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The importance of safety issues in Traditional Chinese Medicine marketing

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L'importanza delle questioni
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Summary

The Chinese Medicine Ordinance has been launched for more than 10 years in Hong Kong. One of major aims of this ordinance is to control the use and sale of Chinese Materia Medica (CMM) and proprietary Chinese Medicine (pCM) products in local markets. However, different types of safety issues were reported continuously over the past 10 years. These issues include the use of confused species of CMM, adulteration of western drugs and the associated analogues in pCM products, false trade description, fake products and microbial contamination. Although the Government put a lot of effort to improve the situation, the Chinese medicine industry and traders do not consider the problem very seriously. The existing situation in the Traditional Chinese Medicine (TCM) market of Hong Kong will be discussed. In order to improve the quality control of CMMs and pCM products in the local market, a local standard namely Hong Kong Chinese Materia Medica Standards (HKCMMS) has been established since 2002 by the Government. Up until now, standards for 96 selected CMMs have been completed and around 100 new standards will be established by end-2012. The progress and impact of these standards on the local TCM market will be discussed.

Riassunto

L'attuale ordinamento sulla Medicina Cinese è stato prodotto più di 10 anni fa a Hong Kong. Uno degli scopi principali di questo ordinamento è quello di regolamentare l'uso e la vendita di Materia Medica Cinese (CMM) e specialità medicinali cinesi (pCM) prodotti nel mercato locale. Tuttavia, negli ultimi 10 anni, sono stati continuamente segnalati diversi tipi di problemi di sicurezza. Questi problemi comprendono l'utilizzo di specie mescolate della CMM, l'adulterazione dei prodotti pCM con farmaci occidentali e con analoghi associati, denominazioni commerciali false, prodotti contraffatti e contaminazioni microbiche. Anche se il governo si è prodotto in un grande sforzo per migliorare la situazione, l'industria della medicina cinese e i commercianti non prendono il problema molto seriamente. In questo lavoro verrà discussa la situazione attuale del mercato della Medicina Tradizionale Cinese (MTC)

di Hong Kong. Al fine di migliorare il controllo qualità dei prodotti CMM e pCM nel mercato locale è stato istituito dal Governo a partire dal 2002 uno standard locale detto Standard in Materia Medica Cinese di Hong Kong (HKCMMS). Fino ad oggi sono stati completati gli standard per 96 CMM selezionati e circa 100 nuovi standard saranno stabiliti entro la fine del 2012. In questo lavoro verrà discusso anche il progresso e l'impatto di questi standard sul mercato locale.

Introduction

Traditional Chinese medicine (TCM) has been used by Chinese people for more than 2000 years for prevention and treatment of diseases as well as health maintenance. Since 1998, TCM has been recognised as a strategic development area by Hong Kong Special Administrative Region (HKSAR). In order to enhance the protection of public health and ensure the safety, quality and efficacy of Chinese medicines, the Chinese Medicine Ordinance (Chapter 549) was passed on 14 July 1999 and the associated regulatory system was established under the Ordinance. Up to February 2011, around 10,500 proprietary Chinese medicine (pCm) products are applied for registration under the Ordinance and sell in the local market. However, herbal dietary supplements without curative or health claim can be sold in local market without any registration. Over the past 10 years, various type of TCM related safety issues

were reported continuously and more than 350 items were recalled from the market. The issues included the use of confused species of CMM, adulteration of western drugs and analogues in pCm products, false trade description, fake products and microbial contamination. The trend of safety issues in TCM market will be discussed in the following section.

To tackle the safety issue, a quality control system for TCM is desired for the local market. In 2001, Department of Health of HKSAR launched a research project namely Hong Kong Chinese Materia Medica Standards (HKCMMS). Standards for around 200 commonly used CMM are being established and the work will be completed by end-2012. Details and progress of HKCMMS project will be introduced.

Current regulatory control of TCM in Hong Kong

There are more than 5,000 medicinal species available in China. In

Hong Kong, 605 medicinal species which includes 31 types of potent/toxic CMM and 574 types of commonly used CMM are listed under Schedule 1 and Schedule 2, respectively, of Chinese Medicine Ordinance. These medicinal species include substances from plant, animal, insect and mineral origin. Details of the medicinal species used in Hong Kong are available from the Bilingual Laws Information System (<http://www.legislation.gov.hk/eng/home.htm>). All items listed under Schedule 1 are restricted uses in Hong Kong. Although import, export and sales of these CMM are regulated by the Ordinance, safety requirement such as maximum permitted levels of heavy metals and pesticide residues is not available in Hong Kong. Some items such fresh ginseng, dried wolfberry fruit and etc. can be served as Chinese herbal medicine or general foodstuff. As compared to Chinese herbal medicine, regulatory limits are available to control the use of colouring matters, sweeteners, metallic contami-

nation, harmful substances and preservatives in food. Requirements of these parameters are listed under the Public Health and Municipal Services Ordinance (Chapter 132) of HKSAR.

Proprietary Chinese medicine products are regulated more stringently than Chinese herbal medicine in Hong Kong. All pCm products must be applied for registration from 3 December 2010 onwards before sold in local TCM market. In general, pCm product must have test reports to demonstrate both product safety and product quality in according to the guidelines from Chinese Medicine Council of Hong Kong during registration (1-2). If pCm product claims to contain any pharmaceutical substance as major ingredient, such product is classified as pharmaceutical products by law and shall be applied registration in according to the requirement as stipulated in Pharmacy and Poisons Ordinance (Chapter 138).

TCM safety issues reported in Hong Kong

During 1999 to 2010, more than 350 TCM related items were recalled from the market by Department of Health of HKSAR. Reasons for product recall includes (1) contamination of heavy metals, pesticide residues and microbial,

(2) adulteration with western drugs, analogues and toxic herbs, (3) misuse of toxic or confused species of herbs, (4) false trade description and (5) fake products. Table 1 summarises the statistic of products recalled during 1999 to 2010 in Hong Kong. Among the cases reported, adulteration of western drugs and analogues in TCM related product caused great concern. However, these reported figures do not actually reflect the situation for safety issues in local TCM market.

Common practice for product quality control in Hong Kong

Up to February 2011, 208 pCm manufacturers including 8 with certificate of Good Manufacturing Practice (GMP) for pCm production are registered under the Ordinance.

Most of pCm manufacturers are small scale company which are owned by Chinese medicine practitioner or operated by a trading agent. Production scale by these manufacturers is around 1,000 to 2,000 items per year with product shelf life of 2 to 5 years. These groups of pCm manufacturers seldom perform safety and quality control testing for their products except during application of registration.

During 2008 to 2011, a product quality compliance program was launched by our university and a local health and beauty chain store. At the early stage of the program, all pCm and dietary supplement suppliers of the chain store were requested to provide up to date testing reports of their products for vetting purpose. Negative feedback was received from the suppliers. Testing reports

Table 1 - Statistic of TCM related product recall during 1999 to 2010 in Hong Kong

Types (including herbs and proprietary Chinese medicines)	No. of cases reported
Microbial contamination	38
Heavy metals	19
Pesticide residues	2
Adulteration of western drugs and analogues	283
Adulteration with other toxic herbs	13
Misuse of toxic species	6
Misuse of confused species	5
False trade description	No statistic
Fake product	No statistic

issued on or before 2004 were provided by the suppliers to demonstrate the safety status for the products that currently sold in the chain store. The suppliers replied that such reports were used for registration purpose. No further test was performed for subsequent batches of product due to high testing cost.

In order to reflect actual product safety status for the items available in the chain store, spy check exercises were initiated from 2009 onward. More than 150 items were randomly sampled for safety testing. Testing parameters include heavy metals content, pesticide residues, microbial level and drug adulteration. Results of spy check exercises showed that 4 products items were found to have microbial contamination and 1 product item was identified to be adulterated with trace amount of sildenafil. The findings indicated that some suppliers did not consider product safety is a critical issue for their business. Importance of product safety shall be further promoted in local TCM market.

Drug adulteration and its trend

Drug adulteration in pCm and dietary supplement products become an emerging threat in local TCM market (3, 4). Both slimming and male sexual enhance-

ment products were identified as high risk products. Manufacturer usually claims these products contain pure herbal substance and have desired curative effect. During 1999 to 2010, 283 cases of product recall were issued by Department of Health of HKSAR. Table 2 summarises the top 10 drugs to be identified from the recall products. Among the cases reported, there is a trend to adulterate the product with drug analogues or multiple drugs.

Drug analogues are chemically modified by replacing or adding functional groups to existing drug. Many drug analogues are available for human consumption via different channels without any aforementioned drug testing process. Their potential adverse effects are numerous and unpredictable. Around 70 products

were reported to be adulterated with different types of analogues. Table 3 summarises typical analogues detected in pCm and dietary supplement products in Hong Kong. In the past, use of drug analogues was not regulated under the Ordinance. Only approved pharmaceutical substance and its salts were permitted in local market. As the number of drug analogues is numerous, it is impossible to include every analogue in the Ordinance. In this connection, the Ordinance was amended on 30 September 2009 to control the use of sildenafil, tadalafil, vardenafil, sibutramine; their salts and any compound containing similar chemical structure of these substances substituted to any degree or without substitution. The IUPAC name is adopted in the Ordinance to de-

Table 2 - Top 10 drugs to be identified from the recall products

Ingredient	Type/Function	No. of times identified in the recall product
Sibutramine ^P	Slimming	118
Phenolphthalein ^P	Laxative	49
Sildenafil	Aphrodisiac	35
Sibutramine analogues ^P	Slimming	26
Acetildenafil	Aphrodisiac	17
Glibenclamide	Anti-diabetic	16
Tadalafil	Aphrodisiac	14
Diclofenac	Anti-inflammatory	13
Fenfluramine ^P	Slimming	9
Paracetamol	Anti-inflammatory	8

^P: Prohibited in Hong Kong

Table 3 - Typical examples of analogues detected in pCm and dietary supplement products in Hong Kong

Ingredient	Related analogues	Name of the controlled substances in ordinance
Sildenafil	Acetildenafil, Hydroxyhomosildenafil, Hydroxyacetildenafil	5-(2-Ethoxyphenyl)-1-methyl-3-propyl-1 <i>H</i> -pyrazolo[4,3- <i>d</i>]pyrimidin-7(6 <i>H</i>)-one
Tadalafil	Aminotadalafil	6-(Benzo[1,3]dioxol-5-yl)-2,3,6,7,12, 12a-hexahydropyrazino[1',2':1,6]-pyrido[3,4- <i>b</i>]indole-1,4-dione
Vardenafil	Pseudovardenafil, Piperidenafil	2-(2-ethoxyphenyl)-5-methyl-7-propylimidazo[5,1- <i>f</i>][1,2,4]triazin-4(3 <i>H</i>)-one
Sibutramine	N-desmethyl-sibutramine	1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutan-1-amine

scribe the chemical structure of these substances. Table 3 lists the IUPAC name for the substance under control in the Ordinance. Adulteration with multiple drugs in pCm and dietary supplement products were also reported in recent year. Typical examples include adulterating sibutramine and phenolphthalein in slimming product and adulterating sildenafil and glibenclamide in male sexual enhancement products (5). Sibutramine/phenolphthalein and sildenafil/glibenclamide belong to different drug groups with different indications and have never been used in the same formulation. The presence of mixture of different ingredients in the same products remains unexplained. Drugs are either added by the manufacturer to the product to enhance the efficacy or contaminated during production. A typical case was reported in 2010 in

which a pCm product was contaminated with sibutramine and phenolphthalein during processing of raw material by a third-party manufacturer.

TCM Poisoning

TCM poisoning is another safety issue commonly reported in local TCM market. According to the information from Hong Kong Poison Control Network, Hospital Authority of HKSAR, 4,338 poisoning cases were reported in 2009 and around 6.7% (291 cases) was related to TCM poisoning. The figure was increase to 8.3% (367 out of 4,420 poisoning cases) in 2010. Most of cases reported were related to the misuse of commonly confused Chinese herbs. Some examples are Sinopodophylli Hexandri Radix et Rhizome was confused with Gentianae Radix et

Rhizoma and Clematidis Radix; Solani Lyrati Herba was confused with Aristolochiae Mollissimae Herba. Reasons for using confused Chinese herbs include confused nomenclature in Chinese, similarity in appearance and complexity of processed products (6).

In recent year, some Chinese herbal medicines were found to be contaminated with aconitum alkaloids such as aconitine from Aconiti Radix and tropane alkaloids such as atropine and scopolamine from Daturae Metelis Flos. These alkaloids are highly toxic cardiotoxins and neurotoxins. In 2010, 7 cases were reported and the questioned Chinese herbs were recalled from the market. After investigation, contamination may be taken place at the cultivation site, during processing of crude herb to decocting pieces or during prescription of Chinese herbal medicines at the retailer store.

Hong Kong Chinese Materia Medica Standards

Due to lack of standards for quality control of TCM in Hong Kong, Department of Health of HKSAR launched a research project namely Hong Kong Chinese Materia Medica Standards (HKCMMS) in 2001. The project aims to establish TCM quality and safety standards for 200 commonly used Chinese material medica (CMM) in local market. Up to now, 61 monographs are compiled as three volumes of standards and have been published in both Chinese and English in 2005, 2008 and 2011 respectively (7-9). Title of monographs available is shown in Table 4. Details of individual monograph are also available at the webpage of Department of Health of HKSAR (http://www.cmd.gov.hk/html/eng/health_info/publication.html).

Nowadays, HKCMMS are adopted by the member state of Harmonisation of Standards and Regulatory Framework of Herbal Medicines, WHO and various pharmacopeia committees as an official reference for safety and quality control of herbal materials.

For phase IV, the six local universities have already finished the development of standards for 35 species including 8 mineral origin materials, and the publication will

Table 4 - Names of monographs in HKCMMS

Volume	Title
Volume 1	(1) Cortex Moutan, (2) Cortex Phellodendri Amurensis, (3) Cortex Phellodendri Chinensis, (4) Radix Angelicae Sinensis, (5) Radix Astragali, (6) Radix Ginseng, (7) Radix Notoginseng, (8) Radix Salviae Miltiorrhizae, (9) Rhizoma Alismatis
Volume 2	(1) Caulis Clematidis Armandii, (2) Cortex Magnoliae Officinalis, (3) Flos Magnoliae, (4) Herba Desmodii Styracifolii, (5) Herba Ephedrae, (6) Radix Achyranthis Bidentatae, (7) Radix Aconiti Praeparata, (8) Radix Angelicae Pubescentis, (9) Radix Aucklandiae, (10) Radix Bupleuri, (11) Radix Codonopsis, (12) Radix et Rhizoma Gentianae, (13) Radix et Rhizoma Glycyrrhizae, (14) Radix et Rhizoma Rhei, (15) Radix Paeoniae Alba, (16) Radix Paeoniae Rubra, (17) Radix Platycodi, (18) Radix Polygoni Multiflori, (19) Radix Saposhnikoviae, (20) Rhizoma Chuanxiong, (21) Rhizoma Cimicifugae, (22) Rhizoma Coptidis, (23) Rhizoma Curcumae, (24) Rhizoma et Radix Notopterygii
Volume 3	(1) Bulbus Fritillariae Thunbergii, (2) Bulbus Fritillariae Ussuriensis, (3) Cortex Eucommiae, (4) Cortex Mori, (5) Folium Ginkgo, (6) Fructus Evodiae, (7) Fructus Forsythiae, (8) Fructus Ligustri Lucidi, (9) Fructus Psoraleae, (10) Herba Andrographidis, (11) Herba Leonuri, (12) Herba Taxilli, (13) Medulla Junci, (14) Radix Glehniae, (15) Radix Ophiopogonis, (16) Radix Panacis Quinquefolii, (17) Radix Polygalae, (18) Radix Pseudostellariae, (19) Radix Puerariae Lobatae, (20) Radix Puerariae Thomsonii, (21) Radix Rehmanniae, (22) Radix Scutellariae, (23) Rhizoma Anemarrhenae, (24) Rhizoma Atractylodis Macrocephalae, (25) Rhizoma Belamcandae, (26) Rhizoma Gastrodiae, (27) Semen Cassiae, (28) Semen Vaccariae, (29) Spica Prunellae

be released in 2012. The laboratory work of phase V is ongoing, and further 104 monographs including potent/toxic species, expensive species such as Cordyceps, Cervi Cornu Pantotrichum and

Croci Stigma will be available by end-2012. Besides six local universities, one research institute from Taiwan will also join this project to establish part of the standards in phase V.

Each monograph in HKCMMS includes source, description, botanical and chemical identification, quality control tests and safety tests. A brief description of each section is listed below.

Source

This section describes the major botanical origin and family name of the medicinal plant and the used part of the plant. The time for collection, the preliminary on-the-spot treatments upon collection are also included. Similar to other pharmacopoeia, only the species are currently available in the local market are included in each monograph.

Description

This section refers to the macroscopic and organoleptic characteristics such as dimension, colour, texture, odour, smell and taste of CMM. A typical photograph is available in each monograph to describe the appearance and major characteristics of CMM.

Identification

In order to verify the identity of a CMM, both botanical and chemical identification methods play an important role in HKCMMS. Botanical identification is performed by using light microscope

to identify major characteristics of transverse section and powder for each CMM. Polarised microscopy technique is also adopted in HKCMMS to highlight some important features such as starch granules, clusters of calcium oxalate and crystal fibres for individual CMM. Colour images of microscopic identification of transverse section and powder together with the corresponding text description are listed in the monograph.

To complementary the biological information from microscopy technique, various chemical fingerprint techniques is adopted in HKCMMS for identification purpose. Commonly used technique includes thin layer chromatographic (TLC) fingerprint and high performance liquid chromatographic (HPLC) fingerprint. Gas chromatographic (GC) fingerprint is used occasionally for identification of volatile substances in CMM.

In phase IV, 8 mineral origin CMMs namely Arsenolite, Arsenicum, Orpiment, Realgar which are mineral drugs of arsenic and Cinnabaris, Calomelas, Hydrargyri Oxydum Rubrum, Hydrargyrum Chloratum Compositum which are mineral drugs of mercury are included in HKCMMS. The chromatographic fingerprint techniques as mentioned above are unsuitable for identification of inor-

ganic substances. Although other analytical technique such as atomic absorption spectroscopy (AAS) and inductively couple plasma mass spectrometry (ICP-MS) may be adopted for identification, only elemental information is available by these methods. In this connection, a new technique namely x-ray diffraction is introduced for identification of mineral drug in phase IV. Any inorganic substance has a unique x-ray diffraction pattern. This technique can identify the major ingredient together with minor impurities in molecular form from the mineral drug.

Quality control tests

Unlike Chinese Pharmacopoeia and other popular pharmacopoeia, each CMM must meet the requirements of maximum limits of foreign matter, ash and water content and minimum limits of extractives in HKCMMS. Limits of these items are established either based on statistic of test results which includes mean, standard deviation and measurement uncertainty of the test or from reputation reference. In general, a more stringent limit is adopted in HKCMMS.

Quantitative analysis of chemical markers in CMM is another important test in HKCMMS. Most of the analysis of chemical markers is based on the HPLC method with ultra-violet detector or evap-

orative light scattering detector. Titration is selected as the method for analysis arsenic and mercury contents in mineral drug. Determination of polysaccharides in CMM is done by ultra-violet spectrometry.

In phase IV, another new technique namely liquid chromatography-mass spectrometry (LC/MS) is the first time introduced in HKCMMS for quantitative analysis of artemisinin in *Artemisiae Annuae Herba*. During method development stage, difficulty was reported by using HPLC method with ultra-violet detector to detect artemisinin. After a lengthy trial, LC/MS is found to be the best option to tackle the problem. LC/MS method is adopted in Chinese Pharmacopoeia 2010 edition for quantitative analysis of chemical markers in *Homalomenae Rhizoma*, *Toosendan Fructus* and *Meliae Cortex* respectively (10).

Similar to other quality control parameters, a minimum limit of chemical markers is established for each CMM except *Clematidis Caulis*. As no suitable chemical marker is available, the assay of *Clematidis Caluis* is absent from the standards.

Safety tests

In HKCMMS, harmonised test methods for heavy metals, pesticide residues and mycotoxins have

been developed by Government Laboratory of HKSAR. Each CMM must meet the requirements of the limits of heavy metals (including arsenic, cadmium, lead and mercury), pesticide residues (20 organochlorine pesticides) and mycotoxins (aflatoxins B₁, B₂, G₁ and G₂). A fixed maximum permitted limit is assigned to each parameter except cadmium.

In phase II, cadmium level of 4 CMMs was found to exceed the predefined limit of 0.3 mg/kg. As a result, an individual limit of cadmium is set to these 4 CMMs namely *Chuanxiong Rhizoma* (< 0.39 mg/kg), *Coptidis Rhizoma* (< 0.70 mg/kg), *Curcumae Rhizoma* (< 0.39 mg/kg) and *Gentianae Radix et Rhizome* (< 0.58 mg/kg). In phase IV, limit of cadmium raised another concern. More and more species of CMM were found to have samples exceed the limit of 0.3 mg/kg during the study. At the same time, European Pharmacopoeia releases a new requirement on heavy metals for herbal drugs in Editions 6.8 in 2010 (11). Limit of cadmium is set to 1.0 ppm (mg/kg) for general herbal drugs. A debate on releasing the limit of cadmium to 1.0 mg/kg for HKCMMS was raised in the committee meeting and the new limit was adopted finally in December 2010.

Besides the parameters as mentioned above, safety limits are es-

tablished for various toxic CMMs. For example, aristolochic acid I and cardiac glycoside shall not be detected from *Clematidis Armandii Caulis* and *Taxilli Herba*, respectively. Meanwhile, maximum total limit of aconitine, hypaconitine and mesaconitine in *Radix Aconiti Praeparata* were also established in the standard.

Hong Kong Chinese Medicine Authentication Centre

In order to foster the Chinese medicine industry to focus on the safety and ingredient in Chinese medicine, Hong Kong Chinese Medicine Authentication Centre was established in 2009 under School of Chinese Medicine of Hong Kong Baptist University. The centre aims to promote Hong Kong as the world TCM product testing centre. Testing service in accordance to the HKCMMS, general safety tests for pCm products, authentication of CMM and advisory service is provided by the centre to CM industry, government department and public.

Product Testing and Certification for Chinese Medicine

As stated in the previous section, CM manufacturer and trader are seldom to perform product test-

ing. In order to promote product testing and introduce new added value for CM products, testing and certification in Chinese medicine has been identified by The Hong Kong Council for Testing and Certification as one of major area for development in the coming 3 years (12). Roadmap for the development is stated in Report of The Hong Kong Council for Testing and Certification which was published in 2010. New accreditation program which is based on the HKCMMS on identification of CMM by microscopic examination, chemical and physicochemical testing for CMM is announced by Hong Kong Accreditation Service in December 2010 and March 2011 respectively. Laboratory in Hong Kong may applied the new accreditation and encourage the CM industry to use this new service.

Conclusion

In conclusion, various types of TCM safety issues were reported during the past 10 years. CM in-

dustry shall be more concerned about product safety and testing. With the availability and implementation of HKCMMS, a better quality control for CMM and product will be achieved and health of consumer will be properly protected. To further improve the situation, migration of production to Good Manufacturing Practice (GMP) is necessary. Government shall put more resource to enforce this area.

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