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RESEARCH ARTICLE

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Comparative study on registration application of proprietary Chinese medicine in the Guangdong-Hong Kong-Macau Greater Bay Area of China

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ABSTRACT

Background: Proprietary Chinese medicine (PCM) is widely used in the Guangdong-Hong Kong-Macau Greater Bay Area (GBA) of China. However, the regulatory frameworks and procedures for PCM registration in the region are not well-established, and there are differences among the three jurisdictions. The study is aimed to compare the legal basis, regulatory guidelines, application requirements, and evaluation criteria in each jurisdiction.

Methods: We conducted a comprehensive review of the registration application processes for PCMs in the Chinese mainland, Hong Kong, and Macau based on publicly available information from respective regulators.

Results: The study found that the registration application process in the GBA was complex and time-consuming, with differences in requirements and procedures among the three jurisdictions. The study also identified several challenges faced by PCM manufacturers, such as the lack of harmonisation of regulatory requirements and procedures and the requirement of package inserts and labelling for PCM products. The study proposed recommendations for improving the registration process and promoting the development of the PCM industry in the GBA.

Conclusion: This study provides a comprehensive understanding of the PCM product license application procedures and requirements in the GBA, coupled with discernment of their similarities and disparities, equips applicants with the knowledge to formulate an appropriate strategy for obtaining product approval. Exploring potential methods for harmonising the regulatory process stands to benefit manufacturers, regulators, and patients by improving efficiency and curtailing costs.

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KEYWORDS Traditional and complementary medicine; proprietary Chinese medicine; traditional Chinese medicine; Chinese medicine regulation; Chinese medicine registration; product license application regulation

1. Introduction

In the context of contemporary demographic shifts, including aging populations and the increasing prevalence of chronic diseases and multi-morbidity, traditional and complementary medicine (T&CM) is poised to remain a vital component of primary health care (World Health Organization, 2018). T&CM is utilised by a significant majority of World Health Organization (WHO) Member States, with over 80% across all regions, and more than 90% in the Eastern Mediterranean, South-East Asia, and Western Pacific regions (World Health Organization, 2019). Traditional Chinese medicine (TCM) is considered a complementary or alternative medical system in Western countries, but it is an essential part of the health system in Asia (Chan et al., 2010). TCM has been integral part to the healthcare landscape for millennia, providing a holistic and systematic approach to maintaining health and treating disease (Xu & Yang, 2009). For example, the coronavirus disease 2019 (COVID-19) pandemic caused a terrible global health problem; TCM treated 91.5% of the COVID-19 cases in China, which showed promising results in improving symptoms and reducing disease deterioration, mortality, and recurrence rates (Luo et al., 2020). TCM is firmly rooted in the cultural fabric of Guangdong, Hong Kong, and Macau, where it enjoys widespread acceptance and application (Li et al., 2018).

The ambit of TCM encompasses an extensive array of items, including traditional Chinese medicinal materials, decoction pieces, proprietary Chinese medicine (PCM), herbal extracts, and healthcare products (Lin et al., 2018). PCM, also known as Chinese patented medicines, refers to TCM formulas or products manufactured and marketed by pharmaceutical companies or individual manufacturers as proprietary products. The composition of PCM may involve a blend of herbal medicines, animal parts, or minerals and is developed based on traditional Chinese medical theory and practices. PCM is frequently utilised to prevent and treat an array of health conditions, such as respiratory diseases, digestive disorders, and skin ailments. Nonetheless, the safety and efficacy of PCM products may vary depending on the manufacturing processes, quality control, and clinical evidence, which are overseen by national or regional authorities according to their respective regulatory frameworks.

In recent years, PCM has exerted a substantial economic influence, as evident in the burgeoning domestic and global markets. The China Customs statistics from 2017 to 2022 illustrate a generally upward trajectory in the combined value of imports and exports (Figure 1). Specifically, the total

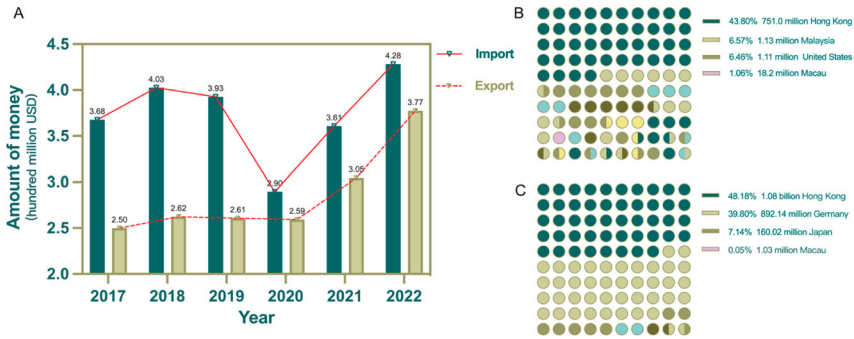

Figure 1. The overview value of import and export of PCM in the Chinese mainland from 2017 to 2022. A: Import and export trend of PCM; B: The PCM main import market overview; C: The PCM main export market overview.

trade volume of the import and export manifested a growth from 2017 to 2018, albeit with a slight reduction in 2019. The outbreak of the COVID-19 pandemic led to a noticeable downturn in 2020, mainly impacting the import values. Nonetheless, the year 2021 witnessed a progressive rebound in the total value of imports and exports, culminating in their peak levels during the observed period in 2022, with the figures standing at 4.282 billion USD and 3.775 billion USD, respectively (General Administration of Customs of the People's Republic of China, 2023).

This widespread use of PCM underscores the necessity for policy development, suitable legal frameworks, safety and monitoring systems, and the incorporation of T&CM products, practices, and practitioners into global health systems. However, the regulation of PCM has been a challenging issue due to the diversity of its products and the complexity of its manufacturing processes.

In the Guangdong-Hong Kong-Macau Greater Bay Area (GBA), which encompasses nine cities in Guangdong province, Hong Kong Special Administrative Region (HKSAR), and Macau Special Administrative Region (MSAR), PCM plays a significant role in the local healthcare industry (State Council of China, 2019; The National Administration of Traditional Chinese Medicine, 2020). Furthermore, the Chinese government and the authorities in Hong Kong and Macau have undertaken significant efforts to reform PCM regulations to ensure their safety, efficacy, and integration with modern healthcare systems (Li et al., 2018). Nevertheless, the regulatory frameworks and procedures for PCM registration in the GBA are not yet well-established, and there are differences among the three jurisdictions. Consequently, this situation poses challenges for PCM manufacturers who intend to register their products and promote their business in the GBA. Hence, there is a pressing need for a comparative study to identify the similarities and differences

among the regulatory frameworks and procedures for PCM registration in the region to provide recommendations for enhancing the registration process and promoting the development of the PCM industry in the GBA. This study endeavours to address the knowledge gap in the regulation of PCM in the GBA and offer insights into the regulatory challenges confronted by PCM manufacturers in the region.

2. Regulatory framework

The official guidelines and regulatory frameworks governing proprietary Chinese medicine in GBA can be accessed through the websites of their respective regulatory agencies (Bureau Macau Government Printing, 2023; Bureau Macau Pharmaceutical Administration, 2023; Center for Drug Evaluation National Medical Products Administration, 2023; Justice Hong Kong Department of, 2023; Kong Chinese Medicine Council of Hong, 2023; National Medical Products Administration, 2023a).

2.1. Legal basis and regulations

2.1.1. The Chinese mainland

In the legal system of the Chinese mainland, the legal documents concerning TCM can be classified into several categories according to different legislative bodies and the authority of the regulations. These include administrative laws and regulations, departmental rules, normative administrative documents, working documents, and others. The regulation of pharmaceuticals in the Chinese mainland is primarily based on the Pharmaceutical Administration Law of the People's Republic of China, which covers various aspects of pharmaceuticals, including their manufacture, distribution, and use (Standing Committee of the Thirteenth National People's Congress, 2019). There is no separate legislation regulating TCM and western medicine. The system of categorising and registering TCM, chemical drugs, and biological products was established based on the regulations on the management of drug registration.

The National Medical Products Administration (NMPA) of China derives its authority from the Pharmaceutical Administration Law of the People's Republic of China, as the principal supervisory body governing TCM in the People's Republic of China (Standing Committee of the Thirteenth National People's Congress, 2019). The NMPA, formerly known as the China Food and Drug Administration (CFDA), is an administrative entity that supervises the regulation of drugs and medical devices within China, explicitly including TCM. Its mandate includes ensuring the safety, efficacy, and quality of medical products within the country. The NMPA operates under the jurisdiction of the State Administration for Market Regulation (SAMR), a ministerial-level

department under the auspices of the State Council of the People's Republic of China. The Center for Drug Evaluation (CDE), a crucial division of the NMPA, serves as the technical reviewer of drugs throughout the various stages of research and development in China (National Medical Products Administration, 2019). The CDE's mandate encompasses the assurance of safety, efficacy, and quality control of pharmaceutical products, a scope that explicitly includes medications utilised within the framework of TCM. In addition to the NMPA, the National Administration of Traditional Chinese Medicine (NATCM) plays a pivotal role in regulating and developing the TCM industry (National People's Congress, 2018). The NATCM assumes an extensive range of duties, which incorporate policy planning, industrial management, and fostering international cooperation for TCM in China.

2.1.2. Hong Kong SAR

Based on the Article 138 of the Basic Law (HKSAR), 'The HKSAR Government shall, on its own, formulate policies to develop Western and Chinese medicine and to improve medical and health services' (The Basic Law of The Hong Kong Special Administrative Region of The People's Republic of China, 2021). Hong Kong began drawing up regulations with discussions and consultations with relevant stakeholders, including practitioners, academics, and industry representatives. These efforts culminated in the establishment of the Chinese Medicine Ordinance (Cap. 549) in 1999 (Hong Kong Legislative Council, 2018). Moreover, pharmaceutical regulation in Hong Kong is legislated based on different categories of pharmaceuticals, characterised by a parallel management structure. TCM is regulated by the Chinese Medicine Ordinance (Cap. 549), while Western medicine is subject to be controlled by the Pharmacy and Poisons Ordinance (Cap.138) (Hong Kong Legislative Council, 2015). Additionally, the regulations governing both TCM and Western medicine in Hong Kong are dispersed among five ordinances, including the Import and Export Ordinance (Cap.60), Public Health and Municipal Services Ordinance (Cap. 132), Undesirable Medical Advertisements Ordinance (Cap. 231), Trade Descriptions Ordinance (Cap. 362), and the Protection of Endangered Species of Animals and Plants Ordinance (Cap. 586) (Council Hong Kong Legislative, 2012; Council Hong Kong Legislative, 2019; Council Hong Kong Legislative, 2021; Hong Kong Legislative Council, 2012; Kong Legislative Council of Hong, 2021). The legal efficacy of various regulations is equivalent, allowing for horizontal supplementation and vertical refinement (Table 2).

The main regulatory authority for TCM in Hong Kong is divided into independent statutory bodies and government departments, primarily consisting of the Chinese Medicine Council and the Chinese Medicine Regulatory Office under the Department of Health within the Health Bureau. The Chinese

Medicine Council, established per the Chinese Medicine Ordinance (Cap. 549), comprises two boards and ten committees. It is responsible for overseeing the regulation of the Chinese medicine profession, ensuring the professional standard of Chinese medicine practice and the qualifications of practitioners. The Chinese Medicine Regulatory Office of the Department of Health is responsible for providing administrative and technical support to the Chinese Medicine Council and its affiliated boards and committees to implement regulatory measures related to the licensing of TCM practitioners and the registration of PCM.

2.1.3. Macau SAR

Before implementing the TCM Pharmaceutical Activities and Proprietary Chinese Medicines Registration Law (Law No.11/2021) in 2022, the Macau SAR adopted a pre-licensing system for pharmaceuticals (Bureau Macau Pharmaceutical Administration, 2021). With the implementation of the new legislation, the regulation of PCM in Macau has entered a comprehensive registration-based supervision system. The legal system for drug regulation in Macau comprises laws and regulations, technical directives, and administrative instructions. Decree No. 59/90/M establishes the pre-registration system for pharmaceuticals, while Decree No. 58/90/M regulates pharmaceutical activities (Governor of Macau, 1990; Legislative Assembly of Macau, 1990). Laws No. 7/89 and Decree No. 30/95/M establish the regulatory system for pharmaceutical advertising (Governor of Macau, 1995; Legislative Assembly of Macau, 1989). Law No. 7/2003 requires an import pre-approval certificate from the Drug Administration for the import of goods such as pharmaceuticals, PCMs, and Chinese medicinal materials (Macau Legislative Assembly of, 2003). Laws No. 4/2014, No. 10/2016, No. 22/2020, and No. 10/2021 all regulate anesthetics and psychoactive drugs. Law No. 12/2022 specifically regulates toxic substances in hazardous materials (Legislative Assembly of Macau, 2022). Subsequent Decree No. 20/91/M, Administrative Regulation No. 1/2009, and Administrative Regulation No. 21/2003 modify Decree No. 58/90/M. Law No. 3/2016 amends Law No. 7/2003 on foreign trade. The laws and regulations related to TCM in Macau are numerous, high-level, and systematic, but the structure is relatively loose.

According to detailed implementing rules (Administrative Regulation No.46/2021) for Law No.11/2011, the Pharmaceutical Administration Bureau is the government department established for drug supervision and management, comprising five offices and six divisions. The Pharmaceutical Administration Bureau is supervised by the Secretariat for Social Affairs and Culture. Its subordinate Registration Office is responsible for the registration of pharmaceuticals, including TCM, as well as the coordination and approval of registration for small-scale medical devices.

Table 1. Comparison of regulatory framework proprietary Chinese medicine in the Chinese mainland, Hong Kong, and Macao.

	Chinese mainland	Hong Kong SAR	Macau SAR
Definition	Proprietary Chinese medicine refers to a category of drugs that are processed or extracted from TCM using certain formulas, and made into certain specifications, which can be directly used for disease prevention and treatment, such as various pills, powders, and granules.	Proprietary Chinese medicine means any proprietary product – (a) composed solely of the following as active ingredients – (i) any Chinese herbal medicines; or (ii) any materials of herbal, animal or mineral origin customarily used by the Chinese; or (iii) any medicines and materials referred to in subparagraphs (i) and (ii) respectively; (b) formulated in a finished dose form; and (c) known or claimed to be used for the diagnosis, treatment, prevention or alleviation of any disease or any symptom of a disease in human beings, or for the regulation of the functional states of the human body;	Proprietary Chinese medicines refer to preparations composed of one or more Chinese medicine ingredients, which are prepared and used according to the theory of TCM and applied to the human body to prevent, treat diseases or alleviate their symptoms.
Regulatory authority	National Medical Products Administration (NMPA)	Chinese Medicine Council Chinese Medicine Regulatory Office	Pharmaceutical Administration Bureau
Classification category	1. Innovative TCM 2. Modified new drug of TCM (MND TCM) 3. Classical Chinese formula pharmaceutical preparations (Classical Chinese formulations, CCF) 4. TCM with the same name and prescription	1. Established medicines 1.1 An ancient prescription 1.2 A modified ancient prescription 1.3 A pharmacopoeia prescription 1.4 other prescriptions originated from the National Drug Standards of the People's Republic of China 2. Non-established medicines 2.1 Health-preserving medicines 2.2 Other medicines 3. New medicines	1. TCM with the same name and prescription 2. Classical Chinese formula pharmaceutical preparations (Classical Chinese formulations, CCF) 3. Modified new drug of TCM 4. Innovative TCM

2.2. Definition and classification

PCM holds distinct definitions across the Chinese Mainland, Hong Kong, and Macau, reflecting variations in the legal and regulatory frameworks of the three regions.

Table 2. Legal basis for control of Chinese medicine

Classification	The Chinese mainland	Hong Kong SAR	Macau SAR
Health	Drug Administration Law (August 27, 2019)	Chinese Medicine Ordinance (Cap. 549)	TCM Pharmaceutical Activities and Proprietary Chinese Medicines
	Regulations for the Implementation of the Drug Administration Law of the People's Republic of China (March 2, 2019)	Chinese Medicine (Fees) Regulation (Cap. 549E)	Registration Law (Law No. 11/2021)
	The Provisions for Drug Registration (January 22, 2020)	Chinese Medicines Regulation (Cap.549F)	Detailed Implementation Rules for the TCM Pharmaceutical Activities and Proprietary Chinese Medicines Registration Law (Administrative Regulation No. 46/2021)
	the Law of the People's Republic of China on TCM (December 26, 2016)	Chinese Medicines Traders (Regulatory) Regulation (Cap. 549G)	Regulates the Activities of the Pharmaceutical Profession and the Pharmaceutical Industry (Decree No. 58/90/M)
		Pharmacy and Poisons Ordinance (Cap. 138)	(Decree No. 20/91/M)
			(Administrative Regulation No. 21/2003)
			(Administrative Regulation No. 1/2009)
			Establishes and Regulates the Registration of Pharmaceuticals Used in Macau (Decree No. 59/90/M)
Trade	Regulations on the Management of Imported Medicinal Materials (May 16, 2019)	Import and Export Ordinance (Cap. 60)	Foreign Trade Law (Law No. 7/2003)
			Amendment to Law No. 7/2003, 'Foreign Trade Law' (Law No. 3/2016)
Commercial	Advertising Law of the People's Republic of China (April 29, 2021)	Public Health and Municipal Services Ordinance (Cap. 132)	Establishes A Series of Rules Regulating Advertising Activities (Law No. 7/89/M)
		Trade Descriptions Ordinance (Cap. 362)	Establishes the Legal System for Pharmaceutical Advertising (Decree No. 30/95/M)
		Undesirable Medical Advertisements Ordinance (Cap. 231)	
Environment	Regulations on the Protection of TCM (September 18, 2018)	Protection of Endangered Species of Animals and Plants Ordinance (Cap. 586)	Regulatory System for Hazardous Goods (Law No. 12/2022)

After comparing the definition provided in Table 1, several commonalities and differences can be identified. First, all three regions acknowledge PCM as preparations or products derived from TCM ingredients. And all definitions encompass the use of these medicines for disease prevention, treatment, and symptom alleviation. Besides, PCM should be prepared in a finished dose form, which is well acknowledged. The definition from Macau, similar to the one from the Chinese Mainland, does not explicitly mention the

types of ingredients that can be used. However, it does emphasise that the preparations of PCMs are done according to the theory of TCM, which is not explicitly stated in the definitions from the Chinese mainland and Hong Kong. The definition provided by Hong Kong is more explicit about the types of ingredients that can be used as active ingredients, which include Chinese herbal medicines and materials of herbal, animal, or mineral origin customarily used by the Chinese. It also explicitly mentions the use of PCM for the diagnosis of diseases and for the regulation of the functional states of the human body, which are not clearly stated in the definitions from the Chinese mainland and Macau.

According to the special provisions for TCM Registration (No. 20, 2023) and Classification of TCM Registration and Requirements for Application Materials (No. 68, 2020), the classification category of PCMs are classified into four categories based on their ingredients and usage history in the Chinese mainland (National Medical Products Administration, 2020; National Medical Products Administration, 2023b). The first three types all belong to new Chinese medicine. The fourth category of drugs with the same name and same prescription is similar to the concept of generic drugs in Western medicine, but it places more emphasis on the comparison of research results rather than the consistency of quality standards. Macau also has four same categories as the Chinese mainland, whereas Hong Kong divides its PCMs into three main categories. The Chinese mainland and Macau's classification both include TCM with the same name and prescription as a separate category, while this is not a distinct category in Hong Kong's system. However, Hong Kong includes a specific category for health-preserving medicines, which is not explicitly mentioned in the Chinese mainland or Macau classifications. An exceptional aspect of the regulatory framework in Hong Kong concerning PCM lies in its distinctive registration groups, which exist alongside classification categories. Both established and non-established medicines can apply for registration under Group I, II, or III. In contrast, new medicines are restricted to applications under Group III only. The requirements for data submission escalate from Group I to Group III, with Group I necessitating the least amount of information and Group III demanding the most extensive data provision. This particular stratification of the registration process underscores the sophistication and rigor of Hong Kong's regulatory approach to PCM.

2.3. Schedule of Chinese material

PCMs have diverse sources, primarily originating from traditional Chinese medical practices. The sources can be categorised into three main groups: (a) herbal materials; (b) animal-derived materials; and (c) mineral materials. In addition to these traditional sources, some PCMs may also include ingredients derived from modern pharmaceutical processes, such as extracts, or

concentrates produced using advanced equipment and techniques. The first part of the 'Pharmacopoeia of the People's Republic of China' contains traditional Chinese medicinal materials and decoction pieces, plant oils and extracts, formulated preparations, and single-flavor preparations. The, 2020 version includes 2711 types of TCMs, which serve as the common basis for the inspection of drugs by the production, supply, use, and management departments of PCMs (National Medical Products Administration; National Health Commission of the People's Republic of China, 2020). The Chinese Medicine Ordinance (Cap. 549) was passed by the Hong Kong Legislative Council on July 14, 1999, and Schedule 1 and Schedule 2 of Cap.549, respectively list 31 kinds of potent/toxic Chinese medicinal materials and 574 kinds of commonly used Chinese medicinal materials. All Chinese medicinal materials in Schedule 1 and 5 kinds of Chinese medicinal materials in Schedule 2 (namely 威靈仙 Veratrum nigrum, 凌霄花 Campsis grandiflora, 製川烏 processed Aconitum carmichaelii, 製草烏 processed Aconitum kusnezoffii, and 龍膽 Gentiana scabra) must be subject to import and export control. However, since Schedules 1 and 2 were compiled, the 'Chinese Pharmacopoeia' has been updated and published five times, yet there have been no changes to Schedules 1 and 2 (Hong Kong Legislative Council, 2018). According to Directive No. 95/2021 of the Secretary for Social Affairs and Culture, the 'List of Chinese Medicinal Materials Used in the Macao Special Administrative Region' was revised in 2021 and divided into three categories. Table I includes 31 kinds of prescription toxic Chinese medicinal materials, Table II-A includes 101 kinds of prescription common Chinese medicinal materials, and Table II-B includes 485 kinds of non-prescription common Chinese medicinal materials (Directive No. 95/2021 of the Secretary for Social Affairs and Culture, 2021).

Upon comparison of List 1 in Hong Kong and Table 1 in Macau, we notice a discrepancy in the classification of certain medicinal ingredients. Specifically, two kinds of Chinese medicinal materials, namely Radix or Rhizoma Podophylli emodis (also known as 鬼臼, 桃耳七, or 八角蓮) and Radix Sophorae Tonkinensis (山豆根), are categorised as toxic in Hong Kong (falling under Schedule-1 toxic Chinese medicinal materials), whereas they are not recognised as such in Macau, where they are classified under Table II-A as common prescription Chinese medicinal materials. Conversely, two medicinal materials, Euphorbiae Pekinensis Radix (京大戟) and Genkwa Flos (芫花), are classified as toxic in Macau (falling under Table I toxic Chinese medicinal materials) but are not recognised as toxic in Hong Kong. In Hong Kong, they are classified under Schedule 2 as commonly used Chinese medicinal materials. Further, seven kinds of medicinal materials exhibit discrepancies in the categorisation based on their processing state. For instance, Hong Kong distinguishes between Unprocessed and Processed Fructus Crotonis (巴豆). The unprocessed form (生巴豆) is listed as a toxic medicinal material

in Hong Kong, whereas its processed counterpart (製巴豆) is included in the list of commonly used medicinal materials. In contrast, Macau does not differentiate between the processed and unprocessed forms of Fructus Crotonis; instead, it classifies Crotonis Fructus as a whole as a toxic medicinal material.

3. Registration system of proprietary Chinese medicine

3.1. Basic requirements for PCM registration

In the Chinese mainland and the Macau Special Administrative Region (SAR), the registration of Classical Chinese Formulations (CCFs) necessitates adherence to several requirements. Firstly, these formulations must align with the catalogs provided by national authorities, such as the 'Catalogue of Ancient Classic Prescriptions (First Batch)' discussed in section 3.1, or other sources of compound preparations (3.2) (National Medical Products Administration, 2023a). In addition, the composition of a classic compound formulation should exclude any ingredients recognised as contraindicated, severely toxic, or toxic. The contraindications are derived from the 'Eighteen Antagonisms' and 'Nineteen Fears', while ingredient toxicity is informed by the 'Regulations for the Management of Toxic Drugs for Medical Use' and the 'List of Chinese Materia Medica Used in the Macau Special Administrative Region' (Department of Social Culture, 2021; State Council, 1988).

Regarding the registration of TCM in Hong Kong, the inclusion of Western medicine ingredients is strictly prohibited. If such ingredients are present, the formulation falls under the purview of the 'Pharmacy and Poisons Ordinance' (Cap.138) and is ineligible for TCM registration (Hong Kong Legislative Council, 2015). Moreover, the product must meet three safety benchmarks: heavy metals or toxic elements, pesticide residues, and microbial limits should not exceed prescribed standards. If the formulation is consumed as food, does not claim therapeutic or health benefits, and contains medicinal ingredients also classified as food, it is considered food. As such, it is governed by the 'Public Health and Municipal Services Ordinance' (Cap.132) and is ineligible for TCM registration (Council Hong Kong Legislative, 2019). Similarly, external preparations used for cleaning, elimination, skincare, and beauty purposes that make no therapeutic or health claims are subject to the 'Consumer Goods Safety Ordinance' (Cap.456) and are also ineligible for TCM registration (Hong Kong Legislative Council, 2020).

3.2. Registration dossier requirements (general, safety, efficacy and quality)

The Common Technical Document (CTD) is a set of specification for application dossier for the registration of medicines and is designed to be used

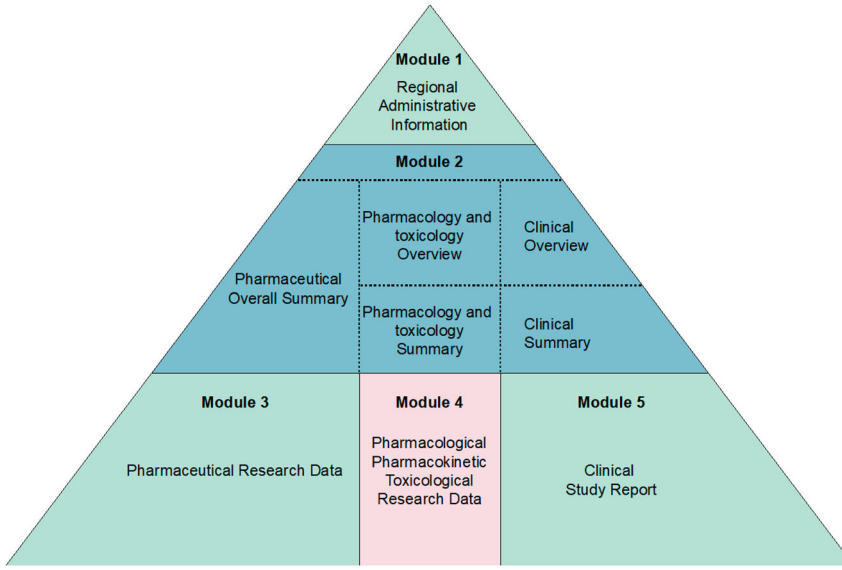

Figure 2. The Common Technical Document (CTD) triangle for TCM.

across Europe, Japan, and the United States. It's harmonised among the regulatory agencies to streamline the process. However, the application of CTD in TCM is a unique challenge because of the complex nature and historical background of TCM. We conducted a common format for TCM application based on the concept of integrating the diverse regulatory environments of the GBA (Figure 2).

The general dossier requirements for PCM registration vary significantly across the Chinese mainland, Hong Kong, and Macau (Table 3). The Chinese mainland necessitates comprehensive product-related materials and certification documents, emphasising the product's heritage and quality assurance. Supplementary information, including applications for accelerated market registration and post-marketing studies, is also considered. Hong Kong's requirements, while less extensive, focus on practical business aspects such as the manufacturing history, sales documentation, and compliance with local laws. Macau's requirements, on the other hand, prioritise international compliance and standards, demonstrated by the mandate for ISO17025, CMA, or CNAS certification for inspection institutions, and the requirement of documents proving adherence to international conventions like the Convention on International Trade in Endangered Species of Wild Fauna and Flora.

For product safety, both Hong Kong and Macau necessitate reports on heavy metals, toxic elements, pesticide residues, and microbial limits – criteria not obligatory in mainland China. However, acute and chronic toxicity test reports are mandatory across all three regions, with the mainland further

Table 3. Comparison of the general dossier requirements

The Chinese mainland				Hong Kong			Macau			
I	II	III	IV	Group I	Group II	Group III	I	II	III	IV
1. Explanatory letter 2. Table of contents 3. Completed application form. 4. Product information-related materials (package insert, packaging labels, product quality standards and production process, key information of ancient classic prescriptions, application materials for approval of the generic name of the drug, inspection-related information, product-related certification documents, and other product information-related materials) 5. Application status (if applicable) 6. Application for accelerating the market registration process (if applicable) 7. Communication meeting (if applicable) 8. Clinical trial process management information (if applicable) 9. Drug vigilance and risk management (if applicable) 10. Post-marketing study (if applicable). 11. Certification documents of the applicant/ manufacturer. 12. Proof of small and micro enterprises (if applicable)				1. Completed Application Form & appropriate checklist 2. Application fee 3. Personal information of the person-in-charge of the company 4. Documentary proofs of manufacture or sales history of the product 5. Copy of manufacturing authorisation issued by the country of origin (if applicable) 6. Copy of free sale documentation issued by the country of origin (if applicable) 7. Product sample and prototype sales pack 8. Label & package insert that have complied with the laws 9. Master formula			1. Completed specialised application form for PCM 2. Identification information and relevant documents of the applicants 3. Copy of declaration of the right to submit a registration application (if applicable) Copy of registration authorisation issued by the country of origin (if applicable) 4. Prototype of package, label, the sample of package insert (The specific source of the prescription and the main function of the treatment must be explained in the package insert of Classic Chinese Formulation, and the daily dose of the prescription medicine should be noted) 5. Sample inspection report. (Inspection institutions must have obtained ISO17025, China metrology accreditation (CMA) or China national accreditation service for conformity assessment (CNAS) certification-related inspection qualifications) 6. Copy of manufacturer's production license issued by country or region (if applicable) 7. Contract manufacturing permission (if applicable)			

(*Continued*)

Table 3. Continued.

The Chinese mainland				Hong Kong			Macau			
I	II	III	IV	Group I	Group II	Group III	I	II	III	IV
							8. Copy of free sale documentation issued by the country of origin (if applicable) 9. Document proving compliance with the convention on international trade in endangered species of wild fauna and flora. 10. Patent protection declaration (if applicable) 11. Data protection declaration (if applicable)			

stipulating irritation, allergy, hemolysis, and toxicological summary reports. Mutagenicity, carcinogenicity, and reproductive toxicity reports are mandated for Hong Kong Group III and mainland Classes III and IV but are exempted for Hong Kong Groups I and II.

Concerning product efficacy, all regions call for a rationale behind the prescription formulation and supporting efficacy materials. Primary and secondary pharmacodynamics studies, safety pharmacology reports, and clinical trial summaries are needed for Hong Kong Group III and mainland Classes III and IV, excluding Hong Kong Groups I and II.

Regarding product quality documentation, all regions require information on the manufacturing method, physicochemical properties of crude drugs, and product specification, method, and certificate of analysis. Accelerated stability test reports are required by all regions except Hong Kong Groups II and III, while real-time stability test reports are required by all regions except Hong Kong Group I.

In summary, there is considerable overlap among the regions but also crucial differences, with the Chinese mainland typically requiring more comprehensive documentation, particularly in product safety and efficacy. Hong Kong has a tiered system (I, II, III) with increasing requirements. Macau's requirements tend to be more streamlined, falling somewhere between Hong Kong Group I and II for most categories.

3.3. Technical guidelines

In the Chinese Mainland, there are 124 guidelines divided into eight primary categories. These encompass everything from administrative processes and

drug information technology to specialised directives for particular diseases and specific populations (Appendix 1, Table S1). Of particular note is the dedicated emphasis on TCM, with distinct guidelines delineating pharmaceutical research, clinical research, and even repeat guidelines for the clinical research of TCM. Such granularity and depth suggest a comprehensive and detailed approach to regulating TCM in the Mainland, reflecting its deep-rooted history and widespread usage within the region.

Contrastingly, Hong Kong's approach, with a total of 43 guidelines, is more streamlined and centres primarily on the PCMs (Appendix 2, Table S2). The Hong Kong SAR guidelines are grouped into three main categories, emphasising the registration of these PCMs, the licensing of Chinese medicine traders, and the adherence to Good manufacturing practice (GMP) specific to PCMs. This focused approach underscores Hong Kong's commitment to ensuring the quality and standardisation of PCMs while also promoting a sustainable trade ecosystem within its borders.

Macau SAR has formulated 34 technical guidelines, with a distinct focus on drug and TCM importation and quality assurance (Appendix 3, Table S3). Key directives, like the 'Documents to be Submitted Prior to Approval of Drug Importation' (Technical Directive No. 02/2000) and guidelines on Radiopharmaceutical and Western Medicine Packaging, emphasise rigorous importation standards and information transparency. Additionally, several directives target TCM specifics, ensuring standardisation and scientific rigour in practices. Complementing these are 12 administrative directives that offer procedural clarity, such as the 'Prohibition on the Production, Import, and Sale of Aristolochia medicinal materials' (No. 6/SS/2004) and a unique provision for Proprietary Chinese Medicines from Hengqin, signifying regional cooperation (No. 191/2021 Administrative Chief Directive).

3.4. Package inserts and labelling for proprietary Chinese medicines

The Chinese mainland guidelines encompass advisories related to components, dosage, specific consumer demographics, potential adverse effects, and precautions. They caution against the excessive or prolonged consumption of particular ingredients and contraindicate usage for certain demographics, such as athletes, pregnant or nursing women, and infants. The policy also stipulates that if certain elements (contraindications, adverse reactions, precautions) within the TCM manual remain ambiguous after three years post the current regulation's enforcement, the product will be denied re-registration (National Medical Products Administration, 2023b). Additionally, it mandates explicit delineation of details pertaining to the incorporated substances or auxiliary materials, administration protocol, usage and dosage, potential risks, drug interactions, and storage procedures.

Hong Kong's regulations mirror those in the Chinese mainland, albeit with greater specificity. The label on a medicinal package must feature information such as the medicine's name, active ingredients, country of origin, registration number, certificate holder's name, packaging specifications, dosage and administration method, expiration date, and batch number (Administration National Medical Products, 2022). Likewise, an accompanying leaflet should encapsulate many identical details along with supplemental information concerning the medicine's functions or pharmacological properties, indications, contraindications, side effects, toxic effects, usage precautions, and storage guidelines.

Similar to the other regions, Macau enforces particular regulations to maintain the accuracy and precision of the content on the packaging, labels, and instruction manuals of medicines (Pharmaceutical Administration Bureau, 2022). The content must be presented in Chinese or Portuguese, and disseminating misleading or false information is prohibited. The typography on the packaging, labels, and instruction manuals should be clear, legible, and precise, with sufficient contrast between the text and the background to ensure readability. The use of transient pigments in printing is discouraged. The measurement units must adhere to international standards.

4. Discussion

One of the primary challenges confronting manufacturers is the absence of standardisation in regulatory requirements across different regions. In some instances, the requisite documentation bears significant similarity, while in others, it diverges considerably. The classification criteria for PCM registration in the Chinese mainland and Hong Kong differ, but both rely on judgments grounded in the historical records of PCMs and encompass evidence of safety, efficacy, and quality. The distinction lies in the nature of evidence required for submission. Given the disparity between population and market size, manufacturers might question the cost-effectiveness of complying with each specific standard and evidentiary requirement set by individual regions. Distinct cities within the GBA adhere to diverse healthcare regulations, and harmonising these disparate regulatory frameworks poses a formidable challenge. Furthermore, securing the necessary approvals for PCM registration can be not only time-consuming but also financially burdensome.

However, with the advent of Macao's comprehensive registration system for TCM and the Chinese mainland's introduction and reform of the Drug Registration Management Measures in 2020, there have been significant strides towards regulatory harmonisation. In August 2021, the NMPA sequentially issued the 'Interim Provisions on the Management of Imported Hong Kong and Macao Drugs and Medical Devices Urgently Needed in Clinical Practice in the Mainland of the Guangdong-Hong Kong-Macao Greater Bay Area'

and the 'Notice of the Guangdong Provincial Drug Administration on Simplifying the Registration Approval of Traditional External Chinese Medicines Already on the Market in Hong Kong and Macao' (Guangdong Provincial Drug Administration, 2021; National Medical Products Administration, 2021). As a result of these measures, drugs, medical devices, and external TCMs registered in Hong Kong and Macao can now be listed in Guangdong under certain conditions via a simplified approval process. Consequently, the registration systems for TCMs in Guangdong, Hong Kong, and Macao are demonstrating a progressive trend towards convergence.

The registration application materials for TCM in Hong Kong and Macao necessitate the inclusion of test reports pertaining to heavy metals, pesticide residues, and microbial limits. The successive iterations of the 'Pharmacopoeia of the People's Republic of China' have instituted a detection system for heavy metals and detrimental elements in TCM, progressively stipulating limit standards for different variants of TCM. This has proven instrumental in the cultivation, processing, production, and market circulation of TCM. However, diverging from the heavy metal limit requirements in Hong Kong and Macao, the 'Pharmacopoeia of the People's Republic of China' does not dictate a uniform limit for all TCMs. Instead, it prescribes separate limits according to different varieties and furnishes uniform limit guidance values for herbal medicines. Compared to the element limit established in Hong Kong and Macao, the existing limit standard system in the Chinese mainland is moderately stringent. Yet, the 2020 edition of the 'Pharmacopoeia of the People's Republic of China' only designates the limits of heavy metals and harmful elements in 28 types of TCMs. This suggests that the scope of monitoring is currently still quite restricted.

The classification of a medicinal ingredient as a prescription toxic Chinese medicinal substance significantly influences the accessibility of PCM after registration. Specifically, when seeking to register a CCF in the Chinese mainland and Macau, it is imperative to strictly eschew the inclusion of toxic medicinal materials. In addition, a PCM composed of ingredients classified as prescription toxic Chinese medicinal substances is typically subject to prescription-only access upon successful registration. This restriction means that such a PCM can only be procured and used under the supervision of a licensed healthcare professional. This strategy ensures the safe and appropriate use of potentially harmful substances and underscores the focus on patient safety and effective treatment in PCM. However, this classification could impact the marketing strategies of the respective PCM product. It also brings to light the inconsistencies in regional regulations concerning the classification of medicinal ingredients based on their processing status. These variations emphasise the differences in regulating and classifying Chinese medicinal ingredients across regions, underscoring the need for harmonised regulatory measures to ensure patient safety and treatment efficacy.

In a comprehensive review of PCMs registrations across different Chinese jurisdictions, mainland China currently lists 59,474 PCMs, with 9,629 in active market circulation, and 1,381 incorporated into the latest national medical insurance drug list (Chun-miao, 2022; Security National Medical Insurance Administration & Ministry of Human Resources and Social, 2023). In contrast, since the initiation of its PCM registration system in 2003, Hong Kong circulates 8,097 PCMs, with 4,832 registered and 3,265 under transitional registration (Chinese Medicine Council of Hong Kong, 2023). Macau, transitioning from a pre-licensing to a registration system in 2022, has 3,861 PCMs in circulation (Bureau Macau SAR Pharmaceutical Administration, 2023). Notably, out of 118 registration applications in Macau, only 20 PCMs are registered, indicating potential regulatory or market dynamics affecting PCM registration and circulation (Macao Daily News, 2023). In response to the distribution of PCMs, Macau has instituted a transitional framework akin to that of Hong Kong, granting a five-year extension to PCMs previously authorised for distribution in Macau prior to compulsory registration. When Hong Kong first introduced its comprehensive registration protocol, it designated June 30, 2009, as the cut-off for transitional registration, thus allotting a four-and-a-half-year grace period. Nevertheless, the process experienced multiple postponements due to the scant number of PCMs achieving successful registration (Office of The Ombudsman Hong Kong, 2018). Consequently, regulatory agencies have further extended these deadlines on numerous occasions. Presently, a significant volume of PCMs continues to be distributed under the aegis of transitional registration. As Macau moves forward with its transitional framework for PCMs distribution, it stands to gain insights from Hong Kong's experiences. The decision to provide a five-year extension reflects a measured approach, taking into account the challenges encountered elsewhere. Yet, the recurring extensions in Hong Kong underscore the inherent complexities associated with registering PCMs. It is likely that Macau will need to invest in building capacity for a streamlined registration process, raising awareness about the standards expected, and providing support for suppliers to meet those standards. Moreover, given the global interest in PCM, there's potential for Macau to set a precedent in creating an efficient and robust regulatory framework for PCM distribution, possibly even serving as a model for other regions.

In this study, our analysis revealed implications for key stakeholders in proprietary Chinese medicine, notably manufacturers, regulators, and patients. For manufacturers, our comprehensive analysis of the regulatory framework and market dynamics offers crucial insights for strategic alignment with regulatory requirements and market trends, potentially guiding innovation and product development that meet emerging health needs. The similarities and differences in the legal systems and regulatory framework of Guangdong, Hong Kong, and Macau can provide valuable

references for regulators. Before implementing reforms or enacting policies, drawing on the three regions' practical experiences can help avoid wasting resources and time. Most importantly, for the regulatory coordination of traditional Chinese medicine products, a harmonised registration process can enhance the accessibility and safety of these products, allowing patients to receive more assured PCMs in a shorter time frame. This not only aids in safeguarding public health but also empowers patients with informed choices in their healthcare. Collectively, these insights contribute to advancing the TCM field, offering a foundation for future research and policy development to optimise the benefits of TCM for all stakeholders involved.

There is a potential limitation of this study that worth noting. In mainland China, the legal and regulatory framework for traditional Chinese medicine registration is divided into national and provincial levels. This study mainly placed focus on the nation-level policy and measures to TCM regulation and registration. However, more specific policies, mentation plans, and initiatives are often formulated and carried out at the provincial level in China. For example, Guangdong Province has enacted local regulations such as the 'Guangdong Provincial Traditional Chinese Medicine Regulations' and departmental rules like the 'Detailed Rules for the Registration and Record-Filing of Medical Institution Preparations in Guangdong Province.' (Drug Administration of Guangdong Province, 2022; People's Congress of Guangdong Province, 2021) Exclusion of this aspect of policy responses in Guangdong province may prevent us from obtaining a comprehensive understanding of the policy landscape regarding TCM regulation.

5. Conclusion

A comprehensive understanding of the PCMs product license application procedures and requirements in the GBA, along with an appreciation of their similarities and differences, will empower applicants to devise a suitable strategy for securing product approval. Investigating avenues for harmonising the regulatory process has the potential to benefit manufacturers, regulators, and patients by enhancing efficiency and reducing costs.

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