



## Future development of global regulations of Chinese herbal products<sup>☆</sup>

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### ABSTRACT

**Ethnopharmacological relevance:** GP-TCM is the first EU-funded Coordination Action consortium dedicated to traditional Chinese medicine (TCM) research. One of the key deliverables of the Work Package 7 in GP-TCM was to investigate information of the existing requirements for registration of TCM products listed by global regulatory bodies. The paper aims to collate data and draw comparison of these regulations. Case studies are also presented to illustrate the problems involved in registering TCM products in different regions worldwide.

**Materials and methods:** A collaborative network task force was established during the early stage of the GP-TCM project and operated through exchanges, teleconferences and focused discussions at annual meetings. The task force involved coordinators, academics who are actively involved with R&D of Chinese herbal medicines, experts on monographic standards of Chinese materia medica, representatives from regulatory agencies, experts from industries in marketing Chinese medicines/herbal medicines and natural products. The co-ordinators took turns to chair teleconferences, led discussions on specific issues at AGM discussion sessions, at joint workshops with other work-packages such as WP1 (quality issues), WP3 (toxicology issues) and WP6 (clinical trial issues). Collectively the authors were responsible for collating discussion outcomes and updating written information.

**Abbreviations:** CHM, Chinese herbal medicine; CMM, Chinese materia medica or Chinese medicinal material; CHP, complex herbal products; EDQM, European Directorate for Quality Medicines & Healthcare; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration (USA); FP7, 7th Framework Programme; GP-TCM, Good Practice in Traditional Chinese Medicine Research in the Post-genomic Era; GxP, good practice guidelines; MHRA, Medicines and Healthcare products Regulatory Agency (UK); R&D, Research and development; SFDA, State Food and Drug Administration (P.R. China); TCM, Traditional Chinese medicine; TGA, Therapeutic Goods Administration (Australia); THMP, traditional herbal medicinal product; WP, work package.

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<sup>☆</sup> The authors and editors of this GP-TCM Work Package deliverable are engaged to create accurate and up to date content reflecting reliable research evidence, guidance and best practice in TCM research and development. They are free from any commercial conflicts of interest. Reference herein to any specific commercial product, process or service, whether by trade name, trade mark, manufacturer or otherwise does not imply its endorsement, recommendation or favouring by the members of GP-TCM, and is not hereby endorsed, recommended or favoured by GP-TCM. The examples of TCM-derived products quoted are solely intended as case-studies of successful registration of herbals, their particular route to market and lessons learnt to date.

**Results:** A global overview of regulations on herbal registration has been compiled during the three years of the consortium. The regulatory requirements for registration of herbal products in the EU and China were compared, and this is extended to other regions/countries: Africa, Australia, Brazil, Canada, Japan, Russia, South Korea, Taiwan, and the United States. A wide variation of the regulations for the categories of herbal products exists: food (functional food, novel foods, dietary food for special medical purpose, foods for particular nutritional use, food supplement); cosmetic, traditional herbal medicine products; herbal medicines for human use and veterinary use.

**Conclusion:** The regulatory issues for registration of herbal products are complicated among the countries and regions worldwide. The information summarised in the text is for reference only. Some regulations which are presented in this review are still in legislation process and may change in due course. Before taking any regulatory action, readers are advised to consult current official legislation and guidance and/or to seek appropriate professional advice. The lessons learnt from global regulation of TCM will provide valuable insights for regulation of other traditional medicine such as Ayurveda and Unani medicine, as well as other forms of indigenous medicine. The WHO is well placed to co-ordinate a consultation process with the aim of putting forward suggestions for harmonisation to key regulatory agencies.

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## 1. The task of Work Package 7 within the GP-TCM consortium

In 2005, the WHO global survey on National Policy on Traditional Medicine and Regulation of Herbal Medicines pointed out that there has been increasing use of complementary and alternative medicines (CAM) in many developed and developing countries. The safety and efficacy of traditional medicine and complementary and alternative medicines, as well as quality control, have become important concerns for both Health Authorities and the public.

GP-TCM (Good Practice in Traditional Chinese Medicine Research in the Post-genomic Era) is the first EU-funded Coordination Action consortium dedicated to traditional Chinese medicine (TCM) research. The Work Package 7 of GP-TCM was assigned the task to collate accurate and reliable information on the regulatory requirements for registration of TCM products in the EU.

At an early stage in the project, it became very clear that stringent government regulation is crucially important to ensure the quality, efficacy and safety of herbal products and ideally standards should be harmonised at international level. Therefore, one of the aims of GP-TCM Work Package 7 (WP7) is to establish a collaborative network towards formulating an easy-to-follow statement on the various regulatory frameworks for herbals, emphasising the synergies and highlighting the differences, in order to contribute to the long term goal of global harmonisation.

In line with GP-TCM's overall objective, the authors of this article have investigated and compared the applicable regulations of Europe and China. To encompass WP7's global outlook, the authors have also considered the regulations and laws of other countries and regions (in alphabetical order): Africa, Australia, Brazil, Canada, Japan, Russia, South Korea, Taiwan and the United States. These country-specific reviews are summarised and compared.

Various traditional medicine practices have been developed in different cultures in different regions, but without a parallel development of international standards and appropriate methods for evaluating traditional medicine. Therefore, sharing national experience and information is crucial. We believe that the lessons learnt from global regulation of TCM will provide valuable insights for regulation of other traditional medicine such as Ayurveda and Unani medicine, as well as other forms of indigenous medicine.

## 2. Overview of herbal regulations worldwide

### 2.1. Europe

With the European Directive 2004/24/EC taking full effect on 30th April 2011, it is now illegal for companies to sell manufactured unlicensed herbal medicines within Europe without the

appropriate license i.e. a Marketing Authorization (MA) or a Traditional Herbal Registration (THR). The UK differs slightly from the rest of Europe in that herbal practitioners are to be regulated as from April 2012 allowing for unlicensed manufactured herbal medicines to be prescribed following a face-to-face consultation.

#### 2.1.1. Overview

The main regulatory body is the European Medicines Agency (EMA) but each Member State also has their own regulatory agency e.g. The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, and The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) in Germany. To date, there is no separate regulation for the registration of TCMs. Instead, there are several different routes to market for herbal products within Europe:

- food (functional food, novel foods, dietary food for special medical purpose, foods for particular nutritional use – PARNUTS, food supplement),
- cosmetic,
- traditional herbal medicinal product (THMP),
- medicine for human use (Well Established Use, full Marketing Authorization), or
- veterinary product.

It is important, therefore, to determine the classification of the herbal product. This may seem to be stating the obvious but many companies and researchers assume that if their product contains herbal actives, automatically it must be registered as a THMP but this is not always the case. The classification of herbal products can often be determined by the overall strategy of the company producing the remedy. For example, classification as a medical device (e.g. ear drops, skin patches) may be possible and more desirable: registration is generally quicker and therefore a company's investment will reach breakeven much sooner than via the 'traditional' route. For the purpose of this article, however, the authors have chosen to focus on the Traditional Herbal Registration Scheme as this has had the greatest impact on the European herbal industry in recent times.

#### 2.1.2. Why did the EU want to regulate herbal remedies?

Increasingly consumers have turned to plant-derived remedies in the belief that these 'natural' products are 'safer' than conventional medicines. The words "natural", "herbal" and "plant-derived" can be misleading and it is important for the public to be reminded that herbal remedies are medicines in their own right. Health Authorities have been concerned about the safety profile and quality of such medicines for a number of years now. For example,

it is well known that St. John's Wort interacts with SSRIs and oral contraceptives. In some national markets, such as Germany, France and Austria, herbal preparations were already well defined under existing laws. However, laws in other markets, such as The Netherlands and the UK were less stringent or, at the very least, less well enforced. So the EU Directive 2004/24/EC was implemented in order to harmonise the regulations, enable the free movement of herbal products within Europe and protect the consumer.

#### 2.1.3. Traditional Herbal Registration Scheme

In March 2004 the European Directive 2004/24/EC was adopted and so the term “traditional herbal medicinal product” (THMP) was established.

The word “traditional” is key: it is important to demonstrate that the herbal medicine or ‘corresponding’ (i.e. comparable) product(s) has been in traditional medicinal use for 30 years preceding the date of the application for the required medicinal indication. 15 years of this usage must have been within the European Union (EU). The latter is not absolutely essential and therefore, if the 15 years of usage in the EU cannot be satisfied but the product(s) meets all the other requirements of the Directive, the Health Authority can refer the product(s) to the Committee on Herbal Medicinal Products (HMPC) who have the discretion to lower the requirement for 15 years’ use (but there is no guarantee of this).

#### 2.1.4. Key requirements of the Traditional Herbal Medicinal Products Scheme (THMPS)

The THMP dossier must follow the Common Technical Document (CTD) format (Fig. 1). The CTD is designed for use in Europe, Japan and America and consists of 5 Modules:

- Module 1: Administrative and prescribing information.
- Module 2: Overview and summary of modules 3–5.
- Module 3: Quality (pharmaceutical documentation).
- Module 4: Safety (toxicology studies).
- Module 5: Efficacy (clinical studies).

This format has also been adopted by several other countries including Canada and Switzerland. The THMPS, however, follows a simplified version of the usual CTD format (see below).

**2.1.4.1. Safety.** This is where the ‘simplification’ of the registration requirements for a traditional herbal remedy can clearly be seen as compared to a conventional pharmaceutical medicine. In this instance Module 4 of the Common Technical Document (CTD) requires bibliographical evidence on safety (including cross referencing to the appropriate Expert Report) and therefore replaces the usual non-clinical study reports. If, however, the herbal substance is included on the Community List (European Medicines Agency, 2011), the need to provide a safety summary to support the application is removed.

If a safety summary is required it must consider:

- all herbal ingredients (+ vitamins or minerals),
- use in pregnancy, lactation etc.,
- potential interactions with other medication, herbal products and/or food.

**2.1.4.2. Confirm ‘traditional use’ of the product.** As with ‘safety’ outlined in point (i) above, this is a key part of the CTD for traditional herbal medicines and consists of bibliographical evidence. It replaces the usual requirement of clinical studies in Module 5 although if studies are available these should be included.

So what is meant by “traditional”? Put simplistically, it is an herbal product which:

- is intended and designed for use without the intervention of a medical practitioner for diagnosis, prescription or monitoring of treatment;
- is taken orally, for external use or inhalation;
- the efficacy must be ‘plausible on the basis of long-standing use and experience’.

Acceptable sources of evidence include:

- information from handbooks of medicine, pharmacy, pharmacology, phytotherapy, herbal medicine, pharmacopoeia;
- official expert committee reports, ESCOP monographs;
- product related documentation (e.g. product brochures); and
- company archive materials (e.g. sales invoices).

**2.1.4.3. Quality.** Even if the herbal substance is included on the Community List (European Medicines Agency, 2011), quality must still be demonstrated. Quality applies from the Field to Finished Product. Good Agricultural and Collection Practice (GACP) and Good Manufacturing Practice (GMP) are examples of some of the required practices and systems which need to be followed. Herbal products must contain the correct ingredients of acceptable quality, free from unacceptable contamination; and the claimed shelf life of the product must be supported. The normal quality requirements applicable to licensed medicines apply. There is also a requirement to hold a manufacturer’s license, a wholesale dealer’s license or a wholesale dealer’s (import) license where appropriate.

As a result of several discussions with those companies operating in the herbal industry as well as with agency representatives, quality appears to be the most challenging aspect of registration with examples of products from India and China using different genera for different batches of the same herbal remedy.

#### 2.1.4.4. Labels and leaflets – readability/user testing (Directive 2001/83/EC).

*“The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use” (European Parliament, 2001b)*

The aim of a readability test is to demonstrate that patients can:

- locate information in the PIL,
- understand it, and
- know how to act on it.

The product labelling and leaflet must include the statement:

*“product X is a traditional herbal medicinal product for use in specified indications exclusively based on longstanding use”*

And the correct certification registration mark must be used: <http://www.mhra.gov.uk/Howweregulate/Medicines/HerbalMedicines/PlacingaherbalmedicineontheUKmarket/TraditionalHerbalMedicinesRegistrationScheme/TraditionalHerbalRegistrationcertificationmark/index.htm>.

**2.1.4.5. Advertising.** Specific advertising requirements (European Parliament, 2007) apply to THMPs over and above other provisions and specific extra wording on advertisements of THMPs are required:

*“Traditional herbal medicinal product for use in (registered indication) exclusively based upon long-standing use as a traditional remedy”*

It is important to remember that THMPs are registered for “use in minor self-limiting conditions that are suitable for self-management and do not require the intervention of a medical

practitioner.” (Medicines and Healthcare products Regulatory Agency, 2011)

2.1.4.6. *Article 16d (European Parliament, 2001a, 2004)*. It is possible to obtain mutual recognition of the registration of a THMP in the EU. Put simply, this is the process by which EU countries may approve the decision made about a THMP by another EU country. A company submits their application to the country chosen to carry out the assessment work which then approves or rejects the application. The other countries then have 90 days to decide to approve the decision made by the original country.

Article 16d of Directive 2004/24/EC (as amended) outlines that:

- mutual recognition shall apply to registration if covered by a Community Herbal Monograph;
- the herbal ingredient is recorded on the Community List; and
- Member States must take into account registration by other Member States.

So far THMP registrations have only been at national level and as yet, companies have not taken advantage of the Mutual Recognition Procedure (MRP).

2.1.4.7. *Enforcement*. The herbal industry is being actively policed not only by the regulatory agencies themselves but also by the competitors and members of the public and it tends to be non-compliant websites and promotional activities which bring companies to the attention of the authorities.

#### 2.1.5. Case study: UK based Chinese company

Early in April 2011, a regulatory consultancy was approached by a Chinese company trading in the UK. The company produces herbal granules and finished product. They were aware of the THMPD and the imminent deadline of 30 April 2011. Unfortunately, they were naïve and thought that as long as they reached compliance at some point in the future, they could continue trading as they were. In addition, the company's employees were confused about the THMPD requirements some of which was due to language and cultural barriers. Some of the confusion arose, however, because they were selling granules as well as finished product but, depending on circumstances, granules can also be deemed to be “finished product”. Further confusion arose because the company had products on the US market and, as a result they had assumed that because they were compliant in the US this ‘compliance’ would translate into Europe. Unfortunately, this assumption was incorrect.

A meeting was held between the company and the consultancy during which it became clear little was in place to ensure compliance with THMPD. In May 2011, the company then received an unannounced visit from the UK's MHRA as a result of Customs and Excise detaining a consignment of what was suspected to be unlicensed medicine entering the UK. At the time of writing this article, this incident remains under investigation and a formal response from the MHRA is awaited.

With the approval of the MHRA, the company continues to provide herbal granules as ingredients to practitioners but all of their finished products have been returned to the manufacturers in China. It has been agreed that they will reassess their business when they have received a formal response from the MHRA and once the regulation of herbal practitioners has been implemented. In preparation for this time (and after receiving further advice) they are in discussion with other similar companies with the aim of forming a co-operative to share the costs for quality and pharmacovigilance activities.

This is a particularly serious case as it involves criminal proceedings. The outcome will be a fine of several thousand pounds and may also result in imprisonment of the company directors.

2.1.5.1. *Case studies using Dantonico® (for human angina) and Phytopyca® (for canine skin health)*.

2.1.5.1.1. *Case study 1 – Dantonico® (Danshen Diwan) for angina produced by Tasly Pharmaceuticals, Co. Ltd., P.R. China*. Although Dantonico® is not a traditional herbal remedy, the authors believe that the product proves to be a useful case study because it demonstrates the complexity (and differences) of the various regulatory pathways worldwide and, in particular, between China and Europe. In turn, this highlights the difficulties facing companies trying to develop plant based medicines whether novel or based on traditional formulae.

Dantonico® was developed as a novel formulation by pharmacists at a military hospital in Tianjin, China, in the early 1990s. The ingredients were chosen based on TCM theory and accumulated clinical experience for treating chronic stable angina pectoris due to coronary artery disease. It contains 2 herbal extracts: *Salvia miltiorrhiza* and *Panax notoginseng* plus *Borneolum syntheticum*. It is marketed (and prescribed by clinicians) in China but the 2 herbs are also known to be used as food ingredients. Interestingly the product has been legally marketed as a food/dietary supplement in The Netherlands for many years (there is documentation confirming that it is imported with approval from the Dutch authorities). The Swedish Medical Products Agency (MPA), however, informed the manufacturer that in their view Dantonico® is classified as a medicine for the following reasons:

- they could not find that the ingredients had been used in food within the EU;
- they found many studies showing the ingredients have pharmacological properties, and
- the monograph in the Chinese Pharmacopoeia showed it is a product intended for medicinal use.

In this instance, the medicinal use established in China was enough to classify Dantonico® as a medicinal product and the option of classification as a food supplement was not possible in the EU.

This example shows an obstacle and challenge for CHMs entering the EU market i.e. the product will be classified as a medicine because of the documented medicinal use in China. At the same time the product does not qualify for the ‘simplified’ registration path (Traditional Herbal Medicinal Product Registration) as documented use is not within the EU.

It is interesting that EU Agencies will recognise medicinal use in China in one context but not in another. Since the first launch of Dantonico® in Vietnam in 1996, it has been legally marketed in more than 26 countries or regions including Russia, South Korea, Mongolia, Singapore, Vietnam, and South Africa as a prescription drug or over-the-counter (OTC), in 32 countries include the United States as dietary supplements, and in Canada as traditional drug labeled with cardiovascular treatment indications. See Table 1 for country-specific approval/initial launch status (correct as of May 2010).

2.1.5.1.2. *Conclusion*. Table 1 clearly demonstrates the significant variances in the classification of the same herb-based product showing the full spectrum from dietary supplement, OTC drug, traditional drug, to prescription drug. It is well known that many herbal ingredients in China, Korea, etc. are classified as “drug and food from the same origin i.e. they can be used as ingredients for food, soft drink, dietary supplement, and medical purpose depend on method of use and normal daily intake amount. How such products are recognised by the different regulatory agencies is the key to their future health benefits to patients and commercial value

to the manufacturer. It seems the method of use and daily intake amount are not considered in the some countries but does in others in classification. Before any consideration can be made for the harmonisation of regulations perhaps first an agreement needs to be reached in the future on the definition, and therefore classification, of these products.

**2.1.5.2. Case study 2 – Phytopica® for canine skin health developed by Phytopharm and initially under licence to Intervet/Schering Plough, UK.** Phytopica® is based on a traditional formula and, although it was planned to obtain European registration for human use, it eventually gained successful registration as a veterinary foodstuff with ‘health claims’ (pre Article 13.5 but originally developed under the principles of this Article). It is important to note that it cannot be used off-label for human patients.

The original 10 plant extract (Zemaphyte®) was developed for human use and progressed into phase III clinical trials. Registration was abandoned as it was too expensive to manufacture to GMP standards (and also required further work). Additional clinical trials of Phytopica® would need to be performed in humans (some had been performed but more would be needed). The original Phytopica® data package is identical to that of a human data package and fully supports human clinical trials. In the end, 3 plant extracts (*Rehmannia*, *Paeonia*, *Glycyrrhiza*) were selected from the original 10 plant extracts based on their pharmacology and usage.

The clinical trials and manufacturing data package were reviewed by the Veterinary Medicines Directorate (the veterinary equivalent of the MHRA), and therefore were to ‘investigational medicinal product standards’ both in the UK and France. Phytopica® was launched as a veterinary foodstuff with ‘health claims’ for the European market because it was a quicker route to market and therefore, could provide an immediate return on investment. These funds were then used to research and develop other potential medicines.

Later, the product was licensed to Intervet/Schering Plough who marketed and sold it in Europe and Asia. It proved difficult to sell in the US due to differing state laws which is why the company only marketed Phytopica® in Europe and not the US.

The manufacturing methods used for Phytopica®, along with the 3-plant extract combination, resulted in a novel product (hence the product was able to be patented) which had not been used as a medicine in China or Europe. As it had no previous history as a medicine, this may well have contributed to the company’s success in launching the product as a veterinary foodstuff.

**2.1.5.2.1. Conclusions.** This case study demonstrates that developing plant extracts for use as a food but which are traditionally used as CHMs can be difficult but not impossible particularly if the plant extracts used are in a different combination. It is understood that if, traditionally, the combination of plant extracts has been used as a medicine in China then it will be classed as a medicine in Europe. If separately the plant extracts are used as a food then it is likely that the product could be developed as food (i.e. a novel food and as a food with health claims (or possibly as a medical food)).

## 2.1.6. Summary

General consensus is that whether a product is a TCM, Ayurvedic or Western herbal, the basic rules are the same i.e. the product will need a suitable product licence or Traditional Herbal Registration. Materials of animal origin and chemical compounds are excluded. It is recognised that there are particular issues with, for example, TCMs in that proving a minimum of 15 years’ traditional use in Europe can be problematical. Interestingly, agencies perceive other factors to be greater ‘stumbling blocks’. For example:

- quality often is not to required standards i.e. Good Agricultural and Collection Practice (GACP), Good Manufacturing Practice (GMP);
- some TCMs contain much more potent ingredients than is permitted under the THMRS; and
- some TCMs make much stronger claims than is allowed.

As from May 2012, it is likely that TCMs will have an alternative regulatory route with the planned introduction of the regulation of healthcare practitioners although, currently, this applies to the UK only.

The THMRS is not the only regulatory pathway in Europe so it is important for companies and researchers to determine what is the most appropriate and beneficial route for their product. Some regulations which are presented in this review are still in legislation process and may change in due course.

## 2.2. China

In China,<sup>2</sup> Chinese herbal products are governed by the State Food and Drug Administration (SFDA) and can be registered as functional food or drugs. Regulatory approval of functional food is the responsibility of the Department of Food License whereas that of Chinese herbal drugs is controlled by the Division of TCMs & Ethno-Medicines under the Department of Drug Registration.

Drugs in China cover not just chemical drugs but also traditional medicines. According to Article 102 of the *Drug Administration Law of the People’s Republic of China (State Food and Drug Administration P.R. China, 2001)*, the definition of drugs is as follows:

“Drugs refer to articles which are used in the prevention, treatment and diagnosis of human diseases and intended for the regulation of the physiological functions of human beings, for which indications, usage and dosage are established, including Chinese crude drugs, prepared slices of Chinese crude drugs, traditional Chinese medicine preparations, chemical drugs substances and their preparations, antibiotics, biochemical drugs, radioactive pharmaceuticals, serum, vaccines, blood products and diagnostic agents.”

### 2.2.1. Laws and regulations

The *Drug Administration Law of the People’s Republic of China (Drug Administration Law)*, enacted in 2001, is the fundamental law governing drug administration in China to ensure drug quality and safety for human beings, to protect the health of people and their legitimate rights and interests in the use of drugs. The *Regulations for Implementation of the Drug Administration Law of the People’s Republic of China* are formulated in accordance with the Drug Administration Law and provide legal framework for the control over drug manufacturers, drug distributors, pharmaceuticals in medical institutions, drug packaging, drug pricing and advertising.

A unique feature of the regulatory system is the *Regulations for the Protection of TCM Products* which provide administrative protections for TCM products manufactured within China (*State Food and Drug Administration P.R. China, 1993*).

### 2.2.2. Distinction between TCM and natural medicinal products

The *Provision for Drug Registration (SFDA order 28)* provides practical guidelines for the registration of drugs (*State Food and Drug Administration P.R. China, 2007*). Drugs will be assessed for

<sup>2</sup> China refers to the mainland China. Chinese herbal products in Hong Kong and Macau are governed by their domestic laws and regulations.

its safety, efficacy and quality. According to this provision, Traditional Chinese Medicines refer to medicinal substances and their preparations used under the guidance of traditional Chinese medical theory; whereas natural medicinal products refer to natural medicinal substances and their preparations used under the guidance of modern medical theory. Traditional Chinese Medicines and natural medicinal products can be classified into 9 categories as follows:

- 1 Active ingredients and their preparations extracted from plants, animals, minerals or other substances which have not been marketed in China.
- 2 Newly discovered crude drugs and their preparations.
- 3 New substitutes to existing Chinese crude drugs.
- 4 New medicinal parts of existing crude drugs or their preparations.
- 5 Active fractions and their preparations extracted from plants, animals, minerals or other substances which have not been marketed in China.
- 6 Preparations of Chinese medicines and natural medicinal compounds, which have not been marketed in China.
  - 6.1. TCM combination preparations.
  - 6.2. Natural medicinal combination preparations.
  - 6.3. Combination preparations consisting Chinese medicines, natural medicinal products and chemical drugs.
- 7 Preparation with altered mode of drug delivery of marketed Chinese medicines and natural medicinal products.
- 8 Preparation with altered dosage form of marketed Chinese medicines and natural medicinal products.
- 9 Generics.

### 2.2.3. Drug standards

Both TCM and natural medicinal products must follow the national drug standards and provincial standards. The former standard is defined by the Pharmacopoeia of PRC (ChP) and specifications approved by SFDA. In the ChP, there are standards for Chinese prepared sliced crude drugs and TCM products. The standards for the herbal granules, being extracts for single herbs or combination classical formulae, will be available in the 2015 edition. Provincial standards are monographs of Chinese *materia medica* and processing of TCM herbal slices approved by individual provinces.

### 2.2.4. Supplementary rules for TCM Registration

In order to follow the rules on the study of TCM, reflect the distinguishing feature of the registration of TCM, regularise the registration of TCM and support the development of TCM and medicine of Chinese minorities, SFDA issued the *Supplementary Requirements on the Registration of TCM* in accordance with relevant requirements of *Provisions for Drug Registration (State Food and Drug Administration P.R. China, 2008)*.

**2.2.4.1. Traditional or historical use.** Under this Supplementary Requirement, TCM combination preparations were further divided into:

- 6.1.1 TCM combination preparations originated from historic, classic and well-known recipes.
- 6.1.2 TCM combination preparations which indication is a TCM syndrome.
- 6.1.3 TCM combination preparations which indication is a combination of TCM syndrome and diseases.

The application data for marketing TCM combination preparation from historic,<sup>3</sup> classic and well-known recipes may be partially exempted based on its formulation source, their composition, function, indication and manufacturing procedures. However, safety data are compulsory.

### 2.2.5. Reasonability in accordance with TCM theory

The SFDA has expertise in assessing the reasonability of Chinese herbal formulation. Depending on the registration classification, applicants may be required to submit non-clinical safety data and phase III clinical trials only. Clinical trials of the herbal formulations have to be conducted in accredited centres for specific disease/system in China. If the drug fails to demonstrate reasonable formulation based on TCM theory, requirements for data submission may follow that of natural medicinal products.

### 2.2.6. Summary

The supervision on TCM in China is as strict as that of chemical drugs and biological products. Registration of TCM is subject to strict technical evaluation and clinical trial. Safety data are compulsory although TCM that demonstrate historical use may have partial application data exempted.

## 2.3. Africa

A recent WHO report (WHO Regional Report dated July 5th 2011 ref AFR/RC61/PR/2) on the status of traditional medicine in Africa indicates the following:

- In 2000 only 10 African countries had laws on use of herbal medicines. By 2010 the figure was 20 countries.
- In 2000 only 4 African countries had a registration system of traditional healers. By 2010 the figure was 15 countries.
- In 2000 only 1 African country had issued a market authorisation for traditional herbals. By 2010 the figure was 12 countries.

The countries which have done most to develop regulations for both the manufacture and use of traditional herbal drugs but also the regulations of traditional healers are:

- Egypt where all herbal medicines are regulated and manufactured with licenses similar to Europe.
- Mali where traditional medicine is integrated into the health system and traditional medicine is prescribed under the national health system.
- Ghana where a herbal pharmacopoeia has been developed, commercially manufactured herbal medicines are regulated by the Food and Drugs Authority and traditional healers are organised into a recognised national association.

Nigeria, Cameroon and Congo also now have national pharmacopoeias and issue market authorisations for commercially manufactured herbal preparations. In many other African countries, including South Africa and Kenya, legislation regulating the use of herbal medicines has been under discussion for many years but has still not been passed by their governments.

The protection of the intellectual properties of traditional healers has become an increasingly important aspect of the regulatory scenario. 8 countries, including South Africa, Ghana and Nigeria, have national laws relating to IPR and traditional medicine. There is, however, a wide gap between the existence of the legislation

<sup>3</sup> Historical TCM formulae refer to those that are still widely used, of proven therapeutic effect and was documented before or during the Qing Dynasty (AD 1644–1912).

and the application of the law in practice (Association of African Medicinal Plants Standards; Denzil Phillips International Ltd.).

## 2.4. Australia

### 2.4.1. Introduction

The Therapeutic Goods Administration (TGA) is the main regulator for Chinese material medica (CMM) and related proprietary Chinese medicines (PCM) (TGA, 2011). Before importing or exporting CMM and PCM, product sponsors must register or list their products in the Australian Register of Therapeutic Goods (ARTG). The TGA maintains the ARTG, a database that includes details of all therapeutic goods that are imported into, supplied in, or exported from Australia. Once a product is successfully listed or registered, TGA will issue a certificate of listing/registering to sponsors who can then make the logistic arrangement for shipping these products.

### 2.4.2. TGA regulatory aspects of complementary medicines

Generally, the therapeutic goods whose supply is regulated by the TGA fall into three categories:

- **Medical devices.** Medical devices are items used on humans for therapeutic benefit and which generally have a physical or mechanical effect on the body or are used to measure or monitor functions of the body.
- **Registered medicines.** Registered medicines are those assessed as having a higher level of risk. The degree of assessment and regulation they undergo is rigorous and detailed, with sponsors being required to provide comprehensive safety, quality and efficacy data. They include all prescription medicines, most 'over-the-counter' medicines and a small number of complementary medicines.
- **Listed medicines.** Listed medicines are considered to have a lower level of risk. They have established ingredients, usually with a long history of use, such as vitamin and mineral products or sunscreens. This category includes about 98% of complementary medicines.

Examples of complementary medicines according to TGA (TGA, 2011).

- Medicinal products containing herbs, vitamins, minerals, and nutritional supplements, homoeopathic medicines and certain aromatherapy products are referred to as 'complementary medicines'.
- Complementary medicines comprise traditional medicines, including traditional Chinese medicines, Ayurvedic medicines and Australian Indigenous medicines.
- Other terms sometimes used to describe complementary medicines include 'alternative medicines', 'natural medicines' and 'holistic medicines'.
- Complementary medicines are generally available for use in self-medication by consumers and can be obtained from retail outlets such as pharmacies, supermarkets and health food stores.
- Most complementary medicines are indicated for the relief of symptoms of minor, self-limiting conditions; many are indicated for maintaining health and wellbeing, or the promotion or enhancement of health.

(Source: TGA, [www.tga.gov.au/industry/cm-basics-regulation-overview.htm](http://www.tga.gov.au/industry/cm-basics-regulation-overview.htm)).

### 2.4.3. The growing use of complementary medicines in Australia

Surveys carried out in 1996 in Victoria and South Australia indicated about 50% of people had recently used alternative

medicines. By early 2009, the National Institute of Complementary Medicine's (NICM) figures indicated that 2/3 of Australians use these medicines each year (Minister for Health and Family Services, 1996). Health professionals may be contributing to the increased usage in Australia. Research undertaken by the National Prescribing Service (NPS) in 2007 showed about 90% of general practitioners had recommended at least one complementary medicine in the last 12 months and almost all surveyed community pharmacists had recommended some kind of complementary medicine over that period (NICM, 2009).

### 2.4.4. The reason for regulating complementary medicines

The belief that complementary medicines are safe because they are 'natural' is considered by the TGA as an important risk. The risks are relatively small when traditional medicines are used correctly, but they are still there, and consumer understanding is generally low. For example, a cross-sectional population survey conducted in Australia found that less than half (46.6%) of traditional, herbal medicine users were even aware that there could be potential risks associated with product use. Not everything that is natural is safe; traditional medicine products must be used judiciously and as indicated, just like any other medication, and with awareness of potential risk.

### 2.4.5. Development of the regulatory framework in Australia

The key events leading to regulatory framework:

- Until the 1980s certain sorts of therapeutic goods were unregulated in Australia. This was the case with most therapeutic devices and with complementary medicines for which there were increasing concerns about quality, safety and the 'extravagant therapeutic claims' that were being made.
- National regulation of complementary medicines commenced with the *Therapeutic Goods Act 1989*. Section 9A of the Act requires the Secretary of Department of Health & Ageing (DoHA) to maintain a register of therapeutic goods. This is the Australian Register of Therapeutic Goods (ARTG), which is at the heart of therapeutic goods regulation in Australia (see the box below).
- A therapeutic good must be on the ARTG before it can be imported into, supplied in Australia or exported, unless it is in a special category of exempt or excluded goods. The importer or manufacturer of the goods (under the Act, the 'sponsor') is responsible for applying to the TGA to have their goods included in the ARTG. The sponsor of a therapeutic good included in the ARTG must be an Australian resident and/or doing business in Australia.

### 2.4.6. The Australian Register of Therapeutic Goods

The ARTG is established under the Act. The Secretary of DoHA is required to maintain the ARTG, comprising three parts:

- (1) **Registered medicines.** These are higher-risk items whose efficacy must be demonstrated before they can be registered. The Act requires them to be evaluated for quality, safety and efficacy before they can be registered. They must display an 'AUST R' number on their label as proof of registration.
- (2) **Listed medicines.** These can be listed unless they fail to comply with quality and safety criteria. They are not evaluated for efficacy. They are generally lower-risk items, usually self-selected by consumers for self-treatment. They must display an 'AUST L' number on their label as proof of listing. Medicines for export only are listed on the ARTG.
- (3) **Medical devices.** These include a wide range of products such as medical gloves, bandages, syringes, condoms, contact lenses, in vitro diagnostic devices, disinfectants, X-ray equipment, surgical lasers, pacemakers, dialysis equipment, baby incubators and heart valves.

Medicines included in the ARTG are divided into three broad categories:

- (1) *Prescription medicines*. These are medicines available only upon prescription by a qualified health practitioner, usually for a serious illness. They must be registered on the ARTG, will usually contain an active ingredient which is a 'scheduled' substance (that is, included in the *Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)*)<sup>46</sup> and their use may involve risks.
- (2) *Over-the-counter (OTC) medicines*. These items, also registered on the ARTG, include mild analgesics, cough and cold preparations and anti-fungal creams. OTC medicines generally have active ingredients less potent than those used in prescription medicines.
- (3) *Complementary medicines* (sometimes called 'complementary and alternative medicines', 'CAM'). Most complementary medicines are listed on the ARTG and include vitamins, minerals, Chinese traditional medicines, herbal, aromatherapy and homeopathic products.

(Source: Therapeutic Goods Act 1991)

## 2.5. Brazil

### 2.5.1. Introduction

Herbal medicine has been regulated in Brazil in some form or another since 1967 with effective regulation being implemented since 2000. Then in 2006 the National Policy of Integrative and Complementary Practices (PNPIC) in the Brazilian Unified Health System (SUS) and The National Policy of Medicinal Plants and Herbal Medicines (PNPMF) were launched. Based on these policies, ANVISA (the Brazilian Health Surveillance Agency) amended the regulations applicable to herbal medicines. Previously there were five key regulations but these have now been succeeded by the recently published RDC 14/10 (Carvalho et al., 2011; WHO Geneva 2011, 2011).

### 2.5.2. Safety, efficacy and traditional use

Herbal products are categorised as 'herbal drugs' (prescription and over-the-counter); functional foods, probiotics, bioactive substances and cosmetics. Medical claims are only allowed if the product is registered as a herbal medicine. It is worth noting that herbal medicines have the same status as any other medicine. This means that they can only be produced by GMP-certified facilities (and the company must employ a qualified pharmacist). Safety and efficacy must be demonstrated by pre-clinical and clinical data, literature, an entry in the "list of simplified registration of herbal medicines" or evidence of traditional use. Traditional use must confirm the safety and efficacy of a product and document at least 20 years of use. *Farmacopéia brasileira* is Brazil's Pharmacopoeia (includes their national monographs) and is legally binding.

### 2.5.3. Quality control

It is a requirement for various tests to be carried out to demonstrate product quality. These tests should confirm, for example, the plant genus and levels of contaminants (e.g. fungi) within acceptable limits. RDC 14/09 states the requirements for quality assurance and in particular, the reproducibility of herbal medicines. Any company submitting a herbal medicine dossier for registration should use the methodologies included in the pharmacopoeias recognised by ANVISA for quality control of herbal materials, excipients and medicine. If the pharmacopoeias are not followed then the company is required to validate the methodologies they have used (ANVISA, 2008).

## 2.5.4. Other regulations

These include

- Restriction of sale criteria i.e. is the medicine to be sold as a prescription medicine or not (Brasil, 2003b).
- Stability study guide (Brasil, 2005a).
- GMP, quality control and outsourcing of storage (Brasil, 2005b, 2007).
- Advertising (Brasil, 2008c).
- Standardisation of Package Leaflet (RDC 47/09)).

The list, RDC 138/03, itemises those medicinal products which do not require a prescription. If the indication described on the product is not included in RDC 138/03 then it can be marketed under prescription only (Brasil, 2003b).

RE 01/05 provides information on stability requirements for both accelerated and long lasting mode with the results determining the product's expiry date and appropriate storage conditions (Brazilian Government, 2010).

## 2.6. Canada

Canada is one of the countries in the western world that has better established system in regulating natural health products (NHPs). In Canada, NHPs are defined as vitamin and mineral supplements; herb and plant-based remedies; traditional medicines like TCM or Ayurvedic (Indian) Medicines; omega 3 and essential fatty acids; probiotics; homeopathic medicines.

All NHPs sold in Canada are subject to the Natural Health Products Regulations (The Government of Canada, 2003), which came into force on January 1, 2004. Under this regulation, all producers of NHPs need to apply for licenses before selling them in Canada. To apply for a licence, the person or company shall submit an application to Natural Health Products Directorate (NHPD), Minister of Health Canada (Health Canada, 2011c) with a package of information. Among others, the application requires the information for each medicinal ingredient contained in the NHP, including its quantity per dosage unit, potency, source material and a statement indicating whether it is synthetically manufactured. It also requires information for non-medicinal ingredients and recommended use. The safety and efficacy of NHPs and their health claims must be supported by proper evidence. It is interesting to note that evidence is not necessarily from clinical trial data but can also be references to published studies, journals, pharmacopoeias and traditional resources. The type and amount of supporting evidence required depends on the proposed health claim of the product and its overall risks.

There is a compendium of monographs established by NHPD (Health Canada, 2011d). The NHPD product licensing system allows applicants to reference the monographs listed in the compendium in support of the safety and efficacy of their products, rather than providing evidence for ingredients that are already known to be safe and efficacious when used under the conditions specified in the monographs.

Once Health Canada has assessed a product and decided it is safe, effective and of high quality, it issues a product licence along with an eight-digit Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM), which must appear on the label. The licensing procedure is to be completed within 60 days after the day on which the application is submitted unless additional information is required by the NHPD. It might be important to notice that the licensing requirements of the *Natural Health Products Regulations* only apply to any person or company that manufactures, packages, labels and/or imports NHPs for commercial sale in Canada. They do not apply to health care practitioners who compound products on an individual basis for their patients, or

to retailers of NHPs. In addition, because Health Canada has not yet evaluated all natural health products currently on the market, products with exemption numbers can also legally be sold in Canada. The exemption number will be listed on the product label in the form EN-XXXXXX. You can search for licensed natural health products using Health Canada's Licensed Natural Health Products Database (Health Canada, 2011a), or for exempted natural health products using Health Canada's Exempted Products Database (Health Canada, 2010). On the other hand, all Canadian manufacturers, packagers, labellers, and importers of natural health products must have site licenses. To get a licence, sites must maintain proper distribution records, have proper procedures for product recalls and for the handling, storage and delivery of their products, and demonstrate that they meet good manufacturing practice requirements. As of December 31, 2010, the NHPD has issued 25,919 product licences (representing over 34,900 products); 1120 site licences; and 6795 exemption numbers (representing over 8300 products). Since 2009, there are about 8000 new applications submitted each year in Canada (Health Canada, 2011b).

## 2.7. Japan

### 2.7.1. Introduction

Kampo is the Japanese traditional medicine which is based on traditional Chinese medicine. Although Kampo has its roots in China, it is a product of Japanese culture and experience. Chinese medicine was first introduced to Japan in the 4th century. Japanese practitioners gradually refined and improved the original formulae. After the 17th century, many of the original formulae were validated through clinical experience, which laid the foundation of Kampo medicine (Goda, 2006).

### 2.7.2. Regulations of herbal medicines

The Ministry of Health, Labor and Welfare is the regulatory agency in Japan responsible for herbal medicines. Pharmaceutical administration in Japan is regulated according to a number of laws among which the *Pharmaceutical Affairs Law* is the supreme law. Issued in the 1950, the *Pharmaceutical Affairs Law* documented national laws and regulations on traditional medicines and its purpose is to regulate matters pertaining to drugs, quasi-drugs, cosmetics and medical devices in order to ensure their quality, efficacy and safety. It also promotes the drug development for orphan diseases (Saito, 2000).

### 2.7.3. Herbal medicine as prescription drugs or OTC drugs

Depending on the medical claims, herbal medicines may be approved as prescription drug or OTC drugs. Prescription drugs have to be produced according to the official quality standards as required by law. As for the Japanese OTC drugs, they are divided into Japanese traditional medicines, 'Kampo' formula, phytomedicines and multi-vitamin preparations. To date, more than 200 'Kampo' formulae have been listed for insurance reimbursement. Herbal crude drugs combined with chemical drugs were also accepted, subject to quality, safety and efficacy tests, as CNS drugs, cold remedies, antipyretics, analgesics, topical drugs, anti-inflammatory drugs, gastrointestinal drugs, cardiovascular drugs and urogenital drugs (Saito, 2000).

### 2.7.4. Prescription-to-OTC Switch

Some products, even though originating from a recognised 'Kampo' formula, may also be defined as an OTC drug depending on its composition, doses, efficacy and direction of use. 'Shosaiko-To' is a typical example of a product which can be both a prescription drug and OTC in the Japanese market (Saito, 2000).

### 2.7.5. Japanese Pharmacopoeia

In Kampo medicine, the decoction formula generally consists of 2–15 different crude drugs. Nowadays, Kampo preparations are mainly distributed in the form of ready-made granules, powders or tablets which contain the spray-dried decoction (dry extract). Therefore, dry extract was selected for admission to the Japanese Pharmacopoeia (Goda, 2006).

The Japanese Pharmacopoeia is divided into 2 sections, namely the crude drugs and their related preparations (Section II) and others (Section I). Therefore, Section II of the Japanese Pharmacopoeia contains the monographs of crude drugs and their related preparations only including that of a number of Kampo formula extract (Goda, 2006). The pharmacopoeia includes herbal crude drugs of both Japanese and European origins.

The Japanese Pharmacopoeia is legally binding. Regulatory requirements for manufacturing are the same GMP rules that apply to conventional pharmaceuticals; these requirements are part of the following regulations: Pharmaceutical Affairs Law, Regulations for Manufacturing Control and Quality Control of Drugs and Quasi Drugs and Regulations for Buildings and Facilities for Pharmacies. The control mechanisms used to ensure the implementation of these requirements are the same as those used for conventional pharmaceuticals; however, details are not available. The regulatory requirements for safety are the same requirements that apply to conventional pharmaceuticals. To ensure the implementation of these requirements, the same rules of approval review, GMP and post-marketing surveillance are used for herbal medicines as for conventional pharmaceuticals (WHO, 2005).

### 2.7.6. Summary

In Japan, regulations for herbal medicines are the same as that for conventional pharmaceuticals. Herbal medicines are regulated as prescription and over-the-counter medicines, dietary supplements (called "health foods") and functional foods. By law, medical, nutrient content and structure/function claims may be made for herbal medicines. Currently, there is an approval system rather than a registration system; at least 1469 herbal medicines have been approved (WHO, 2005).

## 2.8. Russia

### 2.8.1. Introduction

Phytotherapy is a separate branch of medicine in Russia and herbal medicinal preparations (HMP) are official medicaments. More than 600 HMP have been registered for medication and included in the Governmental Register of Medicinal preparation (Shikov et al., 2011; Register Russia, 2011).

### 2.8.2. Laws and regulations

All aspects relating to the development, preclinical and clinical studies, evaluation, state registration, standardisation and quality control, manufacturing, preparation, storing, transporting, importing and exporting, advertising, releasing, selling, using, and disposing of pharmaceutical preparations (including HMP) are regulated by Federal Law No. 61 FZ (dated 12.04.2010) "About circulation of drugs". In case preparations of TCM have medicinal indication they are recognised as HMP and governed by above mentioned law.

A drug master file for a HMP for the purpose of state registration should be prepared according to the Federal Law No. 61 FZ and regulations and the legislation, including

- Decree No. 759n of Ministry of Public Health and Social Development of Russian Federation dated on August 26th 2010 "Procedure for submission of the documents necessary for the

state registration forming the drug master file for a pharmaceutical product created for medical use”.

- Decree No. 750n of Ministry of Public Health and Social Development Russian Federation dated on August 26th 2010 “The rules governing the evaluation of pharmaceutical products for medical use and the decision of the expert committee”.
- Decree No. 388 of Ministry of Public Health and Social Development of Russian Federation dated on 01.11.2001. About the state quality standards of medicinal preparations.

### 2.8.3. Classification of HMP in Russian Federation

Herbal medicinal preparation is the finished product and pertains to a medical preparation containing herbal materials and/or herbal preparations as its active ingredients. Depending on the processing method used, the pharmaceutical formulations can be classified into the following categories (Severtsev et al., 2003):

1. Medicinal plant materials are dried or sometimes newly gathered parts of medicinal plants (rarely, integral plants) used for the production of medical drugs. Medical species are mixtures of a few kinds of crushed or integral plant materials with salts and ethers as additives.
2. Summarised non-refined or galenic formulations contain, along with biologically active substances, a number of concomitant substances. In the course of production, inactive ingredients are removed from galenic formulations. These include herb infusions and decoctions, tinctures, extracts and elixirs.
  - Infusions and decoctions are liquid medicinal preparations representing aqueous extracts from medicinal plant materials, as well as aqueous solutions of dried or liquid extractions (concentrates).
  - Tinctures are medicinal formulations in the form of alcoholic and aqueous/alcoholic extracts from medicinal plant materials (1:5 or 1:10) produced with no heating or removal of extractant.
  - Extracts are concentrated extractions from medicinal plant materials in the form of liquid (1:1), stick (moisture < 25%), or dried (moisture < 5%) mass.
  - Elixirs are liquid medicinal formulations in the form of a transparent mixture of alcoholic/aqueous extractions from medicinal plant materials with medical drugs, sugars and flavors as additives.
3. Novo-galenic formulations are phyto-preparations containing a mixture of biologically active substances that are free from inert and concomitant ingredients. They contain a mixture of alkaloids, coumarins, etc. Novo-galenic preparations also include such substances as flamine (dried extract of *immortelle* flowers containing flavonoids), ergotal (mixture of ergot alkaloid phosphates), adonisid (extracted from *Coronaria* grass), etc.
4. Active pharmaceutical ingredients (API) – individual compounds isolated from plants (serotonin, morphine, rutin, lysergin, etc.). These compounds have direct action and a majority of them are used for the preparation of injection formulations.
5. Combined phyto-preparations contain, along with the substances extracted from plants, synthetic, endocrine and other types of ingredients such as “Allokhoh” (based on dry extracts from garlic and nettle with coagulated active coal as additive), “Besalol” (contains viscous extract of belladonna and phenylsallylate), “Valocormyde” (based on the tincture of valerian, lily of the valley and belladonna with sodium bromide and menthol as additives), etc.

### 2.8.4. Registration of medicinal preparations and HMP

The registration procedure for pharmaceutical preparations is clearly described, including all steps and deadlines in Federal Law

No. 61. The maximum period of registration is 210 days. The application requirements for state registration of pharmaceutical preparations and documents of the drug master file are the same for domestic and foreign manufacturers. HMP is assessed for its safety, efficacy and quality.

The activities related to the evaluation of pharmaceutical preparations in the framework of the Federal Law are implemented by the Federal State Organization FGU “National Center of expertise of preparation for medicinal application” of the Ministry of Public Health and Social Development of the Russian Federation. Anything related to pharmaceutical preparations comes under the jurisdiction of the “Centre for Evaluation and Control of Finished Pharmaceutical Products” which comprises of four divisions and one test center for pharmaceutical products quality evaluation.

All applications for registration of pharmaceutical preparation in Russian Federation are subject to evaluation (Decree No. 750n of Ministry of Public Health and Social Development Russian Federation dated on August 26th 2010).

### 2.8.5. Drug standards

Pharmaceutical preparations must follow the national drug standard. State standard OST 91500.001-00 “Standards for quality of medicinal drugs – basic provisions” was introduced in the Russian Federation by the Decree No. 388 of Ministry of Public Health and Social Development of Russian Federation dated on 01.11.2001. This standard sets out the categories, development procedures, wordings, filing, expertise, approval and designation of quality standards for pharmaceutical preparations. The provisions of the standards are binding upon developers and producers of medicinal/herbal drugs, as well as upon the companies involved in the expertise of the quality standards of medicinal drugs.

The 12th State Pharmacopoeia of Russian Federation is main state quality standard of pharmaceutical preparations. The first part was published in 2007 and it includes the description of analysis methods and pharmaceutical substances. The second part includes specific pharmacopoeial monographs for individual drugs and it was submitted for approval by the Ministry of Public Health and Social Development of the Russian Federation in 2010 (Severtsev et al., 2003; Shikov et al., 2011).

### 2.8.6. Summary

Herbal medicinal preparations are official medicaments in Russia and regulations for HMP are the same as that for pharmaceuticals. More than 600 HMP have been registered for medication and included in the Governmental Register of Medicinal preparation. All aspects of handling of pharmaceutical preparations (including HMP) are regulated by Federal Law No. 61 FZ “About circulation of drugs”. In case preparations of TCM have medicinal indication they are recognised as HMP and governed by above-mentioned law.

## 2.9. South Korea

### 2.9.1. Introduction

Although the medical system in Korea is divided into two systems: a modern medical system and a Korean traditional medical system, medicines are controlled by a single regulatory system established by the Pharmaceutical Affairs Act. The Korea Food and Drug Administration (KFDA) is in charge of establishing standards and pre-market approval, post-market inspection, and management of the product quality system for herbal medicines.

### 2.9.2. Regulation

The Pharmaceutical Affairs Act, passed in 1954, deals with pharmaceutical affairs including herbal medicines. Other regulations concerning the control of herbal medicines are ‘Regulations on the demand/supply, distribution, and product management of herbal

medicines' (Ministry of Health and Welfare Notification) and 'Regulations for Imported Medicines' (KFDA Notification).

### 2.9.3. Standardisation of herbal medicines in Korea

Standards for commonly used herbal materials and preparations are included in the 'Korean Pharmacopoeia', 'Korean Herbal Pharmacopoeia', and 'Korean Pharmaceutical Codex'. In terms of the safety of herbal medicines, the amount of hazardous substances such as heavy metals, pesticides, and aflatoxins are restricted by the 'Regulations on Limits and Test Methods for Residues and Contaminants in Herbal Medicines'.

Traditional medicine (TM) has a long history as an important means in curing diseases in Eastern Asia. Despite this fact, TM has been often disregarded as non-scientific and even excluded in view of western medicine. Recently, however, new evidence has been discovered through elaborate scientific approaches with some cases even successfully leading to new drug development, both at the level of extracts and pure substances. The formulae for TMs comprised a single herb or several herbs have great potential as active ingredients of drugs. Nevertheless, the ambiguity of the origins of the herbs makes them more difficult to be utilised for either clinical or industrial purposes, and thus, both standardisation and modernisation of TMs is essential.

Since 2005, a collaborative study has been conducted to establish a method for the standardisation of herbal medicines through the support of the Korea Food & Drug Administration (KFDA). One of the specific aims of this project is to establish the unique chemical principles of herbal medicines based on their pharmacological activities. Thus far, a total of 64 herbal medicines have been investigated and about 30 more plant drugs will be investigated over the next four years.

Many facts about medicinal plants have been identified and new methods for quality control have been reported. Nevertheless, all these things cannot be included in the pharmacopoeia. The purpose of this research project is to lay a foundation for workers engaged in this area to discriminate between inferior and superior herbal medicines using scientific methods. Once the research project is successfully completed, herbal medicines with a high standard of quality are expected to be distributed on the market.

### 2.9.4. Pre-marketing approval of herbal medicines

To manufacture herbal medicinal products, one must obtain the permission of the KFDA by submitting data on the standards and test methods, safety, and efficacy according to the 'Regulations for the approval and registration of herbal medicines'. Preparations with the same ingredients, dosages, and efficacy that are included in the ten traditional Korean medicinal references, indicated by the Ministry of Health and Welfare Notification, do not need to submit data on the safety and efficacy of the preparation.

### 2.9.5. Herbal materials as health functional foods

Herbal medicinal materials have also been used as a source of food and health functional foods. A lot of health functional foods such as red ginseng products are used in Korea. The manufacturing of health functional foods must be approved by the KFDA according to the 'Health Functional Food Act'.

### 2.9.6. Summary

For the purposes of consumption, herbal materials can be used as sources of food, health functional foods, or drugs. In each case, they are controlled by different legal systems, the 'Food Sanitation Act' (food), 'Health Functional Food Act' (health functional food), or 'Pharmaceutical Affairs Act' (medicine). As medicine, herbal medicines need to have a high standard of quality as well as be safe and have efficacy.

## 2.10. Taiwan

In Taiwan, regulations on TCM are under the jurisdiction of the Committee on Chinese Medicine and Pharmacy (CCMP), Department of Health (DoH). The national health insurance (NHI) has been implemented in Taiwan since 1995, covering western medicine, TCM and dentistry. By the year 2005, all TCM pharmaceutical manufacturing facilities have met GMP standards as required by the government. Currently, there are 117 TCM pharmaceutical manufacturing facilities in Taiwan producing various preparations such as concentrated extract granules or powder, pills, capsules. However, only concentrated extract granules and powders are covered by the insurance. Decoctions of traditional herbs are not covered by NHI. In other words, patients receiving raw herbal decoctions have to pay out of their own pockets. Moreover, only traditional formulae that have been listed in classical TCM literature can apply for registration and licensing without clinical efficacy/safety data. Registration and licensing of traditional formulae require them to meet the DoH's "Standards of Examination and Registration for Medicines (revised in September, 2005, in accordance with Paragraph 4 of the Pharmaceutical Act)". With increasing concerns from the consumers, as of August, 2011, the DoH issued a rule that all concentrated Chinese medicinal preparations (including formulae and single herbs) should contain total heavy metals no more than 30 ppm; additionally total microbe number should be less than 105 cfu/g, and *Escherichia coli* or *Salmonella* spp. should be undetected.

All new or innovated formulae must apply for registration and licensing according to the "Guideline on Examination and Registration of New Chinese Medicines", issued by the DoH in June 1998. Briefly, for Chinese medicines listed in classical Chinese TCM literatures to apply for Chinese medicines with new therapeutic efficacies (indications) or new administrating routes must provide data on clinical efficacy. For Chinese medicines unlisted in classical TCM literatures, data on clinical efficacy, safety and quality control must be provided at the time of application. Eighteen TCM clinical trial centers have been set up to perform clinical trials on TCM preparations. Similarly, application for registration and licensing of botanical drugs (not traditional Chinese herbs) should generally provide data on clinical efficacy, safety and quality control (CCMP, 2011).

## 2.11. The United States

### 2.11.1. Introduction

In the United States, FDA regulated product categories under the Federal Food, Drug, and Cosmetic Act ("the Act") or Public Health Service Act ("PHS Act") included the following:

- Cosmetic;
- Device;
- Dietary supplement;
- Drug, as well as "new drug" and "new animal drug;"
- Food; and
- Food additive.

A botanical product (including those marketed in other countries as herbal medicines/Chinese herbal medicines) may be subject to regulation as a biological product, cosmetic, drug, device, or food (including food additives and dietary supplements) under the Act or the PHS Act (FDA, 2011b).

These statutory definitions also cover herbal medicine/botanical products. Neither the Act nor the PHS Act exempts CAM products from regulation. This means, for example, if a person decides to produce and sell a Goji juice product to promote optimal health, that product is a food subject to the requirements for foods in the

Act and FDA regulations, including the hazard analysis and critical control point (HACCP) system requirements for juices in 21 CFR part 120. If the Goji juice is intended for use as part of a disease treatment regimen and intended to label the product's function as such instead of for the general wellness, the Goji juice product would also be subject to regulation as a drug under the Act. For the Goji product to become an approved new drug for a disease treatment, then the sponsor should reference FDA's Guidance for Industry-Botanical Drug Products to demonstrate its safety and efficacy through well-designed clinical studies, and meet other regulatory requirements for new drugs (e.g. assurance of quality and consistency of the product).

### 2.11.2. Botanicals as FDA regulated products

- Cosmetic

Cosmetic, regulated by FDA's CFSAN, the center also regulates food, food additives, and dietary supplement. Many botanicals are used in cosmetics without particularly describe their functions on the label. Green tea and Aloe vera are among the commonly used ingredients in cosmetics.

- Food

Some Chinese herbs are marketed and available as regular food/spice e.g. ginger, star anis, and garlic. Some TCM herbs that are not commonly used as spices in the West may also be found from ethnic stores (and Asian markets) e.g. Ginseng, Astragalus root, Dan-Kuei (Dang-Gui). Certain food may be permitted to bare general "health claims".

- Dietary supplement

Under Dietary Supplement Health and Education Act (DSHEA, 1994), most of the Chinese herbs (except several of the most toxic herbs, minerals, and certain animal products) and many traditional Chinese medicine products are permitted to be marketed as dietary supplements, provided that those products comply with the labelling requirements for dietary supplements. CFSAN does not publish the list of grandfathered herbal dietary supplements, but the book *Herbs of Commerce* (1992) is a common reference by industry as one of the references to indicate that an herb has been marketed before DESHA becoming effective. For those TCM products marketed in the US, the disease claims from the traditional uses are not permitted on the label of the products. Otherwise, the marketer/manufacture will be considered as marketing of non-approved drugs.

Newly formulated TCM products can be marketed as dietary supplements in the US, but the sponsor is recommended to check CFSAN's website or contact CFSAN directly to determine whether a new dietary ingredient (NDI) is needed. For example, pomegranate skin has been used in TCM, and the herb can be marketed as a dietary supplement. However, a concentrated extract of pomegranate skin was requested to be qualified as a NDI to demonstrate the proposed dose of the product for safety. The sponsor eventually provide data to confirm that the daily dose of the pomegranate extract contains equivalent amount of polyphenols as 8 oz of pomegranate juice, and thus the product was determined to be safe for being marketed as an NDI.

Acupuncturists/herbalists in the US, use TCM products based on a one-to-one practitioner-client consultation. These products are regulated as dietary supplements without any labeled disease claims on the product labels. FDA will take actions on certain herbal products, if the product is deemed unsafe (e.g. contain certain toxic or otherwise banned herbs e.g. Ephedra).

- Drug

In 2000 FDA published the Guidance for Industry-Botanical Drug Products (draft) to illustrate its current thinking on how to develop a botanical mixture into a botanical new drug. According to the principles of the Guidance (finalised in 2004) (FDA, 2011a), a botanical product, including those used in CAM or

Chinese medicine, can be further developed through clinical trials and non-clinical studies to become an FDA approved drug through investigational new drug application (IND) and new drug application (NDA) processes without further purification nor identification of active compounds from the botanical mixture. FDA recognised and reference previous human use of botanical (herbal) products and foreign clinical trial data as part of the safety and efficacy evaluation. However, it is unlikely that botanical drugs can be approved based solely on "traditional use".

- Since the publication of the guidance, over 400 pre-INDs and INDs have been submitted to CDER, FDA, most of which are intended for phase I and II studies to investigate the preliminary safety (or efficacy) of the products, few are intended for phase III trials which will have a potential of leading to botanical NDAs. So far, only one botanical NDA has been submitted and subsequently approved. About a quarter of the INDs are intended to study botanical products that are originated with TCM herbs.

### 2.11.3. Discussion and conclusions

Herbal medicines/botanicals are not defined as regulatory product categories under the Act or PHS Act. FDA regulates TCM products as either food, food additive, dietary supplements, cosmetics, drugs, devices, or biologics, according to the Act, and PHS. Act. Most TCM products (include TCM raw herbs) are currently marketed/used in the US as food, dietary supplements, and/or as ingredients of cosmetics.

TCM products and raw herbs can be further developed as new drugs through IND/NDA processes. FDA references previous human use in TCM and other herbal medicine systems to speed up early phase clinical trials of botanicals without requesting standard animal toxicology data, if the previous human use of the product is deemed to be safe. However, the overall requirements for NDA of a botanical drug product are not significantly different from those of pure small molecule new molecular entities (NMEs). FDA recognises the challenges to demonstrate the quality and therapeutic consistency of a complex botanical product. The current thinking at the FDA is to adopt comprehensive approaches, which may include one or more of the following, robust chemistry, manufacturing, and control (CMC), clinically relevant bioassays, multiple-batch clinical trials, based on the particular situations of the to-be-studied botanical product (Chen et al., 2008).

## 3. General discussion

A major challenge is how to define an herbal medicine and, in particular, a traditional herbal medicine. For example, garlic (*Allium sativum*) is eaten as a food/spice throughout the world and is often used knowingly to help lower cholesterol and to treat certain cancer symptoms. In Europe, garlic is classified as a food, herbal supplement, herbal medicine, food supplement and as a pharmaceutical medicine. In Brazil, garlic is classified as a "phytotherapeutic agent"!

An important question arising from our research is whether it is possible to develop a model for universal harmonised registration of herbals. It is conceivable that harmonisation of monographic standard and mutual recognition of herbals across the globe may be an easier way to proceed. For example, the root of *Polygala tenuifolia* (a Chinese materia medica called "Yuanzhi" in Chinese) has been widely used as a memory enhancer for people in Asian countries for many years (Xu et al., 2011), and it is also included in many traditional prescriptions used for treatment of amnesia and dementia. However, other *Polygala* species in Europe have no recorded medicinal applications, except *Proteus vulgaris* (known as Common Milkwort), the whole herb being used as an infusion to increase the flow of a nursing mother's milk. If different *Polygala* species

in EU have memory-enhancing effects like *Polygala tenuifolia* root used in China, this might be used for the demonstration of traditional use under 30/15 year rule. It was proposed that interested parties should contact their National Authority and propose to the European Directorate for Quality Medicines & Healthcare (EDQM) for the inclusion of relevant Chinese herbs into the EU pharmacopoeia monographs. In a similar manner, European herbs can be considered for inclusion in Chinese Pharmacopoeia. Presently the registration procedures in the EU and China for herbal products are quite different (see Figs. 2–4 shown in Appendix).

It is noteworthy that EDQM Working Group for TCM is establishing monographs for CMM with the Hong Kong Chinese Materia Medica Standards Office (HKCMMS – where an International Advisory Board is overseeing the standards involving the advices from recognised academic, scientists working in registration bodies and experts from Australia, Canada, China, EU, Japan, Thailand and USA) with Pharmacopoeia of the People's Republic of China (Chinese Pharmacopoeia). This may eventually produce a path for harmonisation of official standards of CMM, the starting materials for manufacturing of Chinese herbal medicines and TCM practice.

#### 4. Concluding remarks

As emphasised in the Introductory Paper (Uzuner et al., 2012) of the GP-TCM *Journal of Ethnopharmacology* special issue, “good practice” is further defined as: (i) collaboration and sharing, and (ii) striving for consensus while respecting differences of opinion. The regulatory issues for registration of herbal products are complicated among the countries and regions worldwide (see Comparison Tables 2 and 3 in Appendix). The information summarised in the text is for reference only. Before taking any regulatory action, readers are advised to consult current official legislation and guidance and/or to seek appropriate professional advice.

The WHO is well placed to co-ordinate a consultation process with the aim of putting forward suggestions for harmonisation to key regulatory agencies etc. As a start, through WHO Collaborating Centres for Traditional Medicine, the following issues could be discussed, agreed and implemented:

- the definition for “traditional herbal remedy” – in some countries they are seen as ‘food supplements’ whilst in others they are deemed to be ‘medicines’ (requiring a full product licence);
- the definition and English terminology of raw herbs, ‘paozhi’ (processing of Chinese material medica) or prepared herbs and ‘granule’ extracts;

- documentation/data and requirements are acceptable globally e.g. suggest removing the 15 year rule for traditional use in Europe and simply retain the 30 year rule whether it be in China, India, Africa, Europe, etc.;
- GxP activities to be of the same standard worldwide;
- more stringent post-marketing surveillance i.e. pharmacovigilance;

Given the exponential decline of the R&D productivity of pharmaceuticals from 1950 to 2008 and the WHO’s encouraging strategy on traditional medicine, it seems that herbal industry, if properly regulated, would play an increasingly important role in global healthcare. Through international collaborations, we may be able to achieve regulation without borders, and today’s herbs may become, or evolve into, tomorrow’s medicines.

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#### Appendix.

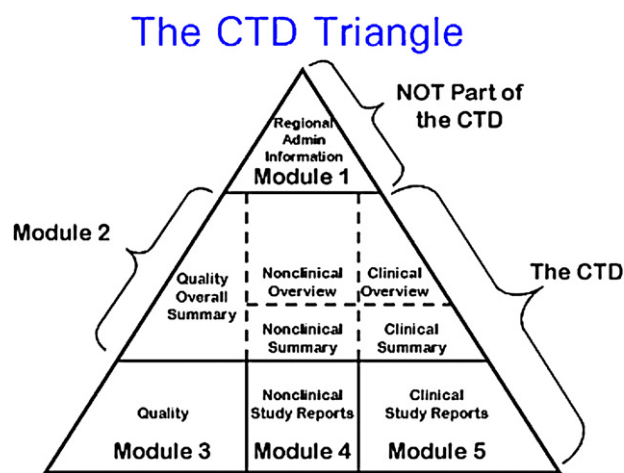


Fig. 1. The CTD triangle.

Courtesy of Wikipedia.

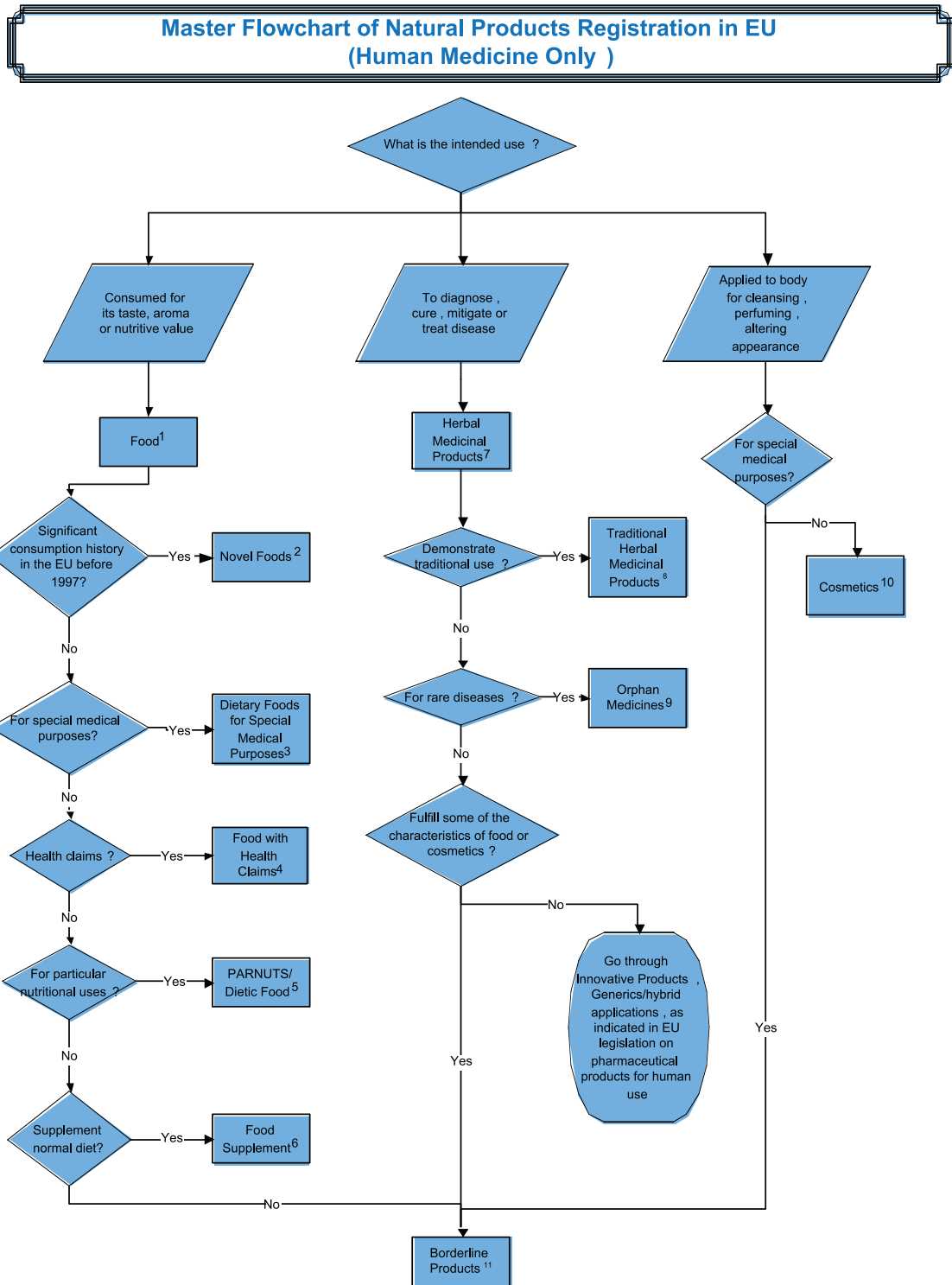
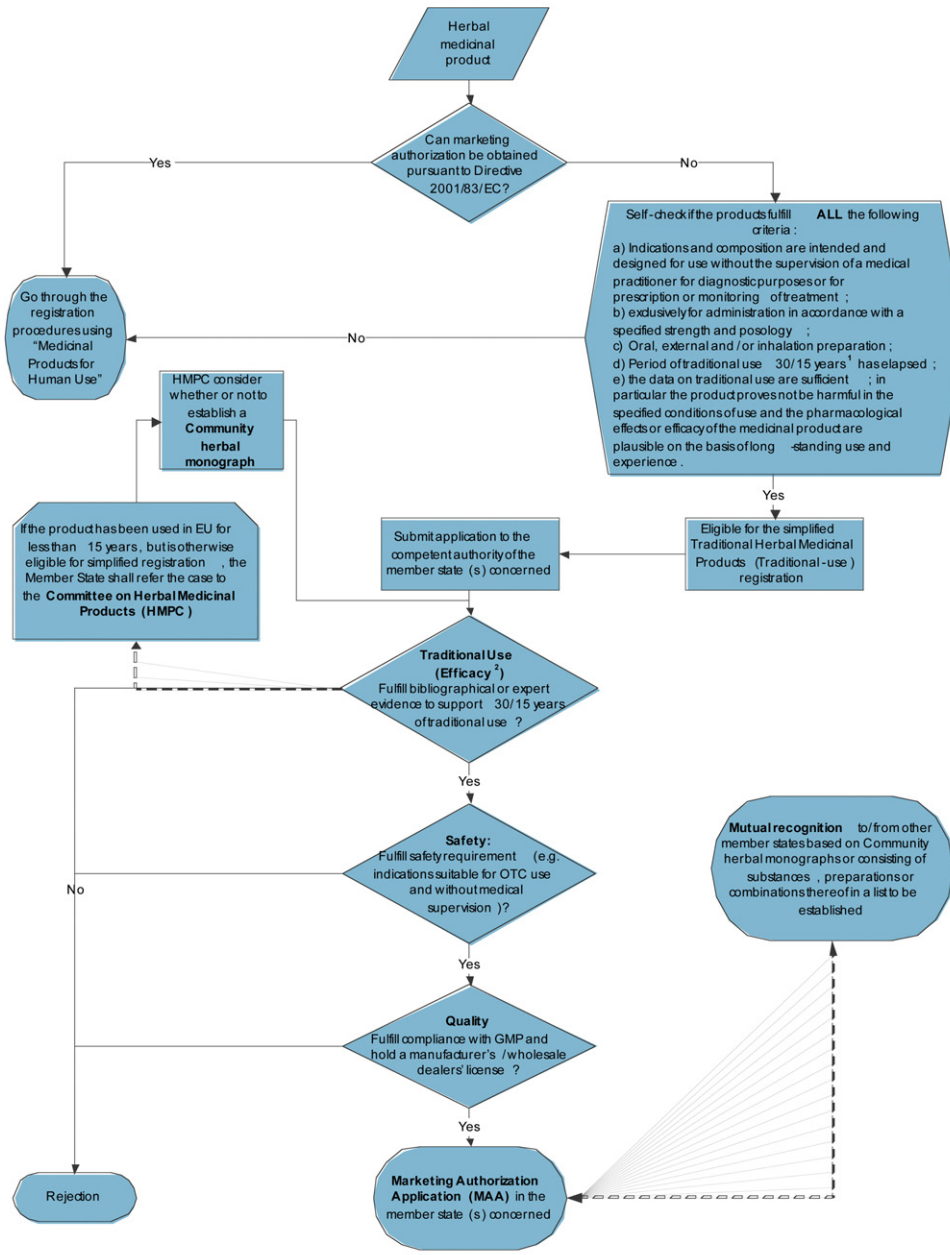


Fig. 2. Registration flowchart of natural products in EU.

**Simplified Registration Procedure for Traditional Herbal Medicinal Products (Traditional -use registration ) in EU**  
 With reference to Directive 2004 /24/EC



**Remark :**  
 1. In medicinal use  $\geq 30$  years &  $> 15$  years of usage within EU  
 2. Efficacy of the medicinal product is plausible on the basis of long standing use and experience, making it possible to reduce the need for clinical trials

Fig. 3. Registration flowchart for traditional herbal medicinal products in EU.

# Chinese Medicine Registration Procedures in China

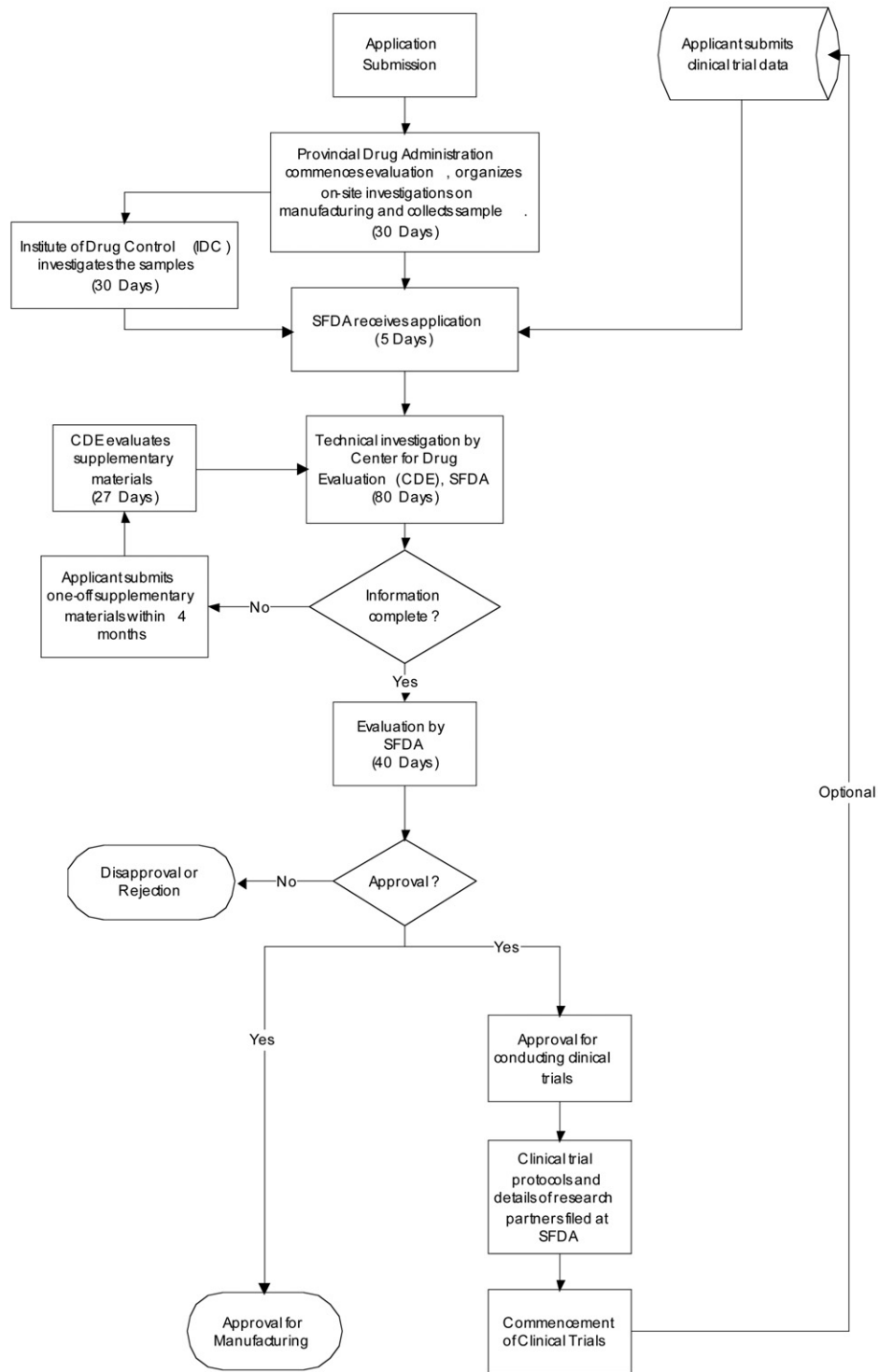


Fig. 4. Registration flowchart in China.

**Table 1**  
Dantonice® development worldwide: international market.

Country/region	Legal status	Approval/time of initial launch
USA	Dietary supplement	September, 2000
The United Arab Emirates	Prescription drug	June, 2001
South Korea	OTC	January, 2002
Cuba	Drug <sup>a</sup>	July, 2002
Singapore	TPM <sup>b</sup>	October, 2002
Mongolia	Drug <sup>a</sup>	Oct, 2002
Namibia	CAM <sup>b</sup>	August, 2003
Kazakhstan	Prescription drug	January, 2004
South Africa	CAM <sup>b</sup>	September, 2005
Vietnam	Prescription Drug	October, 2005
Russia	Prescription drug	December, 2005
Ghana	CAM <sup>b</sup>	March, 2006
Nigeria	CAM <sup>b</sup>	December, 2006
Zambia	CAM <sup>b</sup>	January, 2007
Kenya	Functional product <sup>c</sup>	March, 2007
India	Functional product <sup>c</sup>	March, 2007
Pakistan	Prescription drug <sup>c</sup>	April, 2007
Congo	Functional product <sup>c</sup>	July, 2007
Botswana	CAM <sup>c</sup>	October, 2007
Thailand	TM <sup>b</sup>	February, 2008
Hong Kong	TCM <sup>b</sup>	March, 2008
Canada	OTC	July, 2008
Malawi	Functional product <sup>c</sup>	December, 2008
Philippines	OTC	July, 2009
Uganda	Functional product <sup>c</sup>	August, 2009

<sup>a</sup> Drug: there is no clear classification between prescription drugs and OTC in some developing countries.

<sup>b</sup> TPM, Traditional Patent Medicine; CAM, Complementary and Alternative Medicine; TM, Traditional Medicine; TCM, Traditional Chinese Medicine.

<sup>c</sup> Functional product: similar to dietary supplement or food supplement.

**Table 2**  
Comparison of herbal regulations in Europe and Asia.

Continents	Europe	Asia			
	EU	China	Japan	South Korea	Taiwan
Regulatory Agency	National agencies in each country (European Medicines Agency provides scientific opinion to assist national agencies in their decision making process)	State Food and Drug Administration (SFDA)	The Ministry of Health, Labor and Welfare	Korea Food and Drug Administration (KFDA)	The Committee on Chinese Medicine and Pharmacy, Department of Health
Major legislation or guidance documents	European Union Directive 2004/24/EC	SFDA Order 28 – Provision for Drug Registration; Supplementary Rules for TCM Registration	Pharmaceutical Affairs Law	Pharmaceutical Affairs Act	Guideline on examination and registration of new Chinese medicines
Category where herbal products can be registered (other than supplements or health food)	Traditional Herbal Medicinal Products, Prescription or OTC drugs	Chinese Medicine and Natural Medicinal Products (9 categories)	Prescription drugs or OTC drugs	Herbal medicines	Chinese medicines
Pharmacopoeia	European Pharmacopoeia	Pharmacopoeia of the PRC	Japanese Pharmacopoeia	Korean Pharmacopoeia, Korean Herbal Pharmacopoeia, and Korean Pharmaceutical Codex	Chinese Pharmacopoeia of Chinese Medicine
Mutual recognition	Yes (for EU Member States only)	No mutual recognition between Mainland China and its Special Administrative Regions such as Hong Kong and Macau	No	No	No
Uniqueness	30/15 years of traditional use; Benefit-risk methodology	Regulations tailored for TCM; State secrets may be granted to certain variety of TCM for interests protection; For ancient classical TCM formula (documented in or before Qing dynasty i.e. before AD 1912), the need of clinical trial safety data may be waived; different categories of Chinese medicine may have different requirement on clinical trials	Over 200 formula are listed as “Standards of Approval for the Kampo Formulation”	Preparations with the same ingredients, dosages, and efficacy that are included in the ten traditional Korean medicinal references, indicated by the Ministry of Health and Welfare Notification, do not need to submit data on the safety and efficacy of the preparation.	Formulas listed in well-established publications can be used as the formulation basis. The well-established publications mentioned in this Chapter refers to “Yi Zong Jin Jian”, “Yi Fang Ji Jie”, “Ben Cao Gang Mu”, “Ben Cao Shi Yi”, “Ben Cao Bei Yao”, China Medicine Big Dictionary and China Pharmacy Big Dictionary.

**Table 3**  
Comparison of herbal regulations in Eurasia, Australia, North America and South America.

Continents	Eurasia	Australia	North America		South America
Country/region	Russia	Australia	Canada	US	Brazil
Regulatory Agency	Ministry of Public Health and Social Development of Russian Federation	Office of Complementary Medicines (OCM), Therapeutic Goods Administration (TGA)	Natural Health Products Directorate (NHPD), Health Canada	Food and Drug Administration (FDA)	The National Health Surveillance Agency (ANVISA)
Major legislation or guidance documents	Federal Law No. 61 FZ (dated 12.04.2010) "About circulation of drugs"	Australian regulatory guidelines for complementary medicines (ARGCM)	Natural Health Products Regulations (under Food and Drug Act)	Federal Food, Drug, and Cosmetic Act; Guidance for Industry Botanical Drug Products	Resolucao-RDC No. 14, de 31 de Marco de 2010 (Resolution RDC No. 14, 31 March 2010)
Category where herbal products can be registered (other than supplements or health food)	Herbal medicinal preparations	Complementary Medicine	Natural Health Product	Botanical Drug Products (food/drug/medical device/cosmetics)	Herbal Medicines (prescription and OTC)
Pharmacopoeia	State Pharmacopoeia of Russian Federation	British Pharmacopoeia	Homeopathic Pharmacopoeia of the United States, the Homöopathische Arzneimittel, the Pharmacopée française or the European Pharmacopoeia	United States Pharmacopoeia (USP)	Brazilian Pharmacopoeia ( <i>FBras. Farmacopéia brasileira</i> )
Mutual recognition Uniqueness	No Herbal medicinal preparation can be classified into 5 different categories, namely Medicinal plant materials, Summarised non-refined or galenic formulations, Novo-galenic formulations, 4. Active pharmaceutical ingredients (API) and Combined phytopreparations	Not stated Level of evidence in supporting efficacy and safety; Early market access for low-risk complementary medicines through Listed medicine system (2 tier-system)	Possible Health claim schedules with reference to US FDA	No Clinical trials in the US required despite traditional use history; Marketing under OTC Drug Monograph versus Approved NDA	No Herbal medicines have the same status as other medicines; safety & efficacy must be demonstrated or 'traditional use' (20 years); very particular requirements for quality and reproducibility of herbal medicines.

**In regulatory affairs, it is prudent to refer to websites because regulations are constantly evolving and being updated. Referral to a website is deemed to be best because it ensures that the reader is taken to the most recent and up-to-date information. If a particular reference is provided, there is the risk that the reader will use out-of-date information when planning their regulatory strategy and ultimately their application.**

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