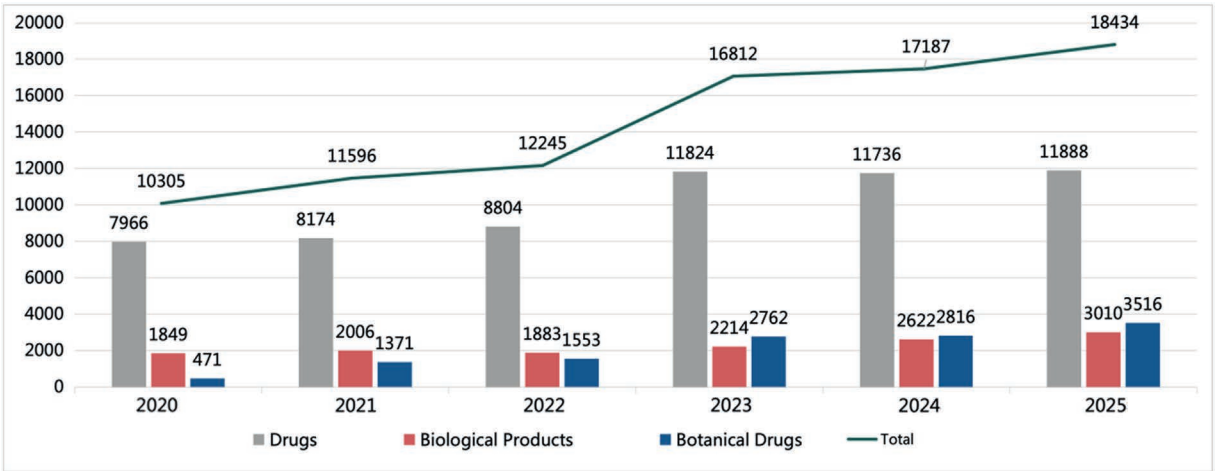

Figure 1 Acceptance status of various drug registration applications from 2020 to 2025[9].

entered a historic leap phase from 2021 to 2025, reflecting unprecedented enthusiasm within the industry for TCM research and development, along with heightened expectations for TCM in preventing and treating complex and chronic diseases.

2.1.2. *Acceptance status of IND and NDA for TCM by registration category*

Figs. 2 and 3 show the overall acceptance trends for investigational new drug (IND) and new drug applications (NDA) of TCM across different registration categories from 2020 to 2025[2,10-12].

Overall TCM registration categories: The total number of IND applications accepted for TCM from 2020 to 2025 was 20, 52, 57, 75, 100, and 140, respectively. Using 2020 as the baseline, the five-year average growth rate $G_{\text{geometric average}} = 47.58\%$ from 2021 to 2025 indicates sustained long-term high growth.The number of NDA applications accepted from 2020 to 2025 was 7, 13, 14, 26, 40, and 54, respectively. Using 2020 as the reference year, the five-year average growth rate $G_{\text{geometric average}}$ from 2021 to 2025 was 50.48%, indicating robust overall growth and a steady high-growth trajectory.

Innovative TCM drugs: The number of IND applications accepted from 2020 to 2025 was 17, 44, 39, 54, 80, and 103, respectively. Using 2020 as the baseline, the five-year average growth rate $G_{\text{geometric average}}$ from 2021 to 2025 was 43.38%, maintaining overall sustained high growth. Number of NDA applications accepted (Units) from 2020 to 2025: 6, 10, 10, 8, 11, and 14. Using 2020 as the base year, the five-year average growth rate $G_{\text{geometric average}}$ from 2021 to 2025 is 18.47%, indicating a steady upward trend.

Improved TCM new drugs: The number of IND applications accepted from 2020 to 2025 was 2, 8, 17, 21, 19, and 36, respectively. Using 2020 as the baseline, the five-year average growth rate from 2021 to 2025 was $G_{\text{geometric average}} = 78.26\%$, exhibiting a stepwise increase. The number of NDA applications accepted for improved TCM drugs from 2020 to 2025 was 0, 0, 0, 3, 1, and 4, respectively. After reaching a positive value for the first time in 2023, the number of improved TCM NDA applications remained at a low level, fluctuating without overall growth or decline.

TCM compound preparations based on ancient classic formulas: The number of NDAs accepted from 2020 to 2025 was 0, 3, 4, 15, 28, and 36, respectively. Since the data for 2020 is zero, using the 2021 baseline as a reference, the four-year average growth rate $G_{\text{geometric average}}$ from 2022 to 2025 was 86.13%, achieving a stepwise expansion starting from zero.

TCM formulations with identical names and formulas: The number of IND applications from 2020 to 2025 was 1, 0, 1, 0, 1, and 1, respectively. Overall, the figures fluctuated at a low level without sustained growth, indicating poor stability. The number of NDA submissions from 2020 to 2025 was 1, 0, 0, 0, 0, and 10, respectively. The overall trend showed prolonged stagnation followed by a late surge, lacking sustainability.

2.1.3. *Annual acceptance status of TCM IND and NDA applications*

Table 2 shows the annual acceptance status of IND and NDA applications for TCM from 2020 to 2025[2,9-18].

In 2025, 140 IND applications were accepted, including 103 for innovative TCM INDs, 36 for modified TCM INDs, and 1 for TCM INDs with identical names and formulas. In 2025, 54 NDA applications were accepted, including 14 innovative TCM NDAs, 4 improved new drug NDAs, 36 classical formula TCM compound preparations NDAs, and 0 same-name, same-formula drug NDAs[9-12,17,18].

In 2024, 100 IND applications were accepted, including 80 innovative TCM INDs (71 varieties), 19 improved TCM INDs, and 1 same-name-same-formula drug IND. In 2024, 40 NDA applications were accepted, including 11 innovative TCM NDAs, 1 improved new drug NDA, and 28 TCM compound preparations based on ancient classic formulas[2].

In 2023, 75 IND applications were accepted, including 54 innovative TCM INDs and 21 modified TCM INDs. In 2023, 26 NDA applications were accepted, including 8 innovative TCM NDAs, 3 modified new TCM NDAs, and 15 NDAs for TCM compound preparations based on ancient classic formulas[13].

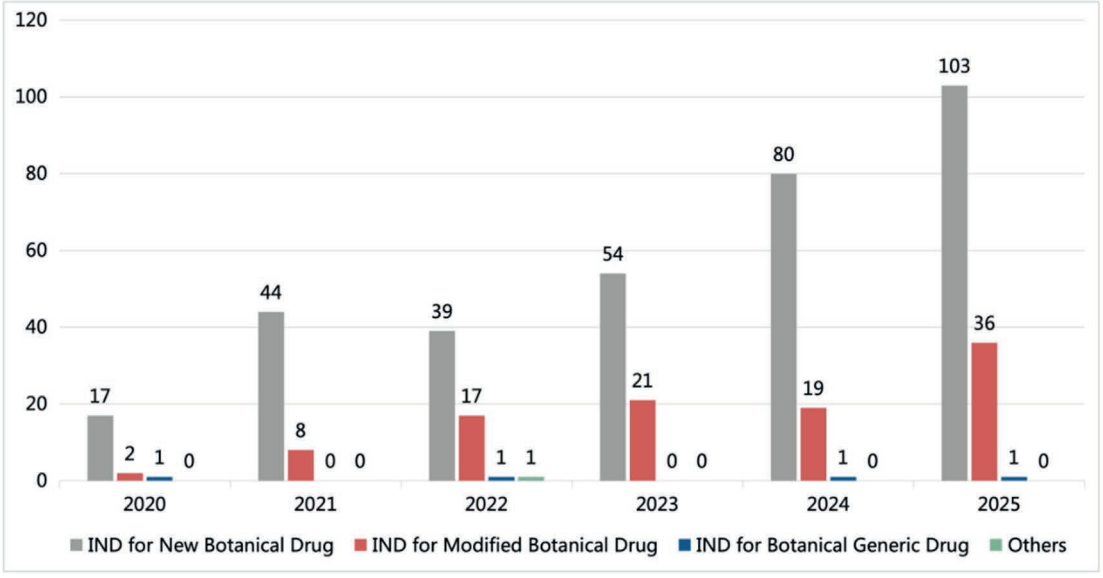

Figure 2 Accepted IND applications for TCMs by registration category, 2020−2025[2,9].

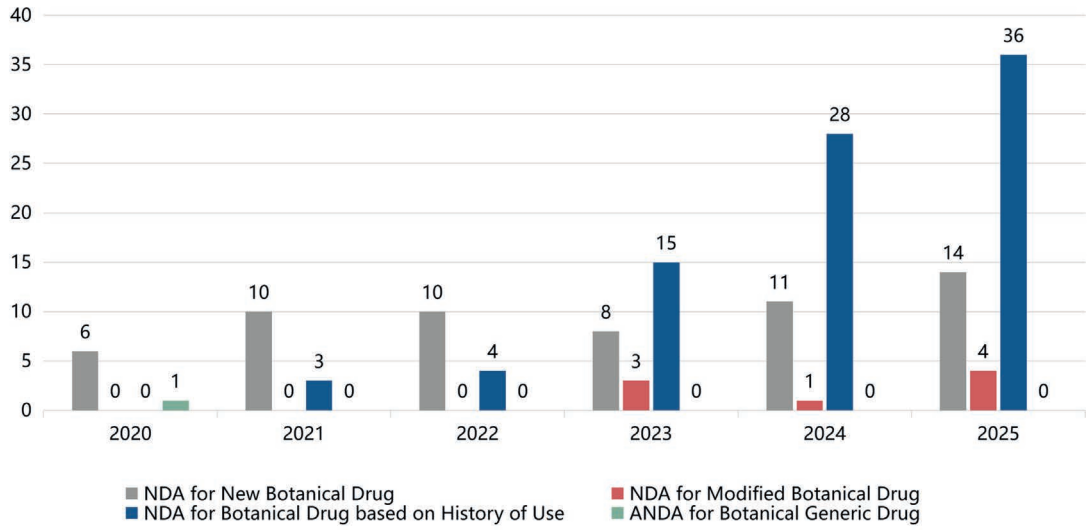

Figure 3 Accepted NDA applications for TCM by registration category, 2020−2025[2,9].

Table 2 Categorized statistics of IND and NDA applications accepted for TCM registration from 2020 to 2025.

Application category		2020	2021	2022	2023	2024	2025
Number of IND applications (accepted applications)	Innovative TCM	17	44	39	54	80	103
	Improved TCM	2	8	17	21	19	36
	Same-name, same-formula medicines	1	0	1[a]	0	1	1
Number of NDA applications (accepted application numbers)	Innovative TCM	6	10	10	8	11	14
	Improved TCM	0	0	0	3	1	4
	Classic prescription formulations	0	3	4	15	28	36
	Same-name, same-formula medicines	1	0	0	0	0	0

[a]For other scenarios (already marketed overseas but not in China).

In 2022, 57 IND applications were accepted, including 39 innovative TCM INDs, 17 modified TCM INDs, and 1 other type*. In 2022, 14 NDA applications were accepted, including 10 innovative TCM NDAs and 4 classical formula TCM compound preparations NDAs[14].

In 2021, 52 IND applications were accepted, including 44 innovative TCM INDs and 8 modified TCM INDs. In 2021, 13 NDA applications were accepted, including 10 innovative TCM NDAs and 3 NDAs for TCM compound preparations based on ancient classic formulas[15].

In 2020, 20 IND applications were accepted, including 17 innovative TCM INDs, 2 modified TCM INDs, and 1 same-name, same-formula drug. In 2020, 7 NDA applications were accepted, including 6 innovative TCM NDAs and 1 same-name, same-formula drug NDA[16].

2.2. Approval status of INDs and NDAs for TCM by registration category, 2020−2025

2.2.1. Overall approval status of INDs and NDAs across TCM registration categories

IND approval status. As shown in Table 3 and Fig. 4, the total number of IND approvals for TCM across various registration categories from 2020 to 2025 were 25, 34, 45, 63, 61, and 115 cases, respectively[2,9-18]. Using 2020 as the reference year, the five-year average growth rate $G_{\text{geometric average}}$ of total TCM IND approvals from 2021 to 2025 $G_{\text{geometric average}} = 35.69\%$, indicating overall steady growth at a medium-to-high pace. Specifically, the number of innovative TCM IND approvals from 2020 to 2025 was 24, 28, 30, 45, 49, and 89, respectively. Using 2020 as the reference year, the five-year average growth rate $G_{\text{geometric average}}$ of

Table 3 Categorized statistics of IND and NDA approvals for TCM from 2020 to 2025.

Approval category		2020	2021	2022	2023	2024	2025
Number of IND approvals (number of accepted applications)	Innovative TCM	24	28	30	45	49	89
	Improved TCM	1	6	13	17	11	25
	Same-name, same-formula medicines	0	0	1	1	1	1
Number of NDAs approvals (number of accepted applications)	Innovative TCMs	4	11	6	7	3	5
	Improved TCM	0	0	0	1	0	3
	Classic prescription formulations	0	3	2	3	11	16
	Same-name, same-formula medicines	0	0	0	1	0	0

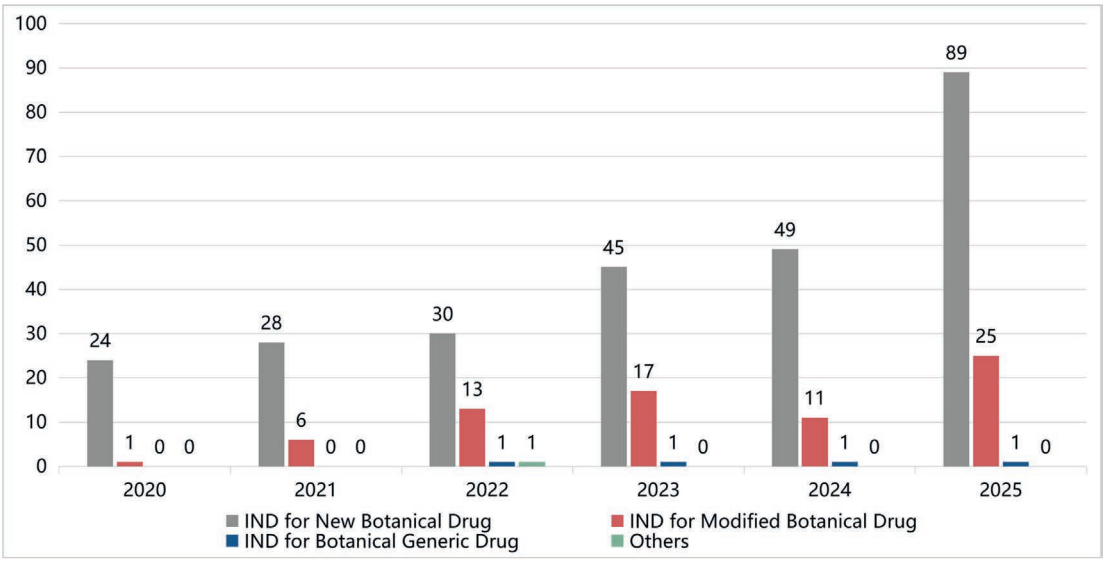

Figure 4 Approval status of TCM INDs by registration category (2020–2025)[2,9-18].

IND approvals for innovative TCM drugs was 29.97%, indicating overall steady medium-to-high growth. The number of IND approvals for modified TCM drugs from 2020 to 2024 was 1, 6, 13, 17, 11, and 25, respectively. Using 2020 as the reference year, the five-year average growth rate $G_{\text{geometric average}}$ for IND approvals of modified TCM drugs was 91.86%, indicating overall steady growth at a medium-to-high pace. The number of IND approvals for drugs with identical names and formulas from 2020 to 2025 was 0, 0, 1, 1, 1, and 1, respectively. Using 2020 as the reference year, the first positive value was achieved in 2022, showing a low-level stable trend overall.

NDA approval status. As shown in Table 3 and Fig. 5, the total number of NDA approvals for TCM across registration categories in 2020–2025 were 4, 14, 8, 11, 14, and 24, respectively. Using 2020 as the baseline, the five-year average growth rate $G_{\text{geometric average}} = 45.41\%$, indicating overall high-speed growth with moderate stability[2,9-18]. Among these, the number of innovative TCM NDAs approved from 2020 to 2025 was 4, 11, 6, 7, 3, and 5, respectively. Using 2020 as the reference year, the five-year average growth rate $G_{\text{geometric average}}$ for innovative TCM drug NDAs approved from 2020 to 2025 $G_{\text{geometric average}} = 8.45\%$, showing a low-speed positive growth

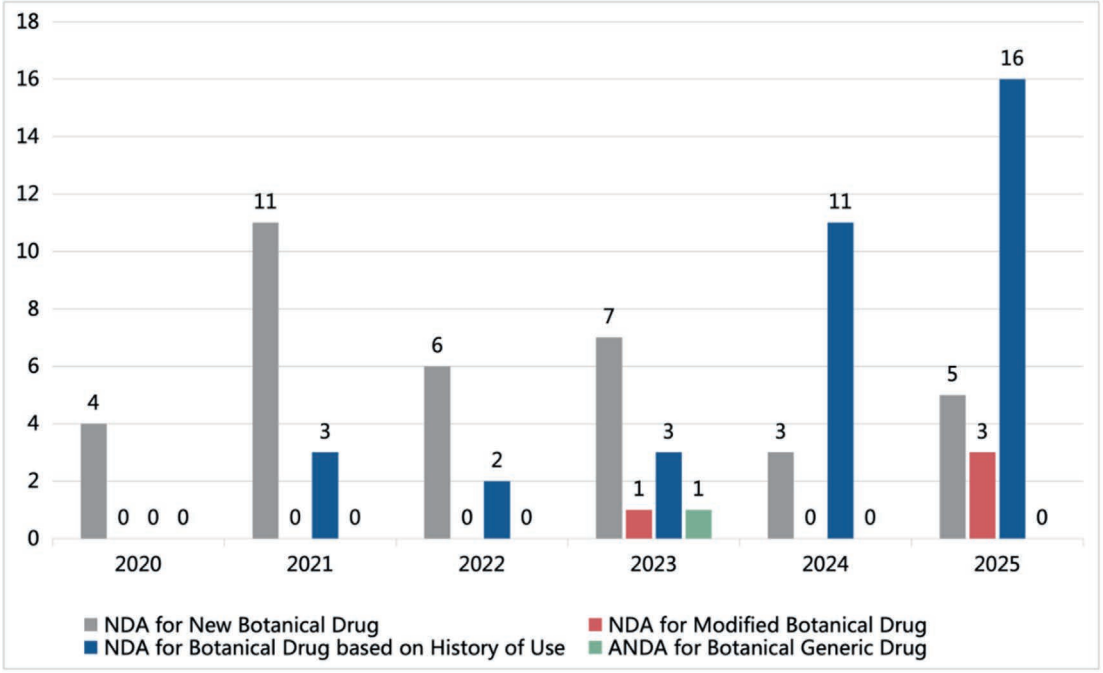

Figure 5 Approval status of TCM NDAs and ANDAs by registration category (2020–2025)[2,9-18].

trend overall with a cumulative increase of 50%. The number of improved TCM drug NDAs approved from 2020 to 2025 (units) were 0, 0, 0, 1, 0, 3 respectively, exhibiting irregular growth patterns but maintaining overall positive growth effects. The number of NDAs approved for compound preparations based on ancient classical formulas from 2020 to 2025 (units) were 0, 3, 2, 3, 11, and 16, respectively. As the data for 2020 is zero, using 2021 as the baseline, the four-year average growth rate $G_{\text{geometric average}}$ for NDAs of ancient classical formula compound preparations from 2022 to 2025 $G_{\text{geometric average}} = 56.51\%$, indicating high-quality growth with strong stability and a sustainable high-growth trajectory after surpassing the zero baseline in 2021. The number of NDAs approved for drugs with identical names and formulas from 2020 to 2025 was 0, 0, 0, 1, 0, 0, respectively, remaining at an extremely low overall level with no foundation for sustained growth.

2.2.2. *Annual approval status of TCM registration INDs and NDAs*

Table 3 shows the annual approvals of IND and NDA applications for TCM from 2020 to 2025[2,9-18].

2025: 115 TCM INDs approved, including 89 innovative TCM INDs, 25 modified TCM INDs, and 1 same-name-same-formula IND. 24 TCM NDAs approved, including 5 innovative TCM NDAs, 3 modified TCM NDAs, and 16 classical formula compound preparations NDA[9-12,17,18].

2024: Approved 61 TCM IND applications, including 49 innovative TCM INDs, 11 modified TCM INDs, and 1 same-name-same-formula TCM IND. Approved 14 TCM NDA applications, including 3 innovative TCM NDAs and 11 classical formula TCM compound preparations NDAs[2].

2023: Approved 63 TCM IND applications, including 45 innovative TCM INDs, 17 modified TCM INDs, and 1 same-name-same-formula TCM IND. Approved 11 TCM NDAs, including 7 innovative TCM NDAs and 3 classical formula TCM compound preparations NDAs[13].

2022: Approved 45 TCM IND applications, including 30 innovative TCM INDs, 13 modified TCM INDs, and 1 same-name-same-formula TCM IND. Approved 8 TCM NDAs, including 6 innovative TCM NDAs and 2 classical formula TCM compound preparations NDAs[14].

2021: Approved 34 TCM IND applications, including 28 innovative TCM INDs, 6 modified TCM INDs, and 0 same-name-same-formula TCM INDs. Approved 14 TCM NDAs, including 11 innovative TCM NDAs and 3 classical formula TCM compound preparations NDAs[15].

2020: Approved 28 TCM IND applications, including 24 innovative TCM INDs, 1 modified TCM IND, and 0 same-name-same-formula TCM INDs. Approved 4 TCM NDA applications, including 4 innovative TCM NDAs, and 0 classical ancient formula TCM compound preparations NDAs[16].

2.3. *Analysis of clinical trial registration and translation for innovative TCM drugs*

2.3.1. *Overall status of clinical trial registration for new TCM drugs*

As shown in Fig. 6, based on available statistical data, the annual total registrations of drug clinical trials in China from 2020 to 2024 were 2602, 3358, 3410, 4300, and 4900 trials, respectively (measured by CTR, same below). The five-year average growth rate $G_{\text{geometric average}} = 17.23\%$, indicating a stable trend of medium-to-high growth. Among these, in 2024, new drug clinical trials registered under acceptance numbers totaled 2539 (51.8%, 2539/4900), while BE filing number-registered clinical trials totaled 2361 (48.2%, 2361/4900). As shown in Fig. 7, chemical drugs dominated China's clinical trials from 2020 to 2024, followed by biological products, while TCM trials accounted for a low proportion. Over the past five years, the percentage of TCM clinical trials was 2.6%, 2.4%, 1.9%, 1.8%, and 2.0%, respectively, fluctuating at a low level with insufficient growth momentum[19-24].

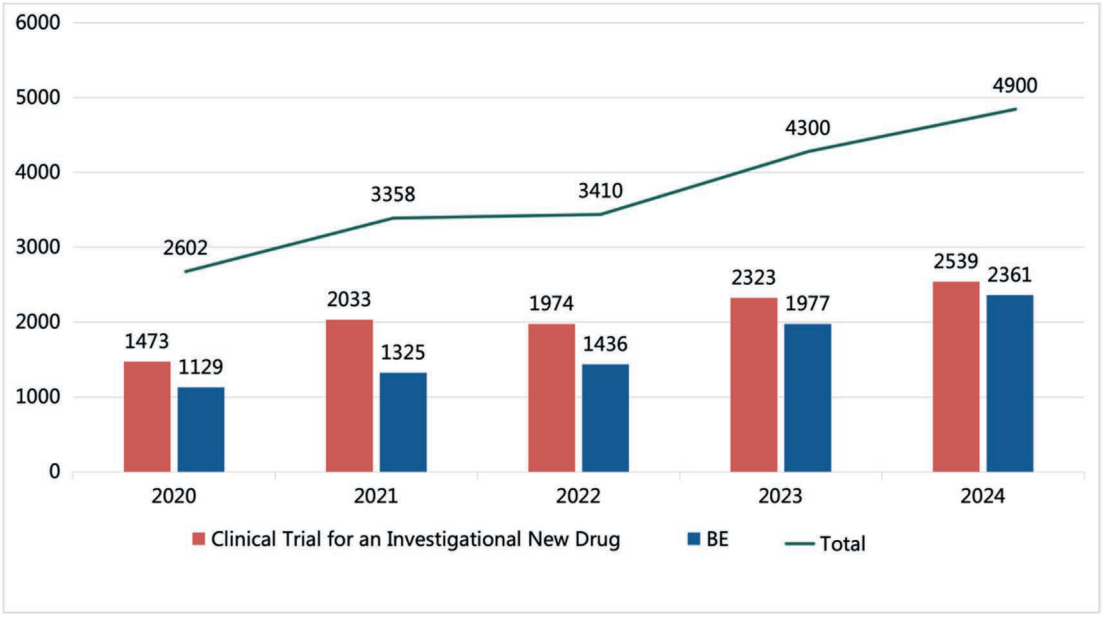

Figure 6 Changes in total clinical trial registrations (CTR-based), 2020−2024[19].

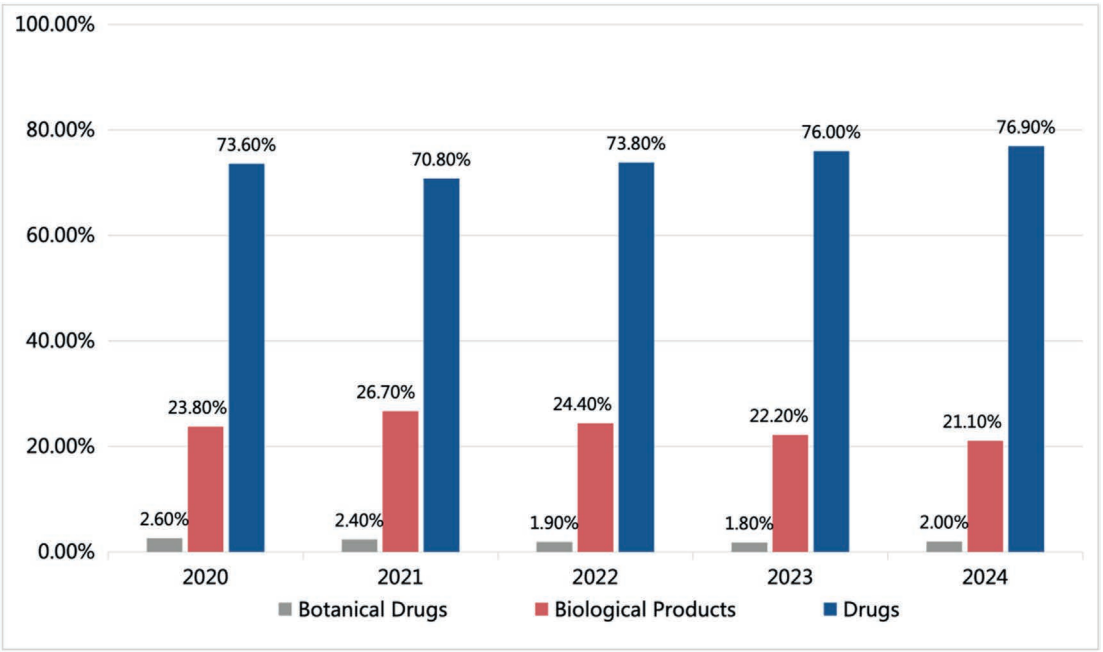

Figure 7 Overall proportion of clinical trial registrations by drug type, 2020–2024[19].

As shown in Fig. 8, among the 2539 new drug clinical trials registered by acceptance number in 2024, chemical drugs, biological products, and TCMs accounted for 1413 (55.7%), 1029 (40.5%), and 97 (3.8%) trials, respectively. A total of 1735 trials were registered for drugs classified as Category 1 innovative drugs (including those under the original registration classification, same below), accounting for 68.3% (1735/2539) of the total. Among these, chemical drugs constituted 52.3% (908/1735), biological products 45.6% (791/1735), while TCM accounted for 2.1% (36/1735). Among the 97 registered TCM clinical trials, Class 1 and the original Class 6 registration classification dominated, representing 37.1% and 36.1%, respectively, followed by Class 2 at 15.5%. As shown in Fig. 9, clinical trials for new TCM drugs primarily focused on respiratory and digestive indications, accounting for approximately 54.6% of all TCM clinical trials. Among these, respiratory indications had the largest share at 36.1%. A total of 114 clinical trials targeting pediatric populations were registered, representing 4.5% (114/2539) of all new drug clinical trials. Among these, 56 involved biological products, 40 chemical drugs, and 18 TCM products, with TCM trials predominantly focused on respiratory system disease indications. In 2024, 97 clinical trials for TCM were registered. Approximately 93.8% of TCM varieties conducted one clinical trial that year. Varieties with two trials included Bai Rui Granules, Jia Shen Tablets, and Xiao Er Jing Xing Zhi Ke Granules. One trial was proactively terminated (due to R&D strategy adjustment[19].

Overall, since initiating and advancing GCP implementation in 2003, China's clinical trial ecosystem has continuously developed and enhanced its quality systems. Similar to the United States,

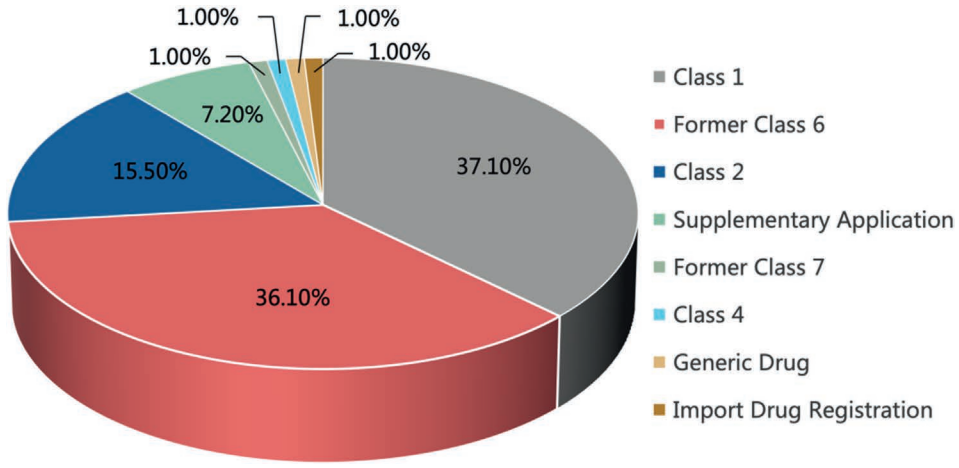

Figure 8 Clinical trial registrations by TCM registration category in 2024[19].

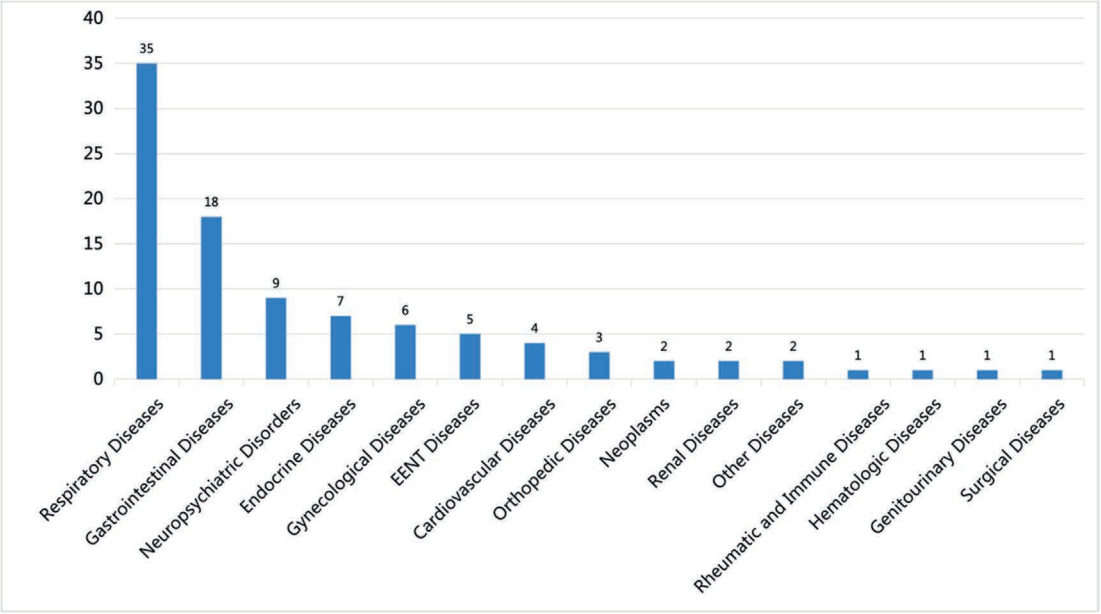

Figure 9 Distribution of clinical trial indications by TCM registration category in 2024[19].

Europe, and Japan, China has established clinical trial quality standards and regulatory frameworks centered on protecting subject rights, ensuring data integrity, and maintaining GCP compliance. Comparing FDA inspection results of Chinese institutions around 2016 reveals that the proportion of "No Action Indicated" (NAI) findings increased from 48.0% during 2009−2015 to 85.0% during 2016−2023. This indicates that China's trial quality is comparable to that of the United States, Europe, and Japan, demonstrating that China's clinical trial quality system, regulatory framework, and standards have reached international benchmarks[25].

2.3.2. From IND to NDA: analysis of clinical translation research for innovative TCMs

The clinical translation rate (often termed clinical R&D success rate or submission success rate) of new TCM drugs from IND approval to NDA approval serves as a core metric for evaluating the clinical R&D efficiency and pipeline quality of new TCM drugs. To date, no universally accepted calculation formula exists within the industry, though the core logic remains consistent. Calculations must be based on clearly defined statistical criteria, time frames, and product classifications, while distinguishing between overall translation rates and stage-specific translation rates. Theoretically, the most ideal scenario involves conducting longitudinal tracking of all IND-approved TCM drug candidates over the long term to monitor their registration studies and submission status. Calculating the proportion that ultimately succeeds in obtaining NDA approval would provide the most intuitive measure of R&D success rate. However, due to the lengthy clinical trial cycles for new drugs, significant time gaps exist between IND approval and NDA approval. This makes obtaining ideal longitudinal point-to-point research results extremely time-consuming and labor-intensive.

Based on the data from Tables 2 and 3 above, this paper calculates and discusses the overall IND approval rate, NDA approval rate (clinical direct conversion rate), and registration application success rate (clinical R&D success rate) for different registration categories of TCM new drugs (IND) and new drug applications (NDA) during a specific time period (cross-sectional analysis).

(1) IND Approval rate. The overall IND approval rate (IND application → IND approval) for all drug categories from 2021 to 2025 is calculated as the ratio of IND applications to approvals.
(2) NDA Approval rate (Clinical direct conversion rate). Calculate the overall NDA approval rate for all drug categories (IND application → NDA approval) from 2021 to 2025 using the ratio of NDA applications to approvals.
(3) Registration application success rate (Clinical development success rate). Calculated as the ratio of IND applications to NDA approvals, representing the overall NDA approval rate for all drug categories from 2021 to 2025 (IND application → NDA approval).

As shown in Table 4, the overall IND approval rate (%), NDA approval rate (%), and registration application success rate (%) for innovative TCM drugs from 2021 to 2025 are 77.55%, 62.26%, and 10.34%, respectively. The overall IND approval rate (%), NDA approval rate (%), and registration application success rate (%) for modified new TCM drugs from 2021 to 2025 were 72.28%, 42.86%, and 2.97%, respectively. The NDA approval rate (%) for compound preparations based on ancient classical formulas from 2021 to 2025 is 50. The overall IND approval rate (%), NDA approval rate (%), and registration application success rate (%) for both innovative and modified TCM drugs combined are 74.46%, 60.00%, and 8.57%, respectively. Although the overall IND approval rates for innovative and modified TCM drugs show little disparity, the NDA approval rate (%) and registration success rate (%) for modified TCM drugs are significantly lower than those for innovative TCM drugs. This stems not from greater R&D difficulty, but from stricter clinical advantage validation requirements. Modified drugs must demonstrate superior efficacy/equivalence compared to original formulations or

Table 4 Success rates for new TCM drug registration and clinical translation, 2021−2025.

TCM Registration Category	Number of IND Applications (A)	IND Approvals (B)	Number of NDA Applications (C)	Number of NDA Approvals (D)	IND Approval Rate (B/A) %	NDA Approval Rate (D/C) %	Registration Application Success Rate (D/A) %
Innovative TCM (1)	319	241	53	33	77.55	62.26	10.34
Improved TCM-based new drugs (2)	101	73	7	3	72.28	42.86	2.97
(1)+(2) total	420	314	60	36	74.46	60.00	8.57
TCM compound preparations based on ancient classic formulas	−	−	86	43	−	50.00	−

marketed counterparts, or address new risks arising from altered medicinal substance bases. The NDA approval rate (%) for classical formula compound preparations is 50.00%. This high approval rate stems from policy incentives, alignment with human experience and review models, rather than lower R&D difficulty. Instead, it reflects a more efficient risk control pathway.

An analysis of the characteristics of Phase II clinical trials for new TCM drugs reveals that from January 1, 2015, to October 1, 2024, a total of 393 Phase II clinical trials involving 336 varieties were registered on the Drug Clinical Trial Registration and Information Disclosure Platform of the Center for Drug Evaluation under the National Medical Products Administration. The analysis found: granules have become the primary dosage form for new TCM drug development, followed by capsules and tablets. These three dosage forms account for 75.3% of the drugs under development. Indications encompass 136 diseases, with the highest number of registered trials targeting respiratory, digestive, and cardiovascular/cerebrovascular systems. Most indications have only one investigational drug. Over 90% of trials employed randomized, double-blind, placebo-controlled designs. Among the 393 clinical trials, 386 (98.22%) employed randomized grouping, while 7 did not use randomization and were single-arm trials. Double-blind trials numbered 371 (94.40%), single-blind trials 2 (0.51%), and open-label trials 20 (5.09%). 356 trials (90.59%) employed placebo controls. 54.96% of trials conducted dose-finding studies, primarily using two dose groups with a 2:1 dose ratio. Sample sizes ranged from 24 to 704 subjects per trial, with 86.01% of trials having an average sample size per group between 31 and 120 subjects[26].

Analysis of the reasons for failure in clinical trials of new TCM drugs indicates that the primary cause lies in the failure to balance the distinctive features of TCM with the requirements of modern evidence-based medicine, resulting from the combined effects of multiple factors. Specific circumstances include: (1) Ambiguity in study design and clinical positioning. Some drug candidates target saturated therapeutic areas, lacking unique advantages over existing therapies—such as chronic cholecystitis and the common cold—and thus failing to demonstrate irreplaceability. The TCM concept of "syndrome patterns" is difficult to translate into quantifiable modern medical indicators. Blindly selecting complex diseases (*e.g.*, advanced tumors) overlooks the holistic regulatory advantages of TCM, making efficacy hard to demonstrate. Alternatively, choosing indications with low incidence rates and recruitment difficulties leads to trial delays. (2) Failure to validate efficacy. This is the primary reason for rejection of marketing applications. Defects in efficacy endpoint design, overreliance on subjective syndrome scoring, and lack of hard endpoints (*e.g.*, mortality, recurrence rates) or objective biomarkers. Inadequate sample size and control group design, failure to adopt non-inferiority designs for formulation changes, or failure of innovative drugs to meet superiority standards, all prevent confirmation of therapeutic benefit. (3) Inadequate safety risk management. This is the primary reason for clinical application rejection. Defective toxicology trial design, lax clinical safety monitoring, non-standardized processing of herbal materials and preparations, and quality fluctuations pose safety hazards. (4) Incomplete quality control systems. Compound formulations lack clear active/indicator components, feature imprecise processes and formulations, and suffer from authenticity and standardization issues in submission documentation. (5) Deviations in trial design and execution. Double-blind design feasibility is low due to challenges in masking characteristics like dosage form (*e.g.*, decoctions, ointments), odor, and color. Poor subject recruitment and compliance, unreasonable protocol design, and inappropriate statistical analysis methods hinder effective interpretation of results[27,28]. Analysis of issues in TCM new drug clinical trial design indicates that from May 2020 to February 2023, a clinical trial institution conducted 18 registration-type TCM clinical trials covering over 10 disease categories across specialties including cardiovascular, respiratory, otolaryngology, endocrinology, neurological disorders, gastroenterology, and surgery. Referencing the Good Clinical Practice (GCP) for Drug Clinical Trials, the Guiding Principles for Ethical Review of Drug Clinical Trials, Guidance Principles for Data Management and Statistical Analysis Plans in Clinical Drug Trials. The review identified 242 issues across six categories: non-compliance with regulatory requirements, unclear protocol descriptions, poor feasibility of trial documents (*e.g.*, protocols and case report forms), inconsistent trial operational requirements across documents or within the same document, drafting errors, and other issues. The roles and safeguards of sponsors, investigators, and institutions in clinical trial design quality were proposed[29].

3. Analysis of approved TCM innovative drug NDAs and case studies (2021−2025)

3.1. Approved NDA varieties of category 1.1 innovative TCM compound preparations

TCM category 1.1 innovative compound preparations refer to formulations composed of multiple herbal slices, extracts, and other ingredients formulated under the guidance of TCM theory. China's classification of TCM compound preparations as category

1.1 innovative drugs represents a breakthrough and milestone in global new drug development regulation, fully reflecting the clinical characteristics, development patterns, and practical realities of TCM compound formulations. As shown in Table 5, from 2021 to 2025, the following formulations were included: Kidney-Nourishing, Heart-Calming, and Spirit-Soothing Tablets; Qi-Boosting and Orifice-Opening Pills; Yinqiao Heat-Clearing Tablets; Xuanqi Bone-Strengthening Tablets; Astragalus and

Table 5 List of approved production varieties for category 1.1 innovative TCMs (compound preparations) from 2021 to 2025.

Drug name	Drug composition	Indications	Approval number
Yishen Yangxin Anshen Tablets	Fried *Ziziphus jujuba* Seed, prepared Polygonum Multiflorum, Mulberry Fruit, Lily Bulb, Salvia root, Ganoderma Lucidum, Poria Sclerotium, Anemarrhena Rhizome, Albizia flower, Chrysanthemum flower	Insomnia	National drug approval number Z20210001
Yiqi Tongqiao Pills	Astragalus, Saposhnikovia, Honey Ephedra, Magnolia flower, *Angelica dahurica*, Atractylodes, Poria, Bupleurum, Angelica, Peony Bark, Schisandra, black Plum, Scutellaria, Licorice	Seasonal allergic rhinitis	National drug approval number Z20210002
Yinqiao Qingre Tablets	Honeysuckle, Kudzu root, Forsythia, Anemarrhena, Isatis root, Burdock Seed, Mint, Cimicifuga, Cicada Shed	Common cold	National drug approval number Z20210003
Xuanqi Jiangu Tablets	Corydalis, whole Scorpion, *Panax notoginseng*, Smilax Glabra, Achyranthes root, prepared Rehmannia root, Astragalus, white Peony root, Polygonum Multiflorum, Stiff Silkworm, Licorice	Mild to moderate knee osteoarthritis	National drug approval number Z20210004
Qizhi Yishen Capsules	Astragalus, Rehmannia, Ligustrum, Hirudo, Fried Bombyx, Eupolyphaga, prepared Rheum, Cynanchum, Clematis, Plantago	Early diabetic nephropathy	National drug approval number Z20210005
Kunxinning Granules	*Rehmannia glutinosa*, *Astragalus membranaceus*, *Curculigo orchioides*, *Epimedium brevicornu*, *Paeonia lactiflora*, Concha Ostreae, *Albizia julibrissin*	Female menopausal syndrome	National drug approval number Z20210006
Huzhen Qingfeng Capsules	*Polygonum cuspidatum*, *Plantago asiatica*, *Ligustrum lucidum*, *Apis mellifera*	Mild to moderate acute gouty arthritis	National drug approval number Z20210007
Jieyu Chufan Capsules	Gardenia, Ginger-processed Magnolia Bark, Ginger-processed Pinellia, Forsythia, Poria, Perilla stem, Trifoliate Orange Peel, Licorice	Mild to moderate depression	National drug approval number Z20210008
Qirui Weishu Capsules	*Panax notoginseng*, Alum, Calcined Hualishih, Wine-processed Rheum	Mild to moderate chronic non-atrophic gastritis with erosion	National drug approval number Z20210009
Qijiao Tiaojing Granules	Astragalus, Donkey-Hide Gelatin, Codonopsis, white Peony, Angelica, herba Hedyotis, Rubia, Citrus, Dipsacus	Menstrual prolongation caused by intrauterine device insertion	National drug approval number Z20220005
Shenge Bushen Capsules	Taisizhen, Kudzu root, epimedium	Mild to moderate depression	National drug approval number Z20220006
Shenyuning Tablets	American ginseng, Curcuma, Fried Ziziphus Seed, Schisandra	Mild to moderate depression	National drug approval number Z20230001
Xiaoer Zibei Xuanfei Syrup	Burdock seed, Mulberry leaf, Mint, Schizonepeta spike, Fritillary bulb, Peucedanum root, Aster root, Fried Zhiqiao, Isatis root, Licorice	Pediatric acute bronchitis	National drug approval number Z20230003
Tongluo Mingmu Capsules	Red Peony root, Astragalus root, Ligustrum Fruit, Eclipta herb, Rehmannia root, Pueraria root,	Moderate non-proliferative diabetic retinopathy caused by type 2 diabetes	National drug approval number Z20230002

(*continued on next page*)

Table 5 (*continued*)

Drug name	Drug composition	Indications	Approval number
	Ginkgo Leaf, Pollen, Rhubarb root, Cassia Seed, Notoginseng root, Earthworm		
Xianglei Tangzu Cream	Centella Asiatica Extract, Polygonum Multiflorum Extract	Wagner grade 1 diabetic foot ulcer with wound cross-sectional area less than 25 cm^{22}.	National drug approval number ZC20230001 (Imported natural medicine), conditional approval
Ercha Shangqing Pills	Catechu, Sophora flavescens root, *Coptis chinensis* rhizome, synthetic musk, borneol, borax, *Schizonepeta tenuifolia*, mint, *Platycodon grandiflorus* root, licorice	Mild recurrent aphthous ulcers	National drug approval number Z20240001
Jiuwei Zhike Oral Liquid	Dwarf tea, Honeyed Loquat Leaf, Ephedra, Bitter Apricot Kernel, Mint, Dried Tangerine Peel, Bamboo Shavings, Fish Grass, Fried Licorice	Acute tracheobronchitis	National drug approval number Z20240002
Qinwei Granules	Eucommia Bark, Clematis root, Angelica root, Ligusticum root	Acute gouty arthritis with wind-dampness and heat pattern	National drug approval number Z20240003
Xiaoer Huangji Granules	*Scutellaria baicalensis*, *Fagopyrum tataricum*, Honeyed loquat leaf, Zhejiang fritillary bulb, *Polygonum cuspidatum*, *Glycyrrhiza uralensis*	For mild acute bronchitis in children aged 3−7 years	National drug approval number Z20250001, priority review
Qifang Bitong Tablets	Astragalus, Saposhnikovia, Atractylodes, Magnolia, Angelica, Alpinia, Notopterygium, Moutan, Cicada Shed, Prunus, Glycyrrhiza	Persistent allergic rhinitis (without seasonal allergen exposure)	National drug approval number Z20250002
Fufang Bina Fuxi Granules	Tianshan Viola, Boxfruit Vine root, Scammony resin, ali red, Rose flower, Licorice extract	Heat-induced cold	National drug approval number Z20250003, priority review
Xiaoer Niuhuang Tuire Patch	*In vitro* cultivated cow bile, honeysuckle, bupleurum, gardenia, coptis, schizonepeta, menthol	Fever (38.5 °C or below) caused by wind-heat syndrome in pediatric acute upper respiratory tract infections	National drug approval number Z20250004
Yangxue Qufeng Zhitong Granules	Astragalus, Angelica, Codonopsis, Fried Atractylodes, Ligusticum, Saposhnikovia, Cimicifuga, Bupleurum, Mentha, Schizonepeta, Notopterygium, *Angelica dahurica*	Frequent tension-type headaches	National drug approval number Z20250006
Shenpu Granules	Dangshen, Daxueteng, Dandelion, Smilax glabra, Zaojiashi, *Polygonum cuspidatum*, Vinegar-processed Corydalis, Wuyao, Danshen, red Peony root, etc.	Chronic pelvic pain resulting from post-pelvic inflammatory disease sequelae	National drug approval number Z20250007

Leeches Kidney-Benefiting Capsules; Kunxinning Granules; Huizhen Wind-Clearing Capsules; Depression-Relieving and Irritability-Easing Capsules; Qirui Stomach-Comforting Capsules; Qi Jiao Diao Jing Granules, Shen Ge Bu Shen Capsules, Shen Yu Ning Shen Tablets, Xiao Er Zi Bei Xuan Fei Syrup, Tong Luo Ming Mu Capsules, Xiang Lei Tang Foot Ointment, Er Cha Shang Qing Pills, Jiu Wei Zhi Ke Oral Liquid, Qin Wei Granules, Xiao Er Huang Jin Zhi Ke Granules, Qi Fang Bi Tong Tablets, Compound Binapuxi Granules, Pediatric Niu Huang Heat-Reducing Patch, Blood-Nourishing Wind-Dispelling Pain Relief Granules, Shen Pu Granules, and other category 1.1 TCM compound preparations have been approved for production. This fully demonstrates the achievements of deepening the reform of TCM registration classification guided by clinical value.

This new drug category exemplifies the development, review, and approval process of the TCM compound formula Shen Ge Bu Shen capsules (National drug approval number Z20220006) for treating depression. Depression is a typical manifestation of depressive disorders, clinically characterized primarily by low mood accompanied by loss of interest and pleasure, decreased energy or fatigue, sleep disturbances, and may also involve anxiety states. Its etiology and pathogenesis remain unclear, though research indicates associations with social, psychological, and biological factors. The formula for Shen Ge Bu Shen Capsules originates from the TCM therapeutic principles of "tonifying qi, nourishing yin, and supplementing the kidneys". It comprises a group of refined active fractions extracted from Radix Pseudostellariae, Puerariae Radix, and Epimedii Herba (namely, Radix Pseudostellariae total polysaccharides, and Puerariae Radix and Epimedii Herba total flavonoids). This case demonstrates distinctive and innovative approaches in the preparation process and quality control of herbal compound formulations. It advances

the transformation of TCM compound development from "empirical formulas" to a modern research model centered on "active component clusters + precise quality control + evidence-based validation", providing a model for the development of TCM for treating mental disorders.

Research innovations of Shen Ge Bu Shen capsules: (1) Extraction and purification employ water extraction followed by macroporous adsorption resin purification, enriching total polysaccharides from Radix Pseudostellariae, total flavonoids from Pueraria root and Epimedium, achieving over 50% purity for the active fraction with stable levels of key components like icariin. (2) Quality control established HPLC fingerprint profiling and multi-component quantitative methods, simultaneously regulating content levels of Radix Pseudostellariae polysaccharides, Puerarin, Icariin, etc., ensuring batch consistency. (3) Core pharmacology: Exerts antidepressant effects by upregulating the expression of the rate-limiting enzyme for 5-HT synthesis (TPH2) in the brain, thereby increasing 5-HT production. This mechanism features a well-defined target and clear pathway, distinguishing it from the multi-target ambiguity characteristic of TCMs.

Review comments on Shen Ge Bu Shen capsules: (1) Pharmacological and toxicological evaluation. Nonclinical pharmacodynamic test results indicate that this product shortens immobility time in mice with reserpine-induced depression models during the tail suspension test and forced swim test, improves ptosis and akinesia behaviors; reduce head-shaking behavior in mice induced by 5-hydroxytryptophan, and elevate brain serotonin and norepinephrine levels. Regarding safety studies, single-dose toxicity tests in mice and 6-month repeated-dose toxicity tests in rats and dogs were completed. No significant toxic reactions were observed at high doses, indicating a certain safety margin. (2) Efficacy evaluation. Phase I, II, and III clinical trials were completed. The Phase III trial supporting the marketing application employed a multicenter, randomized, double-blind, double-dummy, placebo-controlled design with parallel groups receiving placebo and fluoxetine hydrochloride capsules. In the pivotal clinical trials, the primary efficacy endpoint was the difference from baseline in HAMD-17 scores. Superiority testing against placebo and non-inferiority testing against a positive comparator were conducted. Current results demonstrate statistical superiority of the investigational drug over placebo and non-inferiority to the positive comparator. (3) Safety evaluation. A total of 516 subjects across Phase I, II, and III trials were included in the safety dataset. In the Phase I tolerability study, adverse reactions following single-dose administration included headache, dizziness, and nausea, while those following multiple-dose administration included heat sensation, dry throat/sore throat, and epistaxis. In Phase II and III trials, adverse events primarily consisted of isolated or multiple elevations in liver biochemical markers. (4) Risk Analysis and Control. No drug-related serious adverse events occurred during the Phase I, II, and III clinical trials. Adverse events classified as possibly related or possibly unrelated to the drug are listed under the "Adverse Reactions" section of the product label. The "Precautions" section of the label addresses the safety risk of potential liver injury, advising caution in patients with hepatic impairment or a history of drug-induced liver injury. (5) Benefit-Risk Assessment. The manufacturing process is fundamentally stable and feasible, with a comprehensive quality control system established. Existing pharmacodynamic results provide preliminary support for the proposed indications. Nonclinical safety studies generally meet the requirements for marketing antidepressants. Phase III clinical trial results demonstrate efficacy superiority over placebo in reducing HAMD-17 scores among patients with mild to moderate depression. Based on expert opinions, this product fundamentally meets the relevant requirements for treating mild to moderate depression. Comprehensive assessment indicates that the benefits outweigh the risks for the target population, demonstrating clinical value[7].

3.2. Category 1.2 innovative TCM (extracts of active components from single herbs and their preparations)

Innovative drugs derived from active components of TCM are classified as Category 1.2 TCM innovations, comprising extracts and formulations obtained from single plants or other substances. As shown in Table 6, from 2021 to 2025, these include icariin, icariin soft capsules (priority review and conditional approval), total flavonoids extract from *Eupatorium fortunei*, total flavonoids capsules from *Plectranthus chinensis*, total flavonoids extract from *Hibiscus rosa*-sinensis flowers, oral patches containing total flavonoids from *Hibiscus rosa*-sinensis flowers, total flavonoids extract from *Ziziphus jujuba*, and tablets containing total flavonoids from *Ziziphus jujuba*.

This new drug category exemplifies the development, review, and approval process of epimedium soft capsules (National Drug Approval Number Z20220001), a novel treatment for hepatocellular carcinoma (HCC). HCC ranks as the sixth most common cancer globally and the fourth leading cause of cancer-related

Table 6 List of approved production varieties for innovative TCM category 1.2 (single-ingredient TCM extracts and preparations) from 2021 to 2025.

Drug name	Drug composition	Indications	Approval number
Icariin soft capsules	Icariin	Indicated for unresectable hepatocellular carcinoma in patients who are unsuitable for or refuse standard treatment, and who have not previously received systemic therapy. Patients must meet at least two of the following peripheral blood composite biomarker criteria: AFP $\geq$400 ng/mL; TNF-α < 2.5 pg/mL; IFN-γ $\geq$ 7.0 pg/mL.	National drug approval number Z20220001 priority review and approval, conditional approval
Guangjinqiancao total flavonoids capsules	Guangjinqiancao total flavonoids extract	Ureteral stones	National drug approval number Z20220002
Huangshukuihua total flavonoids oral patch	Huangshukuihua total flavonoid extract	Mild recurrent oral ulcers	National drug approval number Z20220001
Zhishi total flavonoid tablets	Zhishi total flavonoids extract	Functional dyspepsia	National drug approval number Z20230004

deaths. China accounts for 55% of global HCC cases, making it the third leading cause of cancer-related deaths in the country. Currently, a significant proportion of advanced HCC patients are unsuitable for existing targeted therapies, systemic chemotherapy, or immunotherapy due to factors such as weakened constitution, poor liver function, and severe disease status, creating unmet clinical needs. Icariin Soft Capsules (Acoladin/Oreshu®) is an innovative small-molecule immunomodulator derived from the traditional Chinese herb Epimedium. Utilizing high-purity icariin extracted from Epimedium, it embodies the TCM principle of "strengthening the body's defenses while expelling pathogens". It received conditional approval from the NMPA in January 2022 for first-line treatment of unresectable hepatocellular carcinoma with specific biomarker enrichment. Its core advantages include precise biomarker selection, well-defined immune regulation mechanisms, and favorable safety profiles, making it a landmark achievement in the modernization of TCM for oncology.

Icariin soft capsules research innovation: (1) The world's first first-in-class TCM 1.2-class small-molecule immunomodulatory drug derived from epimedium, indicated for first-line treatment of unresectable hepatocellular carcinoma selected through biomarker screening. With "immunomodulation + low toxicity" as its core advantages, it exhibits no direct cytotoxic effects, making it more suitable for liver cancer patients often presenting with concomitant hepatic insufficiency. (2) Clear core target mechanism: Directly binds MyD88/IKKα to inhibit the TLR−MyD88−IKK−NF-κB inflammatory pathway, reducing production of inflammatory mediators like TNF-α and IL-6 while downregulating the IL6−JAK2−STAT3 pathway. It inhibits TNF-α activation of the IKK−NF-κB pathway, reduces PD-L1 expression, suppresses MDSC activity, and activates IFN-γ-positive $CD8^+$ T cells to exert antitumor immune effects. Downstream, it achieves antitumor effects through dual regulation: suppressing the pro-tumor inflammatory microenvironment and rebuilding the anti-tumor immune microenvironment. (3) The extraction and purification process employs supercritical CO_2 extraction + column chromatography purification to obtain high-purity icariin monomer, with batch-to-batch content variation $\leq$2% for precise quality control.

Icariin soft capsules review comments: (1) Pharmacological and Toxicological Evaluation. Nonclinical pharmacodynamic studies indicate icariin exhibits tumor-suppressive effects in mouse models of hepatocellular carcinoma *in situ* and inhibits *in vitro* proliferation of human hepatocellular carcinoma cells. Icariin tested negative in the Ames test, CHL cell chromosome aberration test, and mouse micronucleus test. No reproductive toxicity associated with icariin was observed in rat fertility and early embryonic development toxicity studies, rat and rabbit embryo-fetal development toxicity studies, or rat perinatal reproductive toxicity studies. In Beagle dogs administered 20, 60, or 180 mg/kg of icariin orally for 9 consecutive months, isolated cases of enlarged mammary glands and nipples were observed in female animals in the medium and high-dose groups. Histopathological examination revealed glandular and tissue hyperplasia with a certain dose-relatedness. Electrocardiogram (ECG) examinations at 9 months in the high-dose group showed T-wave inversion and ST-segment depression in 4/8 animals. (2) Pharmacokinetic Evaluation. Epimedium extract soft capsules utilize corn oil as an excipient and employ an oil-phase dissolution process to overcome the compound's water-insolubility. Its pharmacokinetic profile was validated through multicenter clinical studies involving healthy subjects and liver cancer patients, demonstrating clear absorption, distribution, metabolism, and excretion (ADME) characteristics with good adaptability to the pathophysiological state of liver cancer patients. The population pharmacokinetic model derived from multicenter clinical studies indicates that age (18−75 years), gender, and body weight (40−80 kg) have no significant impact on the pharmacokinetic parameters of icariin, eliminating the need for dose adjustment based on these factors. Only hepatic function classification and hypoalbuminemia emerged as significant covariates affecting pharmacokinetics, providing quantitative support for the clinical recommendation of "use with caution in patients with hepatic impairment". (3) Clinical Efficacy Evaluation. The pivotal Phase III clinical trial supporting this product's market approval, "Acladine versus Huachansu in First-Line Treatment of Advanced Hepatocellular Carcinoma: A Multicenter, Randomized, Double-Blind, Double-Simulation Phase III Clinical Trial" (Protocol No.: SNG1705ICR-1) employed a randomized, double-blind, double-simulation design with 283 enrolled subjects. In the enriched population, the median overall survival (OS) in the icariin group was significantly superior to that in the huachansu group, with better safety and lower incidence of adverse reactions such as diarrhea and fatigue. Employing a composite biomarker enrichment design, this is the first drug globally approved in the liver cancer field using this approach, enabling precision treatment selection. Phase II demonstrated improved OS in advanced HCC patients, with significant correlation to immune biomarkers. (4) Clinical safety evaluation. Across Phase I, II, and III trials, 269 subjects in the icariin group contributed to the safety dataset. Adverse events primarily included Grade 1/2 gastrointestinal reactions, abnormal blood counts, and liver/kidney biochemical indicators; Common adverse reactions ($\geq$5% incidence) included elevated aspartate aminotransferase, elevated serum bilirubin, diarrhea, decreased platelet count, decreased appetite, elevated alanine aminotransferase, elevated serum alkaline phosphatase, proteinuria, decreased white blood cell count, elevated γ-glutamyltransferase, nausea, and fatigue. Grade $\geq$3 adverse reactions primarily include elevated γ-glutamyltransferase, elevated serum bilirubin, and elevated aspartate aminotransferase. (5) Risk analysis and control. All adverse reactions and serious adverse events identified during clinical trials of this product have been included in the package insert risk warnings. For patients with abnormal liver function, abnormal renal function, gastrointestinal diseases, low platelet count/coagulation disorders/anemia/hypophosphatemia, myocardial ischemia or infarction, breast hyperplasia or endometrial hyperplasia, HBV viral load $\geq 10^4$ copies/mL (2000 IU/mL), use in pregnant or lactating women, contraception, and pediatric use. (6) Benefit-Risk Assessment. Based on risk-benefit assessment, existing studies and data support the marketing authorization of this product for unresectable hepatocellular carcinoma in patients who are unsuitable for or refuse standard therapy and have not previously received systemic treatment, provided they meet at least two of the following peripheral blood composite biomarker criteria: AFP $\geq$400 ng/mL; TNF-α $<$2.5 pg/mL; IFN-γ $\geq$7.0 pg/mL. This product received conditional marketing approval based on interim analysis data from a randomized controlled Phase III clinical trial in an enriched population. Full approval for this indication is contingent upon planned confirmatory trials demonstrating the product's clinical benefit. (7) Post-marketing requirements. Full approval for this indication is contingent upon planned confirmatory trials demonstrating clinical benefit. Relevant studies, including clinical trials, must be completed by the specified deadline and submitted *via* a supplemental application. Progress must be communicated in

a timely manner during clinical trials in accordance with relevant regulations, and periodic safety update reports must be submitted throughout drug development[7].

Further analysis of the approval process for innovative TCM products since 2020 indicates that among the 28 innovative TCM products approved for marketing between January 1, 2020, and March 31, 2025, three underwent technical review under the priority review procedure, and two were approved for marketing under the conditional approval procedure. For instance, Mulberry Branch Total Alkaloids Tablets, Icariin Soft Capsules, and Pediatric Golden Cough Relief Granules were approved through priority review, while Icariin Soft Capsules and Xiangle Tang Foot Ointment were approved conditionally. The review period for marketing applications granted priority review was shortened from 200 days under the standard procedure to 130 days further accelerating the market launch of these drugs[30]. Notably, the review and approval of the "Three Medicines" (Jinhua Qinggan Granules, Lianhua Qingwen Capsules/Granules, Xuebijing Injection) and the "Three Formulas" (Qingfei Paidu Granules, Huashi Baidu Granules, Xuanfei Baidu Granules) during the COVID-19 pandemic exemplified emergency review practices and landmark reforms in TCM registration. Supported by a "three-combination" evidence system, the "Three Medicines" followed the pathway for expanding indications of marketed drugs and emergency filing, while the "Three Formulas" completed accelerated approval as new drugs based on ancient classical formulas, establishing a paradigm for emergency transformation of TCM[31].

4. The significance of TCM regulatory science as an emerging discipline

4.1. The emergence and development of regulatory science for TCM

The term "regulatory science" was first proposed by Dr. Alan Moghissi of the U.S. Environmental Protection Agency (EPA) in 1970 to describe the emerging challenge of making regulatory decisions within statutory timelines based on novel scientific evidence that defied traditional requirements. In 2010, the U.S. Food and Drug Administration (FDA) outlined the fundamental framework and definition in its report "Advancing Regulatory Science for Public Health". Pharmaceutical regulatory science is defined as the science of developing new tools, standards, and methodologies to evaluate the safety, efficacy, quality, and performance of products regulated by the FDA. In April 2019, China's National Medical Products Administration (NMPA) issued the "Notice on Implementing the China Drug Regulatory Science Action Plan". Through innovations in regulatory tools, standards, and methodologies, this plan aims to effectively address prominent issues affecting drug innovation, quality, and efficiency, accelerating the modernization of China's drug governance system and capabilities. In recent years, driven by major global drug regulatory authorities including the United States, the European Union, Japan, and China, regulatory science has evolved into an emerging strategic frontier discipline of the 21st century. It has significantly promoted global technological innovation and the market application of drugs, becoming the scientific foundation for regulatory agencies to fulfill their responsibilities[5,32-38].

As shown in Table 7, the term "regulatory science for TCM" first appeared in the National Medical Products Administration's (NMPA) "Action Plan for China's Pharmaceutical Regulatory Science" in April 2019. In December 2020, the NMPA's "Implementation Opinions on Promoting the Inheritance and Innovative Development of TCM" proposed strengthening research on regulatory science for TCM, actively advancing innovation in regulatory concepts, systems, and mechanisms, and enhancing the transformation and application of research outcomes. In January 2023, the NMPA issued the "Several Measures on Further Strengthening Scientific Regulation of TCM to Promote Its Inheritance and Innovative Development", requiring vigorous development of regulatory science for TCM to advance the practice of Chinese-style modern drug regulation and the construction of a scientific regulatory system for TCM with Chinese characteristics[6,39]. From 2023 to 2024, the CDE will conduct regulatory science research on TCM, promptly translate research findings into technical guidance principles for TCM, accelerate the construction of a "three-combination" review evidence system, and advance the review of new TCM drugs with proven clinical value[2,4]. In May 2023, the NMPA's TCM regulatory science research team and related technical teams, led by Zhao Junning, systematically elaborated on the concept and scientific connotations of TCM regulatory science (TCMRS)[36]. In July 2023, the book Chinese traditional medicine regulatory policies, regulations, and technical guidance, compiled by the NMPA and edited by Junning Zhao, was published by China medical press. In February 2024, the TCM regulatory science coalition (TCMRSC) operational mechanism was established and commenced activities. In August 2024, the world's first large-scale academic monograph on TCM regulatory science, edited by Zhao Junning, was published by China medical science and technology Press[4]. Also in August 2024, the "14th Five-Year Plan" innovative textbook for higher education institutions, TCM Regulatory Science reviewed by Zhao Junning and edited by Tang Jianyuan was published by People's medical publishing house[40]. On April 25−26, 2025, the 781th academic symposium of the Xiangshan science conference was successfully convened, focusing on "Key Scientific Issues in TCM Regulatory Science and Translational Research on New Tools, Standards, and Methods".

In summary, the past five years have been a pivotal period for the formation and development of regulatory science for TCM. As a new paradigm and pathway for the integrated development of Chinese and Western medicine, the exploratory practice of regulatory science for TCM has achieved successful innovation in new tools, standards, and methods, as well as the successful transformation of research outcomes. This has provided strong support for the innovative research and achievements in new tools, standards, and methods for TCM regulatory science have been successfully translated. This provides novel theoretical frameworks, approaches, and methodological support for the National Medical Products Administration (NMPA) in formulating policy documents such as "Several Measures to Further Strengthen Scientific Regulation of TCM and Promote Its Inheritance and Innovation", "Special Provisions on TCM Registration Management", "Special Provisions on TCM Standard Management", and "Special Provisions on TCM Production Management", as well as reviewing and issuing technical guidance principles for new TCM drugs. This advances the registration review of TCM Investigational New Drug (IND) and New Drug Applications (NDA) and fosters the healthy development of the industry. The "Construction and Transformative Application of the Regulatory Science System for TCM" was honored as one of the Top Ten Academic Advances in TCM for 2023 and received the First Prize for Scientific and Technological Progress from the Chinese Pharmaceutical Association in 2025[41].

Table 7 Milestones in the development of regulatory science for TCM (2019−2025).

Timeline	Key regulatory science developments for TCM
April 2019	The National Medical Products Administration issued the "Notice on Implementing the Action Plan for Pharmaceutical Regulatory Science in China," marking the first official use of the term "TCM Regulatory Science"
September 2020	NMPA issued the "Classification of TCM Registration and Requirements for Application Materials"
December 2020	NMPA issued the Implementation Opinions on Promoting the Inheritance and Innovative Development of TCM
June 2021	NMPA issues "Notice on Implementing the Second Batch of Key Projects Under the China Drug Regulatory Science Action Plan"
September 2021	Zhao Junning and Wang Hainan published the book "Translating TCM: Approaches and Methods for the Innovation and Translation of New TCM Formulations"
July 2022	The First National Conference on Scientific Regulation of TCM convened in Beijing
January 2023	The National Medical Products Administration issued the "Several Measures on Further Strengthening Scientific Regulation of TCM to Promote Its Inheritance and Innovative Development"
February 2023	The National Medical Products Administration issued the special provisions on the registration management of TCM
June 2023	The Drug Registration Department of the NMPA organized research and completed the "Research Report on the Development Strategy for Regulatory Science in TCM"
July 2023	Organized by the NMPA, the book "Regulatory Policies, Laws, and Technical Guidelines for TCM in China," edited by Zhao Junning, was published and distributed by China medical press
July 2023	The Second National Conference on Scientific Regulation of TCM was held in Shanghai.
November 2023	The Center for Drug Evaluation of the NMPA hosted the "Seminar on Regulatory Science Research for TCM: New Tools, Standards, and Methods for Review and Approval of New TCM Drugs"
February 2024	The First Thematic Working Meeting of the TCM Regulatory Science Research Alliance was held in Tianjin
March 2024	The China Association of Chinese Medicine recognized the "Preliminary Establishment and Application of the Regulatory Science System for TCM" as one of the "Top Ten Academic Advances in TCM for 2023"
July 2024	The National Medical Products Administration issued the "Special Provisions on the Management of Chinese Medicine Standards"
August 2024	The Third National Conference on Regulatory Science for TCM convened in Beijing
August 2024	The First Major Monograph on TCM Regulatory Science, edited by Zhao Junning, was published and distributed
August 2024	Edited by Tang Jianyuan and reviewed by Zhao Junning, the "14th Five-Year Plan" innovative textbook for higher education institutions, regulatory science of TCM, has been published and distributed
December 2024	The State Pharmacopoeia Commission issued the "Public Notice on the Draft Standard for the Guidance Principles for Aristolochic Acid I Testing in Chinese Patent Medicines"
April 2025	Xiangshan Science Conference Session 781: Key scientific issues in TCM regulatory science and translational research on new tools, standards, and methods
June 2025	National Medical Products Administration: "Administrative measures for regulatory science innovation research bases" (Guo Ya Jian ke Wai [2025] no. 11)
August 2025	National Medical Products Administration issues "Special Provisions on the Supervision and Administration of TCM Production"
September 2025	"Construction and Application of Regulatory Science System for TCM" Awarded first Prize for scientific and technological progress by the Chinese pharmaceutical association in 2025

4.2. Scientific essence of TCM regulatory science and mechanism of the TCM regulatory science research alliance

4.2.1. Scientific definition of TCM regulatory science

In May 2023, the TCM Regulatory Science Research Team and related technical teams at the National Medical Products Administration, led by Zhao Junning, first defined and systematically elaborated the scientific connotation of TCM regulatory science in China. They formulated development strategies and key pathways for TCM regulatory science, prioritizing the advancement of new tools, methods, and standards for TCM evaluation, as well as translational recognition procedures for TCM regulation. This further contributes to resolving foundational, critical, cutting-edge, and strategic technical challenges in TCM regulation.

Definition of TCM regulatory science (TCMRS): An emerging science that leverages the unique dual attributes of TCM products—both as TCM and pharmaceuticals—to develop new tools, standards, and methods tailored to TCM characteristics. This is achieved through interdisciplinary integration of knowledge and technologies from Chinese and Western medicine, regulatory science, and other fields TCMRS evaluates the safety, efficacy, quality, and overall risk-benefit profile of regulated TCM products, including raw herbs, processed herbal slices, and proprietary Chinese medicines[36].

The essence of TCMRS: (1) A new field. TCMRS is both an application of pharmaceutical regulatory science within the TCM regulatory domain and the outcome of convergence research integrating knowledge and technologies from Chinese and Western medicine, life sciences, regulatory science, and management science. It fills gaps and drives development. (2) New Strategy. Introducing convergence research and regulatory science into TCM oversight stems from the National Medical Products Administration's (NMPA) dual responsibilities: strengthening drug safety regulation and promoting the inheritance and innovation of TCM. This represents a transformative measure by regulatory authorities to proactively adapt to new realities in TCM—including upholding traditional principles while innovating, advancing scientific development, driving industrial growth, meeting health demands, and competing internationally. (3) New Paradigm. Given the "complexity" and "variability" of regulating TCM throughout its entire lifecycle—"from raw herbs to processed slices to finished products"—achieving scientific

oversight of its "safety, efficacy, and quality consistency" presents greater challenges compared to single-component small-molecule chemical drugs[38].

As illustrated in Fig. 10, regulatory science for TCM, as an emerging discipline, exhibits three core characteristics: First, it emphasizes the integration of TCM theory with modern scientific and technological approaches, respecting traditional experience while employing contemporary scientific methods. Second, it prioritizes multidisciplinary collaboration, spanning pharmacy, medicine, chemistry, biology, management, and law. Third, it serves the full lifecycle regulation of TCM, ensuring quality assurance throughout the entire process from source control to clinical application[39].

4.2.2. Alliance mechanism for TCM regulatory science researchers

In accordance with the National Medical Products Administration's (NMPA) Implementation Plan for Comprehensively Strengthening the Construction of the Regulatory Science System, which calls for "promoting the establishment of a collaborative innovation system for regulatory science led by drug regulatory authorities with comprehensive societal participation", and the 2024 National Drug Regulatory Management Work Conference's directive to "establish a new mechanism for translating TCM regulatory science research", experts and scholars from government, industry, academia, and research institutions in the fields of TCM innovation and regulation have reached a consensus through preliminary research and expert deliberation. This consensus drives the establishment of the TCM Regulatory Science Researcher Alliance (TCM Regulatory Science Coalition, TCMRSC). This initiative aims to draw upon successful global regulatory science research models to comprehensively enhance the development of new tools, standards, and methodologies for TCM regulation, facilitate the translation of research outcomes, and strengthen the disciplinary framework. The coalition will deliberate on review and approval criteria for innovative TCM products, advance clinical application of such products, improve post-market monitoring capabilities for suspected adverse reactions, and promote the inheritance and innovation of TCM.

Thematic working meetings serve as a key activity within the TCM Regulatory Science Coalition's operational framework. Typically initiated by topic proponents, these meetings focus on scientific challenges, common issues, or focal points across the entire TCM regulatory chain, or on the latest research achievements of participating members in regulatory science. They also organize studies on hot scientific topics of shared industry interest. Formats include but are not limited to: research interviews, thematic working meetings, and specialized research projects. To date, the TCMRSC working mechanism has convened three thematic meetings in Tianjin, Beijing, and Chengdu[42].

First TCMRSC Thematic Meeting (TCMRSC 24-1): On February 26, 2024, the National Key Laboratory of Modern Chinese Medicine Innovation at Tianjin University of TCM convened the inaugural thematic meeting of the TCM Regulatory Science Research Alliance working mechanism in Tianjin. This meeting served as an exploratory effort to advance TCM regulatory science research. It focused on regulatory science issues concerning "extract feedstock" and "substitutes for rare and endangered TCM materials"—topics of widespread industry concern—providing scientific intellectual support for related regulatory challenges[43].

Second TCMRSC Thematic Meeting (TCMRSC 24-2): On October 25, 2024, the Key Laboratory of TCM Research and Evaluation under the National Medical Products Administration at Beijing University of Chinese Medicine initiated the second thematic meeting of the TCMRSC working mechanism in Beijing. Discussions centered on "regulatory science issues concerning the development and regulation of new TCM drugs based on disease prevention". Experts unanimously agreed that TCM drugs for disease prevention embody the strengths of TCM and hold significant importance for implementing the Healthy China strategy. The development and evaluation of such drugs require innovative approaches and methodologies, while their translation necessitates collaborative innovation among regulatory authorities, universities, research institutes, hospitals, and enterprises[44].

Third Thematic Meeting of TCMRSC (TCMRSC 24-3): On November 28, 2024, the Affiliated Hospital of Chengdu University of TCM convened the third thematic meeting of the TCMRSC working mechanism in Chengdu. Discussions centered on "Key Scientific Issues in the Clinical Translation of Syndrome-Based New TCM Drugs". Experts engaged in in-depth discussions on

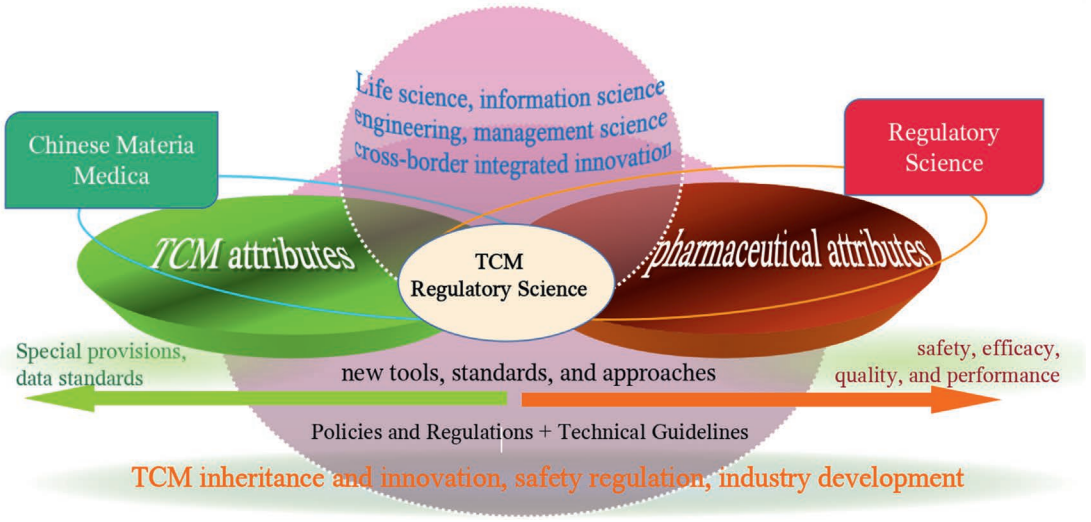

Figure 10 Core characteristics of regulatory science for TCM as an emerging discipline.

critical scientific issues including clinical trial methodologies, research quality control, and clinical efficacy evaluation for syndrome-based TCM drugs. These discussions provided novel approaches and methodologies for the R&D and regulation of such drugs laying a foundational groundwork for establishing a technical evaluation system tailored to the characteristics of TCM[45].

4.3. Research achievements and application of regulatory science in TCM

4.3.1. Technical guidance principles for new TCM drug research play a key role in new drug development

As shown in Table 8, since 2015, the CDE has issued over 100 technical guidance principles related to TCM, including 55 specifically targeting TCM. From 2020 to 2025, TCM regulatory science gained significant attention and rapid development as an emerging interdisciplinary field. Research and application of new tools, methods, and standards in TCM regulatory science achieved breakthroughs, with 38 technical guidance principles specifically for TCM formulated and released. Technical guidance principles for new TCM drug research provide unified new standards and methods for drug developers, researchers, and regulatory authorities. They support the evaluation of TCM efficacy based on TCM theory and clinical practice experience, innovatively establishing a TCM registration review evidence system that integrates "three elements": TCM theory, human experience, and clinical trials. This provides clearer guidance and standards for the development and review of new TCM drugs playing a pivotal role in new drug research[46-49].

4.3.2. The "Three Integrations" TCM registration review evidence system promotes the development of TCM compound preparations

The “Three Integrations” (TCM Theory - Human Experience - Clinical Trials) for TCM registration review centers on a progressive evidence chain. This approach breaks the impasse of applying chemical drug standards to TCM formulas. By synergizing clinical experience with theoretical frameworks, it reduces R&D costs, shortens development cycles, enhances clinical value and quality control, and accommodates the distinct needs of different R&D types—including TCM formulas, active components, and classic prescriptions. It provides an efficient pathway for transforming classic formulas, empirical prescriptions, and hospital-prepared formulations, significantly boosting R&D success rates and industrialization efficiency[50-54].

CDE issued a series of technical guidance principles, including: Guidance Principles for Communication and Exchange Under the "Three Integrations" Evidence System for Registration Review (Trial) Technical Guidance Principles for Collecting and Organizing Human Experience in the Development of New TCM Compound Preparations (Trial) Technical Guidance Principles for Pharmaceutical Research of New TCM Compound Preparations Based on Human Experience (Trial), Technical Guidance Principles for Preparing TCM Theoretical Documentation for New Compound Preparations (Trial), and other series of technical guidance principles have been released. This indicates that the "Three Integrations" approach represents an evidence system upgrade based on integrated Chinese and Western medicine methodologies, thereby better accommodating the complexity of TCM compounds. The evidence system upgrade manifests in: (1) Quantification of human experience data. The 2025 CDE Principles for Collecting and Organizing Human Experience Data for TCM Compound Preparations require structured, traceable data to address the "non-quantifiable" nature of traditional experience, providing robust evidence for registration. (2) Refined quality control. Integrating characteristic profiling, process quality control, and stability principles to establish a "theory—process—quality—efficacy" linkage, enhancing batch-to-batch consistency and reducing industrialization risks. (3) Diversified Efficacy Evaluation. Encouraging indicators like symptom scales, PROs, and TCM syndrome scoring aligns with the "multi-target, holistic regulation" characteristics of compound preparations, highlighting differentiated clinical value (*e.g.*, toxicity reduction through combination therapy).

As shown in Table 9, the weighting of the three-pronged evidence approach varies across different R&D types. This approach is not a simple summation of components but rather a progressive, complementary evidence chain construction. It adapts to the distinct needs of different R&D categories—such as TCM compound formulas, active fractions, and classical formulas—to establish a closed-loop evidence chain anchored by "theoretical grounding, experiential empowerment, and experimental validation": (1) TCM Theory. As the foundation of formula composition, it explains pathogenesis, therapeutic principles, and the roles of sovereign, minister, assistant, and messenger herbs, clarifying clinical positioning and applicable syndromes. (2) Human Experience. The core bridge, leveraging real-world data (formulas from renowned senior TCM practitioners, institutional preparations, and historical applications of classic formulas) to optimize dosage, treatment duration, and target populations, providing rationale for non-clinical/clinical exemptions. (3) Clinical Trials. Precise validation, designing differentiated protocols (*e.g.*, direct confirmatory trials) based on the first two components. Focuses on TCM-specific therapeutic effects (*e.g.*, symptom improvement, quality of life, synergistic efficacy with reduced toxicity) rather than merely replicating Western medicine’s hard endpoints.

4.3.3. Technical documentation requirements for TCM registration impart new dimensions to TCM drug development

The classification of TCM registration has evolved through the 1985 "Measures for the Approval of New Drugs", the 1987 "Supplementary Provisions and Explanations on Issues Concerning TCM in the <Measures for the Approval of New Drugs>", the 1992 "Revised and Supplementary Provisions on TCM in the New Drug Approval Measures", the 1999 "New Drug Approval Measures", the 2002, 2005, and 2007 "Drug Registration Management Measures", and the 2008 "Supplementary Provisions on TCM Registration Management". This phase did not yet include the concept or classification of innovative TCMs. The State Council’s Opinions on Reforming the Drug and Medical Device Review and Approval System (State Council Document [2015] No. 44), issued on August 18, 2015, redefined "new drug" from "a drug not previously marketed in China" to "a drug not previously marketed either in China or abroad." Based on the originality and novelty of the material basis, drugs were classified into new drugs and generic drugs, with new drugs further divided into innovative drugs and modified new drugs. The policy encouraged drug innovation guided by clinical value. On October 8, 2017, the General Office of the CPC Central Committee and the General Office of the State Council issued the Opinions on Deepening the Reform of the Review and Approval System to Encourage Innovation in Drugs and Medical Devices (Hall Document [2017] No. 42). This document proposed "establishing and improving a

Table 8 Technical guidance principles for TCM research published from 2015 to 2025.

No.	Technical guideline name	Release date	Category
1	Guidance principles for clinical research on new TCMs for the treatment of malignant tumors	2015/11/03	Clinical
2	General principles for clinical research on new TCMs	2015/11/03	Clinical
3	Technical guidance principles for clinical research on new TCMs for the treatment of primary osteoporosis	2015/11/03	Clinical
4	Technical guidelines for clinical research on new TCMs for stroke treatment	2015/11/03	Clinical
5	Technical guidance principles for irradiation sterilization of TCMs	2015/11/09	Pharmacy
6	Technical guidance principles for clinical research on new TCMs for influenza treatment	2016/09/29	Clinical
7	Technical guidance principles for research on production process changes of marketed TCMs	2017/09/11	Pharmaceutical
8	Technical guidance principles for naming generic names of Chinese patent medicines	2017/11/28	Pharmacy
9	Technical guidance principles for specification description of Chinese patent medicines	2017/12/25	Pharmacy
10	Technical guidance principles for the evaluation of TCM resources	2017/12/25	Pharmacy
11	Technical guidance principles for clinical research on new TCMs for irritable bowel syndrome	2017/12/27	Clinical
12	Technical guidance principles for clinical research on new TCMs for functional dyspepsia	2017/12/27	Clinical
13	Technical guidance principles for clinical research on new TCMs for cough-variant asthma	2017/12/27	Clinical
14	Technical guidance principles for clinical research on new TCMs for chronic heart failure	2017/12/27	Clinical
15	Technical guidance principles for clinical research on new TCMs for rheumatoid arthritis	2017/12/27	Clinical
16	Guidelines for the clinical evaluation of liver injury caused by TCMs	2018/06/12	Clinical
17	Technical guidance principles for clinical research of new TCM formulations based on syndrome patterns	2018/11/04	Clinical
18	Technical guidance principles for real-world evidence to support pediatric drug development and review (trial version)	2020/08/27	Clinical
19	Technical guidance principles for quality standards research of new TCM (trial)	2020/10/12	Pharmaceutical
20	Technical guidance principles for the processing of new TCM herbal preparations (trial) https://www.cde.org.cn/zdyz/domesticinfopage?zdyzIdCODE=125d334cb1d57b896dd140be855f12ea	2020/10/12	Pharmacy
21	Technical guidance principles for quality control research of new traditional Chinese medicine herbal medicinal materials (trial)	2020/10/12	Pharmacy
22	Technical guidance principles for pharmaceutical research at each stage of new TCM drug development (trial)	2020/11/04	Pharmaceutical
23	Technical guidance principles for uniformity research of TCMs (trial)	2020/11/05	Pharmacy
24	Pharmaceutical documentation requirements for communication meetings during new TCM drug research (trial)	2020/11/10	Pharmaceutical
25	Technical guidance principles for production process research of TCM compound preparations (trial)	2020/11/27	Pharmaceutical
26	Technical guidance principles for research on bioeffect detection of TCMs (trial)	2020/12/17	Pharmacy
27	Technical guidance principles for clinical research on new TCMs for chronic constipation	2020/12/31	Clinical
28	Technical guidance principles for clinical research on new TCMs for diabetic kidney disease	2020/12/31	Clinical
29	Technical guidance principles for quality research of new TCMs (trial)	2021/1/15	Pharmaceutical
30	Technical guidance principles for research on pharmaceutical changes of marketed TCMs (trial)	2021/04/02	Pharmaceutical
31	Technical guidance principles for pharmaceutical research of TCM compound preparations managed as classical prescriptions (trial)	2021/08/31	Pharmaceutical
32	Guidance principles for preparing TCM theoretical documentation for new compound preparations (trial)	2021/10/15	Clinical
33	Guidelines for preparing Instructions for TCM compound preparations based on ancient classic formulas (trial implementation)	2021/10/15	Clinical
34	Technical guidance principles for samples used in toxicological studies of new TCMs (trial)	2022/01/07	Pharmaceutical
35	Guidance principles for clinical development of new TCM compound preparations based on human experience (trial)	2022/04/29	Clinical
36	Guidance principles for communication and Consultation under the "three integrations" registration review evidence system (trial)	2022/04/29	Clinical

(*continued on next page*)

Table 8 (*continued*)

No.	Technical guideline name	Release date	Category
37	Technical guidance principles for evaluating the clinical efficacy of new TCMs for chronic gastritis (trial)	2022/12/21	Clinical
38	Technical guidance principles for the clinical efficacy evaluation of new TCMs for gastroesophageal reflux disease (trial)	2022/12/21	Clinical
39	Technical guidance principles for research on identical-name and identical-formulation drugs (trial)	2022/12/27	Pharmaceutical sciences
40	Technical guidance principles for the clinical development of new TCM compound preparations related to malignant tumor treatment (trial)	2023/04/14	Clinical
41	Technical guidance principles for the preparation of new TCM drugs for clinical trials (trial implementation)	2023/07/25	Pharmaceutical
42	Technical guidance principles for pharmaceutical research of other TCM compound preparations derived from ancient classic formulas (trial)	2023/07/25	Pharmaceutical
43	Technical guidance principles for pharmaceutical research of new TCM compound preparations based on human experience (trial)	2023/10/18	Pharmaceutical
44	Technical guidance principles for clinical development of new TCM drugs related to diabetic retinopathy (trial)	2023/11/14	Clinical
45	Technical guidance principles for characteristic spectrum research of TCM preparations (trial)	2024/02/27	Pharmacy
46	Technical guidance principles for stability studies of TCM preparations (trial)	2024/02/27	Pharmacy
47	Technical guidance principles for clinical development of new TCMs for pediatric constipation (trial)	2024/03/01	Clinical
48	Guidance principles for preparing pharmaceutical application materials for compound Chinese medicinal preparations managed as classical prescriptions (trial)	2024/04/23	Pharmaceutical
49	Technical guidance principles for evaluating the clinical efficacy of new TCMs for tension-type headache (trial)	2024/050/6	Clinical
50	Technical guidance principles for research on modified TCM new drugs (trial)	2024/05/15	Clinical
51	Technical guidance principles for quality control research in the production process of oral TCM preparations (trial)	2024/06/24	Pharmacy
52	Technical guidance principles for research on artificial preparations of endangered animal-based traditional Chinese medicinal materials (trial)	2024/12/11	Pharmacy
53	Technical guidance principles for research on substituting or reducing endangered medicinal ingredients in marketed TCM formulas (trial)	2024/12/11	Pharmacy
54	Technical guidance principles for collecting and organizing human experience in the development of new TCM compound preparations (trial)	2025/12/29	Clinical
55	Requirements for preparing application materials for modifying safety information in the instructions for marketed TCMs	2025/12/30	Clinical

Table 9 Reference for evidence weighting in the "Three Integrations" approach for different development categories of new TCM drugs.

Development category	TCM theory	Human experience	Clinical trials	Core characteristics
Classic Prescriptions 3.1 Category	+++++	+++++	−	Theory + experience-driven, exempt from clinical trials
Emergency TCM Category 3.2	+++++	++++	+++	Rapid theoretical response, immediate accumulation of experience, simplified clinical trials
Medical Institution Empirical Formulas Category 1.1	++++	++++	++++	Empirically empowered, exempt from non-clinical efficacy studies, clinically validated distinctive therapeutic effects (partial clinical trial exemption)
Active Components of TCM Category 1.2	+++	++	+++++	Theoretical anchoring guides extraction direction, experience mitigates risks, clinical validation confirms efficacy of active components
TCM Monomers Category 1.2	++	+	+++++	Theoretical modernization interpretation, experience-backed safety, clinical integration with precision medicine

registration management system and technical evaluation system tailored to the characteristics of TCM, balancing the preservation of TCM's traditional strengths with the requirements of modern drug R&D. Innovative TCM drugs should emphasize novel therapeutic effects". On August 26, 2019, the newly revised Drug Administration Law was adopted at the 12th Session of the 13th National People's Congress Standing Committee. It formally categorized TCM registration into: innovative TCM drugs, improved TCM drugs, compound preparations based on ancient classic formulas, and drugs with identical names and compositions. On January 22, 2020, the State Administration for Market Regulation promulgated the "Measures for the Administration of Drug Registration" (Order No. 27), with Article 4 explicitly stating that "TCM registration shall be classified into innovative TCMs, modified new TCMs, compound preparations based on ancient classical formulas, and medicines with the same name and formula. "On September 28, 2020, the National Medical Products Administration (NMPA) issued the "Classification of TCM Registration and Requirements for Application Materials" as a supporting document to the newly revised "Measures for the Administration of Drug Registration". This document categorizes TCM into innovative TCM drugs, improved TCM drugs, compound preparations based on ancient classical formulas, and drugs with the same name and formula, while detailing the requirements for application materials[1,7].

Effective January 1, 2021, the NMPA's newly issued "Classification of TCM Registration and Requirements for Application Materials"[55] no longer emphasizes solely the content requirements for "active ingredients" and "active parts" as in the original registration classification management. It no longer relies exclusively on material basis as the basis for categorizing registration types. Instead, it follows the development patterns of TCM, reflects the characteristics, R&D patterns, and actual conditions of TCM, and promotes the establishment and improvement of a registration management system and technical evaluation standard system that conforms to the characteristics of TCM. This reflects the deepening of the achievements of the reform of TCM registration classification guided by clinical value[56]. Concurrently, the CDE conducted systematic research on Category 3 "TCM Compound Preparations Based on Ancient Classic Formulas" within the current "Measures for the Administration of Drug Registration. "Based on the "three-combination" registration review evidence system approach, it proposes adding a new category "3.2 Other TCM Compound Preparations Derived from Ancient Classic Formulas" and outlines corresponding registration management technical requirements. This introduces a distinct R&D model from innovative TCM drugs, accelerating the transformation of outcomes from classic formulas inherited through long-term clinical practice, renowned TCM practitioners' experience formulas, and hospital preparations. This fully addresses clinical treatment needs in TCM practice[56,57].

5. Reconstruction and innovation promotion of TCM regulatory policies: Accelerating the establishment of an excellent regulatory system for TCM

5.1. Macro-level policies, regulations, and normative documents

As shown in Table 10, the new round of reforms by drug regulatory authorities during 2021−2025 further optimized the drug supervision system. Relevant departments and institutions involved in TCM regulation were strengthened, enhancing regulatory capabilities. The General Office of the State Council, the National Medical Products Administration (NMPA), and the National Administration of TCM (NATCM) established a specialized system of administrative normative documents for TCM regulation. They continuously improved the regulatory framework tailored to TCM characteristics and developed incentive measures for new drug registration[1].

5.2. Special provisions related to TCM registration management

As shown in Table 11, guided by macro-level policies, regulations, and normative documents from relevant national authorities, complementary specialized regulations tailored to the characteristics of TCM have been introduced. These include the Classification of TCM Registration and Requirements for Application Materials, Special Provisions on the Registration Management of TCM, Special Provisions on the Standard Management of TCM, and Special Provisions on the Supervision and Management of TCM Production. These regulations represent a major milestone, as they significantly adjust the classification of TCM registration and innovate the evidence system for review, thereby establishing a more scientific and rational classification system for TCM registration. Concurrently, efforts are accelerating to finalize the Catalog of Ancient Classic Prescriptions (Second Batch) and the Key Information Form for Ancient Classic Prescriptions. This continuous refinement of the regulatory framework tailored to TCM characteristics advances the development of a scientific regulatory system for TCM that aligns with its unique nature[1].

Addressing longstanding industry criticisms regarding TCM review and approval—such as "applying Western standards to Chinese medicine", "excessive focus on chemical constituents", and "inefficient review processes"—the National Medical Products Administration (NMPA) has conducted specialized research and targeted breakthroughs in recent years. This has yielded notable achievements in TCM regulation[1,6]: (1) Tailor-made regulations for TCM break down the barriers of "applying Western standards to Chinese medicine". The NMPA issued policies to promote TCM innovation, including the Implementation Opinions on Promoting the Inheritance and Innovation of TCM, Several Measures to Further Strengthen Scientific Supervision of TCM and Promote Its Inheritance and Innovation, Special Provisions on the Registration Management of TCM, Special Provisions on the Standard Management of TCM, and technical guidance principles developed by the CDE. These policies fully recognize the role of "human experience" in supporting the safety and efficacy of TCM, accelerating the establishment and refinement of a "three-combination" review evidence system. (2) Reforming TCM registration classifications to overcome the technical bottleneck of "ingredient-centricism". The NMPA issued transformative regulations—the Measures for Drug Registration Administration and the Classification of TCM Registration and Requirements for Application Materials—which for the first time explicitly defined the concept and classification of innovative TCM drugs. TCM registration is now categorized into four types: innovative drugs, modified new drugs, classical formula preparations, and drugs with identical names and formulas. The new classification no longer relies solely on material basis for categorization and de-emphasizes the previous requirements for "active ingredients" and "active parts" in terms of content. This approach reflects the characteristics, R&D patterns, and practical realities of TCM,

Table 10 Macro policies and regulatory documents for the review and approval of new TCM drugs, 2020−2024.

Release date	Document name	Incentive measures
December 21, 2020, National Medical Products Administration (NMPA Notice [2020] no. 27)	Implementation opinions on promoting the inheritance and innovative development of TCM	Adhere to a clinical value-oriented approach. Promote the development of compound preparations based on classical ancient formulas. Foster innovation in TCM. Encourage secondary development. Strengthen safety research on TCM. Reform the registration classification system for TCM. Establish a "three-combination" review evidence system. Reform and improve the review and approval system for TCM.
January 22, 2021, General Office of the State Council (State Council Document [2021] no. 3)	Several policy measures on accelerating the development of TCM with distinctive characteristics	Respect the inherent principles of TCM research and development, refine the classification system for TCM registration, and clarify submission requirements. Streamline the review and approval process for new TCM drugs with established human application experience. For eligible innovative TCM drugs, modified TCM drugs, classical ancient formulas, and drugs with identical names and compositions, explore the implementation of management mechanisms that exempt them from non-clinical safety studies and certain clinical trials in accordance with laws and regulations. Fully leverage modern technologies such as data science to establish a TCM registration review evidence system integrating TCM theory, human experience, and clinical trials. Actively explore establishing a real-world evidence system for TCM. Streamline the registration and approval process for compound preparations based on ancient classic formulas. Improve the technical research guidance principles for comprehensive quality control throughout the development of new TCM drugs.
May 10, 2021, General Office of the State Council (State Council Document [2021] no. 16)	Implementation opinions on comprehensively strengthening the capacity building of drug regulation	Follow the development patterns of TCM, establish a distinctive TCM review evidence system integrating TCM theory, human experience, and clinical trials, emphasize the application of evidence-based medicine, and explore real-world evidence research for drugs. Optimize the registration classification of TCM formulations, strengthen the management of innovative drugs, modified new drugs, classical TCM compound preparations, and drugs with identical names and formulas. Improve the technical guidance principle system, enhance full-process quality control, and promote the inheritance and innovation of TCM.
December 30, 2021, National Medical Products Administration and 7 Other Departments (Guo Ya Jian Zong [2021] no. 64)	National plan for drug safety and promotion of high-quality development during the 14th five-year plan period	Establish a review and approval system tailored to the characteristics of TCM. Scientifically address the unique theoretical framework of TCM by exploring an evidence-based review system oriented toward clinical value, integrating traditional Chinese medical theory, human experience, and clinical trials. Strengthen the application of evidence-based medicine and explore the role of real-world evidence. Accelerate the refinement of technical requirements for reviewing new TCM drugs based on classical formulas, renowned TCM practitioners' prescriptions, and hospital-prepared formulations with established human experience. Continuously refine the technical guidance principles for comprehensive quality control research throughout the development process of new TCM drugs. Explore the inclusion of TCM decoction pieces with unique processing methods into the scope of TCM variety protection.
March 3, 2022, General Office of the State Council (State Council Document [2022] no. 5)	The 14th five-year plan for the development of TCM	Optimize the clinical evidence system for TCM. Establish a TCM registration review evidence system integrating TCM theory, human experience, and clinical trials. Actively explore establishing a real-world evidence system for TCM. Explore filing and approval

Table 10 (*continued*)

Release date	Document name	Incentive measures
		management for TCM decoction pieces and optimize registration management for TCM preparations in medical institutions. Advance the formulation and release of a directory of classical TCM formulas and accelerate the verification of key information for included formulas.
January 3, 2023, National Medical Products Administration (NMPA Notice [2023] no. 1)	Several measures on further strengthening scientific regulation of TCM to promote its inheritance and innovative development	Comprehensively strengthen quality management across the entire TCM industry chain, accelerate review and approval processes throughout the entire procedure, enhance product services throughout the entire lifecycle, advance global regulatory cooperation, and promote all-round innovation in regulatory science. Deepen the practice of Chinese-style modern drug regulation and the construction of a scientific regulatory system for TCM with Chinese characteristics.
July 31, 2023, National Medical Products Administration (NMPA) (Guo Ya Jian ke Wai [2023] no. 27)	National medical products administration plan for comprehensively strengthening the regulatory science system	Innovate new models for integrating Chinese and Western medicine in regulatory science research for TCM. Focus on developing multidisciplinary theories and methodologies for TCM regulatory science. Organize research on efficacy, safety, quality, and risk-benefit assessment technologies tailored to TCM characteristics to provide technical support for establishing a TCM review and approval system aligned with TCM features. Develop a pharmaceutical evaluation technology system suited to TCM characteristics. Continuously advance research on TCM quality control technologies to overcome bottlenecks in advanced characterization and systematic control of the complex quality systems inherent in TCM.
October 17, 2024, National Medical Products Administration, National Administration of TCM (no. 129, 2024)	Announcement on matters concerning support for the development of substitutes for rare and endangered traditional Chinese medicinal materials	Mainly covers aspects such as "focusing on key varieties, encouraging R&D innovation, strengthening industry-academia-research collaboration, streamlining registration pathways, enhancing technical guidance, accelerating review and approval, and strengthening post-market supervision".
December 30, 2024, General Office of the State Council (state Council Document [2024] no. 53)	Opinions on comprehensively deepening the Reform of drug and medical device supervision to promote high-quality development of the pharmaceutical industry	Improve the distinctive Chinese medicine review evidence system integrating traditional theories, human experience, and clinical trials, and establish mechanisms for medical institutions to systematically collect and organize human experience data. Develop a regulatory framework tailored to the characteristics of Chinese medicine.
March 15, 2025, General Office of the State Council (Guobanfa [2025] no. 11)	Opinions on enhancing the quality of TCMs to promote high-quality development of the TCM industry	With improving the quality of TCMs as the foundation, technological innovation as the support, and institutional and mechanism reforms as the guarantee, achieve standardized cultivation and stable supply of commonly used Chinese medicinal materials. Accelerate the construction of a modern industrial system to form a high-quality development pattern for the TCM industry that equally emphasizes inheritance and innovation, features a rational layout and structure, utilizes advanced equipment and manufacturing, ensures reliable quality and safety, and possesses strong competitiveness. This will better enhance people's health and well-being and serve the modernization with Chinese characteristics.

while establishing comprehensive technical requirements aligned with the new classification system. (3) Accelerated Review and Approval Mechanism Transforms "Low Review Efficiency". Driven by multiple policies promoting the inheritance and innovation of TCM, clinical trial applications and marketing applications for innovative TCM drugs have significantly increased in recent years. The new review and approval mechanism shifts the previous "end-stage acceleration" to "full-process acceleration". The development and submission of innovative TCM drugs now follow a review management system centered on

Table 11 Relevant regulations on TCM registration management.

Release date and issuing authority	Document title	Incentive measures
September 27, 2020, National Medical Products Administration (no. 68, 2020)	Classification of TCM registration and requirements for application materials	TCM registration is categorized into innovative TCMs, modified new TCMs, compound preparations based on ancient classical formulas, and medicines with identical names and formulas. The first three categories are classified as new TCMs. The registration classification does not indicate the level of drug development or therapeutic efficacy; it solely reflects differing requirements for registration application materials across categories.
February 10, 2023, National Medical Products Administration (no. 20 of 2023)	Special provisions on the administration of TCM registration	The special provisions serve as a normative document bridging the "measures for the administration of drug registration" and the series of technical guidance principles for drug development. Its content addresses both administrative management matters related to TCM registration and the specialized technical aspects of TCM review and approval. The special provisions clarify the principles and technical requirements for the rational application of TCM human experience, as well as the development of registration categories such as innovative TCM drugs, improved TCM drugs, compound preparations based on ancient classical TCM formulas, and drugs with identical names and formulas. Through necessary technical requirements, the special provisions further implement the accelerated advancement of a TCM review evidence system integrating TCM theory, human experience, and clinical trials (hereinafter referred to as the "three integrations"). They embody new concepts and reform measures in TCM registration management while strengthening guidance for TCM development, demonstrating strong practical applicability.
May 9, 2024, National Medical Products Administration, National Administration of TCM (no. 61, 2024)	Administrative measures for regionally customary medicinal materials	Regionally customary medicinal materials balance their characteristics as both "regionally customary" and "medicinal". This emphasizes their customary history—specifically, being documented in "herbal compendia, medical texts, local gazetteers, etc."—while also highlighting their regional medicinal use. These materials are defined as "traditional Chinese medicinal materials not included in national drug standards, lacking drug registration standards, yet possessing long-standing medicinal usage practices in specific local areas."
July 9, 2024, National Medical Products Administration (no. 93 of 2024)	Special provisions on the management of Chinese medicinal product standards	Focusing on establishing "the most stringent standards", this regulation sets forth provisions at both policy and technical levels. It integrates general requirements for drug standard management with the unique characteristics of TCM products, stipulating fundamental principles for the research and formulation of TCM standards, specific requirements for various TCM quality standards, standard revisions, implementation, and other aspects. It clarifies responsible entities and standardizes key processes.
March 25, 2025, National Medical Products Administration (no. 32 of 2025)	Announcement on matters concerning the implementation of the 2025 Edition of the *Pharmacopoeia of the People's Republic of China*	The 2025 Edition of the *Pharmacopoeia of the People's Republic of China* (hereinafter referred to as the "*Chinese Pharmacopoeia*") has been promulgated by Announcement no. 29 of 2025 issued jointly by the national medical products administration and the national health commission, and shall take effect on October 1, 2025.
2025-08-25, National Medical Products Administration (Announcement no. 79 of 2025)	Special provisions on the supervision and administration of TCM production	Holders of drug marketing authorizations (hereinafter referred to as "holders") and TCM manufacturers shall adhere to the principles and characteristics of TCM, strictly comply with laws and regulations in production, and ensure that the entire production process of TCM consistently meets statutory requirements.

clinical efficacy, featuring regulatory guidance upfront, communication during the process, and review decisions at the end. By engaging in communication with drug review authorities at key R&D milestones—including pre-IND, post- -II -phase clinical trials, pre- -III -phase clinical trials, and pre-NDA stages—the pace of R&D and submission has accelerated, placing innovative TCM drugs on the "fast track" for approval. (4) Formulations based on ancient classic prescriptions enhance accessibility and affordability of TCM products. According to the "Classification of TCM Registration and Requirements for Application Materials" (State Administration of Market Regulation Announcement No. 68, 2020), these are subdivided into "3.1 Compound TCM Preparations Managed According to the Directory of Ancient Classic Prescriptions" and "3.2 Other Compound TCM Preparations Derived from Ancient Classic Prescriptions". These classical formulas typically originate from ancient Chinese medical texts, have undergone long-term clinical validation, possess clear therapeutic effects, and are grounded in profound theoretical foundations. A series of policies have been introduced to encourage the research and development of classical formula preparations and simplify their registration process, thereby promoting the inheritance and innovative development of TCM. Particularly during the COVID-19 pandemic, the importance of classical formula preparations in rapidly and reliably producing urgently needed medicines and preventing drug shortages has been further emphasized.

5.3. International comparative perspective: Establishing an excellent regulatory system for TCM

5.3.1. Comparison of international regulatory policies and technical requirements for herbal medicines

Globally, TCM, herbal medicines, and natural medicines constitute vital components of traditional medicine systems. They possess a long history of medicinal use and play significant roles in modern disease treatment. Different countries and regions employ varying classifications and common names. China uniformly refers to them as "TCM", while Southeast Asia, Europe, Africa, and the Arab world often use "herbal medicine". In Japan, they are commonly known as "Kampo medicine", in South Korea as "Korean medicine", and in the North American market, they are frequently termed "herbal medicine" or "natural medicine". Statistics indicate that over 180 countries and regions currently import or utilize herbal medicines and related products, benefiting approximately 4 billion people. With societal development and technological advancement, shifts in disease patterns, healthcare models, and consumer attitudes are underway, fueling a global trend toward "returning to nature" and "cherishing natural remedies". Currently, 60% of the population in developed countries has received herbal medicine treatment, particularly for chronic conditions. In developing countries, the proportion of herbal medicine users is even higher. The definition and regulatory scope of herbal medicines form the cornerstone of registration oversight, directly determining the applicable regulatory pathways for products. The reality is that obtaining timely drug approvals across different countries is extremely challenging and burdensome, reflecting the challenges posed by varying regulatory expectations and requirements among national authorities.

Currently, TCM has spread to 196 countries and regions. Globally, over 180 countries and regions import or utilize herbal medicines and herbal products, with users numbering as high as 4 billion—accounting for approximately 80% of the world's total population. As a major producer of TCM, China's herbal products have penetrated markets worldwide, exported to numerous countries and regions including Japan, South Korea, Germany, the United States, Canada, and Australia. Export categories encompass diverse types such as plant extracts, Chinese herbal materials and decoction pieces, proprietary Chinese medicines, and health supplements. Among these, plant extracts constitute the largest proportion, followed by Chinese herbal materials and decoction pieces, proprietary Chinese medicines, and health supplements. Therefore, international coordination and policy convergence regarding regulatory frameworks for TCM natural medicines are not only necessary but also crucial[39]. It is essential to examine core regulatory documents issued by the NMPA, FDA, EMA, and PMDA—China's "Classification of TCM Registration and Requirements for Application Materials" (2020), the U.S. "Guidance for Industry: Development of Herbal Medicinal Products" (2016 revision), the EU's "Traditional Herbal Medicinal Products Registration Procedure Regulation" (2004/24/EC), and Japan's 1975 "Recognition Standards for Over-the-Counter Kampo Preparations". Such comprehensive comparative research can provide a clear roadmap for establishing a globally leading regulatory system for TCM with Chinese characteristics, promoting high-quality development and facilitating international registration applications. As shown in Table 12, regulatory policies and technical requirements for herbal medicines in China, the United States, the EU, and Japan share common ground while exhibiting significant differences. We must collectively address the substantial challenges posed by regulatory and standard disparities[58,59].

5.3.2. Strategic objectives and system development for excellence in TCM regulation

Amid the industrialization, modernization, and internationalization of TCM, the development of TCM regulatory systems and capacity building are entering a strategic window of opportunity for global integration and coordinated regulatory advancement. The NMPA's 2024 Work Priorities explicitly state the continued implementation of the "Several Measures for Further Strengthening Scientific Regulation of TCM and Promoting Its Inheritance and Innovative Development" (Guo Ya Jian Ya Zhu [2023] No. 1). This aims to accelerate the development of a globally leading TCM Excellent Regulatory System (TCM-ERS) with Chinese characteristics and tailored to TCM's unique features, while establishing a mechanism for translating TCM regulatory science research into practice[6,36,38].

The TCM Excellent Regulatory System (TCM-ERS) builds upon scientific TCM regulation to establish a novel, scientific, efficient, and authoritative regulatory framework supported by innovations and applied research in TCM regulatory science. Its cornerstone lies in developing an evaluation and approval system tailored to TCM characteristics, guided by traditional Chinese medical theory to foster the inheritance and innovation of TCM. Strengthen research and translation of clinical value evidence integrating TCM theory, human experience, and clinical trials. This reflects the "quality−efficacy" transmission patterns across the entire chain—from raw/authentic medicinal materials and processed herbal slices to compound preparations—accelerating the market entry of new TCM technologies and products to meet clinical needs. Global leadership hinges on high-quality development and high-level opening-up. Supported by comprehensive innovation in TCM regulatory science, this system aims to achieve accelerated review and approval throughout the regulatory process, safety oversight across the entire industrial chain, lifecycle regulatory services, and coordinated global regulatory cooperation[8,60].

Table 12 Comparison of regulatory policies and technical requirements for herbal medicines in China, the United States, the European Union, and Japan.

Comparison item	China	United States	EU	Japan
Scope of regulation	The broadest scope, encompassing animal-based and mineral-based medicines potentially present in traditional Chinese herbal formulas. It covers raw herbs, processed herbal slices, extracts, TCMs, and natural medicines, providing differentiated registration pathways for various types of new TCM products.	Relatively pragmatic, encompassing plant-based ingredients, algae, fungi, and their mixtures. However, its exclusion clauses are explicitly defined, reflecting a principle of caution: Excludes products containing animal or animal-derived components, minerals (trace additions permitted); excludes raw materials derived from genetically modified plants; excludes fermented products; excludes highly purified components (which are regulated as chemical drugs).	The most stringent category upholds the "purity" of herbal medicines. It is primarily divided into herbal medicinal products (HMP) and traditional herbal medicinal products (THMP). Its definition emphasizes that "the active ingredients are solely or exclusively plant-based components or extracts".	Standardized formulations based on classical prescriptions from China's Eastern han to Ming dynasties (*e.g.*, Shanghan Lun, Jingui Yaolue) and Japan's localized adaptations, produced *via* modern techniques. Emphasizes the integrity of the prescription and fixed ratios. Classified by usage scenario into three categories: Medical Kampo preparations (146 types prescribed by physicians), general Kampo preparations (294 types sold in pharmacies), and pharmacy preparations (185 types self-manufactured by medical institutions).
Quality control	Emphasis is placed on comprehensive process management integrating traditional and modern approaches, establishing a holistic quality standards system spanning raw herbs, processed herbal slices, extracts, and finished preparations.	The "integrated evidence chain" concept employs a systematic quality control approach guided by clinical endpoints, emphasizing "bridging studies" to demonstrate quality consistency through multiple interconnected evidence links.	Highly reliant on mature monograph systems (including European Pharmacopoeia monographs and EMA herbal monographs), with refined classification management: Standardized extracts (known active ingredients), quantified extracts (known marker compounds), and other extracts (unknown composition).	Requires thin-layer chromatography identification methods for all herbal ingredients in prescriptions; where unfeasible, sufficient experimental justification must be provided. Mandates that herbal ingredients with specified content levels in the Japanese Pharmacopoeia must comply in Kampo formulations, with at least three components subject to assay.
Non-clinical research	The exemption or simplification mechanism based on "human experience" has formed a distinct "Chinese approach".	Based on comprehensive risk assessment, the following five factors are considered: Prior human experience, existing clinical research data, known or suspected risks of the drug, the drug's development stage, and the design of the proposed clinical study.	Relatively simplified, the core is to demonstrate safety through literature and expert reports.	In new drug development, due to stringent approval requirements, Japanese Kampo companies rarely venture into the new drug field.
Clinical research	Pioneered the "three-combination" system for evaluating new TCM drugs, integrating TCM theory, human experience, and clinical trials.	The core concern is therapeutic consistency, which serves as the final link in the "overall evidence chain". Requirements are extremely stringent and specific: Multi-batch, multi-dose clinical designs; "de-formulation trials" for compound herbal medicines; and acceptance of traditional Chinese medical terminology.	Evidence is based entirely on traditional usage, not new clinical trials. Indications are strictly limited to mild conditions with clear diagnoses that can be self-managed, excluding severe diseases like cancer, cardiovascular disease, or diabetes.	Investigator-initiated trials (IITs) conducted by enterprises/researchers, aimed at clinical scientific exploration and evidence-based medical research.

Strategic Objectives of the TCM Excellence Regulatory System: As a vital component of China's "scientific, efficient, and authoritative" drug regulatory framework, the TCM Excellence Regulatory System focuses its strategic objectives on three interrelated dimensions: Chinese characteristics, TCM-specific features, and global leadership[8]. Specifically: (1) Chinese Characteristics. While drawing extensively from the experiences of international regulatory bodies such as the FDA and EMA, it also grounds itself in the practical realities of China's pharmaceutical industry development. It rationally proposes a "localized adaptation" practice pathway, providing a feasible reference plan for constructing a regulatory science system with Chinese characteristics. We must innovate a hybrid decision-making model for scientific regulation, balancing professional authority, policy and regulations, and social reputation to better fulfill the role of guardian of public health.We must adhere to the coordinated development and governance of healthcare financing, medical services, and pharmaceuticals to better leverage the role of TCM in addressing challenges such as technological innovation, industrial drivers, evolving health needs, and public health emergencies like COVID-19. (2) Characteristics of TCM. Establish an evaluation and approval system tailored to the unique features of TCM. Guided by TCM theory, promote the inheritance and innovation of traditional medicine. Strengthen research and translation of clinical value evidence through the "three integrations" (TCM theory + human experience + clinical trials). Emphasize TCM's distinctive theories on medicinal properties (toxicity) and drug combinations, its unique compound formulations, and quality and safety control methods. Accelerate the market entry of new TCM technologies and products to meet clinical needs. (3) Global Leadership. Global leadership is founded on high-quality development—where innovation is the primary driver, coordination is an inherent characteristic, green practices are the norm, openness is an essential path, and sharing is the fundamental purpose. It is an imperative for advancing high-level opening-up. A globally leading TCM regulatory excellence system must be underpinned by comprehensive innovation in TCM regulatory science, achieving accelerated review and approval throughout the regulatory process, safety oversight across the entire industrial chain, lifecycle regulatory services, and coordinated global regulatory cooperation.

As shown in Fig. 11, the construction and top-level design of the TCM excellence regulatory system comprise two components: the upper layer encompasses strategic objectives, development approaches, priority initiatives, and supporting specialized administrative regulations centered on regulatory administrative affairs; the lower layer comprises new tools, standards, methodologies, and a series of technical guidance principles underpinned by TCM regulatory science. Systematic design across five dimensions—regulatory frameworks, organizational structures, technological innovation, industrial development, and international influence—refines work content and core indicators to ensure the achievement of globally leading strategic objectives.

Evidently, establishing an exceptional regulatory system for TCM necessitates further strengthening research on new tools, new standards, and new methodologies for TCM regulatory science. This includes establishing a national coordination mechanism for full-chain TCM regulation, an international collaboration mechanism for TCM regulatory science researchers, and a global coordination mechanism for TCM registration standards and regulation. It also involves refining the regulatory and technical framework—including laws, departmental rules, normative documents, and technical guidance principles—to align with TCM characteristics. Furthermore, it supports the translation of basic research into regulatory applications, underpins evidence-based TCM regulatory decision-making, and builds an efficient, China-specific TCM regulatory organizational system.

6. New approach methodologies (NAMs) and TCM new drug research

6.1. Screening of TCM, natural medicines, and their active components for new drug discovery

Based on a comprehensive analysis of China's innovative drug R&D landscape and regulatory support system, Zhao's team[61] observed that China's strengths in biotechnology primarily manifest in the development of TCM, chemical drugs, and biological agents. Leveraging large-scale public investment and a state-supported manufacturing infrastructure, China has achieved significant progress in drug R&D efficiency, production capabilities,

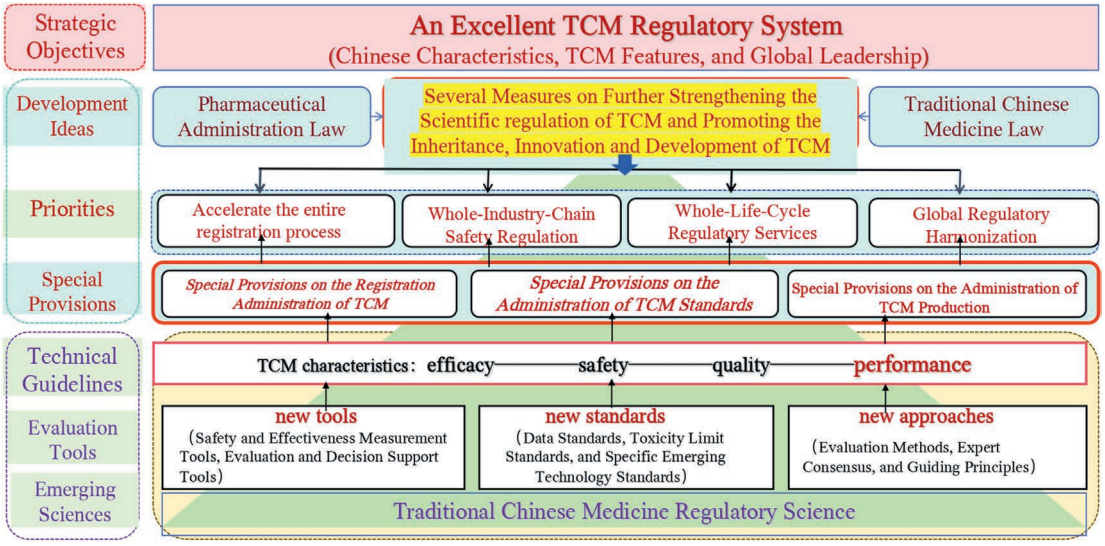

Figure 11 Construction and top-level design of an excellent regulatory system for TCM.

and cost control. TCM and its active ingredients serve as vital resources for drug discovery. To overcome the bottleneck of limited compound libraries (*e.g.*, TCMSP, TCMID), Yu et al.[62] and Chen et al.[63] constructed the world's first billion-level gene-encoded natural diversity components repository (GNDC), providing a rich source for efficient drug screening.Regarding targets, receptor proteins—such as G protein-coupled receptors (GPCRs), nuclear receptors, and ion channels—have become core targets in modern drug development. Chen et al.[64] introduced artificial intelligence into GPCR ligand discovery and optimization; Yang et al.[65] established a genome-wide pan-GPCR cell library and integrated PRESTO-Tango, CRISPR/Cas9, and cell membrane chromatography technologies to construct a high-throughput drug screening and functional validation platform; Bi et al.[66] explored traditional drug target discovery strategies from a systems perspective and proposed a novel drug development concept oriented toward GPCRs.Given the high compatibility between the multi-component, multi-target, and multi-pathway action characteristics of TCM and the complexity of GPCR signaling networks[67], utilizing GPCRome as a target library for TCM holds great promise for significantly advancing the elucidation of its mechanisms and the development of new drugs. Building upon this foundation, Zhang et al.[68] proposed a novel "drug-target co-screening" strategy. Leveraging the genome-wide pan-receptor and GNDC component databases, this strategy integrates multi-omics, artificial intelligence, and high-throughput screening technologies. Systematically applied to disease-target discovery, TCM drug design and evaluation, multi-target mechanism elucidation, and pharmacological theory research, it provides an innovative methodological framework and technical support for TCM drug discovery and evaluation. These strategies and screening systems overcome the limitations of traditional unidirectional screening models, aiming to efficiently identify novel drugs from TCM sources while enhancing R&D efficiency and success rates. They inject fresh perspectives and methodologies to address critical challenges such as unclear targets and undefined mechanisms in TCM, driving deep integration between traditional TCM research and modern technology. This approach facilitates elucidating TCM mechanisms of action and the material basis of its efficacy, establishing a new paradigm for TCM drug development and modernization research.Given the complexity of herbal medicines, Zhou and Gao[69] proposed integrating the principles of phenotype-driven drug discovery (PDD) with target-driven drug discovery (TDD) techniques, establishing a high-throughput phenotype-target-coupled drug screening (PTDS) framework. This approach enables both precise elucidation of drug mechanisms and accelerated discovery of first-in-class drugs derived from natural compounds.

6.2. Novel formulation-based drug discovery (FDD) strategy for complex diseases

The high investment and high failure rate in new drug development, known as the "Eroom's law", indicates a significant translational gap in current drug research. This gap arises from simplifying complex human systems into studyable models (reductionist approach) and ultimately returning to complex human systems for efficacy validation (systems approach)[70]. Current understanding of human diseases has shifted from monopathogenic theories to the scientific logic of systems medicine. In recent years, global innovative drug development has increasingly focused on multi-target drug design (MTDD) to address the challenges of developing new treatments for complex diseases. TCM formulas, as personalized drug combinations for clinical disease treatment with over 3000 years of history, meet human needs for systemic disease regulation through multi-drug combinations, multi-component interactions, multi-target effects, and network-based regulatory mechanisms. They have garnered significant attention for demonstrating clinical value in treating complex diseases, chronic conditions, and emerging infectious diseases.

Recent studies reveal that active components in TCM typically exist not as free monomers but rather as self-assembled nanoparticles (SANs) or exosome-like nanoparticles (ELNs) to exert synergistic pharmacological effects. Formula-derived nanoparticles of TCM (FDN), derived from TCM formulas or their constituent drugs, include TCM exosomes (TCM-Exo), TCM decoctosomes (TCM-Deco), TCM pillosomes (TCM-Pillo), TCM carbon quantum dots (TCM-CDs), TCM bencaosomes (TCM-Benc), exhibit novel physical, chemical, and biological properties at the nanoscale. These carrier-free, self-assembled nanoscale aggregates serve as ideal delivery vehicles for the complex bioactive constituents of TCM. They enhance bioavailability, improve drug targeting, reduce toxicity, and enable the delivery of all or multiple bioactive components from TCM formulas, facilitating cross-regulatory effects. The synergistic effects inherent in FDN's unique multiscale hierarchical structure—combining complex component combinations, micro/nano-body structures, and multi-target functional regulation—form a "multi-layer regulation"−"pharmacological integration"−"Moderate Regulation" system response mechanism. This enables multi-level, three-dimensional targeted regulation of complex disease dynamic networks from lower to higher orders—spanning "point (key targets)−line (signaling pathways)−plane (hub nodes)−body (disease networks)"—to achieve synergistic multi-component, multi-target therapeutic effects[71,72].

Zhao Junning, Chen Chunying, and colleagues innovatively proposed the Formula-derived Nanoparticles Drug Discovery (FDD) strategy and methodology, establishing a comprehensive disciplinary framework encompassing "fundamental theory−core technology−principle elucidation−drug evaluation" alongside a shared technological platform, which has seen initial application. Unlike current high-failure-rate approaches like Phenotypic Drug Discovery (PDD), Targeted Drug Discovery (TDD), and MTDs strategies, FDD emerges as a novel drug discovery paradigm tailored for complex disease treatment. Originating from the wisdom of Chinese formulae's sovereign−minister−assistant−messenger principles, it advances through the discovery of carrier-free self-assembling formula nanoparticles to new strategies for creating multi-target advanced therapeutics, innovatively integrates traditional Chinese formula combination theory, long-term human experience data, and modern nanotechnology methods. This approach screens and discovers FDNs with specific functions and excellent pharmacological effects, prepares FDN nanomedicines for holistic multi-component targeted delivery, and achieves the synergistic integration of PDD and TDD. It provides novel insights and solutions for overcoming technical challenges in multi-target compound drug development—such as selecting multiple active molecules and combining multiple targets—and for advancing new drug discovery. This approach significantly enhances the success rate of multi-target compound drug development, offers fresh perspectives for elucidating the mechanisms of compound drugs in managing complex diseases, and provides scientific regulatory insights for advanced therapeutic products. It better addresses challenges posed by systemic human diseases,

particularly multi-etiological complex conditions like diabetes, neurodegenerative diseases, cardiovascular diseases, and cancer[73,74].

6.3. The profound impact of model-informed drug development (MIDD) on evaluating new TCM drugs

In recent years, the pharmaceutical industry has witnessed numerous original and disruptive technological breakthroughs. The integration of medical big data and artificial intelligence (AI) has ushered in a new era of digital and intelligent healthcare. Organoid/organ-on-a-chip technology and bio-3D printing have spearheaded revolutionary advances in biopharmaceutical innovation and regenerative medicine. Innovations such as gene editing, induced pluripotent stem cell technology, and synthetic biology have opened new pathways for clinical diagnostics and novel drug development[75]. In April 2025, the FDA released a public roadmap for reforming nonclinical safety evaluation, explicitly stating that "New Approach Methodologies" (NAMs) will become a crucial supplement to the nonclinical evaluation system. These methodologies include AI-based computational models, organ-on-a-chip systems, organoid models, and other human-relevant testing systems, designed to support human safety and risk assessments at multiple levels. In December 2025, the U.S. Senate passed the FDA Modernization Act 3.0 (S.355), signaling the impending end of the nearly century-long "animal testing-centric" paradigm in global drug R&D. "Human-relevant technologies" such as AI modeling, organoids, and organ-on-a-chip will formally take the lead in nonclinical drug evaluation, ushering in a historic restructuring of the industry's regulatory framework. Its core principle is that "regulations must support alternatives to animal testing", granting non-animal models clear operational feasibility and predictability in drug review. The FDA 3.0 Act does not impose a blanket ban on animal testing but instead reconstructs regulatory language and frameworks to integrate it with cutting-edge technologies like AI models, organoids, and organ-on-a-chip into a more scientific evaluation system, providing explicit regulatory support for non-animal models. The revision's key lies in uniformly replacing regulatory terminology: expressions like "animal testing/data/research/models" in regulations are comprehensively substituted with corresponding "non-clinical" items[76-78]. In June 2025, the Center for Drug Evaluation (CDE) of China's National Medical Products Administration (NMPA) issued the landmark document "Technical Guidance on Model-Guided Rare Disease Drug Development". Data sources include but are not limited to non-clinical research data, real-world data, literature data, and pre-marketing clinical trial data. Non-clinical research data encompasses, among others, genetic, molecular, cellular, organoid, organ-on-a-chip, and animal study data. Real-world data encompasses records from clinical practice in authentic healthcare settings (*e.g.*, electronic health records) and various observational study data. Literature data includes, but is not limited to, research data on comparable drugs and drugs targeting the same molecular targets. Pre-marketing clinical trial data covers data from trials for the target indication and other indications under development. Key technologies involved include organoids, organ-on-a-chip, and computational models. Promoting high-quality development of the TCM industry and ensuring high-level safety oversight represent two major public health missions undertaken by the NMPA in advancing the inheritance and innovation of TCM. In recent years, TCM new drug development has strengthened the "evidence-based review system combining TCM theory, human experience, and clinical trials" (the "three-combination" review system) to support clinical trials and marketing applications. Driven by new methodologies (NAMs) such as AI modeling, organoids, and organ-on-a-chip, opportunities have emerged for evaluating the efficacy and safety of TCM new drugs and advancing drug development, thereby overcoming inherent limitations of traditional animal testing.

Recent advances in artificial intelligence (AI), including image recognition, natural language processing (NLP), and computer vision, demonstrate particular potential in addressing key challenges in drug development. Notably, large language models (LLMs) such as ChatGPT, DeepSeek, Grok, and Gemini, alongside generative AI like Sora, have exhibited capabilities surpassing human intelligence in certain scenarios. In recent years, AI has become a transformative force in drug discovery, revolutionizing traditional approaches including target identification, virtual screening, de novo design, ADMET (absorption, distribution, metabolism, excretion, and toxicity) prediction, synthetic planning, and automated synthesis and drug discovery. By leveraging advanced algorithms and technologies, researchers can now accelerate the discovery of novel therapeutics, enhance prediction accuracy, and reduce the overall time and cost associated with drug development. However, no AI-developed drug has yet entered Phase III clinical trials, highlighting the complexity of drug development. A key challenge is the scarcity of high-quality training data, attributed to high acquisition costs, privacy regulations, and limited data sharing—particularly for rare diseases or novel drug targets—which hinders AI's effectiveness in identifying targets, biomarkers, and other functionalities. Furthermore, existing datasets often suffer from missing information, errors, and biases, further diminishing AI reliability. Drug discovery experiments may yield inconsistent results, while cost-saving measures can lead to incomplete data. Additionally, underrepresentation of "negative" data in the literature—such as unsuccessful experiments and negative trial outcomes—hinders comprehensive understanding of drug−target−disease interactions, efficacy, and other clinical characteristics[79]. TCM, characterized by its multi-component, multi-target, and systemic regulatory properties, demonstrates unique advantages in intervening complex diseases. However, its intrinsic mechanisms are highly intricate, featuring significant nonlinear interactions among components, posing long-standing challenges in mechanism elucidation, target identification, and modern translation. Advancements in artificial intelligence, particularly the mature application of machine learning, deep learning, and large-scale modeling methods in complex data analysis, have introduced new research paradigms for systematically deciphering TCM[80]. Chen's team[81] established the TCM database TCMBank using natural language processing and other technologies. This database provides information on 9192 herbs, 61,966 components, 15,179 targets, 32,529 diseases, and their interrelationships. Based on deep learning algorithms, it predicts drug interactions and potential adverse reactions from Chinese and Western medicine combinations. This enables researchers to construct a multidimensional "drug−component−target−disease" network and employ machine learning to predict the probability of interaction between components and targets[81]. Based on the original "network target" theory, Li's group conducted in-depth research integrating artificial intelligence and network pharmacology. They successfully established a methodological framework for network relationship mining, network target localization, and network target navigation. This led to the development of the Chinese and Western

Medicine Molecular Network Navigation System—the UNIQ (Using Network Target for Intelligent and Quantitative Analysis on Drug Actions) system. This system establishes a multi-level network spanning "phenotype−cell−molecule−drug" for both Chinese and Western medicine, enabling a panoramic interpretation of TCM's scientific principles. Utilizing the UNIQ system, they predicted effective therapeutic drugs for key pathways in diseases like rheumatoid arthritis. Integrating TCM theory with the academic experience of renowned senior practitioners, they optimized the Qingluo Decoction to develop a new prescription: Jiawei Qingluo Decoction. Based on the platform and big data, a multimodal multi-omics AI algorithm (AI-TWM) integrating Chinese and Western medicine was developed to decipher diagnostic and therapeutic patterns related to gastritis-to-cancer progression. This established an intelligent "ultra-early" gastric cancer identification system, providing crucial evidence for risk warning and prevention of gastritis-to-cancer progression[82,83]. Cheng's group established a large-scale dataset of mitochondrial dynamic phenotypes in cardiomyocytes under drug effects by integrating AI algorithms such as pedestrian re-identification and random walk analysis independently developed new tools including MitoReID, scRank, and scCube. They successfully identified effector cells and action targets for active components in TCMs such as tanshinone IIA and epicatechin, overcoming limitations of traditional omics technologies like low efficiency and insufficient resolution. This achievement enables intelligent identification of action targets for TCMs based on phenomics and single-cell transcriptomics data. This advancement provides new tools for large-scale omics data and offers novel methodologies for elucidating the scientific essence of TCM[84]. Cheng's group proposed a novel TCM development model—targeted formula design—based on targeted transcriptomics technology. They constructed a large-scale database of medicinal molecular effects and developed the Intelligent Prescription Generation System (IPGS), applying artificial intelligence and omics-driven large-scale TCM molecular efficacy databases for intelligent formula design. Using viral and immune dysregulation signaling pathways in severe COVID-19 patients as targets, they quantitatively evaluated 125 TCM formulas nationwide for COVID-19 treatment. The study assessed the regulatory effects of 166 herbal ingredients on 11 viral pathways in human macrophage cell lines. Results revealed that 98 formulas downregulated viral pathways, demonstrating potential to suppress cytokine storms. This provides internationally recognized scientific evidence for TCM's role in COVID-19 treatment[85].

The newly developed human-relevant experimental systems primarily include models such as human cells and tissues engineered *in vitro*, model organisms, and organoids. These aim to simulate physiological environments and disease states within the human body, supporting drug development and research into disease mechanisms. Since the first organoid was cultured from tissue in 2009, related research has gradually matured and diversified. These tissue-like three-dimensional (3D) structures can be generated from various sources, including differentiated pluripotent stem cells, fetal and adult primary tissues, and primary and metastatic tumors[86]. Cao et al.[87] investigated the effects of the anti-tumor formula ZMYL on ovarian cancer organoids. This formula simultaneously targets drivers of tumorigenesis (*e.g.*, cell cycle regulators) and immune checkpoints (*e.g.*, the CXCL10-mediated T-cell recruitment pathway) within ovarian cancer organoid models, offering a novel strategy for precision treatment of ovarian cancer. Zhu et al.[88] established an ischemic stroke model using brain organoids derived from human pluripotent stem cells. They validated that Dengzhi Shengmai Capsules regulate lipid metabolism, hormonal responses, cytoskeletal organization, and expression of neurodevelopment-related proteins following cerebral ischemic injury, exerting beneficial effects on ischemic stroke. Organ-on-a-chip devices serve as "organ simulators" integrating microfluidic technology and biosensors. For instance, heart-on-a-chip systems enable real-time monitoring of drug effects on myocardial contractility[89], while blood−brain barrier chips assess drug permeability or toxicity[90]. Lin et al.[91] established microfluidic liver and kidney chip models to comprehensively evaluate the hepatotoxicity and nephrotoxicity of Bupleurum and Rheum. They validated that the trends in pathway alterations associated with lipid metabolism disorders induced by Rheum and Bupleurum in animals were consistent with those observed in microfluidic liver and kidney organ-on-chips. Zhao et al. proposed a novel method for detecting and evaluating minor toxicity/activity in TCM, addressing the limitations of conventional toxicological testing in reflecting the "complex toxicity" and safety risks associated with TCM's "complex composition". Based on the luminescent bacteria Microtox technology, they developed fully automated detection equipment for minor drug toxicity and risk early warning, along with a TCM quality control testing kit. This approach enables simultaneous acquisition of multiple quantitative parameters such as IC_{50} values, standard toxicant reference values, and concentration−response curves. It also serves as a bio-fingerprint spectrum for drug toxicity, tests toxic efficacy and potency, comprehensively characterizes drug toxicity profiles, and functions as a sensitive indicator for quality control and risk early warning. This approach supplements and enhances existing quality control standards, ensuring the safety and efficacy of TCM clinical applications. Microtoxicity testing was conducted on 29 herbal materials (including *Aconitum carmichaeli*, *Aconitum kusnezoffii*, and *Strychnos nux*-vomica), 18 herbal injections (such as *Carthamus tinctorius* injection, *Panax ginseng* and Ophiopogon injection, and *Salvia miltiorrhiza* injection), and 3 proprietary Chinese medicines (including Hyperthyroidism Relief Capsules, Nasal Sinus Relief Oral Liquid, and Duliang Soft Capsules). This achieved the standardization, automation, intelligence, and informatization of microtoxicity and risk warning detection for herbal materials, herbal slices, and proprietary Chinese medicines. This holds significant importance for further enhancing the quality of Chinese medicine and ensuring the safety of clinical drug use[92-94].

In summary, "non-clinical trials" for TCM focus more on "human-relevant technologies" such as AI modeling, organoids, and organ-on-a-chip for evaluating TCM efficacy and safety. For TCM compound formulations with sufficient theoretical support and human experience, pharmacodynamic studies may be exempted when applying for clinical trials and/or marketing authorization. For new TCM drugs where human experience is insufficient to support clinical trials, non-clinical pharmacodynamic studies must be conducted prior to clinical trial applications. Pharmacodynamic research should closely align with the drug's clinical positioning and/or therapeutic indications. For single-component TCM formulations, primary pharmacodynamic studies should include mechanism-of-action research. For products supported by the "three-combination" evidence system for clinical trial and marketing authorization applications, interpreting TCM principles through modern science during clinical trials and post-marketing, and elucidating TCM efficacy characteristics and/or mechanisms of action using modern pharmacological research

methods, can provide support for more targeted, safe, and rational clinical use[95,96]. Therefore, the complexity of TCM determines that no single model can resolve all nonclinical evaluation issues; the focus should be on the holistic evidence system. Upgrading to a higher-order model centered on "reconstructing nonclinical evaluation portfolios around human relevance", the role of animal studies shifts from being the "sole core evidence" to becoming part of the overall risk assessment. Sponsors must increasingly address whether the submitted nonclinical evidence reasonably supports judgments about human risks.

7. Summary: further discussion on TCM innovation and regulatory challenges

In 1996, the State Science and Technology Commission and the State Administration of TCM initiated research on the "Strategy for Modernizing TCM", explicitly proposing four major strategies for implementing the "Science and Technology Industrial Action Plan for Modernizing TCM": (1) Research and development of modern TCM. (2) Establish a TCM research and development system. (3) Foster a science-driven TCM industry. (4) Promote TCM's entry into international markets [97]. Over the subsequent three decades, China achieved significant progress in TCM basic research, TCM resource conservation and sustainable utilization, TCM standardization and industrialization, new drug development, and the internationalization of TCM. The 2006 National Medium- and Long-Term Science and Technology Development Plan (2006−2020) deployed 16 major national science and technology projects. Among these, the Major New Drug Innovation Project was jointly organized and implemented by the former National Health and Family Planning Commission and the Logistics Support Department of the Central Military Commission, spanning from 2008 to 2020. This initiative focused on advancing technological upgrades and clinical re-evaluation of major TCM varieties, achieving breakthroughs in core technologies such as precise clinical positioning of TCM formulations and digitalized end-to-end quality control It comprehensively enhanced TCM production techniques and quality standards, fostering over 500 TCM varieties with annual sales exceeding 100 million yuan each, thereby accelerating the internationalization of TCM[98-100]. Statistics indicate that scientific research output in the TCM field experienced rapid growth from 2014 to 2023, achieving a compound annual growth rate (CAGR) of 10.6%, significantly surpassing the global medical field's CAGR of 3.5% during the same period. Since 2022, annual global TCM research output has exceeded 30,000 papers, with 14.2% of TCM research papers being highly cited—also higher than the global average. Research in TCM is no longer confined to complementary and alternative medicine. It has long transcended traditional disciplinary boundaries, increasingly intersecting with fields such as oncology, immunology, genetics, and molecular biology. This convergence drives the development of innovative drug delivery mechanisms and advances the modern application of active components in TCMs[101].

With the widespread application of emerging R&D technologies—such as AI-enhanced drug discovery, nanomedicine, DEL technology, organoid technology, human cell lines, organoids, organ-on-a-chip, and microfluidics—in replacing animal models for developing new TCM drugs, alongside innovations in TCM production, including novel approaches to obtaining drug substances, advanced process control and automation, additive manufacturing, modular systems, and integrated, flexible, distributed manufacturing networks, national drug regulatory authorities and technical review departments inevitably face numerous challenges encompassing specialized knowledge, technical capabilities, innovation promotion, health needs, safety oversight, and cultural heritage preservation. The tension between technological innovation and regulatory management is evident[6,39,102,103]. First, from the perspective of production innovation, the development of new TCM drugs is driven by both R&D technological innovation and advanced production technologies. The significant pull from industry and investment inevitably raises concerns within the sector that stringent regulation may hinder innovation. Second, from the perspective of scientific project management, the high uncertainty of new drugs poses significant challenges to management mechanisms. National major science and technology projects prioritize the realization of technological innovation in their management. The traditional linear performance management system can only optimize project performance itself but suffers from strong lag and difficulty in adaptation. Project management urgently requires dynamic management transformation. Based on a thorough deconstruction of the high uncertainty inherent in major national science and technology projects, we must analyze the management practices of the Major New Drug Innovation Program. This involves constructing an uncertainty model from three dimensions: project timeline, project process, and project output[104]. Third, from the perspective of drug safety regulation and health protection, the rapid advancement of innovative technologies necessitates vigilance against risks and safety hazards. Establishing safety oversight tailored to the characteristics of TCM is particularly crucial. Addressing long-standing industry criticisms regarding TCM review and approval—such as "applying Western standards to Chinese medicine", "excessive focus on ingredients", and "inefficient review processes"—requires integrating scientific research and regulatory science into TCM oversight. This accelerates the development of a globally leading, China-specific TCM regulatory system that aligns with TCM characteristics, reflecting the responsibility and mission of national TCM regulatory authorities. We must fully respect the characteristics and development patterns of TCM, innovate a "three-combination" evidence system for TCM registration review, and achieve high-level safety regulation while promoting high-quality industrial development[1]. In short, the impact of incentive or disincentive measures on new drug innovation is evident. Although the contradictions and challenges between technological innovation and safety regulation pose obstacles, none may be greater than insufficient, counterproductive, or adverse incentives[105]. Beginning in July 2025, a new 10-year Major New Drug Development Program will focus on national priorities, targeting the research and development of new drugs for four major chronic diseases, major infectious diseases, pediatric diseases, rare diseases, and special therapeutic scenarios. The overall task design of this major initiative is structured around four key areas: First, the creation of major new drug varieties, concentrating on diseases categorized as "two major and three special" to align with medication needs; Second, basic research oriented toward new drugs, discovering and validating new drug targets, innovative treatment methods, establishing new research paradigms, and developing distinctive theories; Third, breakthroughs in key core technologies, concentrating on major shared technologies and frontier-leading innovations essential for drug creation to upgrade modern pharmaceutical engineering capabilities. Fourth, resource platform development, establishing national-level critical resource platforms and core databases to

support drug innovation, conducting strategic research on pharmaceutical R&D, formulating medical innovation policies, and comprehensively advancing high-quality development in the sector. By 2035, establish a self-reliant, efficient, and robust national drug innovation system. Achieve breakthroughs in major core technologies for developing new biopharmaceuticals, chemical drugs, and TCMs. Create a portfolio of high-level innovative drugs with clinical value tailored to China's disease spectrum. Advance China's comprehensive innovation capabilities across the entire drug R&D chain to the forefront globally[106].

In summary, driven by the dual engines of "regulatory science" and "policy restructuring", China's development of new TCM drugs has accelerated significantly over the past five years. Both the quantity and quality of IND and NDA registrations for new natural TCM drugs have shown rapid growth, effectively meeting the public's health demands for TCM products and addressing unmet clinical needs of patients. As the key authority overseeing drug regulation, product approval, and the adoption and implementation of new technologies and products, the NMPA evaluates drug marketing applications based on safety, efficacy, and quality control. The ultimate goal of this comprehensive assessment is to ensure overall benefits outweigh risks. Benefit-risk assessment is crucial throughout a drug's lifecycle management, directly determining market approval, appropriate usage, and patient health outcomes. The most vital role of regulatory science is to conduct risk-benefit assessments for innovative products, balance stakeholder interests, and provide support for risk management. The NMPA's technical guidance principles for benefit-risk assessment of new drugs established qualitative assessment frameworks for chemical drugs and biological products. However, for uncertainties and complex scenarios—including the principles for constructing benefit-risk assessment systems for TCM, indicator frameworks, and the unique aspects of such evaluations—there remains an urgent need to develop new tools, standards, and methodologies for TCM regulatory science. The primary challenge in managing the registration of new TCM drugs lies in resolving conflicts between traditional TCM theories and modern pharmaceutical attributes. It is crucial to balance traditional medical theories, the rapid advancement of emerging technologies, and the robustness of the drug regulatory framework. Innovatively constructing a benefit-risk assessment system and standard system for new TCM drugs is particularly important[107].

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Author contributions

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Conflicts of interest

The authors declare no conflicts of interest.

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