Harmonization of monographic standards is needed to ensure the quality of Chinese medicinal materials
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Abstract
This article provides an overview on the regulations of Chinese medicinal materials (CMMs) in various countries and regions. Harmonization of CMM monographs would provide standards for the quality control of CMM products and play an important role in the modernization and globalization of Chinese medicine. A harmonized regulatory system would improve the quality of CMMs thereby ensuring the safety of the products and assisting Chinese medicine practitioners in their practice. The fast growing demand worldwide for traditional medicines calls for harmonized monographic standards to safeguard the safety and quality of CMM products.

Background
Seventy to eighty percent of the world population relies on non-conventional medicines (mainly of herbal sources) as their primary health care [1]. Chinese medicinal materials (CMMs) have the highest turnover-trading-figure among all herbal medicines [1].

At present there is a lack of methodology for the quality control of CMMs. Most pharmacopoeias merely state the minimum requirements to safeguard public safety. To prevent adulterated CMMs, manufacturers must adopt adequate quality control of international standards for harvesting, collecting, processing and packing of the crude herbs and final products. Licensing and registration of herbal medicine are required to enforce the quality assessment of CMMs. Specific monographic profiles of CMMs can standardize the authentication and quality assessment for CMM manufacturers worldwide.

Herbal standards around the world
Differences among national or regional regulations on import and export of medicinal plants can affect the quality control of herbal products. Same medicinal plant products may be classified as food, food-supplements, functional food, nutriceuticals or prescription herbal medicines in different countries or regions. The key features of such diversified national and regional practices due to different monographic standards on CMM products are summarized in Table 1.

World Health Organization
Over the years, the World Health Organization (WHO) has introduced monographs of medicinal plants used around the world. WHO also maintains a list of herbs that are widely used in primary health care in various countries as a result from the WHO Guidelines for the Assessment of Herbal Medicines which promotes the development of monographs to standardize the quality control of herbal medicines. Twenty-five monographs encompassing 28 plants have been published in Volume I [2] and mono-
Table 1: Pharmacopoeia or standards of various countries or regions that have monographic standards for CMMs

| Pharmacopoeia and monograph | Authority | Status    |
|----------------------------|-----------|-----------|
| WHO Monographs on Selected Medicinal Plants | World Health Organization | Unofficial |
| Chinese Pharmacopoeia | State Food and Drugs Administration, China | Official |
| Australian Regulatory Guidelines for Complementary Medicines | Therapeutic Goods Administration, Australia | Official |
| European Pharmacopoeia | European Directorate for Quality Medicines and Healthcare | Official |
| Hong Kong Chinese Materia Medica Standards | Department of Health, Hong Kong, China | Official |
| Japanese Pharmacopoeia | Pharmaceutical Affairs, Japan | Official |
| Thai Herbal Pharmacopoeia | Thai Food and Drug Administration, Thailand | Official |
| British Pharmacopoeia | British Pharmacopoeia Commission, UK | Official |
| American Herbal Pharmacopoeia (AHP) | USA | Unofficial |

graphs of 30 plants have been included in Volume II [3]. WHO emphasizes that these publications are not 'intended to replace official compendia such as pharmacopoeias, formularies, or legislative documents but to promote harmonization in the use of herbal medicines with respect to levels of safety, efficacy, and quality control' [3].

Mainland China

China's first drug control law was promulgated in 1984 [4]. According to the law, production of a new drug is subject to approval by the Drug Regulatory Department under the State Council. The drug regulatory department has compiled a list of crude Chinese medicines. A manufacturer may start producing a drug after a registered number is granted. If a manufacturer modifies the production process, approval from the authorities is necessary. Pharmacopoeia of the People's Republic of China [5] is compiled by the Drug Regulatory Department according to the national drug standards in China [6]. The Drug Administration Law of the People's Republic of China was implemented in 2002 [7].

Good Agricultural Practice (GAP) is also applicable to the quality control of Chinese crude drugs [8] as it includes quality aspects such as macroscopic/microscopic authentication, chemical identification, bioactive compounds and metal elements, as well as pesticide detection. Microscopic examination/authentication identifies the characteristics of tissues, cells or cell contents in sections, powders or surface on slides of CMMs. Chemical identification should include high performance liquid chromatography (HPLC) fingerprints and Fourier transform infrared spectroscopy (FTIR) in investigation stage [9]. Bioactive compounds should be assayed [10]. In China, the authorities have implemented GAP for the cultivation of over 80 species of commonly used CMMs in regions where CMM plants are traditionally cultivated. Outside China CMM plants are cultivated to meet the increasing demand; however, no consensus in methodology has been reached as to how effective regulation can reflect the multi-bioactivity aspects of CMMs [11].

Australia

Therapeutic Goods Administration (TGA) under the Commonwealth Department of Health is the national therapeutic goods control authority in Australia. The Australian Regulatory Guidelines for Complementary Medicines (ARGCM) [12] is used to regulate Chinese medicine which is classified as a complementary medicine [13]. The regulatory framework for complementary medicines in Australia is a two-tier one, classifying registered medicines into high risk or low risk groups [14]. Risk assessment is conducted on ingredients, indications and claims, dosage form, significance of side effects and effects of prolonged use or from inappropriate self-medication. Therapeutic Goods Act 1989 requires that therapeutic goods available in Australia should be included in the Australian Register of Therapeutic Goods (ARTG), unless they are specifically exempted from this requirement by Schedule 5 of the Therapeutic Goods Regulations 1990 [13].

Continental Europe

In 1964, Belgium, France, Germany, Italy, Luxembourg, the Netherlands, Switzerland and the United Kingdom signed the Convention on the Elaboration of a European Pharmacopoeia which has been ratified in 31 European states [15]. European Pharmacopoeia is now a standard reference for both European and non-European countries [16] and published by the European Directorate for the Quality of Medicines and Healthcare (EDQM) [17]. European Pharmacopoeia is known for its universal requirement of all medicines regardless of their origins [15]. About 130 herbal medicines including drugs and drug preparations are included in the European Pharmacopoeia [15]. All necessary tests and assay methods described in the monograph were rigorously validated according to the Technical Guide [18]. In response to toxicity incidences of herbal products, the European Commission requested that the monographs on herbal drugs used in traditional Chinese medicine should be developed to achieve a modern quality standard according to the European Pharmacopoeia, and listed the herbal drugs subject to investigation [19]. Currently the emphasis has been placed on compiling a list of all herbal drugs subject to investigation. The European
Pharmacopoeia Commission is producing more and more monographs and elaborating monographs on proprietary drugs [19].

Hong Kong, China
In 1999, the statutory status was accorded to Chinese medicine in Hong Kong and the Chinese Medicine Council of Hong Kong (CMC) was established [20] to regulate Chinese herbal medicines with assistance from the Chinese Medicine Division of the Department of Health [21]. All proprietary Chinese medicines (PCMs) manufactured or sold in Hong Kong must be registered. For PCMs registered under ‘new drug category’, additional supporting information such as acute/chronic toxicities should also be provided [20].

In 2001, the Department of Health published the Hong Kong Chinese Materia Medica Standards (HKCMMS) [22] which is currently the only standard that has comprehensive limits for heavy metals, pesticide residues and mycotoxins across all monographs (Table 2). All analytical methods and parameters under the HKCMMS were advised by the International Advisory Board (IAB) after considering all the data generated by research efforts from experts of the six universities in Hong Kong. In addition, a Scientific Committee, consisting of IAB members and representatives of the participating universities and government departments, were set up to resolve technical issues and examine research results. All limits were determined with ten samples and with reference to the Chinese Pharmacopoeia, British Pharmacopoeia, European Pharmacopoeia, Japanese Pharmacopoeia and US Pharmacopoeia [22] (Table 2).

Japan
In Japan, Kampo medicine refers to Chinese medicine and Japanese indigenous medicine [23]. Kampo formulae had been non-prescription medicines until 1985 when certain Kampo medicines became classified as prescription medicines and are therefore subject to clinical evaluation [24]. A total of 148 Kampo formulae have been approved for clinical use in Japan. The monographs of the top 20 Kampo extracts have been published in the latest version of the Japanese Pharmacopoeia as the official standards for the medically significant herbal substances [25].

Thailand
In Thailand, medicinal plant materials or crude drugs used in traditional medicines are exempt from registration for easy public use [26]. Prior to the production of any traditional medicine, manufacturers must apply for the manufacturing licenses from the Thai Food and Drug Administration [27]. The registration requires information on the raw material or ingredients, method of process, dosage and quality control. Furthermore, safety information related to acute, sub-chronic and chronic toxicity test as well as clinical trials results should be provided [28]. Thai Herbal Pharmacopoeia is published by the subcommittee on the establishment of the Thai Herbal Pharmacopoeia under the supervision of the Thai Pharmacopoeia Committee [29]. Thai Herbal Pharmacopoeia covers 23 monographs of Thai medicinal plant materials and three herbal preparations. Currently, compliance with the GMP and other standards for the manufacture of traditional medicines are voluntary; however, traditional medicines submitted for registration must pass the limited tests of microbiology, heavy metal and pesti-

| Table 2: Hong Kong Chinese Materia Medica Standards recommended limits of heavy metals, pesticide residues and mycotoxins |
|---------------------------------------------------------------|
| **Heavy metal** | **Limits** |
| Arsenic | 2.0 mg/kg |
| Cadmium | 0.3 mg/kg |
| Lead | 5.0 mg/kg |
| Mercury | 0.2 mg/kg |
| **Pesticide** | **Limits** |
| Aldrin and Dieldrin (sum of) | 0.05 mg/kg |
| Chlordane (sum of cis-trans- and oxychlordan) | 0.05 mg/kg |
| DDT (sum of p,p"-DDT, o,p"-DDT, p,p"-DDE and p,p"-TDE) | 1.0 mg/kg |
| Endrin | 0.05 mg/kg |
| Heptachlor (sum of heptachlor and heptachlor epoxide) | 0.05 mg/kg |
| Hexachlorobenzene | 0.1 mg/kg |
| Hexachlorocyclohexane isomers (α-, β- and δ-hexachlorocyclohexane) | 0.3 mg/kg |
| Lindane (γ-Hexachlorocyclohexane) | 0.6 mg/kg |
| Quinotzene (sum of quinotzene, pentachloroaniline and methyl pentachlorophenyl sulphide) | 1.0 mg/kg |
| **Mycotoxin** | **Limits** |
| Aflatoxin B₁ | 5 μg/kg |
| Aflatoxins (sum of B₁, B₂, G₁ and G₂) | 10 μg/kg |
Pharmacopoeia
Radix et Rhizoma Glycyrrhizae

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already in the AHP [35]. AHP has published several mon-
herbs and other botanical ingredients, not necessarily
nomenclatures [34]. AHP also produces monographs on
supplements. AHP offers standard herbal monographs
(AHP) publishes monographs for herbs used as dietary
products is composite herbal formulae (Fufang) for
individualized treatment. If the quality of CMMs is not
standardized, treatment variability will exist in addition to
other variables. It is imperative, therefore, for regulatory
agencies worldwide to set up harmonized regulatory con-
trols over the manufacture and trade of CMMs.

At present, the British Pharmacopoeia contains 13 mono-
graphs of traditional herbal medicines which facilitate
assessment of registration applications and gives a refer-
ence standard to inform the manufacturers and importers
of the UK regulations. For the first time, a monograph of
Radix et Rhizoma Glycyrrhizae (Gancao, Liquorice root), a
Chinese medicinal herb, was introduced into the British Pharmacopoeia. Furthermore, collaboration has been
established between the British and Chinese Pharmacopoeias in order to exchange information on quality standards for medicines, develop test methods, identify
common adulterants or impurities and to authenticate herbal materials [32].

United States
In the United States, CMMs are classified as supplementary
products regulated by the Dietary Supplements Health
and Education Act (DSHEA) [33]. A manufacturer must
guarantee that the product is safe and properly labeled.
While approval from the Food and Drug Administration
is not required, new dietary ingredients are required for
pre-market safety review [33]. Overall, the regulation for
dietary supplements is less stringent than that for drugs.

In the United States, the American Herbal Pharmacopoeia
(AHP) publishes monographs for herbs used as dietary
supplements. AHP offers standard herbal monographs
whereby a genus and species may be identified according
to the Linnean system of botanical classification and
nomenclatures [34]. AHP also produces monographs on
herbs and other botanical ingredients, not necessarily
already in the AHP [35]. AHP has published several mon-

Discussion
The present article provides an overview on the regulations of
CMMs in various countries and regions. Each
dividual regulation system focuses on specific issues. In
the United States, regulation places its emphasis on source
herbal materials. In the European Union, procedures
focus on authentication of herbal materials. The European
Medicine Evaluation Agency comprising EU member
states was formed for managing the European Pharma-
opoeia. A Technical Guide was issued with all technical
details on the scientific works developed for those medic-
inal materials under regulations. In Australia, TGA regu-
lates all the registered products in terms of the quality,
safety and efficacy. In the UK, regulation focuses on safety
evaluation. In China, the regulation is directed to proper
formulation of CMM products according to traditional
Chinese medicine theory. Under the present systems
herbal manufacturers can submit their products according
to the ease of getting registration in the regions where they
can market or sell their products. One of the Chinese med-
icine practices is composite herbal formulae (Fufang) for
individualized treatment. If the quality of CMMs is not
standardized, treatment variability will exist in addition to
other variables. It is imperative, therefore, for regulatory
agencies worldwide to set up harmonized regulatory con-
trols over the manufacture and trade of CMMs.

Conclusion
The fast growing demand worldwide for traditional med-
icines calls for harmonized monographic standards to
safeguard the safety and quality of CMM products.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
All authors took part in the discussion before drafting the
present article. KSYL and SSZ did literature review on
national standards. KC provided information on current
aspects in various sections. All authors read and approved
the final version of the manuscript.

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