Chinese Traditional Medicine Journal

ISSN: 2693 6356
2024 | Vol 7 | Issue 1

# Integrating traditional Chinese (herbal) medicines into risk-based regulation - With focus on non-clinical requirements to demonstrate safety

Vivian Liu. nqan Fung

*Independent Scholar, 2 Woodward Place, St Ives, NSW, 2075, Australia*

***Keywords:***
**Proprietary and traditional Chinese herbal medicines**
**Internationalization Nonclinical**
**Drug regulation and registration reform Certificate of pharmaceutical product**

**Abstract—**

All parties involved in Hong Kong's (China) public health system agree that TCM plays a significant role. The government, academic institutions, and industry of Hong Kong (China) must work together if the city is to play a pivotal role in exporting Chinese pharmaceuticals to international markets. The opportunity for well-established and traditional herbal medicines to demonstrate a 'acceptable safe' status for registration in the European Union has been opened up with the release of the final version of the European Medicines Agencies guidance document. This document details the acceptance of minimum requirements to nonclinical packages in bibliographical applications. Regardless of whether they are eligible to be registered under the streamlined approach inside the European Union, many traditional Chinese medicines may be shown to be safe to use with this basic nonclinical package. For qualifying proprietary Chinese medicines (pCm) with a long history of usage, this article envisions integrating a streamlined assessment method into the current drug regulatory system in Hong Kong (China). Less demand for scientific resources is required for such integration that uses the minimal nonclinical package based on bibliographical data or expert reports to prove safety for pCm with a lengthy history of usage. 'First hand' evaluation in Hong Kong (China) for qualifying pCm gives local

## Introduction:

Chinese herbal medicines was gained in the last decade. Yet, after ten years of growth, a negative growth in the value of TCM as imports and exports was reported in China for the first time.[2] It is believed that among all the barriers, differences in the standards of evaluation accepted by drug regulation authorities including: the definition/classification of herbal products, paths of market entry, Good Manufacturing Practices (GMP) compliance, and evidential requirements for demonstrating efficacious and safe use based on product history non-clinical and clinical studies, are key elements that hampered the internationalization of TCM.[3]

These inconsistencies in drug evaluation standards do not merely have an impact on how a pharmaceutical manufacturer strategizes their worldwide registration plan, but can potentially cause misinterpretations that result in inappropriate assessment of herbal products. In countries that are dependent on Certificate of Pharmaceutical Product (CPP),[1] herbal products may be used as medicines even when the product has not been assessed as a medicine. Such countries accept the review of scientific and clinical dossiers from CPP issuing countries as quality assurance that the medicinal products they imported meet a stipulated acceptable level of safety and health in their healthcare sector.[4]

Depending on the criteria set by different authorities, a herbal product considered to be a dietary supplement and regulated as a food product in one country, may be considered as food supplement, a therapeutic good (complementary medicine or prescription medicine) or even a substance in another jurisdiction. For example, while melatonin is regulated in the

United States (US) as a dietary supplement, it is a national health product in Canada and a prescription medicine in Australia.[5] Dehydroepiandrosterone (DHEA) is readily available as a dietary supplement in the US, while in many other jurisdictions it is regulated as a controlled sub- stance.[5] This heterogenicity in how CPP issuing countries define herbal products poses a concern to CPP dependent countries as some drug regulatory authorities in CPP issuing countries require few or less stringent registration requirements. As a result, the same herbal products can be marketed in a different category in different countries with a CPP, resulting in potential safety issues for the public's health.[6,7]

## Safety, quality and efficacy of traditional Chinese and herbal medicines controlled

As a result of the prevalence of poor scientific studies on Chinese herbal medicines and the lack of a systematic investigative approach in the past, medical professionals have been concerned about their efficacy and safety.[8] Over the past decade, with the support from the Chinese government, the Chinese clinical trial registry was set up to ensure clinical trials are conducted based on international standards and with higher quality.[9] This allows the anticipated effectiveness of TCM to be verified with means of proper understanding by Western countries.

Safety continues to be an essential attribute in the pharma- ceutical industry. There is a common misconception by the public that natural means safe and that herbal medicines are harmless.[1] It is however, the inherit risk of an herb itself that contains unknown toxic compounds, albeit low, do exist. The lack of regulatory registration/evaluation based on international risk-based standard limits the safe control/use of herbal medicines.[10] Hence incidents on overdosing (since safe levels of intake from dose-response data may not be established), adverse health effect caused by drug interaction or loss of efficacy continue to happen when common herbal medicines are taken together.[11] Manufacturing errors, in which one herb is mistakenly replaced with another or being contaminated with other undeclared plant and animal material, heavy metals (such as arsenic, lead, and cadmium), pesticides, microorganism or toxic compounds are not uncommon. Cases of adulteration have also been reported, Western medicines (such as the blood-thinner warfarin and the non-steroidal anti-inflammatory agent diclofenac) were mixed with herbals to enhance their efficacy. These resulted in serious complications including organ damage.[10e13]

It is unquestionable that stringent requirement should apply to registration of any medicinal products with new herbal substances/ herbal preparations. There is a desire among the medical community for a full evaluation of new herbal products. Compre- hensive, thorough evaluation for new herbal medicinal products to ensure good set of quality, safety and efficacy (QSE) should be conducted like Western medicines with new chemical entities. However, if herbal medicinal products of long history of use are considered as 'new' medicines and the same stringent registration process applied, it inevitably hampers the interest of pharmaceu- tical companies to register and earlier, different classification categories are used in herbal market their products globally. The hesitation in recognizing the long history of clinical experience for traditional Chinese and herbal medicines as evidence of safety has long limited the growth of TCM globally.

To combat this, a tailored approach to register traditional and herbal medicinal products involving dossiers that incorporate long standing evidence of safety and efficacy has long been considered.[14] The need for better quality assurance in drug development has been of focus for years. It is recognized that in view of the complexity of quality assurance of herbal medicines and that long history of use do not represent products with good quality. To achieve quality assurance, a comprehensive quality dossier and other common fundamental principles including GMP must be provided. Pharmacovigilance should always be required regardless of the life history of an herbal medicinal product.[15] However, for safety and efficacy dossiers, a simplified version could be consid- ered acceptable. It is important that no consumption of medicines should cause harm. Good safety profile of any medicinal product is an expected feature and has grown in its importance over proof of efficacy in the past years.[16] Between safety and efficacy data, the requirements in nonclinical safety testing is relatively less certain. The basic goals of a comprehensive conventional nonclinical studies package in drug development include, identifying the pharmacological properties in the establishment of comparative physiology between animals and humans, calibrating the safe initial dose permissible for first human exposure, and identifying the biological markers that predict potential adverse effects for clinical monitoring. There is a general acceptance that some of the above unknowns are indeed addressed or partially addressed in herbal medicals due to a long history and prevalence of use.[14] This is the basis of the tailored approach.

Much effort has been made to modernization of TCM world- wide. For example, in 2004, through Directive 2004/24/EC, the registration procedure for traditional medicinal products was simplified. It is based on submission of full quality dossiers sup- ported with bibliographical data or expert report on well- established or traditional applications of herbal medicines respec- tively.[15] Legislations regarding herbals by the European Union (EU) in 2011 and the Traditional Herbal Registration Scheme in the United Kingdom further strengthened the quality of herbal prod- ucts to pharmaceutical quality standards.[17] Some regulatory bodies including the US Food and Drug Administration (USFDA) have placed special emphasis on batch-to-batch quality and therapeutic consistency.[3] In China, enormous efforts are dedicated in advancing as well as consolidating TCM's scientific grounding and clinical practice. The international community have also contributed on- going collaborative works such as the 'Herbalome Project' which aims to examine mainstay TCM formula and Chinese herbs for their structure, function and chemical composition.[18] The project helps to establish the resource library and contribute to the World Health Organization (WHO)'s classification on TCM. In 2018, the WHO revealed that by 2022, TCM would be included in its 11th revision of the International Statistical Classification of Diseases and Related Health Problems, a document that offers standardized diagnostic classification for clinical and research purposes[19].As noted and Chinese medicines, the terms 'established' and

'traditional' for herbal medicine use in EU[20] can be different from those use in other countries, such as Hong Kong (China),[21] therefore, care should be taken as different registration requirements apply.[22]

In 2019, the European Medicines Agencies finalized minimum package, and hence encourages more eligible herbal medicines to reach international risk-based standard.[16,23] Included in this guideline are herbal medicines that have seen well-established usage EU-wide for the minimum of 15 years or in traditional medicinal use for a minimum of 30 years, including 15 years within the EU.[20] It provides guidance on the minimum nonclinical package to demonstrate 'acceptably safe' for EU regis-tration purposes. The document recognized that human experience with traditional herbals of long usage history may obviate the need to conduct acute and chronic toxicity tests. However, this does not apply to reproductive toxicity, genotoxicity and carcinogenicity tests. It is because these areas of major concern can only be dealt with through careful conduct of nonclinical studies. The minimum nonclinical package for the simplified registration consists of:

1. General aspects, including investigation of the effects on drug metabolizing enzymes
2. *In vitro* and *in vivo* genotoxicity assays
3. Long-term rodent carcinogenicity (for products intended to be continuously used for >3 months or intermittently for >6 months)
4. Reproductive and developmental toxicity (for products used by women of childbearing age)

The package takes into consideration the frequent use of herbal medicines in conjunction with conventional Western medicine, therefore making clinical and kinetic interaction major areas of concern. Drug interaction studies to investigate the effects on drug metabolizing enzymes, as mechanistic and genetic evidence, are key nonclinical studies in herbal medicines registration. This in-cludes identifying cytochrome P450 enzyme involved, lower sig-nificant interaction and potential genetic issues.[24]

Special toxicity studies, like the genotoxicity assays, are needed because it allows early identification of potential carcinogenic to human. In combination with long history of clinical experience, this non-clinical package provides an acceptable safety profile for sub-chronic use of traditional herbal medicines. For those that request for specific targeted therapeutic indications or have demonstrated cause for concern, test on carcinogenicity and/or reproductive/developmental toxicity may be required.[23]

There are still many herbal products not registered within the EU since the introduction of the simplified procedure in 2014,[17] with the minimum nonclinical package being finalized, it is antic-ipated that this refined simplified procedure will further promote safe use of traditional herbal products and enable free EU-wide movement.[15]

## Opportunities and challenges for Hong Kong (China) in internationalization of TCM

In Hong Kong (China), TCM is a vital part of the mainstream medicinal consideration. Conjunctive use of Western drugs and TCM are commonplace within the Hong Kong (China) public.[25] With the drive from the Hong Kong (China) Government and the increase in consumer demand worldwide, Hong Kong (China) is placed with the opportunity to lead the internationalization of herbal products and the challenge to preserve their therapeutic value as medicines.

guidelines for documenting herbal medicines of well-established use or traditional origins in non-clinical ways. It reaffirms its acceptance of the waiving of a thorough toxicological assessment with the

Government and businesses are the main drivers for regulatory reform. Strong policy drivers are core factors in translating idea into practice. Resistance to policy changes tends to be high when stakeholders and users are confused with how the changes may affect them and whether the changes would be positive.

Hong Kong (China) is well positioned in creating a good envi-ronment for the growth of TCM globally. The Hong Kong (China) Government has already set key initiatives to develop TCM. This includes promoting research, clinical TCM practice and conducting clinical trials in China. The setup of the first Hong Kong (China) Chinese medicines hospital will further support the established academic exchange allowing more local TCM trainee to gain first-hand experience from TCM practitioners in China.[26,27]

Implementation of new regulatory measures is complex. Early stakeholder engagement, including community, industries, in-stitutes and affirmative financial support are crucial to a successful reform. The benefit of promoting Hong Kong (China) to be a TCM hub, including having early access to Chinese medicines and enhancement of import and export trade business need to be communicated early. Concerns, including the high cost incurred for complying with the requirements for providing the QSE of Chinese medicines should also be addressed. Financial support assisting licensed TCM manufacturers in conducting safety tests and re-searches could be promoted.

It is recognized that language is a barrier in promoting TCM globally. Translating scientific information of Chinese medicine is paramount in this amalgamation.[3,28] Only a miniscule portion of this tradition has been translated in English. The theory of Chinese medicine functions on a different paradigm to that of modern sci-ence and cannot be fully captured within its context or discourse. It requires of the translator an intimate knowledge of the subject matter at hand.[28,29] The sociocultural context of Hong Kong (China) is influenced by the convergence of East and West. It has the advantage of having Chinese being the national language and has inherited the cultural and philosophical understanding of TCM direct from the People's Republic of China.[30]

As a Special Administrative Region, Hong Kong (China) has the advantage of having a different pharmaceutical regulatory system from the People's Republic of China. The regulation of TCM in Hong Kong (China) is also separated from its Western medicines. This provides the flexibility for Hong Kong (China) to make policy changes in developing new registration process for Chinese medi-cines without affecting the existing system for both Chinese and Western medicines.

To maintain a creditable system, a scientific approach when making policy changes in regulating Chinese medicines must be maintained. Product assessment and registration is a major step for marketing and to ensure pharmaceutical products meeting appropriate standards of QSE. Drug regulation process is complex and resource intensive. Limitation in scientific and clinical exper-tise and resources is not uncommon in Asian countries. In Singapore, the national drug regulatory agency, Health Sciences Authority managed this limitation by engaging both internal and external evaluators. It further adopted a

risk based approach by implementing a full registration process with three evaluation routes for Western medicines. This approach is confidence based. It leverages on the evaluations conducted by selected competent drug regulatory agencies. Thus, allows flexibility in utilizing its expertise according to the depth of evaluation required yet ensuring robustness in the evaluation system.[31] With years of effort in bringing international standards into the drug regulatory pro- cess, Singapore is accepted as a regulatory member, together with China, Taiwan (China), Republic of Korean and Brazil, of the Inter- national Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). The ICH is a global platform for discussion of drug registration with regards its technicalitie

and science. In Singapore, regulation of herbal medicines is subject to less stringent registration requirements than Western medicines.[32]

## Regulation of Chinese herbal medicines in Hong Kong (China)

In Hong Kong (China), the term herbal medicines mean essentially herbal species that do not undergo any manufacturing to change their form. Proprietary Chinese medicines (pCm) are Chinese herbal medicines that have undergone some degree of manufacturing to be made into tablets, powder, liquid, *etc*. They are used to treat many medical problems, including gynecological and gastrointestinal disorders.[33] The term pCm is clearly defined under the Chinese Medicines Ordinance.[2] All pCm are categorized into established, non-established and new medicines.[21] They must be registered with the statutory Pharmacy and Poisons Board before they can be legally marketed. Secondary review[3] is conducted to ensure all pCm meet the registration requirements prescribed by the Board regarding their safety, efficacy and quality.[35,37] Much efforts have been placed by the Hong Kong (China) government on improving the quality control and post marketing surveillance of pCm. Unlike registration of Western medicines which compliance with GMP standards is mandatory,[38] manufactured licensed pCm, at present, is voluntary.[39] A timetable will soon be set for the mandatory compliance of pCm manufacturing to the standards of GMP.[40] To assist the accreditation process, regulatory services has been put in place to provide quality testing and assessment based on the *Pharmacopeia of the People's Republic of China* and the *Hong Kong Chinese Materia Medica* Standards.[41] For safety control, post registration monitoring of pCm in detecting any unfortunate adverse events has long been carried out in Hong Kong (China).[41] Since 2009, this surveillance program plays an important role in predicting and preventing the occurrence of adverse drug reactions especially when nonclinical safety data on drug interaction and pharmacogenomic studies are lacking or insufficient.[37]

A strong regulatory infrastructure is essential in ensuring pCm products uphold high quality standards and safety, make true and non-misleading claims, and have appropriate and reasonable marketplace accessibility. The key regulatory barrier in Hong Kong (China) is the requirement for two CPPs as proof of quality and safety before a pCm can be registered for marketing. The intention of CPP is to provide quality assurance and to substitute the review of scientific and clinical dossiers to allow products to be registered in shorter timeframes. However, in Hong Kong (China), the requirement does not fully substitute an internal review of QSE. More test results and summary reports are required with further queries may be raised and together with the waiting time to obtain the CPP from the issuing countries, it defies the intention of requiring CPP submission in allowing patients to have earlier access to the medicines. For Hong Kong (China) to play a bridging role in leading China's internationalization of TCM, the registration process of pCm should consider becoming independent from the requirement of CPP for quality and safety assurance.

Hong Kong (China), have long been recognized as a country having a reasonably established clinical practices and basic scientific research and development for TCM. With its current focus on improving quality control and enrichment in clinical expertise, the area that worth further strengthening will likely be the nonclinical assessment capacity when the feasibility of conducting review for a simplified registration for eligible pCm with long history of use is to be explored.

The waiver of a thorough evaluation with a minimum nonclinical package in bibliographical applications for EU registration purpose represents a golden opportunity for Hong Kong (China) to take its first entry to evaluate pCm with long history of use not previously registered and marketed in other countries. Although the objective of having an EU simplified procedure aims to ensure a freedom of movement for herbal medicines within the EU, it does provide a framework of a minimum package to demonstrate 'acceptable safety'. It is important to note that although the EU simplified registration for traditional herbal medicinal products does include TCM, this particular registration process has set tight limitations. It is restricted to TCM that has been in the EU for at least 15 years with administration pathways restricted to oral, inhalation and external use.[20] Therefore, there are a great number of TCM that are prevented from attaining registration as traditional herbal medicinal products according to the outlines of the EU.[22] In other words, the 'minimal nonclinical package' route of registration does not apply to most TCMs. Projecting the same principle to a Hong Kong (China) society, there are much wider range of TCM products satisfying minimal nonclinical package demonstrating 'acceptably safe' for pCm that have been in traditional medicinal use throughout a period of at least 30 years, including 15 years in China or Hong Kong (China). The establishment of a TCM registration process in Hong Kong (China) would pave the future for better recognition and growth of the TCM market beyond Hong Kong (China) and the region.

One of the limitations in Hong Kong (China) drug regulation is the lack of number in expertise. The recognition of pharmacovigilance and long-standing use of pCm as evidence of an accepted safety profile to support a range of pharmacology and toxicology, including safety pharmacology, pharmacokinetics, single and repeat dose toxicity, toxicokinetics, immunotoxicity and local tolerance studies,[23] reduce the nonclinical package significantly. This

[2] The definition of pCm is defined under the Chinese Medicines Ordinance.[34] pCm means any proprietary product e(a) composed solely of the following as active ingredients e(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) of paragraph 3 (a) 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.

[3] Secondary review requires approval of drugs based on the reviews conducted by two reference ICH drug regulatory authorities. These countries are the US or Europe and Japan.[35] The Certificate of Pharmaceutical Product from these countries are the evidence of approval. Most countries, including Hong Kong (China), require this certificate/document to proof that the medicinal products they imported meet a stipulated acceptable level of safety and health in their healthcare sector.[36]

notably lessen the demand on nonclinical expertise/evaluators and allow a much-needed focus on capability building in address- ing the major concern in reducing kinetic and clinical interaction concern in reducing the number of adverse events due to use of pCm concomitantly with other medicines.

To implement a primary (first-hand) yet simplified evaluation route based on international practice within drug registration process for pCm in Hong Kong (China), a progressive approach can be adopted. For example, a new independent center can be set up to complement the regulatory role of the existing drug regulatory agency before the evaluation capability is achieved. The indepen- dency and flexibility in funding and structural reform will allow the new set up to focus only on the scientific evaluation on pCm of long history of use, while building up its drug evaluation capabilities, particularly in pharmaceutical chemistry, pharmacology, toxicology and clinical disciplines. Recognizing its own limited resources in pharmaceutical sciences professionals, the use of both internal and external expertise is worth considering. Both local and overseas from local universities, hospitals and research institutes can be engaged as external evaluators to conduct drug evaluation and participate in capabilities building. It is worth noting that a sustainable development of such regulatory capacities will provide encouragement for growth in research and development within Hong Kong (China) by the pharmaceutical industries and in the future, establish Hong Kong (China) as the origin for new and innovative pCm.

Having an option to approve pCm with long history of use based on international standard while maintaining the existing review process, incur minimum burden to the registration of both Chinese and Western medicines. This new evaluation route not only will allow both local and overseas pCm with long history of use to obtain marketing authorization in Hong Kong (China) within the timeframe like other regulatory agencies that conduct the simpli- fied evaluation. It will also allow the approved pCm to expand its market globally using the CPP issued by the Hong Kong (China) Government when the necessary conditions are met. With this, the pCm trade sector will be better positioned and able to provide users an earlier access to increased variety of quality and safer medicines. In the long term, the building of this infrastructure will encourage the modernization of pCm and the improvement in drug evaluation capabilities will become the platform for further grow in the drug regulatory system in Hong Kong (China).

There are opportunities and challenges for Hong Kong (China) to conduct first-hand review on eligible traditional pCm with long history of use. With the simplified EU registration process and the finalised minimum nonclinical package for traditional herbal me- dicinal products, it is a good time to strengthen the drug registra- tion and regulatory infrastructure of Hong Kong (China). The internal and external factors to the growth, success and threats to globalising pCM with long history of use are listed in Table 1.

## Concluding remarks

Most herbal products that are currently available in the global market have yet to be subjected to drug approval process to demonstrate their safety and effectiveness, the final release of the minimum package of nonclinical in bibliographical applications provides an avenue to further reduce cost and resources in con- ducting extensive animal studies to fulfilling the safety re- quirements for the EU regulatory authorities. With this mechanism, more well-established and traditional herbal medicines could be encouraged to register and obtain marketing authorization in EU and worldwide.

Hong Kong (China) has relatively stringent documentary re- quirements for marketing pCm among the Asian cities.[3] However, its secondary review process while assuring QSE meeting interna- tional standard, requires a substantial amount of time in registra- tion and marketing authorization of pCm. This has been a significant obstacle to the pharmaceutical traders and users in Hong Kong (China).

For Hong Kong (China) to be promoted to be a TCM hub and fulfilling its major role in leading the internationalization of pCm, a concerted regulatory effort in building a sound registration process, a good network for conducting epidemiological/clinical studies as well as post-marketing experience is essential.

With the support from the government and the maturing GMP compliance framework for pCm, there is an opportunity for Hong Kong (China) to develop an additional registration process to approve pCm of long history of use based on the simplified pro- cedure established in the EU. Hong Kong (China) possesses the

Table 1
Opportunities and challenges for Hong Kong (China) to conduct first-hand review on pCm with long usage history based on the EU simplified registration process.

Strength
1. Clear direction from Government to support the growth of TCM
2. Strong financial business infrastructure to support Hong Kong (China) as Chinese medicine registration hub
3. Independent Chinese and Western medicine regulatory framework, and hence having more flexibility in making policy changes in adopting new evaluation and registration processes for Chinese medicine without the need to implicate Western medicine framework
4. Large pool of Chinese medicines in traditional medical use of at least 30 years, including 15 years in Hong Kong (China)
5. Existing GMP accreditation process for manufacture of pCm, and post marketing surveillance program
6. Good scientific and clinical expertise to enrol as internal or external evaluators
7. Inherit good cultural and philosophical understanding of Chinese medicine
8. Good regulatory network with Asiaepacific countries

Weakness
1. Hong Kong (China) has insufficient global impact in the area of drug registration
2. Inexperience in conducting first-hand/full evaluation of pCm, particularly in the area of nonclinical assessment
3. Relying on CPP from other countries for registration of Chinese medicine
4. Limited financial commitment from licensed TCM manufacturers

Opportunities
1. EU's acceptance of waiving the full ICH nonclinical evaluation with a minimum package to demonstrate safe use of traditional herbal products
2. Adopt the EU simplified registration process with minimum nonclinical package to be an option to register eligible pCm with long usage history
3. Less demand on regulatory/evaluation capacity/capability under the simplified registration process
4. Be the first country to conduct full review and globalise eligible pCm as Hong Kong (China) registered traditional pCm based on the EU recognised simplified registration process
5. To becoming a CPP independent country for traditional pCm with a recognised simplified registration process
6. To promote the use of Hong Kong (China) issued CPP/marketing authorisation of eligible traditional pCm for their registration of use and marketing in Southeast and Asiaepacific countries
7. To explore advantages and synergise the use of Chinese and Western medicine by analyzing differences in their origin for human health between Chinese and Western medicine
8. Preserve therapeutic values of TCM

Threats
1. Change in EU position on the acceptance of simplified registration and the use of minimal nonclinical package as a demonstration of

safe use of traditional herbal medicines
2. Other countries not receptive with EU position for minimum nonclinical package
3. Other countries do not accept the waiver of full nonclinical package for registration of TCM in Chinese society. Demand for submission of additional ethnical/non- Chinese data to demonstrate safety and efficacy
4. Immature drug regulatory framework to support pre- and post-marketing authorisation on safe use of medicines
5. Non-acceptance by Western medical profession
6. Diminishing global interest in TCM

Abbreviations: pCm: proprietary Chinese medicines; EU: European Union; TCM: traditional Chinese medicine; GMP: Good Manufacturing Practices; CPP: Certificate of Pharmaceutical Product; ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

academic capabilities to strengthen its drug evaluation capabilities to accept QSE dossier submission. The use of both internal and external expertise is a good option to expand the pool of expertise available in specialized area. An integration of a new evaluation route into an existing CPP dependent registration process has been successfully implemented in other countries. The advancement of Hong Kong (China) to be a location that can provide QSE assurance for the eligible pCm without waiting for reassurance from other countries' CPP will encourage local manufacturers to export and open their products to the global market. Understanding and translating Chinese medical texts is complex. An inherited knowl- edge of the philosophical and holistic approach of TCM could progressively result in a faster evaluation and approval timeframe than the Western countries in a worldwide simultaneous submis- sion. Supported by Hong Kong (China)'s internationally recognized business infrastructure, a constructive drug regulatory reform could lead Hong Kong (China) to provide patients' earlier access to pCm, facilitate importation and exportation of pCm, and most importantly allows the therapeutic values of these herbal medicinal products to be preserved with health care professionals in a better position to make informed decisions about pCm usage alongside with Western medicines.

References


1. Zhou X, Li CG, Chang D, Bensoussan A. The current state of Chinese herbal medicine and the main obstacles to its safety and effectiveness. E14. Published in Medicines (Basel) 2019;6(1).
2. Lin AXE, Chan G, Hu Y, + more. Globalisation of TCM: the present state of the market, obstacles to globalisation, and recommendations for the future. (Chinese Medical Journal, 2018) 13:9.

3. Li JT, Zhu JF, Hu H, et al. Foreign sales of traditional and complementary medicine goods: breaking into the pharmaceutical industry. Chinese Medicine. 2018;13:50.
(4) The World Health Organization's Federation of Pharmaceutical Business Groups. The current state and future prospects of the certificate of pharmaceutical product (CPP) procedure. The file "Final- Position-ElectronicCPP_formed-July-2016.pdf" was last modified in 2019, according to the IFPMA website. November 18th, 2018.
5. Joint work by Dwyer, Coates, and Smith. Issues with regulation and available resources for research on dietary supplements. The article is published in Nutrients on 2018-01-09.
6, Alostad AH, Steinke DT, and Schafheutle EI. Five countries' herbal medication registration systems were compared internationally to help shape future regulations: the UK, Germany, USA, UAE, and Bahrain. The pharmaceutical journal published an article in 2018 with the DOI: 32(1): 39–49.
7. Sharma S. The present state of herbal products: a review of regulations. Journal of Pharmaceutical and Bioallied Sciences, 2015, 7, 293–296. Huang HC, Hu J, Zhao W, Zhang YL, Zhang L, and Zhang JH. A study of the Cochrane database including studies on Chinese herbal remedies. Publication: PloS One. 2011;6(12), e28696. Wu TX, Li Yp, Liu GJ, and colleagues—9. The purpose, role, and functioning of the Chinese clinical trial registry. Medical Evidence, 2011;4(3):165–167.
10. The WHO's Global Health Report. The World Health Organization's 2005 worldwide assessment on traditional medicine and the regulation of herbal medicines on a national level. This information was last updated in 2019. Released in May of 2005. Evaluated on October 21st. Sachsel-Galor S and Benzie IFF; 11. An overview of herbal medicine including its background, practice, regulation, trends, and areas for further study. Vol. 1, edited by Benzie IFF and Wachtel-Galor S. Herbal Medicine: Biomolecular and Clinical Aspects. Chapter 1 from Boca Raton, FL: CRC Press/Taylor & Francis, 2011.
12. The authors are Backyar, Musgrave, Marker, and Bunce. In what ways may herbal remedies endanger Australians? The medical journal of Australia published an article in 2017 with the DOI: 206/2:86e90.
13 Xu YM, Ng SLP, Patel DN, et al. An analysis of all adverse events recorded in Singapore with dietary supplements between 2010 and 2016. Current Medical News (Lausanne) 2018;5:167.
14. The World Bank, UNICEF, UNDP, and WHO. Non-clinical safety testing approach. Chapter: Nonclinical Safety Testing, Fourth Edition, 2004. you may find it at this URL: http://apps.who.int/medicinedocs/en/m/abstract/Js

19828en/. Retrieved on November 7, 2019.
15. The Health and Medicines Agency of the European Union. Pharmaceuticals derived from plants.The European Medicines Agency (EMA) has published guidelines for herbal medical products. Retrieved on November 7, 2019.
16. The authors are Moreira DL, Teixeira SS, Monteiro MHD, De-Oliveira ACAX, and Paumgartten FJR. Herbal supplements: their long-standing usage and potential side effects. Review of Brazilian Pharmacology. 2014;24: 248–257.
17.Everyone from Dickinson to Kennedy to Raynor to Knapp to Thomas to Adami was involved. How has the UK's Traditional Herbal Registration (THR) system affected the information given with over-the-counter herbal products? This article is from BMC Compl Alternative Med (2019;19(1):85).
18.Names of authors: Xu QH, Bauer R, Hendry BM,... A journey towards updating TCM for the current day. 132. BMC Complementary and Alternative Medicine. 2013;13:
19.Health Organisation of the World. Today, the new International Classification of Diseases (ICD-11) was released by the World Health Organisation (WHO). Worldwide Health Organisation (WHO) announces new international classification of diseases (ICDS-11) in June 2018. The date of access is October 19, 2019.
Twenty-one. The European Medicines Agency for Health and Well-Being. Discussing the rules and regulations set forth by the European Union (EU) for herbal remedies with a long history of use, including those with a "non-European" origin. The text may be found at the following location: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/questions-answers-european-union-framework-traditional-herbal-medicinal-products-including-those-non_en.pdf; 2014. Retrieved on November 7, 2019.
21. The Legislative Council of the People's Republic of China's Hong Kong Special Administrative Region. Health services panel paper; report from the subcommittee on proprietary Chinese medicine registration. The following document was accessed on October 21, 2019: https://www.legco.gov.hk/yr11-12/english/panels/hs/hs_rpcm/reports/hs_rpcmcb2-1040-e.pdf.
Knooss and Wiesner (22). A look at conventional medicine's globalisation via the lens of the EU's regulatory framework. European Medicines Agency Science, Medicines, and Health. Engineering. 2019;5(1):22–31. Standards for the non-clinical documentation required by applications for the registration or marketing authorization of traditional herbal medicines with a long history of use. 2018. Retrieved from https://www.ema.europa.eu/en/non-clinical-documentation-applications-marketing-authorization-registration. Last updated on November 7, 2019.
The FDA of the United States is number twenty-four. Adverse medication responses that are preventable: with an emphasis on drug interactions. "Preventable Adverse Drug Reactions: Focus on Drug Interactions" (June 2018), https://www.fda.gov/drugs/drug-interactions-labeling/.
Retrieved on November 12, 2019.
25. Lam TP. How some Hong Kong Chinese see the relative merits of Wes

tern treatment and traditional Chinese medicine. Panel on Health Services. 2001. Journal of Epidemiology and Community Health. 55(10): 762–766. Chinese territory including the special administrative zone of Hong Kong's Legislative Council. Recent Developments in Clinical Chinese Medicine; 2018. November 9, 2019. Retrieved from https://www.legco.gov.hk/yr18-19/english/panels/hs/agenda/hs20181217. htm. Office for the Regulation of Chinese Medications, State Health Department (27). The Hong Kong SAR administration. Growth of Hong Kong's Chinese screen industry. Check out this website: http://www.cmd.gov.hk/html/eng/aboutus/development. html.the 21st of October, 2019.
No. 28: Oaster B. The difficulties of translating from Chinese to Western medicine. "Chinese medicine translation" on https://www.daytranslations.com/blog in 2017. Evaluated on November 12, 2019.
Chapter 29: Pritzker, Hui, and Zhang (Hong et al., 2018). Considerations in the translation of Chinese medicine."CM-Considerations-4.10.14-FINAL.pdf" from 2014, found at https://cewm.med.ucla.edu/wp-content/uploads/.
www.ncbi.nlm.nih.gov/books/NBK92773/-_ch1_sec2_. Retrieved on November 12, 2019.
Wang YY 30. What makes traditional Chinese

medicine scientific in the current day. Traditional Chinese Medicine Journal, 2019;6(3):195–200. Thirty-one. Tan ST, Chan VSW. Analysing the NDAs that the Centre for Drug Evaluation has received for review. Health Sciences Research: Priorities and Opportunities was the subject of the first scientific seminar hosted by the Health Sciences Authority in 2002 in Singapore. The authors of the piece are Yee SK, Chu SS, Xu YM, and Choo PL. Singaporean oversight of Chinese patented pharmaceuticals. Journal of Health Policy, 2005, 71(2), 133–149. 33. The Australian state government's Department of Health and Human Services in Victoria. Herbal medication from China. Retrieved November 12, 2019, from https://www.betterhealth.vic.gov.au/health/ConditionsAndTreatments/chinese-herbal-medicine.
Office for the Regulation of Chinese Medicines, State Health Department (34). The executive branch of

SAR of Hong Kong. Chinese Medical Practice Regulations. Accessed October 24, 2019, from https://www.cmro.gov.hk/html/eng/important_info/regulation.html.
Committee for the Facilitation of Business; 35. The business facilitation advisory group convened for the third time. Part 2 of the agenda will include the steps to take after receiving feedback and suggestions from the Hong Kong pharmaceutical association. Retrieved October 20, 2019, from https://www.gov.hk/en/theme/bf/advisory/intro/papers. htm.
Global Health Organisation (WHO) (36). WHO Certification system on the quality of pharmaceutical items moving in international commerce: questions and answers (Q & A). The following information was retrieved on November 9, 2019: https://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/qas_certif_scheme_2012.pdf?ua¼1., 2010.
BioSpectrum Bureau is number 37. The process for registering a medicine in Hong Kong. (2012, November 12) https://www.biospectrumasia.com/regulatory/26/3216/how-to-get-your-drug-registered-in-hong-kong.html.
Department of Health, Chinese Medicine Regulatory Office (38). The ruling party in

the Special Administrative Region of Hong Kong. Registration of pharmaceutical items imported into the country must adhere to PIC/S GMP standards. here: https:// www.drugoffice.gov.hk/eps/do/en/popup_Impl_PICS_GMP_Req_Reg_Imprt_
Phrm_Prod_en.htmlthis date (November 11, 2019).
1. Office for the Regulation of Chinese Medicines, State Health Department. The Hong Kong SAR administration. The gold standard for quality, good manufacturing procedures (GMP) applies to proprietary Chinese medicines. Accessed November 11, 2019, from http://www.cmd.gov.hk/html/eng/health_info/pamphlet/GMP_for_
Proprietary_Chinese_Medicines.html in 2017. Second, the Chinese government's health department's medicine regulatory office. Hong Kong Special Administrative Region's administrative body. Chinese medicine merchant licencing > producer certification (good manufacturing practice for proprietary Chinese medicine). The website for the licenced practitioner examination is http://www.cmchk.org.hk/pcm/eng/main_
licen_cert.htm. The date of access is November 5, 2019.

thirdly, services and information provided by the government. Hong Kong's administration. LCQ15: Chinese medicine regulation. 2010. Retrieved from https://www.info.gov.hk/gia/general/201004/28/P201004280141.htm. Retrieved on March 18, 2020.