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RESEARCH

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Advancing human-use experience for real-world evidence for the registration of traditional Chinese medicine products in China

Mingge Xia[1], Yan Xue[1], Luwei Zhu[2], Xianwen Chen[1], Carolina Oi Lam Ung[1,3,4], Sheng Han[5,6], Yunfeng Lai[7*] and Hao Hu[1,3,4*]

Abstract

Background The registration application of traditional Chinese medicine (TCM) products as new drugs often meets the challenges of lacking clinical evidence from randomized controlled trials (RCT). In recent years, China has introduced a new evidence system for the review and approval of TCM products, which proposed using human-use experience (HUE) for real-world evidence (RWE) to support the safety and effectiveness of TCM.

Purpose This study aimed to comprehensively analyse the regulatory concerns, policy guidances, and approved cases of using HUE to register TCM products.

Methods Literature search and thematic analysis were conducted to identify and synthesize the regulatory concerns. A documentary analysis of policy guidances was employed to present the evolving regulatory framework for incorporating HUE into TCM registration in China. Case studies of approved TCM products using HUE to support registration were conducted, and the study design, study population, and postmarked requirements of these cases were analyzed.

Results Four main themes and 12 sub-themes regarding regulatory concerns of applying HUE in the registration of TCM products were identified. The 4 main themes are HUE quality, HUE applicability, HUE governance, and HUE regulation. Six policy documents and seven technical guidances were released to facilitate the application of HUE in TCM registration, founding a practical regulatory framework for TCM product registration. In China, six cases that employed HUE to support registration were approved. Of these, five cases utilized HUE to support direct registration, while one utilized HUE to lay the foundation for subsequent phase III clinical trial. Regarding study design and data types, retrospective observational studies were the predominant approach and electronic health records from the hospital information systems were the most commonly used data source. Among the five cases of direct registration, three relied solely on retrospective observational studies, while two conducted small-sample prospective studies in conjunction with retrospective observational studies.

*Correspondence:
Yunfeng Lai
yunfeng.lai@hotmail.com
Hao Hu
haohu@um.edu.mo
Full list of author information is available at the end of the article

Conclusion HUE can be advanced to generate RWE for the safety and effectiveness of TCM products, which provides potential support for registering new TCM products. Leveraging HUE for registration can shorten research and development period, reduce development costs, and promote innovation, ultimately driving the growth of the TCM industry. However, several challenges remain in using HUE to support the registration of TCM products in China, including difficulties in data accessibility, lack of standardized protocols for HUE collection and reporting, and obstacles in transforming TCM preparations from hospitals into new TCM products using HUE. Furthermore, ensuring high-quality HUE requires future attention to data applicability, data infrastructure, and research design.

Keywords Human-use experience, Real-world evidence, Traditional Chinese medicine, Regulatory decision

Introduction

The registration application of traditional Chinese medicine (TCM) products as new drugs often meets the challenges of lacking clinical evidence from randomized controlled trials (RCT) [1, 2]. TCM products typically include a combination of herbs, animal ingredients, and minerals materials. The methods used in their manufacturing and the standards for quality management can vary greatly from those applied to chemical and biopharmaceutical drugs [3]. Additionally, TCM has a unique theoretical system and approach to diagnosis and treatment, making it difficult to evaluate the safety and efficacy through RCT [2].

In recent years, the concept of real-world evidence (RWE) has gained traction in the field of drug development and regulatory decision-making. RWE, derived from real-world data (RWD), encompasses extensive data sources beyond RCT, such as electronic health records, insurance claims, patient registries, and observational studies [4]. The utilization of RWE has been increasingly recognized for its potential to complement RCT by providing additional insights into the safety and effectiveness of medical products in real-world settings. This paradigm shift has been particularly notable in the regulatory frameworks for chemical and biopharmaceutical drugs, where RWE has been employed to support registration applications and post-marketing surveillance [5, 6]. With thousands of years of history, TCM has amassed vast empirical knowledge and a significant repository of RWD through its application in disease prevention and treatment. This presents an intriguing opportunity for integrating evidence from RWD into its regulatory framework. However, despite the growing acceptance of RWE in the broader pharmaceutical landscape, its application in the registration of TCM products remains underdeveloped and less explored.

The nature of TCM implies its integral requirements of clinical practices [7]. In recent years, China has proposed a new evidence system for the review and approval of TCM products, which emphasized the combination of TCM theory, human-use experience (HUE), and clinical trials (referred to as"Three Combinations") [8]. Of these, HUE refers to a holistic and integrated approach considering the eligible population, clinical targeting, usage and dosage, efficacy and safety profiles, and clinical benefits of TCM formulas or preparations accumulated during clinical practice. Data of HUE is mainly comprised of clinical practice data, which is, in essence, identical to the concept of RWD. Obtaining HUE involves gradually exploring and clarifying real-world data on the efficacy, safety, and clinical benefits of TCM products [9]. HUE can help fill the gaps left by traditional RCTs by offering insights into treatment effectiveness in diverse, real-life populations, capturing long-term outcomes, and reflecting routine clinical practices that RCTs, with their controlled settings and strict inclusion criteria, often overlook [4]. By adopting a comprehensive and systematic approach to incorporating HUE, regulatory authorities can better examine the registration applications of TCM products, ensuring their safety, efficacy, and quality. Furthermore, this integration can potentially shorten the research and development cycle, reduce costs, and enhance the overall efficiency of TCM product development.

While some trial guidance documents are being launched, China is still in the initial and exploratory stage of making better use of HUE to support the development and registration of TCM products. Lin et al. [10] discussed the opportunities and challenges encountered by clinical pharmacists of TCM in the development of new drugs under the"Three Combinations"system. Yang et al. [11] shared considerations about using real-world study and human use experience in research and development of new TCM drugs. However, studies focused on regulatory considerations of HUE are limited. There is an urgent need for regulatory agencies to strengthen the regulatory system of “Three Combinations” by clarifying the requirements and standards of HUE to facilitate the development of TCM.

Therefore, this study aimed to comprehensively analyse the regulatory concerns, policy guidances, and approved cases of using HUE to register TCM products. Specific objectives include: (1) to synthesize regulatory concerns from the published articles related to the use of HUE in TCM products; (2) to identify and examine the policy

guidances to present the evolving regulatory framework for incorporating HUE into TCM registration applications in China; (3) to analyse cases where HUE was applied to support the registration of TCM products. It is expected that the findings of this research will contribute to the regulatory science subfield of drug registration to enrich the practices of advancing the HUE for RWE in registration applications of complementary and alternative medical products.

Methods

Research design

The study employed a mix-methods approach, including literature search and thematic analysis of published articles, documentary analysis of government policies and technical guidance documents issued by regulators, and case studies on the use of HUE in the registration applications of TCM products, as shown in Fig. 1.

literature search and thematic analysis

Firstly, we searched the PubMed, Web of Science, CNKI, and WANFANG databases for and included articles related to the application of HUE or RWE in the registration and regulatory decisions of TCM products (The search term identifiers and search strategy were provided in the supplementary table). The exclusion criterion included: (1) commentaries, study protocols, letters, editorial material, and conference abstracts or posters; (2) studies unrelated to registration or regulatory decisions; (3) article content does not involve TCMs product; (4) the language is neither English nor Chinese.

For the included articles, qualitative study findings were synthesized using applied thematic analysis to identify the regulatory concerns of using HUE in the registration application of TCM products [12]. Data was extracted from the aim, results and discussion sections of each article and documented using Microsoft EXCEL. We used a descriptive narrative approach to present the findings according to each theme of regulatory concerns. The synthesis of findings is presented in the results section of this study.

Documentary analysis on government policies and technical guidances

By searching official Chinese government websites, the study reviewed the government policies and technical guidance documents regarding the generation, evaluation, and application of HUE or RWE for registration and regulatory decisions of TCM products. The official sources reviewed included: The State Council, The People's Republic of China (http://english.www.gov.cn/), The National Administration of Traditional Chinee Medicine (http://www.natcm.gov.cn/), The National Medical Products Administration (NMPA) (https://www.cde.org.cn/) and The Center for Drug Evaluation of NMPA (http://english.nmpa.gov.cn/). We applied documentary analysis

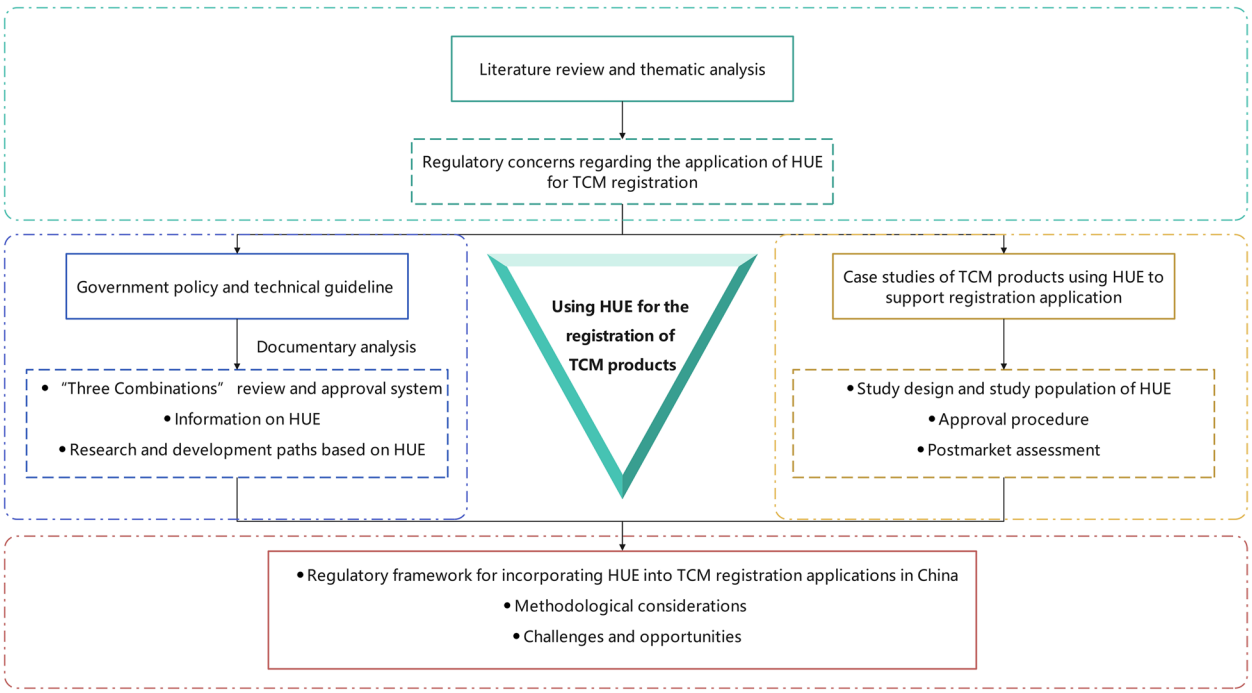

Fig. 1 Research design

to extract information from these documents and summarized the evolving regulatory framework for incorporating HUE into TCM registration applications in China.

Case study

Finally, cases of using HUE to support registrations were collected from official Chinese government websites. Additional searches were conducted to obtain related empirical studies for more detailed information. The following information was extracted from the included case: product name, year of approval, approval institution, type of regulatory decision, classification of TCM registration, and HUE used for registration application. The study design, study population, and postmarked requirements of HUE were further explored. Data extraction from eligible documents and studies was conducted independently by two researchers. Any disagreements between the two researchers were resolved through discussion and with the help of a third researcher. Data were extracted and documented by Microsoft Excel.

Results

Results from thematic analysis of recent literature

Included studies

After a systematic search in the databases, 455 articles were identified. The automatic and manual duplication removal discarded 34 records. After title-abstract screening and full-text assessment, 37 articles related to using HUE to support registration application of TCM were included, of which 4 in English and 33 in Chinese (Fig. 2).

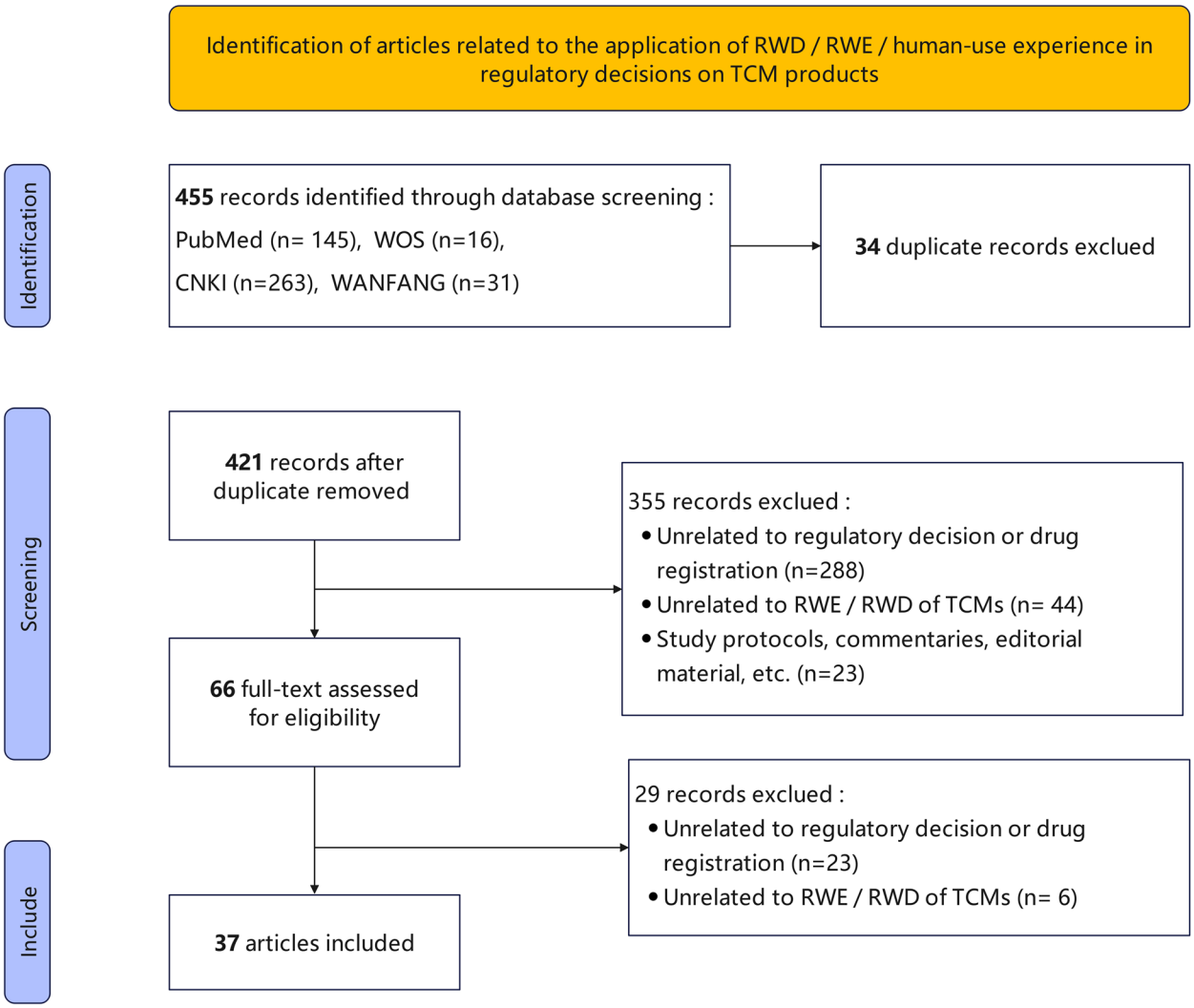

Fig. 2 Flow-chart of article selection

Regulatory concerns regarding the application of HUE for TCM registration

Using thematic analysis, we identified 4 main themes and 12 sub-themes of regulatory concerns regarding the use of HUE for TCM registration, as shown in Table 1. The 4 main themes include HUE quality, HUE applicability, HUE governance, and HUE regulation.

Among these, HUE quality is the primary concern, which was mentioned in more than half of the included literature [11, 13–36]. Quality is a fundamental element in determining whether HUE can be used to support regulatory decisions, and the quality of HUE directly affects the strength of evidence for HUE. Moreover, three sub-themes under the theme of HUE quality were identified: 1) standardized collection and curation of data; 2) appropriate study design and statistical analysis; and 3) report and reasonable interpretation of results. The standardized collection and curation of data are essential for ensuring high-quality datasets. Appropriate study design and statistical analysis are critical for interpreting data collected in real-world settings, establishing causal relationships, testing hypotheses, and generating regulatory-grade HUE to guide policymakers and regulators in decision-making. Clear reporting and reasonable interpretation of HUE findings can further enhance the clarity and completeness of HUE studies.

The applicability of HUE is another main theme, emphasizing the integrity of HUE and TCM products, clear clinical targeting and applicable population, multidisciplinary collaboration, as well as the harmonization and standardization of HUE/TCM terminology. The consistency between HUE and TCM products lies in the alignment of a proposed new drug with practical outcomes observed in HUE. This includes prescription composition, function indications, usage and dosage, preparation method, and primitive medicinal materials [17, 20, 26, 34, 35, 11, 37]. Clinical targeting refers to the indications of the target population of TCM products, which should be accurate. Besides, the applicable population should be clearly defined, including information such as gender, age, disease condition, course of disease, stage, and TCM syndrome. Clear clinical targeting and applicable population are essential for the successful development of new drugs [22, 26, 36, 38]. Multidisciplinary collaboration among stakeholders is also important, as advancing the integration of HUE into TCM registration necessitates collaborations among industry professionals, clinical practitioners, research institutions, and regulatory authorities.

HUE governance and HUE regulation are another two main themes concerned by scholars. HUE governance focuses on the data sources of HUE information, as well as ethical compliance and privacy protection of patient information [15, 16, 18, 22, 35, 39]. HUE regulation emphasizes the optimization of policy and technical guidelines, communication with regulatory authorities, and the post-marketing requirement [24, 30, 31, 40]. Post-market requirement plays a critical role in all phases of a drug's lifecycle. For TCM drugs using HUE to support registration applications, challenges are magnified as HUE often involves greater bias and confounding factors compared to RCT. Therefore, post-market requirements should be strongly emphasized in the approval process, particularly for TCMs containing toxic herbs or incompatible components [29, 41].

Table 1 Themes and sub-themes of regulatory concerns regarding the application of HUE for TCM registration

Main themes	Sub-themes
HUE quality	• Standardized collection and curation of data
	• Appropriate study design and statistical analysis
	• Report and reasonable interpretation of results
HUE applicability	• Consistency between HUE and TCM products
	• Clinical targeting and applicable population
	• Multidisciplinary collaboration
	• Harmonizing and standardizing HUE/TCM terminology
HUE governance	• Data sources
	• Ethical compliance and privacy protection
HUE regulation	• Optimization on policy and technical guideline
	• Communication with regulatory authorities
	• Post-marketing requirement

Findings from documentary analysis on government policies and technical guidelines

In recent years, China has issued a series of policy and technical guidance documents to guide the research, development, and registration of TCMs, aiming to construct a more holistic evidence system for evaluating and registering TCM products that align with their unique characteristics. Our search on the official Chinese government websites resulted in six policy documents and seven trial versions of technical guidance documents related to the application of HUE. These documents'detailed information and main contents were extracted and summarized in Tables 2 and 3.

Three combinations: the novel review and approval system tailored for TCM product

In October 2019, the State Council of China issued the *Opinions on Facilitating the Inheritance, Innovation and Development of Traditional Chinese Medicine*, which purported to reform and improve the management of TCM registration, optimize the classification of TCM

Table 2 Government policies regarding the application of HUE for registration and regulatory decisions of TCM products

Years	Institution	File names	Main contents
2019	The State Council	*Opinions on Facilitating the Inheritance, Innovation and Development of Traditional Chinese Medicine*	• Reforming and improving the management of TCM registration • Optimizing the classification of TCM registration • Improving the methods and technical standards for evaluating the safety and efficacy of TCM in alignment with its unique characteristics • Accelerating the establishment of a review and approval system of TCM registration combining TCM theory, HUE and clinical trials
2020	NMPA	*Implementation Opinions on Facilitating the Inheritance, Innovation and Development of Traditional Chinese Medicine*	• Emphasizing the role of HUE in supporting safety and effectiveness of TCM, and establishing the review and approval system of TCM registration combining TCM theory, HUE and clinical trials • Enhancing the normative collection and curation of HUE, standardizing the requirement for registration materials • Introducing RWE to support the registration application of TCM • Encouraging the implementation of patient-centered assessment of TCM
2021	The State Council	*Notice on Accelerating the Development of Traditional Chinese Medicine Characteristics*	• Establishing the review and approval system of TCM registration combining TCM theory, HUE and clinical trials • Exploring the RWE system of TCM
2021	The State Council	*Opinions on Comprehensive Strengthening of Drug Regulatory Capacity Building*	• Attaching importance to the application of evidence-based medicine and exploring real-world research on TCM
2023	NMPA	*Notice on Several Measures to Further Strengthen the Scientific Regulation of Traditional Chinese Medicines and Promote the Inheritance, Innovation and Development of Traditional Chinese Medicines*	• Encouraging medical institutions to adopt big data, artificial intelligence, real-world research, and other technical approaches to carry out research on TCM preparations in terms of clinical orientation, applicable population, dosage and administration, course of treatment, and evaluation indicators reflecting the characteristics and advantages of TCMs • The supporting role of HUE in the safety and effectiveness of TCM preparations shall be leveraged to support the transformation of medical institutions' TCM preparations with definite curative effects, obvious characteristic advantages, and few adverse effects into medicinal products
2023	NMPA	*Special Provisions for Traditional Chinese Medicines Registration*	• Clarifying the registration classification and requirement of TCM • Specifying the status and scope of HUE in TCM development and registration • Providing guiding recommendations for the rational application of human-use experience • Encouraging the implementation of real-world studies, novel biomarkers, alternative endpoint decisions, patient-centered drug development, adaptive design, and enrichment design to evaluate the efficacy of TCM

Table 3 Technical guidelines regarding the application of HUE and RWE for registration and regulatory decisions of TCM products

Years	Institution	Guidelines	Main contents
2020	NMPA	*Technical Guideline on Using Real-World Evidence to Support Drug Development and Regulatory Evaluation(Trial)*	• Clarifying the relevant definitions of RWE • Proposing to utilize RWE to support the clinical development of TCM with human-use experience
2021	NMPA	*Technical Guideline on Using Real-world Data to Generate Real-world Evidence (Trial)*	• Clarifying the sources and current status of RWD • Providing specific requirements and guiding recommendations for RWD in terms of curation, evaluation, governance, standards, safety compliance, and applicability
2022	NMPA	*Technical Guideline for Clinical Research and Development of New Drugs of Traditional Chinese Medicine Compound Preparations Based on Human Use Experiences (Trial)*	• Information on human-use experience • Curation and evaluation of clinical practice data of human-use experience • Strategies for clinical research and development of TCM based on human-use experience • Clinical study design based on human-use experience
2022	NMPA	*Technical Guideline for Communication under Registration Review Evidence System Based on "Three Combinations" (Trial)*	• Core issues discussed at the communication meeting for TCM registration under the"three combination"system
2023	NMPA	*Technical Guideline on the Design and Protocol Development of Real-World Studies for Drugs (Trial)*	• Introducing main types of designs for RWS and framework of RWS protocols • Providing considerations for RWS designs, including feasibility of RWS, representativeness of the target population, hybrid study design, and target trial emulation
2023	NMPA	*Technical guideline for communication of real-world evidence support to drug registration applications (Trial)*	• Core issues discussed at the communication meeting • Requirement for communication materials
2023	NMPA	*Technical Guidelines on Chemistry, Manufacturing, and Controls (CMC) Studies of New Drugs of Traditional Chinese Medicine Compound Preparations Based on Human Use Experiences (Trial)*	• Providing recommendation for applicants to conduct CMC research of new drugs of TCM compound preparations based on HUE, mainly focused on formulation, preparation process, dosage form, quality standard and control, stability and bridging study

registration, and facilitate the establishment of a review and approval system for TCM registration that integrates TCM theory, HUE and clinical trials [42].

At the end of 2020, NMPA issued the *Implementation Opinions on Facilitating the Inheritance, Innovation and Development of Traditional Chinese Medicine,* which emphasized the role of HUE in supporting the safety and effectiveness of TCM [43]. The document proposed enhancing the normative collection and curation of HUE and called for the development of methods and technical standards to evaluate TCM efficacy in alignment with its unique characteristics. It also encouraged the adoption of patient-centered evaluation approaches and the exploration of RWE to support TCM registration applications.

Subsequently, additional policy documents were released to further promote the "Three Combinations" system, as summarized in Table 2. In 2023, the *Special Provisions for Traditional Chinese Medicines Registration* was released [44]. These provisions clarified that HUE, when accompanied by reasonable and sufficient data analysis and correct interpretation of results, could be used as evidence to support registration applications of TCM products. The policies further emphasize the importance of HUE in supporting the effectiveness and safety of TCM. Collecting and synthesizing HUE data to generate reliable evidence that can be employed for assessment becomes a crucial step in TCM research and development.

Classification of TCM registration

According to the *Special Provisions for Traditional Chinese Medicines Registration,* registration of TCMs is divided into four categories: innovative TCMs, modified new TCMs, compound preparations of TCMs based on ancient classic prescriptions, and TCMs with identical names and formulas (as marketed TCMs), as shown in Fig. 3.

Innovative TCMs refer to the new TCMs prescription preparations that have clinical value and have not been marketed, and whose prescriptions are not included in the *National Drug Standards*, *National Drug Registration Standards*, or *Directory of Ancient Classic Formulas of Traditional Chinese Medicines* issued by the National Administration of Traditional Chinese Medicine. For the registration of innovative TCMs, besides sufficient evidence of effectiveness and safety, randomized controlled clinical trials shall be carried out in principle before being approved.

Modified new TCMs refer to preparations that change the administration route and dosage form of marketed TCMs, with clinical application advantages and characteristics, or added functions and indications. The

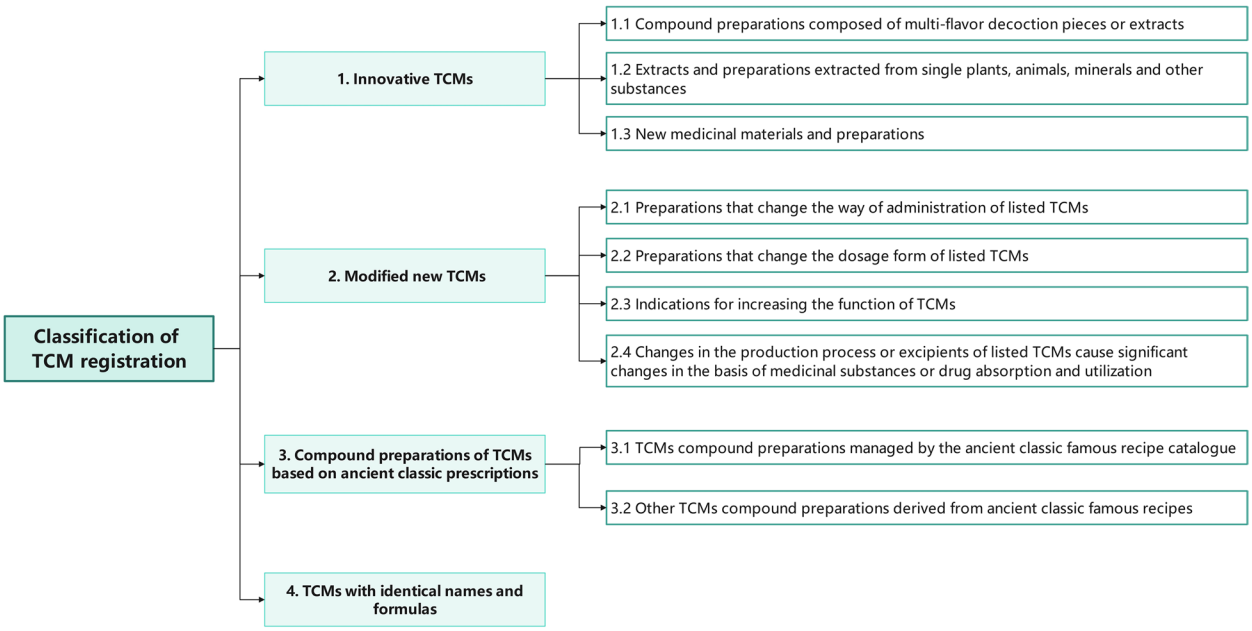

Fig. 3 Classification of TCM registration

research and development of modified new TCMs shall have a clear justification for modification. If the new application is to add indications to a marketed TCM with the support of HUE, data on non-clinical efficacy trials are not required.

The third category in the classification is compound preparations of TCMs based on the ancient classic prescriptions, which refer to the prescriptions recorded in ancient TCMs classics that conform to the regulations of the *Law of the People's Republic of China on Traditional Chinese Medicines* and are still used in current practice, these products often have definite curative effects and have obvious characteristics and advantages. This category adopts the review procedure relying on expert opinions, with HUE playing an important role in supporting safety and efficacy for this category. The review committee of experts, mainly composed of TCM experts, academicians, and regulators, conducts a technical review on the preparation, and gives technical review opinions on whether to approve it for the market.

Information required for HUE

According to the *Technical Guideline for Clinical Research and Development of New Drugs of Traditional Chinese Medicine Compound Preparations Based on Human Use Experiences (Trial)* released by NMPA, HUE is generated in the process of clinical practice of fixed TCM formulas or TCM compound preparations supported by TCM theory, after the formula ingredients (including base, medicinal site, preparation), dosage, clinical targeting are basically clear, accumulated by a longer period of time and a larger population range of clinical use [45]. HUE primarily comprises of four key aspects of information: (1) the source and evaluation of formulas, (2) essential pharmaceutical data, (3) clinical usage, and (4) clinical practice data (Fig. 4).

The source and evolution of formulas of TCM compound preparations encompass the source of formulas, the underlying TCM theories, formula ingredient's dosage, dosage form, intended functional indication scope, applicable populations, dosage and administration, treatment duration, and whether they include toxic herbs or incompatible components. Essential pharmaceutical data includes but is not limited to: formula ingredients (including base, application site, and preparation methods), dosage form, preparation process, and its changes and evolution. Clinical usage refers to the complete clinical use of TCM compound preparations from the original formula to the preparation under application and its evolution. It involves details such as the medical institutions where they are used, the initial date of use, the departments involved, the primary target population, the number of patients treated, the doses administered, and adverse reactions. For clinical practice data, primarily originate from clinical records stored in hospital information systems and medical record databases, encompassing structured and unstructured data, and digital and non-digital medical records.

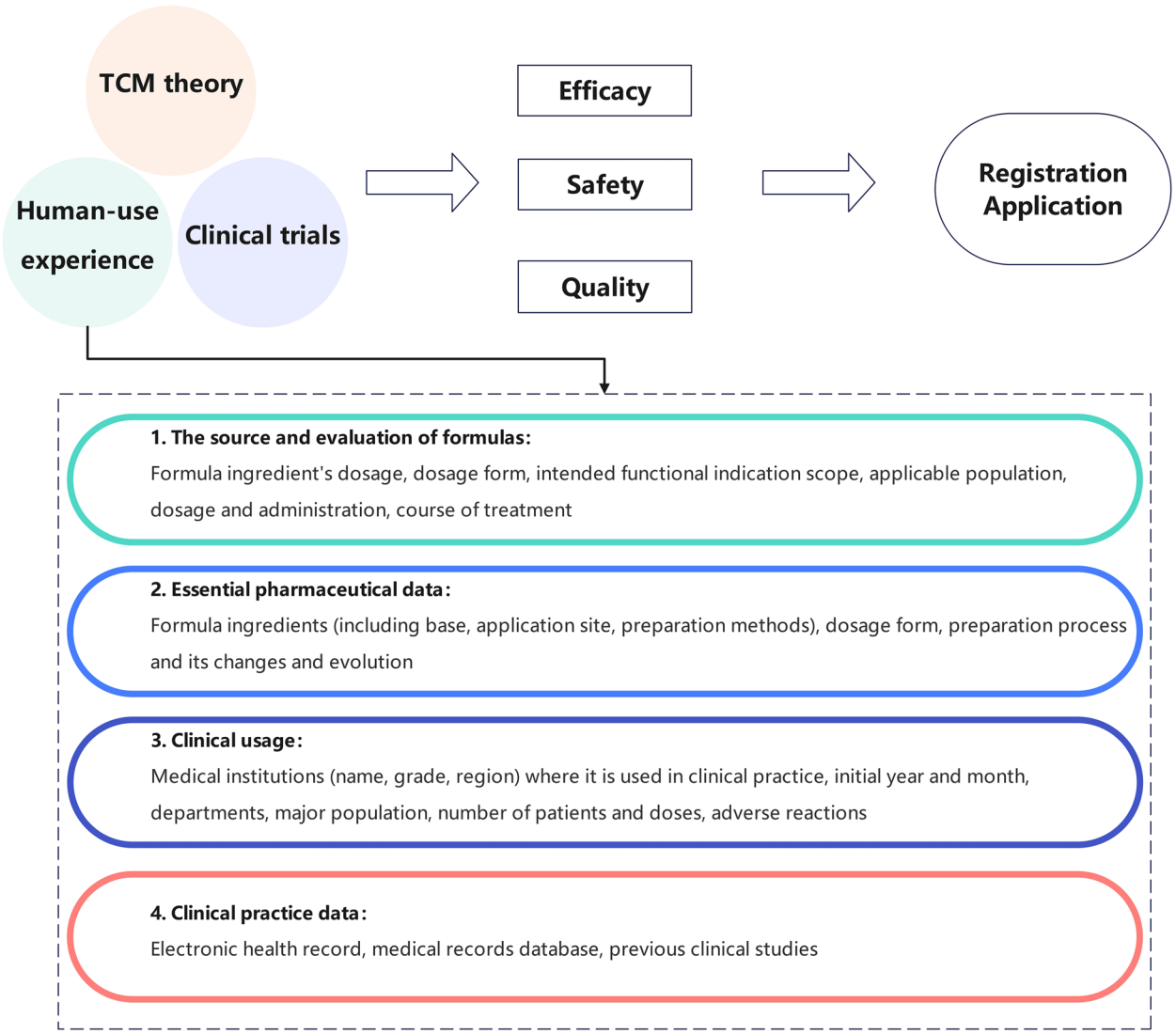

Fig. 4 The "Three Combinations" review and approval system and information on HUE

Evidence based on HUE to support TCM development and registration

Based on the registration classification and situations of HUE, NMPA provided several research and registration paths of new TCMs for recommendation in *Technical Guideline for Clinical Research and Development of New Drugs of Traditional Chinese Medicine Compound Preparations Based on Human Use Experiences (Trial)* (mainly for TCM in 1.1 and 3.2 registration classification), as shown in Fig. 5 [45]. According to the recommended paths, evidence from HUE to support the registration of new TCM can be generally categorized into two categories: direct support for registration and laying the foundation for subsequent clinical studies. For HUE data, following the appropriate study design and statistical analysis, if the results can provide sufficient evidence of efficacy and safety within the proposed functional indication, dosage, and administration, they may directly serve as key evidence to support the product's registration after communication with regulatory agencies, as the Path Five in Fig. 5.

Nevertheless, if the results from the research based on HUE are insufficient to demonstrate drug efficacy and safety or fail to fully and accurately address the scientific questions necessary for marketing approval, further clinical studies are needed to gather more robust evidence (Path Two, Path Three, Path Four, and Path Seven in Fig. 5). When HUE is employed to inform the design of these subsequent studies, several critical elements should be identified through data analysis. These elements include the applicable population, the scope

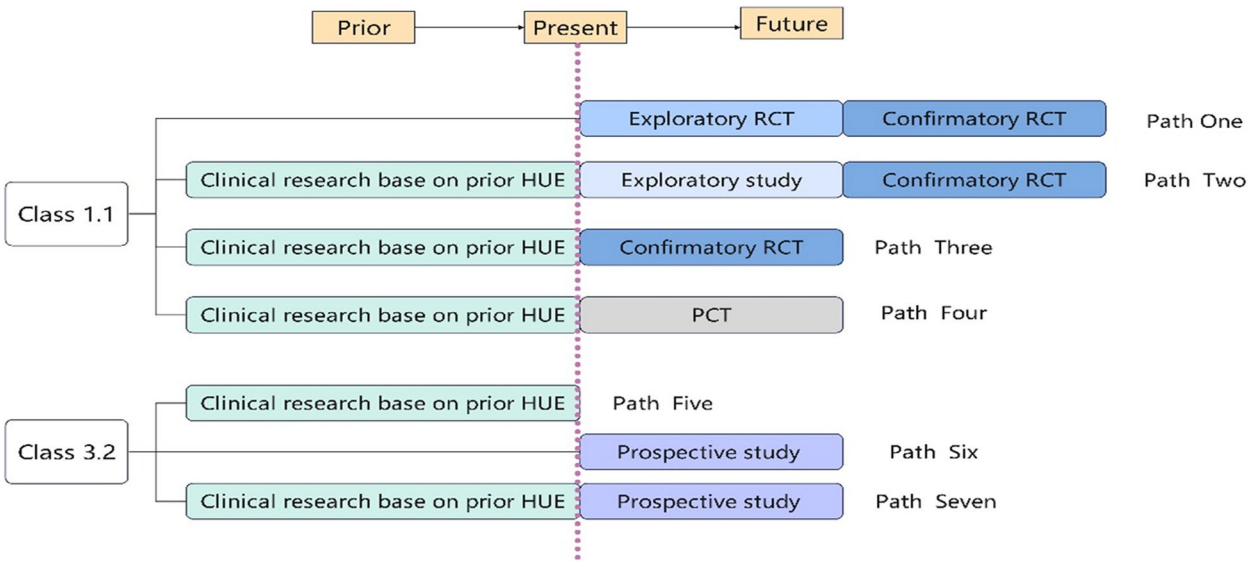

Fig. 5 Clinical research and development strategy for TCM products based on human-use experience. Source: National Medical Products Administration. Technical Guideline for Clinical Research and Development of New Drugs of Traditional Chinese Medicine Compound Preparations Based on Human Use Experiences (Trial). 2022

of functional indications, drug dosage and administration, the primary endpoint, the observation period, follow-up points, and specific parameters or effect sizes needed for sample size estimation. Moreover, if the HUE data are of high quality and adequate, their analysis results, alongside the results of subsequent clinical studies, can jointly serve as evidence for regulatory decision-making.

The type of subsequent clinical studies should be decided on a case-by-case basis. If high-quality HUE data are available and the results are positive, a confirmatory RCT or PCT can be initiated directly. Otherwise, exploratory clinical studies must be conducted first. These exploratory studies can be interventional or observational, and their outcomes will guide the decision on whether further confirmatory trials are necessary. It is important to note that clinical research and development of TCM compound preparations should still follow the conventional pathway without any foundation of HUE-based studies.

The cases of TCM using HUE to support registration application

By searching official Chinese government websites and literature, we finally identified 6 cases in which HUE was utilized to support the registration application of TCM products, as shown in Table 4. Of these, Cases 1–5 utilized HUE to support direct registration, while NMPA approved Case 6 to move directly to Phase 3 studies due to prior HUE.

Using HUE to support direct registration

Case 1–3: In the process of fighting against COVID-19 pandemic, TCMs demonstrated effectiveness on COVID-19 symptoms alleviation and were widely used to treat COVID-19 patients in China [46]. Due to the synergistic effect of multiple components and multiple targets, TCM offers a comprehensive therapeutic effect in antiviral, anti-inflammatory, antipyretic, and immune regulation functions, thereby having the potential to improve the multiple symptoms caused by COVID-19 [47, 48]. Among them, Qingfei Paidu granules (QFPD), Huashi Baidu granules (HSBD), and Xuanfei Baidu granules (XFBD) are the most effective anti-coronavirus prescriptions used by many clinicians and experts since the outbreak of COVID-19. The three TCM prescriptions are all derived from classical TCM formulas used for symptomatic relief of respiratory illnesses and were included in the *National Guidelines for the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* by the National Health Commission in 2020 [49]. They have shown great effectiveness in alleviating symptoms and reducing the progression of mild and moderate COVID-19 cases to severe cases. Based on the human use evidence from clinical practice, NMPA approved these three TCM prescriptions through a special and emergency response procedure on March 2, 2021 [50]. This was the first time that HUE was used to support new TCM registration in China.

QFPD was the first prescription that authorities promoted nationwide and also the most widely used one

Table 4 Cases of TCM products using HUE to support registration application

Case number	TCM product	Regulatory decision	Classification of TCM registration	Approval procedure	Year of approval	Human-use experience
1	Qingfei Paidu Granules (*QFPD*, 清肺排毒颗粒)	New medicine approval	3.2 Other TCMs compound preparations derived from ancient classic famous recipes	Special and emergency response procedure	2021	• Study type: multicenter retrospective observational study • Data source: EHR from more than 60 medical institutions in 28 provinces • Study population: 3715
2	Huashi Baidu G*ranules (HSBD,* 化湿败毒颗粒)	New medicine approval	3.2 Other TCMs compound preparations derived from ancient classic famous recipes	Special and emergency response procedure	2021	Study 1 • Study type: single-center non-randomized controlled trial • Study population: 60 Study 2 • Study type: retrospective case series study • Data source: EHR from Wuhan Jinyintan Hospital • Study population: 55 severe COVID-19 patients
3	Xuanfei Baidu G*ranules (XFBD,* 宣肺败毒颗粒)	New medicine approval	3.2 Other TCMs compound preparations derived from ancient classic famous recipes	Special and emergency response procedure	2021	Study 1 • Study type: retrospective observational study • Data source: EHR from Hubei Provincial Hospital of Integrated Chinese and Western Medicine and Wuhan Hospital of Traditional Chinese Medicine • Study population: 41 Study 2 • Study type: pilot randomized clinical trial • Study population: 42
4	Sanhan Huashi Granules (散寒化湿颗粒)	New medicine approval	3.2 Other TCMs compound preparations derived from ancient classic famous recipes	Normal procedure	2022	• Study type: retrospective cohort study • Data source: using the real-time Internet information collection application and Centers for Disease Control for the Wuchang District, patient data were collected through patient self-reports and follow-ups • Study population: 721 mild and moderate COVID-19 patients

Table 4 (continued)

Case number	TCM product	Regulatory decision	Classification of TCM registration	Approval procedure	Year of approval	Human-use experience
5	Wenyang Jiedu(WYJD, 温阳解毒颗粒)	New medicine approval	3.2 Other TCMs compound preparations derived from ancient classic famous recipes	Normal procedure	2024	• Study type: retrospective observational study • Data source: EHR from Hankou Hospital in Wuhan • Study population: 477
6	Antiwei Granules(ATW, 安体威颗粒)	Approval for phase 3 clinical trial	1.1 Compound preparations composed of multi-flavor decoction pieces or extracts	Normal procedure	2024	• Not found

EHR Electronic health record

during the anti-epidemic battle in Wuhan. It was derived from a combination of classical TCM formulas, and a systematic review and meta-analysis indicate that it can effectively alleviate symptoms and shorten the recovery time of patients [51]. To support its registration application, a multicenter retrospective observational study of QFDA was conducted to evaluate the safety, treatment pattern, and effectiveness of QFPD in the real-world setting. A total of 3,715 cases were included from over 60 medical institutions across 28 provinces in China, and analyses were conducted on these real-world data to form high-quality HUE [29]. Following Path Five in 3.2 registration classification, QFPD used evidence based on HUE to support direct registration application and received approval from NMPA following a special review and approval procedure under emergent events of public health. After its approval, a randomized controlled trial was conducted to further assess the clinical effectiveness of QFPD [52].

Similar to QFPD, HSBD, and XFBD also received approval following Path Five in the 3.2 registration classification. XFBD was derived from classical formulas that have shown effective treatment of infections by corona viruses [53]. A pilot randomized clinical trial has shown that the disappearance rate of clinical symptoms was significantly reduced ($P< 0.05$) in the experimental group using XFBD compared to the control group [54]. Besides, a retrospective observational study including 41 cases shows that XFBD has good efficacy and safety in the treatment of severe COVID-19 cases by alleviating inflammation and clinical symptoms, promoting the absorption of lung inflammation, and reducing mortality [55]. After its approval, a prospective, non-randomized controlled trial was conducted to further evaluate the efficacy and safety of XFBD in the treatment of COVID-19 [56].

For HSBD, before its approval, a prospective, single-center, non-randomized controlled trial was conducted to evaluate the efficacy and safety of HSBD and Lopinavir-Ritonavir treatment in adult patients with COVID-19. The results indicate that compared to Lopinavir–Ritonavir treatment alone, the combination of Lopinavir–Ritonavir and HSBD displayed advantages in terms of the clinical remission time and rate of release from quarantine [57]. Furthermore, a retrospective case series study including 55 severe COVID-19 patients at early stage of the epidemic showed that HSBD can promote lung lesion opacity being absorbed, thereby mediating inflammation [58]. After being approved, a prospective single-center, open-label, randomized, controlled clinical trial was conducted to assess and compare the efficacy and safety of HSBD, Paxlovid, and the combination in treating high-risk patients infected with SARS-CoV-2 Omicron [59]. Additionally, a single-center, open-label, parallel-group randomized controlled trial was carried out to assess the efficacy and safety of HSBD in pediatric patients with laboratory-confirmed mild COVID-19 [60].

Case 4–5: Sanhan Huashi granules (SHHS) was derived from traditional Hanshiyi herbal formula and composed of 20 Chinese herbs [61]. To assess the effect of SHHS on preventing the progression to severe conditions in patients with mild and moderate COVID-19, a retrospective cohort study was conducted at a quarantine station in Wuhan. Patient data were collected through self-reports and follow-ups using a real-time Internet information collection application by the Centers for Disease Control for the Wuchang District. A total of 721 mild and moderate COVID-19 patients were enrolled in the study, and the results showed that SHHS can reduced the progression of mild and moderate COVID-19 to a severe disease status [62]. On 9 Oct, 2022, NMPA approved SHHS in 3.2 registration classification following Path Five [63]. After its approval, a randomized, active-controlled, open-label, multi-center trial was conducted to further compare the effectiveness and safety of SHHS and nirmatrelvir–ritonavir in treating adults with mild-to-moderate COVID-19. The result indicated that SHHS significantly shortened the median time to sustained clinical recovery compared to nirmatrelvir–ritonavir (6.0 (95% CI, 5.0 to 6.0) vs. 8.0 (95% CI, 6.0 to 9.0) d; $P= 0.001$), particularly for individual symptoms including fever, sore throat, cough and fatigue [64].

Wenyang Jiedu Granules (WYJD, formerly known as Fuzheng Jiedu) is derived from Si Ni Tang and Tou Du San, and was used for the treatment of COVID-19 patients. A retrospective study indicated that the use of WYJD reduced the 28-day mortality ($P= 0.049$) and shortened the duration of fever (4 days vs. 7 days, $p= 0.002$) [65]. On 23rd August 2024, WYJD was approved by NMPA following Path Five.

Laying foundation for subsequent Phase 3 clinical trial

Case 6: Antiwei granules was derived from Zhang Zhongjing's "Shang Han Lun", with the effects of relieving the symptoms of cold and coughing. In 2023, Antiwei granules was approved by NMPA to directly conduct a Phase 3 clinical trial with sufficient prior HUE [9]. This case followed Path Three for its clinical study and registration, which allows for the direct conduct of confirmatory randomized controlled trials if there is sufficient high-quality HUE and positive study results.

Discussion

Regulatory framework for incorporating HUE into TCM registration applications in China

In recent years, China has been actively promoting reform on the regulation of TCM, and released relevant

guidelines and policy support to incorporate new methods into the development and evaluation of TCM products. The"Three Combinations"review and approval system, introduced by NMPA, represents a significant advancement in the registration framework for TCM products. This system aims to evaluate TCM products that align with their unique characteristics, and integrates three critical components: TCM theory, HUE, and clinical trial. As a foundational basis for using TCM in clinical practice, TCM theory primarily reflects the reasonable explanation of functional indications, that is, the rationality of"Theory-Diagnosis-Formula-Medicine"[45]. HUE is generally accumulated in clinical practices with certain regularity, repeatability, and clinical value. It encompasses the insights and summaries of usage in specific populations, dosage, efficacy and safety profiles, prescription characteristics, and the clinical benefits of TCM formulas or preparations generated from clinical practice. The inclusion of HUE is particularly noteworthy as it allows for incorporating data from the real world, which can provide insights into the effectiveness and safety of TCM products. This is very important for TCM products as they often have complex mechanisms of action and multifaceted therapeutic effects that may not be fully captured by RCT. It should integrate the TCM theory and summaries of HUE for clinical trials to further conduct studies on unresolved efficacy and safety issues. Various research and development strategies, along with flexible study designs, can be adopted as needed. Based on evidence from HUE, non-clinical effectiveness studies and phase 1/2 clinical trial may be exempted when relevant requirements are met within the "Three Combinations" system. This can potentially shorten the research and development cycle, decrease costs, and enhance the overall efficiency of the research.

Although the use of HUE in the registration of TCM products in China is still in the early stage, the successful cases demonstrated its prospects. By the end of 2024, NMPA approved 6 TCM drugs that used HUE for registration application. Of these, 5 drugs utilized HUE to inform new medicine registration, while one utilized HUE to lay foundation for subsequent Phase 3 clinical trial. Drugs using HUE to directly support registration are typically backed by large-sample retrospective studies or prospective studies, with findings published in academic journals to demonstrate their safety and efficacy. In contrast, drugs utilizing HUE as a foundation for subsequent clinical studies often rely on unpublished research with smaller sample sizes, requiring further trials to validate their safety and effectiveness. For the HUE of approved cases, retrospective observational studies are the main study design, and electronic health records from hospital information system are mostly used data type. Two drugs (HSBD and XFBD) have conducted small sample prospective studies, and submitted applications in conjunction with retrospective observational study for registration. Currently, NMPA has not approved any TCM products to add functions or indications based on HUE. This may be due to the broad indications and function scopes of TCM products. A recent study has investigated the mechanism of indication expansion for Daning tablets under the"Three Combinations"review and approval system [66], while future research should focus more on expanding the application of HUE in regulatory decision-making.

In the aspect of post-market assessment, among these cases approved by NMPA, the first three cases (QFPD, HSBD XFBD) were approved through a special review and approval procedure. This procedure is designed for public health emergencies that pose a threat to people or have already occurred [51]. Although this procedure does not require post-market assessment like the conditional approval designation, all three drugs underwent post-market assessment to further clarify their effectiveness and safety. One possible reason for this could be that these drugs were intended for marketing overseas, but there is no established process for using HUE or RWE for herbal medicine registration in other countries [67]. As a result, evidence from RCT may be necessary for their attempts to gain approval in foreign markets.

Methodological considerations of using HUE to support TCM registration

Data curation and statistical analysis are essential steps to form high-quality HUE evidence. Clinical data of HUE is generally derived from historical or prior sources, such as electronic medical records or past clinical studies. However, these data are often incomplete, with inconsistent standards and description methods, making it challenging for direct analysis. To meet the requirements for generating clinical evidence and the data submission standards, these data must undergo a standardized curation process, in which data curation and data quality evaluation are the major contents [45]. For data curation, the curation of previous clinical data mainly includes but is not limited to: data security processing, data extraction, data cleaning, data conversion, data transfer and storage, and data quality control. In terms of data quality evaluation, it is generally divided into two steps. First, a preliminary assessment determines whether the source data meet the basic analytical requirements, including compliance with ethical review regulations, data security, and privacy protection. This step also evaluates the accessibility of the data, the completeness of key variables, and whether a sufficient sample size can be ensured after curation. Second, the fitness of the data post-curation is

assessed, focusing on two main aspects: relevance and reliability. Relevance examines the coverage rate of key variables, the accuracy associated with treatment and clinical outcomes, the representativeness of the target population, and the integration of various source heterogeneous data. Reliability, on the other hand, encompasses several factors such as completeness, accuracy, transparency, quality control, and quality assurance of the data.

Another primary consideration is the study design of HUE research, which must account for the inherent variability and complexity of RWD. Unlike RCT, real-world studies often lack randomization and control groups, which can introduce biases and confounding factors. Therefore, it is crucial to employ advanced statistical methods and study designs, such as propensity score matching, instrumental variable analysis, and sensitivity analyses, to mitigate these issues and enhance the credibility of the findings [68]. Since the data of HUE is mainly comprised of clinical practice data in real-world setting, the guideline documents of RWD and RWE regarding study design and could be referenced for HUE.

Consistency between HUE and TCM products is also important when using HUE to support registration. For TCM products developed based on ancient classic prescriptions, the essential pharmaceutical data submitted for registration should be consistent with the HUE. This includes formula ingredients, preparation methods, application site, dosage form, and preparation process. Moreover, the clinical targeting and applicable population should also be consistent [36].

Ethical and regulatory considerations also play a pivotal role in the methodological framework for using HUE in TCM registration. Ensuring patient privacy and data security is essential, particularly when dealing with sensitive health information. Compliance with regulations is mandatory. Moreover, obtaining informed consent from patients for the use of their data in research is a fundamental ethical requirement.

Finally, the interpretation and reporting of HUE findings require careful consideration. Transparency in the reporting of study methods, data sources, and analytical techniques is crucial to allow for reproducibility and critical appraisal of the research. The use of standardized reporting frameworks, such as the reporting of studies conducted using observational routinely collected health data (RECORD) statement, can enhance the clarity and completeness of HUE studies.

Challenges and opportunities in the application of HUE

Despite some achievements in recent years, substantial challenges remain in using HUE to support registration application of TCM products in China. The primary obstacles include difficulties in data accessibility. Currently, there is still a lack of comprehensive databases for TCM. HUE data is often dispersed across various sources, including different hospitals, individual practitioners and fragmented literature sources, making it hard to compile and curate data systematically [9]. It's noteworthy that all the six approved drugs mentioned above were authorized for treating influenza symptoms, and their HUE are all collected during COVID-19 pandemic. The pandemic created an urgent need for information to support public health, treatment plans, and vaccine development. This urgency led to many high-quality real-world studies, enabled by multi-collaboration, data sharing, digital health technologies, and innovative research designs [69]. However, with the pandemic's end, conducting high-quality HUE studies faces challenges. These include a lack of large databases in the TCM field and reduced collaboration and data sharing among medical institutions. Therefore, to improve data accessibility, the development of patient registries or research databases, and multi-collaboration needs to be promoted.

Moreover, there is a lack of standardized protocols for HUE collection and reporting. The terminology in TCM is complex and diverse, with different practitioners often using varying terms for similar conditions. Additionally, the composition of herbal ingredients can vary based on their origin, preparation methods, and practitioner interpretation, further complicating the data collection process [70]. Without standardized protocols, the methods of data collection and reporting can differ significantly between studies, leading to variations in data quality and reliability. A researcher from center for drug evaluation of NMPA summarized considerations in reviewing the registration materials of TCM products, which pointed out that most of the HUE materials submitted for drug applications are incomplete, lacking information such as preparation methods, applicable population, and safety data. Additionally, the authors noted that the fitness of the data was not fully considered, especially for retrospective studies [71]. Therefore, standardized protocols for collecting and reporting HUE information are essential to ensure consistency, reliability, and accuracy in both clinical practice and research. Besides, the use of standard TCM terminologies, such as the *International Standard Terminologies on Traditional Chinese Medicine* introduced by the WHO in 2022, should be encouraged among TCM practitioners [72]. This can significantly enhance the standardization and global harmonization of TCM terminology, and further contribute to the collection and analysis of HUE.

Finally, the role of HUE in transforming TCM preparations from hospital (also called as in-hospital TCM preparation) into new TCM products should be further emphasized. TCM preparations from hospital, as

a unique and important form of preparations in China, have a long history of human use and serve as a bridge between clinical experience prescriptions and new TCM products [73]. Generally, these types of TCM preparations are only allowed to be used in the institutions where they are produced, after receiving recordation from the provincial medical products administration. Since the proposal of the "Three Combinations" review and approval system, the idea of transforming preparations used in medical institutions into new drugs based on HUE has been increasingly valued by drug research and development organizations. In the past few years, some TCM preparations from hospital have received recordation with evidence from HUE, such as Toujie Quwen granules and Tianchan Xifeng Granules [9, 74]. Although some progresses have been made, the overall situation in using HUE to support the development and registration of TCM preparations from hospital still awaits further improvement. This includes limited personnel capabilities and suboptimal quality of collected HUE [39, 75]. To promote high-quality HUE research on TCM preparations from medical institutions, more supporting regulations and relevant technical requirements need to be released. Additionally, innovative study designs, such as patient-reported outcomes measurement, may be suitable for the collection and analysis of HUE for TCM preparations from hospital and should be further explored.

Strengths and limitations

The innovative aspect of this study lies in its comprehensive exploration of the regulatory framework for using HUE in the registration of TCM products in China. We systematically reviewed recent articles and identified the regulatory concerns related to the use of HUE in TCM products. By analyzing government policy documents and technical guidelines from the official website, we summarized the evolving regulatory landscape for incorporating HUE into TCM registration applications in China. Additionally, we provide a case study on instances that included HUE in their registration application, which could provide insight into regulators' thinking as they evaluated the data.

We also recognize that there are limitations in our study. First, applying HUE to support the development and registration of TCMs is still in its infancy, with limited literature and practical examples available. Second, the regulatory concerns regarding the application of HUE for TCM registration were synthesized based on published literature, without incorporating opinions from regulatory authorities. This omission may limit the comprehensiveness of our analysis, as regulatory authorities often provide critical insights into practical implementation and compliance requirements. Finally, our study focuses on policies and cases at the national level, with cases collected from official NMPA government websites. To obtain a more comprehensive landscape of the HUE used in regulatory decision-making, registration documents and information at the provincial level, such as TCM preparations from hospital, could also be included in the future studies.

Conclusion

In conclusion, the application of HUE in TCM product registration represents a transformative shift in regulatory practices. By embracing a comprehensive and systematic approach by integrating the HUE, regulatory authorities can better support the registration of TCM products, ensuring their safety, efficacy, and quality. The insights derived from this study provide a foundational basis for ongoing improvements in the regulatory frameworks, fostering innovation and enhancing the global acceptance of TCM. As the field continues to evolve, collaboration among stakeholders, including regulators, researchers, and industry professionals, will be crucial in advancing the integration of HUE in TCM registration and ensuring that traditional wisdom is complemented by modern scientific rigor.

Abbreviations

HUE	Human-use experience
TCM	Traditional Chinese medicine
RCT	Randomized controlled trial
RWE	Real-world evidence
RWD	Real-world data
NMPA	The National Medical Products Administration

Supplementary Information

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Supplementary Material 1: Supplementary table. Search term identifiers. Supplementary Table. Search strategy for articles about using RWE for registration and regulatory decisions of TCM products.

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Clinical trial number

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Authors' contributions

HH, YFL, COLU and SH conceptualized the study. MGX, LWZ, YX, and XWC conducted the collection and analysis. MGX wrote the main manuscript. YX and HH revised the manuscript.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

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The authors declare no competing interests.

Author details
[1]State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Taipa, Macao. [2]Department of Medical Insurance, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China. [3]Centre for Pharmaceutical Regulatory Sciences, University of Macau, Taipa, Macao. [4]Department of Public Health and Medicinal Administration, Faculty of Health Sciences, University of Macau, Taipa, Macao. [5]Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University, Beijing, China. [6]International Research Center for Medicinal Administration, Peking University, Beijing, China. [7]School of Public Health and Management, Guangzhou University of Chinese Medicine, Guangzhou, China.

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