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Implementation of Traditional Chinese Medicine (TCM) Research Outcomes - Product Transformation

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Abstract

The transformation of Traditional Chinese Medicine (TCM) research outcomes is a complex process involving close communication and collaboration between the industry, the academia, the research institutions and governmental regulatory office, aiming to bring innovative scientific achievement of TCM to market. This paper discusses the registration requirements for TCM products in the Guangdong-Hong Kong-Macao Greater Bay Area and highlights regional differences, emphasizing the importance and challenges of transforming research outcomes. Despite the growing research interests in TCM universities, the actual conversion rate of research outcomes from these academic institutions is still much lower than that of pharmaceutical research circles. Stronger cooperation between TCM experts and enterprises is required.

The ultimate goal of TCM research and development is to transform research outcomes into marketable drugs. Different regions have varying market access requirements, which affect research and development costs and timelines. Analyzing the registration systems governing TCM transformation in Mainland China, Hong Kong and Macao, this paper provides solid reference for the effective transformation of TCM research outcomes. It is hoped that the proper establishment of transformation mechanisms which thoroughly observed the regulatory requirements would lead to the healthy development of the TCM industry.

Keywords: Traditional Chinese medicine • Research outcomes • Registration • Transformation • Medical institution preparations

Introduction

The process of transforming Traditional Chinese Medicine (TCM) research outcomes is essentially the process of bringing them to market. It is also a process of close communication and collaboration between the academia, research institutions, the industry and the governmental regulatory office, with the ultimate goal of creating economic and social value. The ultimate objective of novel TCM drug development is to transform research outcomes into marketable drugs.

How to accelerate the transition of innovative scientific outcomes in TCM from "Publications" to market and how to align research data with market listing requirements have become key crucial issues in the transformation of research outcomes. Understanding the complexity and regional differences in registration requirements for health products is essential for the transformation of research outcomes. This paper specializes on TCM research and development and focuses on how research outcomes can become marketable products.

TCM academic units are the pivotal forces in TCM scientific research. Each year, they undertake a large number of research projects, acquire reasonable research fundings, keep building modern research facilities and recruit abundant talent so that scientific bases for TCM scientific research are developed. However, can those TCM research outcomes be successfully transformed into marketable Chinese patent medicines? In developed countries, the success rate of converting pharmaceutical research outcomes into products is between 50% and 70%, while in China, the overall is less than 30% [1]. The conversion rate is low in the health sector. Although Chinese universities achieve between 6,000 and 8,000 scientific research outcomes annually, less than 10% are actually transformed and industrialized. This indicates a situation where many research outcomes exist, but few are applicable in practice, resulting in a significant waste of scientific resources [2].

Despite the abundance of TCM research achievements, very few are practically applied. In the process of transforming TCM research outcomes, universities and research institutions, as the providers of scientific results, are mainly responsible for innovation and development, while enterprises, thirst for reliable scientific results, are primarily responsible for industrialization and product promotion. How well these two sides connect determines whether the research outcomes can be successfully transformed.

Overview of TCM (Natural herbal medicine) R&D and market access requirements in different regions

In February 2019, the Chinese Government issued the *Outline Development Plan for the Guangdong-Hong Kong-Macao Greater Bay Area* [3]. Since then, universities and research institutions have successively settled in the Greater Bay Area, greatly promoting research and development in the region. Consequently, questions have arisen on how to transform research results into products with economic and social value. Taking TCM research as an example, the ultimate goal of TCM R&D is to develop proprietary Chinese medicine (pCm), special medical supplements and health foods that can promote human health and prevent and treat diseases, ultimately registering and launching them on the market in the Greater Bay Area, extending international markets.

The research results of Chinese herbal medicine or natural herbal medicine include pCm, health foods, functional foods and special medical supplements. Different research outcomes have different application targets and market access requirements also differ, leading to varying R&D costs. For example, the R&D costs for pCm are significantly higher than those for

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health foods and the indications of consumption are also vastly different. Due to the different political and governing systems, the Greater Bay Area has three different registration systems, each with unique requirements for registration data.

Mainland China: The reform of the TCM registration classification aligns with the development of TCM R&D, promoting the development of new TCM drugs. The 2007 version of the Drug Registration Management Measures classified TCM registration into nine categories:

1. Extracts and their preparations from plants, animals, or minerals that have not been sold domestically.
2. Newly discovered medicinal materials and their preparations.
3. New substitutes for medicinal materials.
4. New medicinal parts of medicinal materials and their preparations.
5. Extracts and their preparations from parts of plants, animals, or minerals that have not been sold domestically.
6. Compound TCM or natural drug preparations that have not been sold domestically.
7. Preparations that change the administration routes of domestic TCM or natural drugs.
8. Preparations that change the dosage forms of domestic TCM or natural drugs.
9. Generic drugs.

The 2020 version of the Drug Registration Management Measures reduced the classification to four categories [4]:

1. Innovative TCM drugs,
2. Improved new TCM drugs,
3. Compound TCM preparations from ancient classical formulas,
4. TCM with the same name and formula.

The first three categories belong to the category of new TCM drugs

Source: NMPA

Hong Kong: Hong Kong's legal and regulatory framework for medicinal products includes separate regulations for TCM and Western medicine. The Chinese Medicine Ordinance and the Pharmacy and Poisons Ordinance form the core framework for drug regulation in Hong Kong.

In addition to these core ordinances, Hong Kong has other supplementary regulations such as the Import and Export Ordinance, the Dangerous Drugs Ordinance and the Undesirable Medical Advertisements Ordinance. Together, these regulations form a comprehensive drug regulatory network in Hong Kong.

The Import and Export Ordinance regulates the import and export of drugs to ensure that all drugs entering or leaving Hong Kong meet legal standards and requirements. The Dangerous Drugs Ordinance strictly controls drugs with potential hazards to prevent abuse or illegal circulation. The Undesirable Medical Advertisements Ordinance combats false and misleading medical advertisements, protecting consumer rights.

These regulations work in tandem to ensure effective regulation of the entire drug lifecycle, from production and import to sales and advertising [5,6].

The registration categories for pCm in Hong Kong are classified into "Established Medicines category," "Non- Established Medicines category," and "New Medicines category."

Established medicines category: Refers to formulations based on ancient prescriptions (from Traditional Chinese Medicine literature before the Qing Dynasty) or those derived from ancient prescriptions (as recognized by the Chinese Medicine Division of the Hong Kong Department of Health) or those listed in national drug standards.

Non-established medicines category: Includes health products and single-ingredient TCM granules. Health products cannot contain newly discovered medicinal materials or new medicinal parts.

New medicines category: Refers to formulations containing newly discovered medicinal materials, new medicinal parts, or extracts from compound TCM formulations.

Macao: On January 1, 2022, the Macao Drug Supervision and Administration Bureau was officially established and the Law on Pharmaceutical Activities and the Registration of proprietary Chinese medicine ("pCm") came into effect. This law was followed by 25 technical specifications for the registration, production and circulation of pCm in Macao.

According to Decree No. 53/94/M, "proprietary Chinese medicine " in Macao refers to products prepared from natural medicinal ingredients under the guidance of TCM theory, intended for the treatment, alleviation, or prevention of human diseases or symptoms.

Macao applies a pre-approval system for Chinese medicine [7] and there is no clear classification for the registration of pCms. Macao's "List of Chinese Medicinal Materials" divides medicinal materials into three subcategories: toxic medicinal materials, ordinary medicinal materials and dual-purpose medicinal materials (both food and medicine). Toxic and ordinary medicinal materials can only be sold in licensed pharmacies. Macao implements a pre-registration system for imported drugs, focusing on reviewing registration data and conducting post-market sampling inspections, without requiring clinical trials (**Table 1**).

Types of TCM (Natural herbal medicine) research outcomes

Proprietary Chinese medicine ("pCm"): In Mainland China, there is no legal definition of "pCms". According to the information released by the *National Medical Products Administration* (NMPA), "pCms" broadly refer to any processed TCM materials, including prepared medicines (such as pills, powders and granules) formulated according to a set of treatment principles.

In Hong Kong, according to the Chinese Medicine Ordinance, "proprietary Chinese medicine ("pCm") " refers to a product that uses pure TCM as the active ingredient, formulated into a dosage form, with therapeutic or health care uses. Some health foods containing non-TCM ingredients do not fall under this ordinance.

In Macao, there is no legal definition for pCms. Decree No. 53/94/M regulates the licensing and operation conditions for companies and pharmacies engaged in the import, export and wholesale of Chinese medicinal materials. Under this decree, any medicine prepared according to TCM theory and pharmacology for preventing or treating diseases or regulating organ functions belongs to Chinese medicine (**Table 2**).

Health foods: China's health food industry began in the 1980s. After nearly 40 years of industrial development, it has evolved from an initial stage of lacking regulatory laws and disorderly growth to gradually forming a comprehensive pre- and post-market regulatory system. This system includes management of raw materials and functional claims, product registration and

Table 1. Pharmaceutical registration authorities in the Guangdong-Hong Kong-Macao greater bay area.

Product Category	Hong Kong	Macao	Mainland China
Chinese Medicines	Chinese Medicine Council of Hong Kong; Department of Chinese Medicine, Department of Health	Macao Drug Regulatory Bureau	National Medical Products Administration
Western Medicines	Drug Office, Department of Health; Pharmacy and Poisons Board	Macao Drug Regulatory Bureau	National Medical Products Administration
Biologics	-	-	National Medical Products Administration

Table 2. Differences between health foods and medications.

Health Foods	Medications
Cannot be for the purpose of treatment, mainly for regulating bodily functions	Have a clear treatment purpose and corresponding indications and functional indications
Cannot have any acute, subacute, or chronic hazards	May have adverse reactions
Can be used long-term	Have a prescribed period of use
Taken orally	Administered *via* injection, external use, oral ingestion, etc.

evaluation, product dosage forms, naming guidelines, product promotion, production and operation licenses and more. The health food industry is gradually entering a period of scientific and standardized development.

Health foods in China refer to products that claim to have specific health functions or are intended to supplement vitamins or minerals. These foods are suitable for specific groups of people and aim to regulate bodily functions, not to treat diseases and must not cause acute, subacute, or chronic harm to humans [8] (**Table 3**).

Functional foods: The current domestic laws and regulations have not yet clearly defined the concept and requirements for functional foods and their regulation still falls under the category of regular foods. Different countries have different understandings of functional foods.

Foods for Special Medical Purpose (FSMP)

The Food Safety Law, revised in 2015, classified FSMP as a category of special foods, clarifying their meaning and legal status and implementing a registration-based management model. Subsequently, in 2016, the Measures for the Registration Administration of Foods for Special Medical Purposes, formulated according to the Food Safety Law, were officially promulgated. As a result, the regulation of FSMP began to become formalized.

Unlike health foods, which do not require clinical trials for registration, the registration of FSMP does require clinical trials, with materials demonstrating product safety, nutritional adequacy and clinical effects for special medical purposes being required. Prior to conducting clinical trials, applicants do not need to obtain clinical trial permits from the National Medical Products Administration (NMPA), but they are responsible for the quality of the products used in clinical trials and the safety of the trials.

Preconditions (Requirements) for the transformation of TCM research outcomes

The *Guangdong-Hong Kong-Macao Greater Bay Area Traditional Chinese Medicine High Ground Construction Plan (2020–2025)* issued by the National Administration of Traditional Chinese Medicine points out the need to "establish a TCM research outcomes transformation base and build a platform for key TCM technology, product development, outcome transformation and application." In recent years, approximately 600 Traditional Chinese Medicine (TCM) scientific and technological achievements have been appraised annually in China, with about 20% to 25% of these achievements winning awards. However, the outcome transformation rate is less than 10%, indicating a low utilization rate and long transformation cycles [9].

The research achievements in Traditional Chinese Medicine (TCM) are abundant, yet their practical applications are relatively limited. In the process of transforming TCM research outcomes, universities and research institutions, as the suppliers of scientific and technological outcomes, are primarily responsible for innovative research and development. On the other hand, enterprises, on the demand side, are mainly responsible for the industrialization and promotion of these outcomes. The effective integration of these two parties directly affects the successful transformation of research outcomes.

Pre-clinical evaluation: Preclinical evaluations include pharmacological and safety evaluations.

Pharmacological evaluation: For innovative Traditional Chinese Medicine (TCM) drugs, the evidence of effectiveness required for entering clinical trials typically includes TCM theory, human clinical use experience and pharmacodynamics studies. For TCM compound preparations, based on the specific circumstances of their prescription source, composition, clinical human use experience and manufacturing processes, pharmacodynamics studies may be appropriately reduced or exempted. If a TCM compound preparation has extensive clinical use experience, the pharmacodynamics studies may be appropriately reduced or exempted according to the level of clinical support provided for the item's effectiveness.

If the prescription composition, processing conditions, clinical indications, dosage and administration method of the compound are basically consistent with previous clinical applications, then the requirement to provide pharmacodynamics study data may be exempted. Especially when the prescription originates from a classic formula or an experienced formula of a Traditional Chinese Medicine expert with extensive clinical experience, such as a national master of Traditional Chinese Medicine or a renowned senior Traditional Chinese Medicine practitioner and the extraction process is solely water extraction of the entire formula, the research process can be simplified and non-clinical effectiveness studies may be exempted [10].

Safety evaluation: Many commonly used traditional Chinese medicinal herbs are toxic. For example, Strychnos nux-vomica, Aconite root and Croton seeds are highly toxic; Arisaema, Pinellia, realgar, Japanese knotweed and Sophora subprostrata are toxic; and many other Chinese medicinal herbs are mildly toxic. In traditional Chinese medicine, there have always been the sayings of "*Nineteen Incompatibilities*" and "*Eighteen Contraindications*." Although the toxicity of Chinese medicine is generally mild, slow-acting and less encountering compared to synthetic chemical drugs, looking from a different perspective, its toxicity could be more complex and harder to safe guard.

According to traditional materia medica records, there are distinctions between drugs that are toxic, non-toxic and those with varying degrees of toxicity (such as highly toxic, toxic and mildly toxic), but there is a lack of objective experimental data. The modern, comprehensive concept of toxicity should include aspects such as acute toxicity, subacute and chronic toxicity and specific toxicities (such as mutagenicity, teratogenicity, carcinogenicity, miscarriage and addiction) (**Table 4**). However, these modern evaluation methods of safety have not yet been fully applied to the safety evaluation of traditional Chinese medicine, which affects its entry into the international market. Although thousands of years of experience have shown that certain mineral-based medicines containing heavy metals, such as cinnabar, are highly effective and considered safe in treating many diseases, the basic research on the safety of these medicines is insufficient and they have yet to gain international recognition and acceptance.

In recent years, toxicological research on Traditional Chinese Medicine (TCM) has been initiated and the necessity of conducting scientific, comprehensive and systematic evaluations of TCM safety has gradually been recognized and accepted. The National Adverse Drug Reaction Monitoring Center has reported certain proprietary Chinese medicines that have caused drug-induced liver injury (such as Zhuanggu Guanjie Pills, Xianling Gubao Capsules and Zhixue Capsules), bringing the safety of TCM into focus [11]. The *National Medical Products Administration* (NMPA) has raised the technical requirements for the preclinical safety evaluation of compound preparations of TCM. In the new Drug Registration Regulation, it is stipulated that toxicological tests for new TCM compound preparations must be conducted at institutions that are certified under Good Laboratory Practice (GLP) standards.

Table 3. Differences between health foods and regular foods.

Health Foods	Regular Foods
Regulate bodily functions and have specific health benefits	Do not emphasize specific functions
Consumed by specific groups of people	Consumed by the general population
Have a specified daily dosage	No specified consumption amount

For products processed using traditional methods and with historical human usage, typically only single-dose toxicity and repeated-dose toxicity test data are required. For products using non-traditional methods but with clinically relevant application data, safety pharmacology, single-dose toxicity and repeated-dose toxicity test data are generally required. For products using non-traditional methods and lacking human usage experience, comprehensive toxicological tests are generally needed (including safety pharmacology, single-dose toxicity tests, repeated-dose toxicity tests, as well as carcinogenicity, mutagenicity and teratogenicity tests and safety test of pharmaceutical preparations) [10].

The term " Triple-Cause Tests " refer to carcinogenicity, mutagenicity and teratogenicity tests, which are typically used to evaluate the safety of drugs, chemicals, or other products, particularly in terms of their effects on cancer, genetic mutations, or developmental abnormalities. These tests are an essential part of drug development, especially before a new drug is marketed and must undergo rigorous toxicological evaluation to determine its long-term health risks to humans.

The methods for pre-clinical safety evaluation encompass acute toxicity, long-term toxicity, local toxicity, genotoxicity, reproductive toxicity, carcinogenicity tests, etc. Specific items and the contents are shown in Table 4.

Clinical Evaluation: Both traditional Chinese medicines (TCMs) and chemical drugs share a common goal of being clinically oriented. However, TCMs are unique due to their extensive clinical history and generalized experience. This rich historical experience not only serves as crucial evidence for the effectiveness and safety of TCMs but also represents a valuable resource that cannot be ignored in the research and development (R&D) process of TCMs. The uniqueness of the R&D process for new TCMs lies in its adherence to a "clinic-laboratory-clinic" cyclical pathway. This process emphasizes discovering problems and extracting experience from clinical practice, conducting scientific verification in the laboratory and finally returning to clinical settings for efficacy confirmation and safety assessment, forming a closed-loop model. This R&D model not only fully leverages the human use history of TCMs but also ensures the scientific rigor of new drug development.

In recent years, the *National Medical Products Administration* (NMPA) of China has consistently strengthened the concept of "clinic-oriented and emphasizing human use history" in the evaluation of new TCMs. The introduction of this concept reflects a deep understanding of the characteristics of TCMs and an accurate grasp of the laws governing the R&D of new TCMs. By reinforcing this concept, the NMPA aims to guide the R&D of new TCMs to better meet clinical needs, improve the quality and safety of new TCMs and promote the healthy development of the TCM industry.

Table 4. Content of safety evaluation for traditional Chinese medicines.

Acute toxicity tests for systemic medications in mice or (and) rats and dogs
Long-term toxicity tests for systemic medications in rats or (and) dogs and monkeys
Acute toxicity tests for dermal medications
Long-term toxicity tests for dermal medications
Irritancy tests for dermal medications
Sensitization tests for dermal medications
Irritancy tests for oral medications
Acute toxicity tests for nasal drops and inhalants
Irritancy tests for nasal drops and inhalants
Acute toxicity tests for rectal and vaginal medications
Irritancy tests for rectal and vaginal medications
Long-term toxicity tests for rectal and vaginal medications
Genotoxicity tests
Reproductive toxicity tests
Carcinogenicity tests
Drug dependence tests

Randomized Controlled Trials (RCTs), recognized worldwide as the gold standard for clinical evaluation, play a crucial role in the R&D of new TCMs. RCTs can scientifically and objectively evaluate the effectiveness and safety of new TCMs, providing solid clinical evidence for their market approval. In the R&D process of new TCMs, the rational use of RCTs, combined with the human use history of TCMs, will help enhance the clinical value and market competitiveness of new TCMs [12].

In the evaluation system for innovative TCMs, real-world study data and RCT data represent different levels of evidence strength. For ensuring the safety and effectiveness of new TCMs, conducting RCTs before market approval is crucial. Through rigorous experimental design, RCTs can minimize bias and interfering factors, providing the most reliable clinical evidence for new TCMs.

In designing clinical trials for TCMs, various methods can be adopted to comprehensively evaluate new drugs. These include a three-arm trial design with both active comparator (i.e., an already marketed and recognized effective drug) and placebo as controls. This design allows for simultaneous comparison of the efficacy and safety of new TCMs with active comparators and placebos, providing a multidimensional assessment of the clinical value of new TCMs.

A superiority design with an active comparator focuses on the relative efficacy and safety of new TCMs compared to known effective drugs. By comparison, it can clarify whether new TCMs are superior or at least non-inferior in efficacy to marketed drugs, providing important evidence for the positioning and market application of new TCMs. A superiority design with a placebo control focuses on understanding the absolute efficacy and safety of new TCMs. In this design, new TCMs are compared with placebos, directly reflecting the treatment effect of new drugs without other interventions and providing clear data support for evaluating the independent efficacy and safety of new TCMs.

In summary, the diversity of clinical trial methods for TCMs provides abundant options for the evaluation of new TCMs. By rationally applying these designs, the effectiveness and safety of new TCMs can be comprehensively and objectively assessed, providing a solid scientific basis for their market approval and clinical application [13].

Quality Standards and Quality Control: To ensure the safety, efficacy and quality controllability of new Traditional Chinese Medicine (TCM) products, it is crucial to establish a comprehensive quality control system covering the entire production process of TCMs, from source control, process control, to endpoint control. This system aims to implement rigorous quality monitoring at every stage, from raw material procurement to finished product delivery, to ensure that new TCM products meet the established quality standards [14]. By constructing this full-process quality control system, the safety, efficacy and quality controllability of new TCM products can be comprehensively improved, providing robust support for the healthy development of the TCM industry [15,16].

Market entry for TCM (Natural plant) R&D results in China

Functional foods: Health foods have a clear legal definition and regulatory framework in China; however, there is currently no official definition for functional foods, which essentially remain ordinary foods. Functional foods are a type of food with specific health-promoting properties. Besides providing sufficient nutrition, they also have beneficial effects on the human body, possessing functions that ordinary foods do not have or do not emphasize, namely, the ability to regulate human physiological activities. Functional foods are suitable for both specific groups of people and healthy individuals. They regulate bodily functions without causing any acute, subacute, or chronic harm to the human body and are not intended for therapeutic purposes [17]. Functional foods in China still lack a clear legal definition and their regulation falls within the category of ordinary foods. There is no need for registration or filing before they are marketed, but functional claims cannot be made. Products primarily communicate with consumers by introducing their formulas and educating them about the functional ingredients.

Health food: Health food refers to food that claims and possesses specific health functions or is intended for supplementing vitamins and minerals. It is suitable for consumption by specific groups of people, has the ability to regulate bodily functions, is not intended for the treatment of diseases and does not cause any acute, subacute, or chronic harm to the human body [18]. In China, a "dual-track" management approach of registration and filing is adopted for health food [19]. For health food using raw materials not listed in the health food raw material directory and for first-time imported health food (excluding those supplementing vitamins, minerals and other nutrients), registration management is required. However, for products using raw materials already listed in the health food raw material directory and for first-time imported health food supplementing vitamins, minerals and other nutrients, only filing is required for marketing. The registration system requires animal or/and human trials, as well as toxicology tests; while products under the filing system do not need to undergo trials, adhering to the raw material directory and dosage requirements stipulated by the state.

Health food in China has a clear official definition and related regulations. Before being marketed for sale, products need to apply for and obtain a health food registration certificate or filing certificate, known as the "blue hat," and health food can make corresponding functional claims based on the registered or filed product information.

Currently, most nutritional supplements can be directly filed with a short approval cycle and low entry barriers, but the product function claims are monotonous and product homogeneity is severe. Specific functional health food can claim up to 24 functions stipulated by the state according to requirements (**Annex 1**) (**Table 5**).

Importing health food for sale through cross-border e-commerce does not require obtaining approval and the entry threshold is low, making it an important channel for imported health food to enter the domestic market. Products manufactured abroad only need to comply with the relevant standards and technical specifications of the country of origin. They do not need to obtain domestic registration certificates or filing certificates, meaning there is no need to apply for the "blue hat" certification. Instead, these products are sold domestically as ordinary food.

Medicines (Proprietary Chinese medicine ("pCm")): Due to the specificity of medicines, their marketing requires a stringent process, namely medicine registration (see **Annex 2, 3**). The ultimate goal of medicine research and development is to bring them to market. Different countries or regions may have varying registration requirements and procedures for medicines, but their basic principles are similar, namely evaluating the safety, efficacy and quality of the medicines [20]. This is the strictest and most difficult form of market entry. Thanks to the unique geographical location and policy advantages of the Guangdong-Hong Kong-Macao Greater Bay Area (GBA), as of March 2023, the Guangdong Provincial Drug Administration has issued 10 mainland medicine registration certificates for traditional external use pCm from Hong Kong and Macao, facilitating the entry of 920,000 bottles of these medicines into the mainland market of the GBA [21].

Ordinary food (Medicine-food homology): Medicine-food homologous products serve as a supplement to Traditional Chinese Medicine (TCM) health foods and represent an effective extension of the TCM health food industry. Both medicine-food homologous products and TCM health foods fall within the category of food, but they differ in terms of functions and applicable scopes. Medicine-food homologous products are ordinary foods that can be consumed by most people, but they cannot be promoted for their health benefits. In contrast, health foods are intended for specific populations and have the function of regulating human bodily functions [22].

Food for Special Medical Purpose (FSMP): Formula foods for special medical purposes refer to formulated foods specifically processed and prepared to meet the special nutritional or dietary needs of people with limited dietary intake, digestive and absorption disorders, metabolic disorders, or specific disease states. Both Formula Foods for Special Medical Purposes (FSMP) and health foods belong to the category of special foods. They have the effect of promoting health and cannot cause harm. Neither can they claim to treat diseases, nor can they replace drugs for therapeutic purposes (Table 6).

Regulatory frameworks for natural products outside the Greater Bay Area

European Union: The European Union (EU) is the most significant regional integration organization globally and the most mature market for herbal medicines in the West. In 2004, the EU issued the Traditional Herbal Medicinal Products Directive (2004/24/EC), which legally established the status of traditional herbal medicines and improved the registration management system for herbal medicinal products. Traditional medicines such as traditional Chinese medicines and herbal medicines are referred to as Herbal Medicinal Products (HMP) within the EU. There are three registration categories for HMP in the EU, including new HMP, well-established use HMP and traditional use HMP. To date, over 2,000 herbal medicinal product applications have been approved for marketing, whereas only a handful of Traditional Chinese Medicine products from China have successfully obtained approval in EU member states.

North America: Health Canada has a relatively high degree of recognition for Traditional Chinese Medicine (TCM), explicitly classifying it as a natural health product within the category of drugs [15]. Since the implementation of Health Canada's new "Regulations for the Registration of Natural Health Products" in 2019, several domestic TCMs, such as "Qingfei Paidu Granules" and "Xuanfei Baidu Granules," which were derived from the "Three Prescriptions" used in the fight against the pandemic, have successfully registered in Canada.

Approximately 85% of the TCM varieties approved in Canada are already marketed domestically. In terms of registration types, the traditional application route is the primary pathway for registering TCM compound preparations in Canada. Approximately 82% of the products use the China Pharmacopoeia and China's national drug standards as supporting evidence for efficacy, safety and/or quality controllability. Relatively few varieties are

Table 5. Types of health food products.

Nutrient supplements category of health food	Products that have been included in the health food raw material directory can be directly filed. Currently, the national health food raw material directory lists 88 raw materials, of which 83 are nutrient supplement raw materials. This means that most nutrient supplement products can be directly filed, resulting in a shorter product approval cycle and lower entry barriers.
Specific functional category of health food	Besides products using five functional raw materials such as Coenzyme Q10, Melatonin, Spirulina, Broken-Wall *G. Lucidum* Spore Powder and *Fish Oil* that can be directly filed, other products require registration. From the distribution of product functions that have already obtained registration approval, they are mainly concentrated on enhancing immunity, leading to issues of product homogeneity.

Table 6. Differences between FSMP and health foods.

	Purpose	Target Population	Ingredients
FSMP	To provide energy and nutritional support	Individuals with special medical conditions or special nutrient requirements	Proteins, fats, carbohydrates, various vitamins, minerals, etc.
Health Foods	To regulate bodily functions	Specific populations, such as individuals with low immunity, elderly people and those needing vitamin supplements	A wide variety of ingredients and in principle, they do not provide caloric energy

registered under the general (non-traditional) application type in Category III, which requires comprehensive evidence of efficacy, safety and quality.

Taiwan: Taiwan Traditional Chinese Medicines (TCMs) [16] refer to pharmaceuticals that do not include those that have been highly purified or chemically synthesized or modified, encompassing traditional Chinese medicines recorded in ancient texts, herbs used in folk medicine or by other countries and pharmaceuticals obtained through traditional or modern extraction methods. The Pharmaceutical Affairs Act [16] is the primary law in Taiwan regulating pharmaceuticals and medical devices. When applying for the registration of a TCM, if the product is a traditional prescription recorded in ancient texts, a non-traditional prescription already on the market, a new compound prescription that does not exceed the scope of traditional use experience, or a properly extracted or partially purified traditional prescription and if there is appropriate human use experience, this data can be used as the basis for directly entering into early-phase exploratory clinical trials for efficacy.

South Korea: In South Korea, plant medicines are classified into Korean medicine and crude drugs based on different medical theories. Korean medicine and modern plant medicines are regulated separately. Simplified registration procedures are adopted for traditional Korean medicines, which do not require clinical trials or pharmacological and toxicological data. However, for other new plant medicine products, complete clinical and non-clinical trial data are generally required.

Thailand: The requirements for registering Traditional Chinese Medicines (TCMs) in Thailand include: having an approval number from China; a free sale certificate; providing samples with a description of their main ingredients; a report on animal toxicity tests; and a clinical report. The requirements for the efficacy instructions and packaging of the medicines are as follows: the functions and indications should be simplified, medicines cannot be named using internal organs or diseases, advertising should not be excessive and efficacy should be stated in a straightforward manner. Registration fees are as follows: 500 Thai Baht for traditional medicines (which must be ancient or refined formulas from China); and 20,000 Thai Baht for new drug registrations. The classification of drug registrations includes: ancient formulas (which are superior quality medicines from classic Traditional Chinese Medicine formulas, manufactured according to traditional processing techniques); traditional medicines processed using modern methods (for which the active ingredients should undergo toxicological testing); naturally extracted drugs (where toxicology and pharmacology can be controlled); and new drugs.

Japan: In Japan, Kampo (Traditional Chinese Medicine) preparations are classified into Kampo preparations for medical use and Kampo preparations for general use. Currently, there are 148 types of Kampo preparations for medical use and 294 types of Kampo preparations for general use. The approval of Kampo medicines in Japan is primarily based on the "Criteria for Recognition of Kampo Preparations for General Use," from which the prescriptions of almost all Kampo preparations sold in the market are derived. This constitutes the foundation for the research and production of Kampo preparations in Japan [23].

According to the relevant requirements for drug registration in Japan, any enterprise can independently determine the finished dosage form, formulate the manufacturing process and establish quality standards within the scope of the prescription composition, dosage and administration, as well as indications specified in the "Criteria for Recognition of Kampo Preparations for General Use." Provided that water is used as the solvent in the manufacturing process, pharmacological and clinical studies can be exempted and a production license can be directly applied for. However, for new medical Kampo preparations that utilize other manufacturing processes or prescriptions not included in the criteria, it is necessary to provide a basis for the rationality of the prescription and conduct pharmacological, toxicological and clinical studies, which cannot be exempted [24].

The application materials required for traditional Chinese medicines (Kampo preparations) to enter the Japanese market generally include: [25]

1) The origin, source and discovery process of the prescription;

2) Usage and application situation in foreign countries;

3) Research results comparing its characteristics with other drugs;

4) Quality standards and drafting instructions;

5) General accelerated stability testing;

6) Acute toxicity testing (provide if necessary);

7) Subacute toxicity testing (provide if necessary);

8) Local irritation testing (provide if necessary);

9) Absorption testing (provide if necessary);

10) Excretion testing (provide if necessary);

11) Clinical trials.

United State of America: Botanical products are widely used in the United States and can be utilized as food, dietary supplements, drugs and cosmetics based on their labeling and intended use. Botanical products intended for diagnosing, curing, mitigating, treating, or preventing human diseases will be considered drugs and regulated accordingly. The "Guidance for Industry: Botanical Drug Product" issued by the FDA in June 2004 defines botanical drug products as drugs for therapeutic use prepared from botanical drug substances (including plant materials, algae, macroscopic fungi, or combinations of these), which can be formulated into various dosage forms such as solutions, powders, tablets, capsules, elixirs, topical preparations and injections. According to Section 505(b) of the Federal Food, Drug and Cosmetic Act in the United States, drugs must undergo new drug approval before they can be marketed.

The category of botanical drugs encompasses Botanical Drug Products (BDP), Botanical Raw Materials (BRM) and Botanical Drug Substances (BDS). According to the "Botanical Drug Development: Guidance for Industry" (December 2016, Revision 1) issued by the United States, botanical drugs include plant-based ingredients, algae, fungi and their mixtures. However, botanical drugs do not include: products containing animal or animal-derived ingredients or mineral components (except for Traditional Chinese Medicine preparations with trace amounts of such ingredients added); raw materials derived from genetically recombinant plants; fermented products; or highly purified components.

The FDA's new drug evaluation process consists of two main stages: the Investigational New Drug (IND) application and the New Drug Application (NDA). After completing preclinical studies of a new drug, the applicant can submit an IND to the FDA. If the FDA does not raise objections within 30 days of receiving the IND, the applicant may proceed with clinical studies of the new drug on their own.

Since botanical drug products are generally mixtures composed of multiple components, their chemical and active ingredients are often uncertain, their biological activities are not significant and they usually have extensive human use experience. Therefore, the clinical trial requirements for botanical drug products should be distinguished from those for chemical drugs. The Guidance takes these characteristics of botanical drugs into consideration and provides some relief from the requirements for Phase I and II clinical trials in the IND. However, the requirements for Phase III clinical trials and NDAs remain the same as those for chemical drugs [26,27].

Discussion

In recent years, the Guangdong-Hong Kong-Macao Greater Bay Area (GBA) has continuously released positive signals for the development of the Traditional Chinese Medicine (TCM) industry, with a series of favorable policies being introduced consecutively. For example, the "*Plan for the Construction of a TCM Highlands in the Guangdong-Hong Kong-Macao Greater Bay Area,*" the "*Work Plan for the Innovative Development of Drug and Medical Device Regulation in the Guangdong-Hong Kong-Macao Greater Bay Area*" (known as the "Hong Kong and Macao Medical Device Circulation"

policy) and the "*Interim Provisions on the Administration of Hong Kong and Macao Medical Products Urgently Needed for Clinical Use in the Guangdong-Hong Kong-Macao Greater Bay Area of Guangdong Province*" have provided robust support for the development of TCM in the GBA. The development of TCM in the GBA is positioned as an important platform for promoting the modernization and internationalization of TCM. By integrating resources, fostering innovation, nurturing talent and deepening cooperation, the GBA aims to become a highland integrating high-quality development in medical services, education, technology and industry. The TCM industry in the GBA is vast, covering various aspects such as the cultivation of TCM materials, TCM research and development, TCM manufacturing and TCM distribution.

The ultimate goal of pharmaceutical research and development is to bring a drug to market. Although there may be differences in the registration requirements and procedures for drugs among Guangdong, Hong Kong and Macao, the basic principles are similar, namely evaluating the safety, effectiveness and quality controllability of the drug [20]. Addressing the registration requirements of different countries or regions, comprehensively planning and implementing various research and tests for the drug, as well as preparing registration documents, are crucial for successful registration. As seen from the above introduction, drug registration (including Traditional Chinese Medicine) is a highly complex process that requires the participation of various professionals, such as pharmaceutical engineers, pharmacologists, toxicologists, clinicians and so on. At the same time, professionals familiar with the drug registration process are needed to summarize the research and tests and compile the drug registration materials.

The research focus of scientific researchers mainly lies on professional title evaluation, project applications and paper publication, with little attention paid to the practicality and scalability of scientific and technological achievements. Meanwhile, Traditional Chinese Medicine (TCM) enterprises lack the capacity to undertake technology transfer and struggle with introducing and assimilating scientific and technological achievements [23].

The drug approval policies, systems, procedures and requirements in Guangdong, Hong Kong and Macao vary and are not mutually binding. Drugs approved in one region cannot be circulated in the others, which restricts the allocation of market resources and is detrimental to industrial development, innovation capability enhancement and the transformation of research results.

Overall, the registration requirements for TCM in Hong Kong or Macao are lower than those of the National Medical Products Administration (NMPA) of China. In terms of registration strategy, priority should be given to registration in Hong Kong or Macao, as successful registration there will greatly benefit future registration applications in the Guangdong-Hong Kong-Macao Greater Bay Area. Understanding the drug registration management systems and regulatory frameworks in Guangdong, Hong Kong and Macao, promoting the alignment of their regulatory systems and accelerating the approval process for overseas products to enter the domestic market will effectively facilitate the implementation of the transformation of TCM research results.

Conclusion

The transformation of TCM research results faces both opportunities and challenges. By understanding the different registration systems in the Greater Bay Area, as well as international regulations, TCM researchers and developers can better navigate the complex pathways required to bring their innovations to market.

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Conflict of Interest

There are no conflicts of interest by authors.

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Appendix 1

List of non-nutrient supplements for health claims of health foods (2023 version).

1	Aids in enhancing immunity
2	Aids in anti-oxidation
3	Aids in improving memory
4	Alleviating visual fatigue
5	Soothes and moistens the throat
6	Aids in improving sleep
7	Alleviating physical fatigue
8	Tolerant to hypoxia
9	Aids in controlling body fats
10	Aids in increasing bone density
11	Improving iron-deficiency anemia
12	Aids in eliminating acne
13	Aids in eliminating skin chloasma
14	Aids in improving skin moisture condition
15	Aids in regulating intestinal microbiota
16	Aids in promoting digestion
17	Aids in promoting regular bowel movements
18	Aids in protecting the gastric mucosa
19	Aids in maintaining healthy blood lipid (cholesterol/triglyceride) levels
20	Aids in maintaining healthy blood sugar levels
21	Aids in maintaining healthy blood pressure levels
22	Providing auxiliary protective action against chemical liver damage
23	Provides auxiliary protective action against ionizing radiation hazards
24	Aids in lead excretion

Appendix 2

Documents required for domestic Chinese medicine registration.

Categories	Contents
Summary	(1) Drug name
	(2) Certificate documents
	(3) Purpose and basis of the study
	(4) Summary and evaluation of main research results
	(5) Draft drug instructions, drafting explanation and latest references
	(6) Draft designs of packaging and labeling
Pharmacy study materials	(1) Overview of pharmacy study materials
	(2) Source of medicinal materials and basis for identification
	(3) Ecological environment, growth characteristics, morphological description, cultivation or cultivation (breeding) techniques,

		processing methods at the place of origin and preparation methods
	(4)	Research materials (methods, data, images and conclusions) and literature on the properties, tissue characteristics and physicochemical identification of medicinal materials
	(5)	Provision of plant and mineral specimens, with plant specimens including flowers, fruits, seeds, etc.
	(6)	Research materials and literature on production processes, as well as sources and quality standards of excipients
	(7)	Experimental data and literature on confirming chemical structures or components
	(8)	Experimental data and literature on quality research
	(9)	Draft drug standards and drafting explanation, along with standard substances or reference substances
	(10)	Inspection reports of samples
	(11)	Experimental data and literature on drug stability studies
	(12)	Basis for selection and quality standards of packaging materials and containers that directly contact the drug
Pharmacology/toxicology study materials	(1)	Overview of pharmacology/toxicology study materials
	(2)	Main pharmacodynamics experimental data and literature
	(3)	Experimental data and literature on general pharmacology studies
	(4)	Acute toxicity experimental data and literature
	(5)	Long-term toxicity experimental data and literature
	(6)	Experimental studies and literature on special safety tests related to local and systemic administration, such as allergy (local, systemic and photosensitivity), hemolysis and local irritation (blood vessels, skin, mucosa, muscles, etc.)
	(7)	Mutagenicity experimental data and literature
	(8)	Reproductive toxicity experimental data and literature
	(9)	Carcinogenicity experimental data and literature
	(10)	Animal pharmacokinetic experimental data and literature
Clinical study materials	(1)	Overview of clinical study materials
	(2)	Clinical study plan and research protocol
	(3)	Clinical investigator's brochure
	(4)	Sample informed consent forms and approvals from ethics committees
	(5)	Clinical study reports

Appendix 3

Comparison of dossier requirements for registration of pCm between Mainland China and Hong Kong.

For Mainland China	For Hong Kong
Overview materials	General documents
Drug name	Completed Application Form & appropriate checklist
Certificatory documents	Application fee
Purpose and basis of the application	Personal information of the person-in-charge of the company
Summary and evaluation of major research results	Documentary proofs of manufacture or sales history of the product
Draft of drug instructions, drafting instructions and latest references	Copy of manufacturing authorization issued by the country of origin (if applicable)
Packaging and label design drafts	Copy of free sale documentation issued by the country of origin (if applicable)
-	Product sample and prototype sales pack
-	Label & package insert that have complied with the laws
-	Master formula
Pharmacological studies documents	Product quality documents
Overview of pharmacological studies documents	Manufacturing method
Source and identification basis of herbal materials	Physicochemical properties of crude drugs
Ecological environment, growth characteristics, morphological description, cultivation or cultivation (culturing) techniques, processing methods, etc. of herbal materials	Product specification, method and certificate of analysis
Draft herbal material standards and drafting instructions, with drug standard materials and related materials	Accelerated stability test report or general stability test report
Plant and mineral specimens (plant specimens should include flowers, fruits, seeds, etc.)	Real-time stability test report
Research materials on production processes, process validation materials and literature materials; source and quality standards of excipients	-
Experimental data and literature materials on chemical composition research	-
Experimental data and literature materials on quality research work	-
Draft drug standards and drafting instructions, with drug standard materials and related materials	-
Sample inspection report	-
Experimental data and literature materials on drug stability research	-
Basis for selection and quality standards of packaging materials and containers directly in contact with drugs	-

Pharmacological and toxicological studies documents	Product safety documents
Overview of pharmacological and toxicological studies materials	Heavy metals and toxic elements test report
Main pharmacodynamic test data and literature materials	Pesticide residues test report
Experimental data and literature materials on general pharmacological research	Microbial limit test report
Acute toxicity test data and literature materials	Acute toxicity test report
Long-term toxicity test data and literature materials	Long-term toxicity test report
Special safety test data and literature materials related to local and systemic administration, including allergenicity (local, systemic and photosensitivity toxicity), hemolysis, local irritation (blood vessels, skin, mucosa, muscles, etc.) and dependence	Local toxicity test report
Genotoxicity test data and literature materials	Mutagenicity test report
Reproductive toxicity test data and literature materials	Carcinogenicity test report
Carcinogenicity test data and literature materials	Reproductive and development toxicity test report
Animal pharmacokinetic test data and literature materials	Summary report on product safety documents
Clinical trial documents	Product efficacy documents
Overview of clinical trial materials	Interpretation and principle of formulating a prescription
Clinical trial plan and protocol	Reference materials on product efficacy
Clinical investigator's brochure	Principal pharmacodynamics studies report
Informed consent form draft and ethical committee approval	General pharmacological studies report
Clinical trial report	Clinical trial protocol and summary report
-	Summary report on product efficacy documents