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The Role of the European Pharmacopoeia (Ph Eur) in Quality Control of Traditional Chinese Herbal Medicine in European Member States

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ABSTRACT

In order to assure the safety and efficacy of the Chinese Medicines in Europe, the quality of TCM herbals should be guaranteed so that they can be freely imported in the European Union and other Western European Countries which are signatories of the European Pharmacopoeia Convention. Consequently, new Ph Eur TCM herbal drug Monographs should be elaborated, based on preexisting Monographs in the Chinese Pharmacopoeia (ChP) 2010.

Such a program has been inaugurated in 2005 by the Ph Eur Groups of Experts 13 A and B (Phytochemistry). Since then good progress has been made, elaborating of about one third of the originally proposed 100 TCM herbals being identified as important monographs for the European Market. Taking into account the many challenges still laying ahead, the establishment of a specialized Working Party (WP) on TCM with specialists and experts from many EU Member States has been decided by the Ph Eur Commission in 2008 which is highly active ever since in the examination and elaboration of new TCM herbal drug monographs, primarily to assure the safety of the European patient and further to provide quality parameters extremely important for all registration and licensing procedures of the respective National Authorities all over Europe.

This paper is a survey of results and difficulties obtained so far which has been encountered meanwhile in the elaboration process by the Ph Eur TCM WP of these monographs and will discuss these in detail. Moreover the role of Ph Eur TCM monographs in the European community is addressed.

Key words: European Pharmacopeia (Ph Eur), Chinese Pharmacopoeia (ChP), Traditional Chinese Medicine (TCM), TCM monographs, herbal drugs and quality control

INTRODUCTION

Since ancient times, all cultures have developed health care strategies, which are often characterized by a holistic approach to living organisms. A holistic approach to living organisms has been the basis of Traditional Chinese Medicine (TCM) from its earliest years[1,2]. The TCM approach is recognizing the uniqueness of each human being and the necessity to develop a *personalized* medication to obtain optimal results based on *multi-component treatments*[3]. Because of this specific feature, TCM becomes more and more popular in treatment and prevention of diseases in other cultures. In the past two decades public interest in herbal therapies (Phytomedicine) has increased significantly in Europe. Traditional Chinese herbal medicines including Chinese crude herbal materials and manufactured herbal products are a frequently used form of traditional medicines. Currently, the practice of TCM is not only popular in China and some Asian regions; but also it is appreciated worldwide. A large-scale study of the Chinese population of Taiwan showed that from 1996 to 2001, more than 60% of all subjects have used Chinese medicine during a 6-year interval. TCMs (85.9%) were the most common modality[4]. It was estimated that more than 1.5 billion people all over the world are trusting in the efficacy and safety of Chinese medicine[5]. In the 'Western World', the term 'alternative' medicine is now often replaced by 'complementary' medicine. This emphasizes the complimentary nature of TCM and Western medical systems. The latest term 'integrative' medicine underpins the gain that can be obtained when Western and complementary modalities are used together[3]. Data provided by the Chinese Import and Export Chamber of Commerce of Medicine and Health Products shows yearly export sales of traditional Chinese herbal medicinal products to the EU of approximately 12 million US dollars over the last four years suggesting a significant amount of TCM products entering EU market. In respect to this, quality control should be one of the important aspects to guarantee the safe use of TCM products for the patient.

The European Directorate for the Quality of Medicines (EDQM) is an organization which belongs to the Council of Europe (head quarter in Strasbourg, France) which is a leading organization that protects public health by:

- enabling the development,
- supporting the implementation, and
- monitoring the application

of quality standards for safe medicines and their safe use. Their standards are recognized as a scientific benchmark worldwide. The European Pharmacopoeia is legally binding in all member states. The activities elaborating quality monographs of Traditional Chinese Medicines for the European consumers/ patients started in 2005 following a decision of the Ph Eur Commission, which stated that monographs on herbal drugs used in Traditional Chinese Medicine should be developed to provide modern quality standards according to the pre-existing Ph Eur standards. Following this decision in 2005, the existing groups of experts 13A and B (Phytochemistry) received a note from the Ph Eur Commission Secretariat to include in their working program Chinese Medicines products listed as monographs in the ChP 2005. It was then stated that the elaboration of monographs on TCM herbals should provide modern quality standards according to the Ph Eur principles which should facilitate and encourage the use by the practitioners and further to provide save and authorized products to the patient.

From legal perspective, the Directive (Directive 2004/24/EC) on Traditional Herbal Medicine Products existing in the European Medicine Agency (EMA) should be the basis for simplified registration procedures[6] from that time onward, based on traditional use and ensuring quality and safety without the need to prove efficacy by clinical studies of the product. Therefore, elaboration of Ph Eur monographs for TCM is fundamentally important for all quality parameters for the TCM product intended to stay/entering the EU market.

Priority setting of TCM herbal drug candidates was proposed according to a number of documented criteria such as toxicity, risk of substitution, adulterations, volume of use etc. A coordination with the work program of the Committee on Herbal Traditional Products (HMP) of the EMA and the existence of a monograph on a related herbal drug in the actual Chinese Pharmacopeia (ChP) was an essential prerequisite. It was also decided that herbal drug preparations and compounded products should not be dealt with for the time being.

A priority setting of individual monograph candidates by both groups 13A and B (expert groups working for European herbal medicine monographs at EDQM) followed the criteria such as order of overall importance in the EU, quality and completeness of an existing monograph in ChP, and the extent of use in the respective EU Member States and finally, the availability of herbal drug samples on the European and on the International Market.

Initially, more than 100 TCM herbal drug candidates were proposed and out of these, about 75 TCM herbal drugs were finally selected and put in the initial Working Program. First start was made with an evaluation of existing ChP monographs followed by an experimental reexamination of the methods, in order to fulfill the guidelines of the Ph Eur.

With regard to these TCM herbal drugs the ChP Monographs could serve as a basis for the Ph Eur Monographs. However, a number of issues had to be addressed since all Ph Eur monographs have to take into account the relevant style and quality parameters currently required for all Monographs of the Ph Eur.

ESTABLISHMENT OF THE TCM WORKING PARTY BY THE PH EUR COMMISSION (EDQM)

After an initial phase of about two years, the Group of Experts 13A and 13B (European Scientists working at EDQM for European herbal drugs) had to stop the activities in elaborating Monographs on Traditional Chinese Medicine Herbals. This was based on the annual reporting of the Working Program to the European Pharmacopoeia Commission at EDQM, it was found that Groups 13A and 13B had only the capacity to work on European Herbal Drugs. This fact was the basis for the creation of a Working Party on Traditional Chinese Medicine in 2008 by the Ph Eur Commission at the EDQM.

Therefore, specialists from all EU Member States were needed and the profile for experts and specialists was then summarized by the European Pharmacopoeia Commission. Consequently the experts/specialists should have:

- Current expertise in pharmaceutical and analytical methods related to quality control of Herbal Drugs and Herbal Drug Preparations and in development of control methods.
- Access to laboratory facilities for verification of methods proposed for inclusion of Monographs.
- Several years of experience in one or more of the following fields:
  - quality control of Herbal Drugs and Herbal Drug Preparation
  - involvement in market surveillance or regulatory affairs oversight of imported TCM Herbal Drugs
  - knowledge of cultivation, harvesting, conservation
  - development of chromatographic separations systems for Herbal Drug constituents
  - knowledge of use of TCM Herbal Drugs

According to these profile for experts and specialists, the different National Authorities were asked to propose candidates which were then nominated by the Ph Eur Commission in the November 2007 Session. Nomination of experts and specialists based on the proposals made by the National Authorities of the EU Member States is carried out by the Presidium of the Ph Eur Commission. Then the Commission nominates the Chairman for the Working Party. The next step was the definition of the Working Program for the newly established TCM Working Party. It is important to note that only the Ph Eur Commission has the right to approve or remove items of the Working Program or to approve requests for revisions.

In 2008, the official TCM working party with 18 scientists with relevant scientific background as members plus the Chairman of the Working Party was established at EDQM. The members are officially elected by the delegations of the European Member States with approval of Ph Eur commission (Table 1). Since then, the scientific team has been working on elaboration of TCM herbal drug monographs for Ph Eur.

According to the rules of procedure, the progress on the Working Program is reviewed once a year by the Ph Eur

Table 1. Members of TCM working party at EDQM

Country	Name	Institute	Expertise
Chairman			
German	Prof. Dr. G. Franz	University	Analytics
Members			
Austria	Prof. Dr. R. Bauer	University	Analytics
Austria	Dr. R. Laenger	EMA	Microscopy
Germany	Mr. E. Stoeger	Industry	
Belgium	Prof. Dr. P. Duez	University	Analytics
Switzerland	Dr. I.M. Bruentrup	Industry	
Switzerland	Dr. Th. Lehmann	OMCL	Analytics
Switzerland	Dr. E. Reich	Industry	TLC/TPTLC
Switzerland	Dr. Sh. Wang-Tschen	Industry	
Germany	Dr. M. Gasser	Industry	Analytics
Germany	Dr. K. Wuthold	Industry	Analytics
France	Prof. Dr. I. Fourasté	University	Microscopy
France	Mr. R. Soussain	OMCL	
United Kingdom	Mr. M. Whaley	NPA	
Italy	Prof. Dr. A.R. Bilia	University	Analytics
The Netherlands	Dr. M. Wang	University	Plant Biology
Poland	Prof. Dr. K. Glowniak	University	Analytics
Turkey	Prof. Dr. S. Harput	University	Analytics
Observes			
Australia	Prof. Dr. K. Chan	University	
China	SATCM/NKL		

Eighteen members plus one Chairman of TCM working party at EDQM, EMA: European medicinal agency, OMCL: Official Medicines Control Laboratories, NPA: National Pharmacopeia Authority of UK SATCM/NKL: Chinese State administration of TCM/ National Key laboratory.

Commission, usually in the March Session, where chairs have to report regularly to the Commission about progress of the Working Program, highlighting items and work that did not fulfill the expected results with explanation of reasons. The Chairman, with the support from the Secretariat at EDQM, is responsible for the progress of the work allocated to each Group of Experts or Working Party. In consultation with the members in the Group of Experts or Working Party, the Chairman establishes the working plan, and the distribution of the work, in concern of the targets, to ensure that the target deadlines are respected.

PROCEDURE FOR ELABORATION OF PH EUR MONOGRAPHS

It should always be kept in mind that a Monograph from any TCM herbal drug should be drafted with the same overall structure as other European Pharmacopoeia Monographs, based on the latest version of the Technical Guide for the Elaboration of Monographs and on the Style Guide. It has to be recalled that all tests and assay methods described in a Monograph must be validated according to the procedures dated in the Technical Guide. All the details of the general Monograph on Herbal Drugs and Herbal Drug Preparations must be taken into consideration for the elaboration of the individual TCM Herbal Drug Monographs.

The general procedures for establishment of a monograph at Ph Eur are outlined in Figure 1A which is different from Ch P procedure (Figure 1B). The Ph Eur Commission decides to elaborate or revise a monograph, followed by the WP to appoint a rapporteur for this specific monograph. The appointed rapporteur will be responsible to prepare a draft monograph based on scientific research and evaluation. Then this draft monograph will be published in Pharmeuropa, an official journal of the Ph Eur. The draft monograph is for public inquiry and National Pharmacopeia Authorities process the comments to the published draft monograph. The WP examines the comments and revises the draft monograph accordingly. Then the revised draft monograph is proposed to Ph Eur Commissions for adoption (named

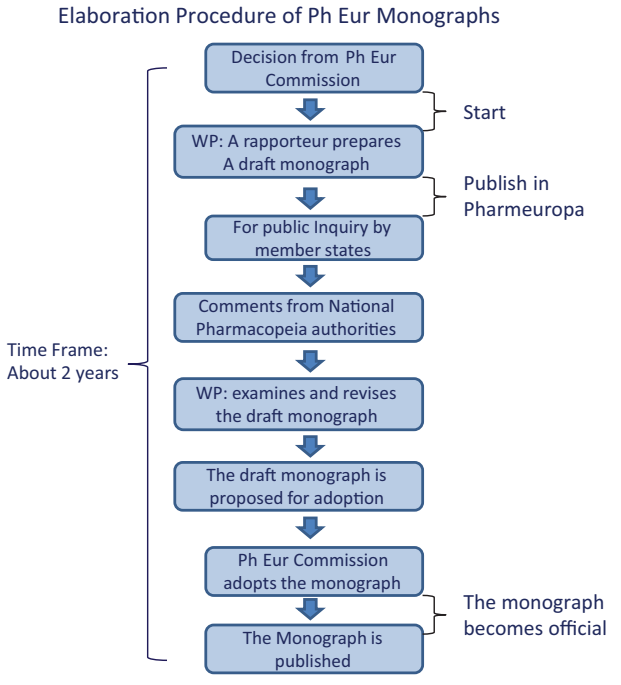

Figure 1A. Elaboration procedure of Ph Eur Monographs.

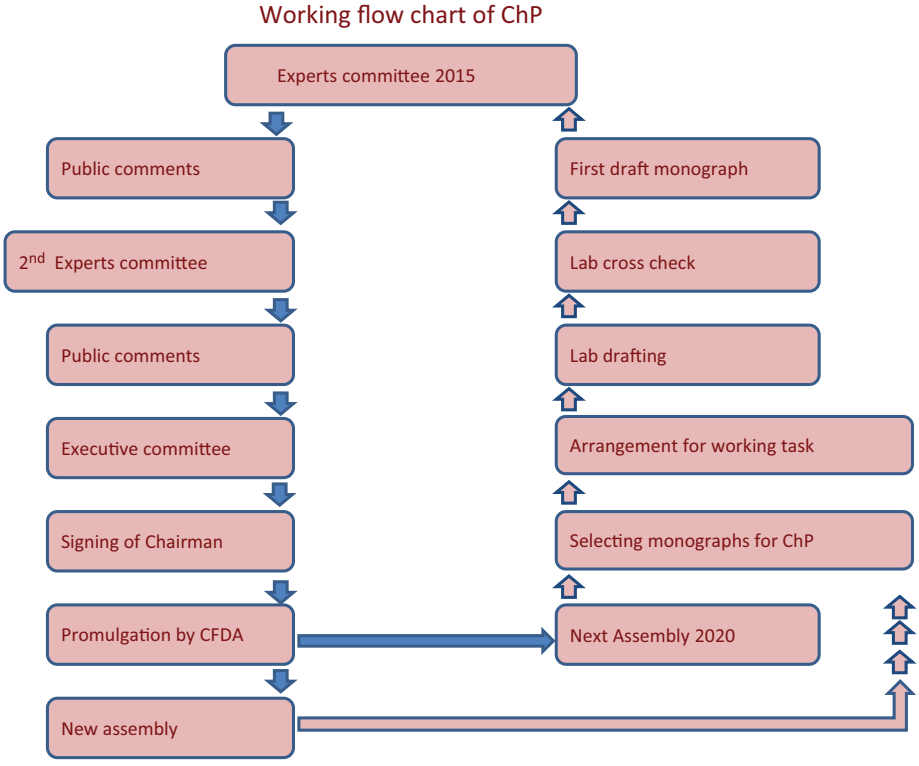

Figure 1B. Working flow chart of Ch P.

COM document). With the approval of the Ph Eur commission the monograph will be published and becomes an official Ph Eur Monograph (Figure 1A). The above mentioned procedure will usually take about two years to complete an official monograph.

WORKING PROGRAM OF THE TCM WORKING PARTY

As the Ph Eur Commission has stated that "monographs on herbal drugs used in Traditional Chinese Medicine should be developed to give a modern quality standard according to European Pharmacopeia principle and to facilitate the encourage use by practitioners for safe, authorized products", therefore the tasks of TCM WP are development of TCM drug monographs that are frequently used in European market. Herbal drugs used in Traditional Chinese Medicine are found in several forms on the European market:

- Crude herbal drugs which have not been submitted to any treatment other than physical treatment such as cleaning, fragmentation and drying.
- Prepared (processed) herbal drugs which have been subjected to one or more treatments such as exposure to dry heat, boiling, cooking in various solutions etc.
- Herbal drugs occurring in a crude and processed form
- Preparations derived from herbal drugs which comprised crude or processed drugs that have been involved in a processing method which necessarily includes other ingredients, such as vinegar, honey, ginger or other excipients.

At present, the TCM Working Party of the Ph Eur Commission is only working on single TCM herbal drugs in a crude and/or processed form. The preparation of the TCM herbal drug monograph in the Ph Eur must always be according to the Ph Eur Style and Technic Guidelines, using ChP (editions 2005 and 2010) as basis but taking into consideration the information from the WHO monographs on selected medicinal plants, and the Hong Kong Chinese Materia Medica Standard (HKCMMS) as well. Some comparisons between Ph Eur and Ch P was made previously[7]. In general a monograph of the actual Ph Eur 8th edition consists of the following chapters: ***Definition***, ***Identification***, ***Test***, and ***Assay***. There is a significant difference in structural organization of all the monographs (see Figure 2) between Ph Eur and Ch P, some information implemented in the ChP are not present in the Ph Eur. Examples of these are the herbal drugs prepared as slices, processing methods, therapeutic property, flavor and taste, meridian tropism, actions, indications, precaution, administrations and dosages. This is because the Ph Eur only deals with quality related matters and not with herbal drug indications and administration of these. In the chapter ***Definition***, the complete scientific name of the plant (including genus, species, subspecies, variety and author) is presented in Ph Eur. As an example, the major difference in the chapter ***Definition*** of a monograph between Ph Eur and Ch P is presented in Figure 3 using the newly published monograph *Polygoni multiflori radix*. In general, the Ph Eur will present the state of the drug such as if it is whole, fragmented, peeled, fresh or dried. Wherever possible, the minimum content of quantified constituents is specified by Ph Eur. The major difference is that there is no information on the systematic name of the respective plant family, collection period and Chinese title, while the Latin

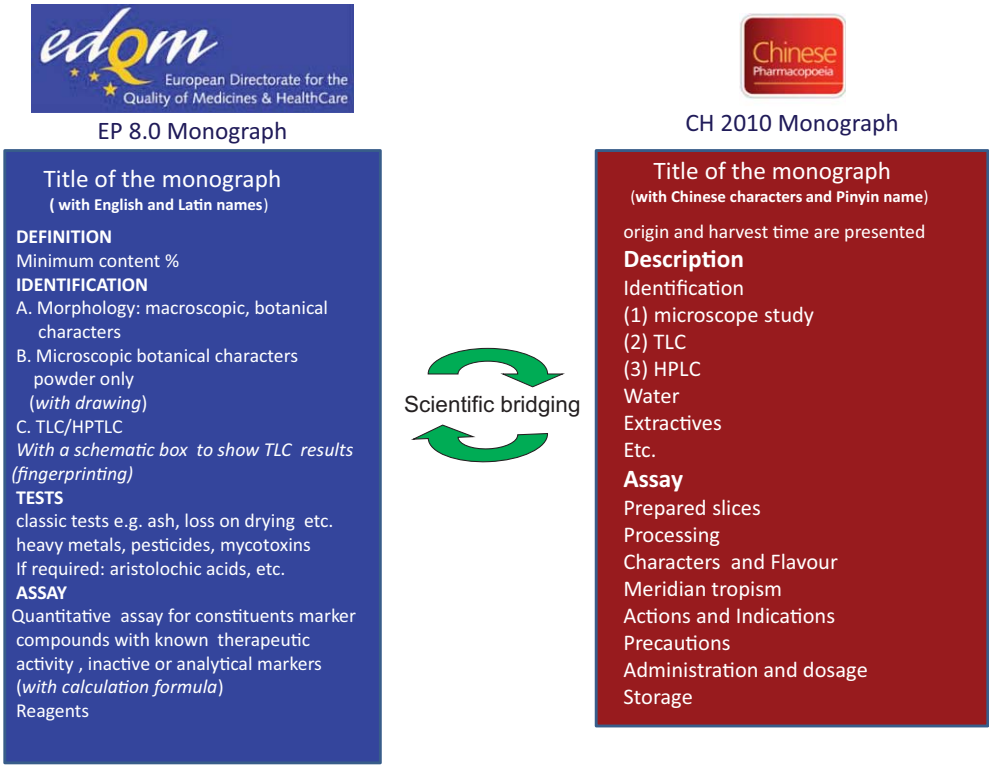

Figure 2A. Difference between herbal drug monographs in Ph Eur 8 and Ch P 2010.

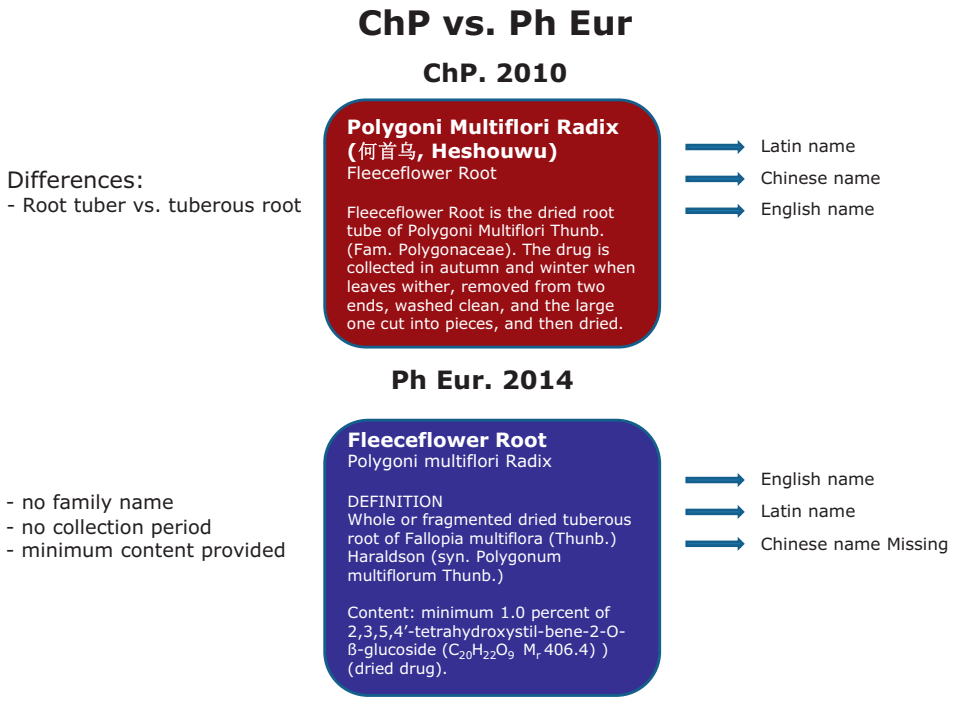

Figure 2B. An example of TCM monograph in Ph Eur and Ch P.

name used for this herbal drug including the new systematic name and possible synonyms of *Polygoni multiflori radix* and minimum content of quality related marker compounds are always provided in the Ph Eur (Figure 3). According to the principles of Ph Eur, the identification of a herbal drug should be relatively simple and be possible to be carried out by e.g. community pharmacies with in general the combination of different methods that allow the identification of a

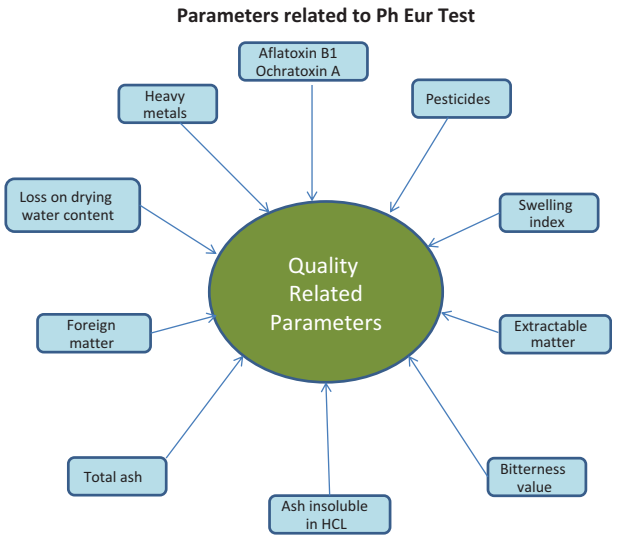

Figure 3. Parameters related to quality control in Chapter of ***Test*** in Ph Eur.

herbal drug without the use of expensive equipment. Both, Ph Eur and Ch P have in common that they present finger printing (TLC and/or HPTLC) and microscopic botanical characteristics. In Ph Eur, a drawing of a microscopy study of the powdered herbal drug and a box type table of results from TLC/HPTLC are presented. However, there is no description of the herbal drug prepared ready for decoction also named "sliced drug" in Ph Eur. Therefore there is also no microscopy study for this type of "sliced drug" in Ph Eur. Within quality related issues, there is a large similarity in scientific information between Ph Eur and Ch P (Figure 2). For Ph Eur, wherever possible, an assay has to be included to determine the constituents based on scientific data supporting therapeutic activity, such as an active therapeutic maker or analytic marker compound.

Markers are chemically defined constituents or groups of constituents which are of interest for control purpose independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation (s) in the Herbal Medicinal Product if that marker has been quantitatively determined in the herbal substance(s) or herbal preparation(s) themselves. There are two categories of markers: 1). Active markers: are constituents or groups of constituents which are generally accepted to contribute the therapeutic activity (with scientific data support); 2). Analytical markers: are constituents or groups of constituents that serve for analytical purposes. Both type of markers are used in Ph Eur assays. The method used for determination of the specific constituent is preferably by LC or GC with a corresponding reference standard Chemical Reference Standard (CRS) or Herbal Reference Standard (HRS) that is established by EDQM. The decision on the choice of the compound as marker should be scientifically justified but also be sustainable for practical purpose in pharmacies. When a marker is used in a monograph of a herbal drug in Ch P (edition 2005 or 2010), in principle, the same marker is used in Ph Eur, except when the assay for this

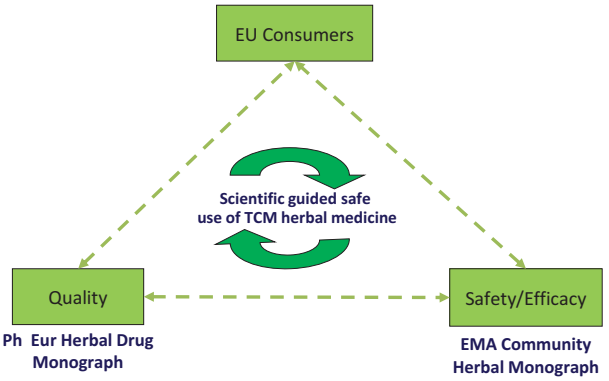

Figure 4. The role of Ph Eur TCM monograph in Europe Ph Eur.

marker is not sustainable or there is already an alternative marker developed in Ph Eur. The analytical results obtained may be presented differently in Ph Eur as compared to Ch P, as is, for example, the case with HPLC assays.

In the Ph Eur chapter ***Test*** various quality control related parameters are presented in Figure 4. The measurements of contaminates such as heavy metals and mycotoxins are not included in the monograph of ChP (ChP. 2005 and 2010). Whilst Ph Eur has clearly stated the methods for measuring aflatoxin B and ochratoxin A in herbal drugs and provides limits for heavy metals (e.g. for lead the maximum is 5.0 ppm; for mercury the maximum is 0.1 ppm and for cadmium the maximum is 1.0 ppm). A more detailed description of Ph Eur's work was reported previously[7].

Up to present, 43 TCM herbal drugs are adopted in Ph Eur 8th edition including supplements 8.1–8.4 (see Table 2) of which 34 monographs are the results of the TCM working party at EDQM. Two monographs (Lycii fructus (2612) and Angelica dahurica root (2556)) were adopted by the Ph Eur Commission and two more monographs (Anemarrhenae rhizoma (2661) and Persicariae tinctoriae folium (2727)) were submitted to the Ph Eur Commission. There are 21 monographs published in the official journal of Ph Eur, Pharmeuropa (Table 3).

INCLUSION OF PINYIN NAMES AND SINOGRAMS IN THE TITLE OF MONOGRAPHS

The English Title of a Monograph consists of the botanical scientific name of the plant which is often a translation of the Latin Title. The plant part used may be included in the title, particularly where different Herbal Drugs are derived from the same plant. In this case it is specified after the scientific name of the plant.

One problem, which partly is resolved by the TCM WP is the introduction of the Chinese Pinyin name as well as the Sinograms for Traditional Chinese Herbal Drugs into the Monographs of the Ph Eur, so that the specialists exactly know what kind of herbs they are dealing with. Reintroducing Chinese Pinyin names will highlight to which

Table 2. Monographs of Chinese Herbs Adopted in the European Pharmacopeia (Ph Eur)

Monograph number	Monograph number	English title	Pinyin	Sinogram
2432	Acanthopanacis gracilistylicortex	Acanthopanax bark	wujiapi	五加皮
2554	Amomi fructus	Amomum fruit	sharen	砂仁
2555	Amomi fructus rotundus	Round amomum fruit	doukou	豆蔻
2661	Anemarrhenae asphodeloides rhizome	Anemarrhena asphodeloides rhizome	zhimu	知母
2556	Angelicae dahuricae radix	Angelica dahurica root	baizhi	白芷
2557	Angelicae pubescentis radix	Angelica pubescens root	duhuo	独活
2558	Angelicae sinensis radix	Angelica sinensis root	danggui	当归
2435	Astragali mongholici radix	Astragalus mongholicus root	huangqi	黄芪
2559	Atractylodis lanceae rhizoma	Atractylodes lancea rhizome	cangzhu	苍术
2560	Atractylodis macrocephalae rhizoma	Atractylodes rhizome, largehead	baizhu	白术
2561	Belamcandae chinensis rhizoma	Belamcanda chinensis rhizome	shegan	射干
2384	Bistortae rhizoma	Bistort rhizome	quanshen	拳参
2386	Carthami flos	Safflower flower	honghua	红花
2430	Citri reticulatae epicarpium et mesocarpium	Mandarin epicarp and mesocarp	chenpi	陈皮
2463	Clematidis armandii caulis	Clematis armandii stem	chuanmutong	川木通
2454	Coicis semen	Coix seed	yiyiren	薏苡仁
2473	Dioscoreae oppositifoliae rhizoma	Dioscorea oppositifolia rhizome	shanyao	山药
2563	Drynariae rhizoma	Drynaria rhizome	gusuibu	骨碎补
2564	Ecliptae herba	Eclipta herb	mohanlian	墨旱莲
2412	Eucommiae cortex	Eucommia bark	duzhong	杜仲
2451	Ephedrae herba	Ephedra herb	mahuang	麻黄
2452	Fraxini rhynchophyllae cortex	Fraxinus rhynchophylla bark	qinpi	秦皮
2566	Isatidis radix	Isatis root	banlangen	板蓝根
2612	Lycii fructus	Barbary wolfberry fruit	gouqizi	枸杞子
2567	Magnoliae officinalis cortex	Magnolia officinalis bark	houpo	厚朴
2568	Magnoliae officinalis flos	Magnolia officinalis flower	houpohua	厚朴花
2383*	Notoginseng radix	Notoginseng root	sanqi	三七
2727	Persicariae tinctoriae folium	Indigo plant leaf	liaodaqingye	蓼大青叶
2477*	Piperis fructus	Pepper	hujiao	胡椒
2453*	Piperis longi fructus	Long pepper	bibo	荜茇
2433	Polygoni multiflori radix	Fleeceflower root	heshouwu	何首乌
2475	Poria	Poria	fuling	茯苓
2439	Prunellae spica	Common selfheal fruit-spike	xiakucao	夏枯草
2434*	Puerariae lobatae radix	Kudzuvine root	gegen (yege)	葛根(野葛)
2483*	Puerariae thomsonii radix	Thomson kudzuvine root	fenge	粉葛
2663	Salviae miltiorrhizae radix et rhizoma	Salvia miltiorrhiza root and rhizome	danshen	丹参
2385*	Sanguisorbae radix	Sanguisorba root	diyu	地榆
2428	Schisandrae chinensis fructus	Schisandra fruit	wuweizi (bei wuweizi)	五味子 (北五味子)
2438	Scutellariae baicalensis radix	Baical skullcap root	huangqin	黄芩
2450	Sinomenii caulis	Orientvine stem	qingfengteng	青风藤
2639*	Sophorae japonicae flos	Sophora flower	huaihua	槐花
2427*	Sophorae japonicae flos immaturus	Sophora flower-bud	huaimi	槐米
2478*	Stephaniae tetrandrae radix	Fourstamen stephania root	fenfangji (hanfangji)	粉防己 (汉防己)

*Herbal monographs were prepared before TCM WP by 13A and 13B groups at EDQM.

therapeutic system the given herbal drug belongs. Most European TCM practitioners always use Pinyin names of these herbal drugs when writing a prescription, and consequently the pharmacists throughout Europe should be encouraged to become familiar with these Pinyin names. When the original names are being removed from the title of the Monograph, this will have an opposite effect. Having the Pinyin names in the Monographs Title will facilitate the work of the Pharmacist and there is no need for any additional reference manuals beside the European Pharmacopoeia. Since some herbal drugs originate from many continents (e. g. Europe and China) the Pinyin name will clearly differentiate between these herbs. For example for *Angelica* sp. where several species are appearing in Europe and China they can easily be differentiated by the Pinyin names.

The argument, that using the Chinese name for TCM Herbal Drugs will lead to misidentification does not hold. Chinese names will never replace the Latin names in the Monograph. They do supply additional information important for exact identification of different herbs of the same genus. Pinyin names thus provide reliable criteria for differentiation in any occasion of doubt. Due to all these reasons it was decided that Pinyin names and Sinograms should appear somewhere in the Ph Eur. The final decision was, that a special chapter should be established, where the TCM Herbal Drugs are being listed with the English-, Latin, French and Pinyin name plus Sinogram. This chapter has been recently published (Pharmaeuropa 26.4, also see table 2) and will be complemented by any addition of a new TCM Herbal Drug which has been accepted by the Commission ready for publication in Ph Eur.

Table 3. Monographs of Chinese Herbs Published in Pharmeuropa Editions 26.3, 26.4 and 27.1

Name of the TCM drugs	Number of Monograph/ in Pharmeuropa
Andrographis herb	(2712)/26.3
Mandarin epicarp and mesocarp	(2430)/26.3
Chinese goldthread rhizome	(2715)/26.4
Eupatorium herb	(2717)/26.4
Dioscorea oppositifolia rhizome	(2473)/26.4
Ephedrae herba	(2451)/26.4
Schisandrae chinensis fructus	(2428)/26.4
Acori calami rizoma	(2456)/27.1
Prunellae spica	(2439)/27.1
Gastrodia rhizome	(2721)/27.1
Peony root, white	(2424)/27.1
Peony root, red	(2425)/27.1
Gardeniae fructus	(2565)/27.1
Polygoni cuspidatum rhizome and root	(2724)/27.1
Lightyellow sophora root	(2440)/27.1
Polygoni orientalis fructus	(2726)/27.1
Zanthoxyli pericarpium	(2656)/27.1
Codonopsidis radix	(2714)/27.1
Eudoia fruit	(2718)/27.1
Platycodonis radix	(2660)/27.1
Uncaria stem with hooks	(2729)/27.1

SCIENTIFIC CHALLENGE FOR BRIDGING PH EUR AND CH P:

Processing of TCM material medica

The materia medica of TCM mainly consists of herbal products such as dried roots, rhizomes, stems, leaves, flowers, fruits and seeds. The major application form in Traditional Chinese Pharmacotherapy is a decoction. Due to the sometimes very voluminous herbal drugs, total drugs are not suitable as raw material for decoctions; they should be processed before usage. The processing of medicinal plant materials has a history as long as Traditional Chinese Medicine itself, The first complete guidebook of herbal preparation goes back to the year 470. The importance of the processing of materials has already been mentioned in the Huang Di Nei Jing (The Yellow Emperor's Internal Classic, 475-221 B.C.) and Shen Nong Ben Cao Jing (Divine Husbandman's Classic of the Materia Medica, *c.* 220 A.D.)[8] Depending on the therapeutic application, the same plant material can be processed differently. In current TCM practice, all the materials are strictly required to be properly processed before using for therapeutic application. Most TCM herbal drugs are in processed form and the purposes of processing are highlighted[9]:

- Achieving drugs of consistent quality and amount for constant and better effectiveness, better storability.
- Reducing toxic effects or undesired side effects.
- Modifying the effect of the herb by traditional, empiric methods.
- Increasing the effect of the herb by traditional, empiric methods
- Modifying molecular structure of the material used to increase solubility.
- Removing unpleasant smells.
- Preparing drug material with completely different therapeutic property as compared with raw the materials.

Understanding the metabolic changes during processing is of great important for quality control of Chinese medicinal herbal materials. Some intensive studies have been done on the processing of e. g. *Rehmannia glutinosa* roots[10,11]. In those studies, the role of processing was to modify the therapeutic properties of the herbal drug *Rehmannia glutinosa* roots that was associated with changes of metabolic profiling during the processing. Effect of processing for reduction of toxicity is another issue for TCM herbal drugs, herewith an example of Aconiti radix is given: this refers to the root part of the medicinal plant that belongs to the genus of the family Ranunculaceae and is comprised of about 400 species of which 166 are endemic in China (http://www.efloras.org/flora_page.aspx?flora_id=2). The most well-known species is *Aconitum napellus* (Monk's hood wolfsbane, aconite). Among them, only two species are used in TCM; *Aconitum carmichaeli* Debx and *Aconitum kusnezoffi* Reichb. The herbal medicines in the Ch P are Radix *Aconitum carmichaeli* (Chuanwu, from the major root of the species *Aconitum carmichaeli* Debx.) and its processed form Radix *Aconitum* Preparata (Zhichuanwu), Radix *Aconitum Kusnezoffii* (Caowu, from the root of *Aconitum Kusnezoffii* Reichb), and its processed form Radix *Aconitum Kusnezoffii* Preparata (Zhicaowu), Folium *Aconitum Kusnezoffii* (Caowuye) and the processed Radix *Aconitum* Lateralis Preparata (Fuzi, the lateral root of the species *Aconitum carmichaeli* Debx.)[9]. In the early ShengNong BenCao Jing, Radix *Aconitum carmichaeli* (Chuanwu) was already recorded as a high risk medicine. Diterpene alkaloids are major chemical components of Radix *Aconitum carmichaeli*. *Aconitum* roots, and some findings[12] demonstrated that proper processing and multi-herbs formulation can reduce the level of toxic components. This also explains that in TCM, some herbal drugs, such as *Aconitum* and *Ephedra* species are never used as single herb for intervention and that aconite is only used when it is processed and in combination with specific matched other herbs. Although some reports about the metabolite changes during processing can be identified in the literature, yet, many processed TCM drugs still require scientific studies.

During processing, not only the metabolites changes are important for quality control, but, various methods are used for processing in TCM as well. Although there is a significant difference between regions in China, in general processing can be classified into 17 different categories[13] (see Table 5.). Under each category there are still different variations and in most case there are no scientific parameters defined to the described categories. Moreover, for the processing, various excipients are used. In Table 6 at least 10 different type of excipients used in TCM processing are shown[13]. The excipients used in TCM herbal drug processing are quite diverse and without scientific parameters for quality descriptions as well.

The most important tasks from the TCM working Party of the Ph Eur will be a joint cooperation between scientists in the field to develop qualitative and quantitative parameters for TCM drug processing procedures, standard operation

protocols (SOP) and defined quality parameters for all excipients used in these procedures.

COOPERATION BETWEEN SCIENTISTS IN EUROPE AND CHINA

Since 2011 the Chinese State Administration of TCM (SATCM) has established a formal cooperation between EDQM, An agreement between both parties was signed in June 2011. The purpose of this cooperation is to promote the cooperation between SATCM of the People's Republic of China and the European Council represented by the EDQM. A mutual cooperation of both parties was established aiming to prepare the quality standards concerning a series of TCM herbal drugs - herbal drug extracts. Both Parties intend to speed up the establishment of high quality standards of TCM in Europe in order to ensure the safety and quality of TCM for the patients.

With the support of Mr. Daning Li from SATCM (former vice director of SATCM), a National Key Laboratory for TCM (NKL-TCM) was established from China side. Scientists in China have joint in the preparation of TCM drug monographs in the TCM working party of EDQM. Chinese scientists supported the following aspects: provide scientific literatures originated from Chinese modern and ancients documents (translating from Chinese language to English language), answer the questions related to TCM drug processing, provide TCM drugs samples, participate in the preparation of TCM monographs by conducting scientific experimental works such as TLC and HPLC studies and development of new quality markers for TCM herbal drugs. From China side, a leading scientist in the field is visiting TCM WP meeting on a regular basis, so that the interactions between scientists from China and Europe are strengthened considerably. Recently, SATCM also suggested new 15 herbal drugs to be added to the Ph Eur TCM WP Working Program (see Table 4).

Table 4. New Chinese Herbs Working List Proposed by SATCM

Name of the TCM drugs	Proposed to Commission by different member states
Arctii fructus	Poland
Corydalis rhizoma	Switzerland
Cyathulae radix	The Netherlands
Eriobotryae folium	Switzerland
Morindae officinalis	Switzerland
Ophiopogonis radix	The Netherlands
Persicae semen	Switzerland
Peucedani radix	Poland
Psoraleae fructus	Germany
Pulsatillae radix	Austria
Scrophulariae radix	Austria
Typhae pollen	Germany
Viticis fructus	Austria
Achyranthis bidentat	The Netherlands
Ganoderma	The Netherlands

ROLE OF TCM HERBAL DRUG MONOGRAPHS IN EUROPE

TCM herbal drug monographs play an important role in quality control for TCM practitioners who are prescribing TCM herbal drugs for their patients/consumers. The present situation in Europe is that the average European TCM practitioner is using 300 TCM drugs in his/her daily practice and the commercial importers provides up to 400 TCM drugs. In European Chinese medicine clinics, there are around 500 TCM drugs being used. The number of quality monographs at this moment is still very limited and cannot serve the needs to EU consumers. To meet the demands of the consumers, much more quality monographs are needed.

Basically there are two types of monographs related to herbal medicine/drugs in Europe. One of them are the EDQM's European Pharmacopeia monographs, which are dealing with quality aspects of the herbal medicine/drugs only. The other type of monograph, named "Community Herbal monographs", is prepared by the European Medicines Agency (EMA) and is dealing with safety and efficiency of herbal medicine/drugs. As both types of monograph play in concert to contribute to the regulation of herbal medicines/drugs in safe use of TCM drugs for consumers in Europe (Figure 2), it is important to have frequently used TCM drugs in the EU to be regulated by both, quality and safety/efficiency rules. Up to now, there are only 10 EMA "Community herbal monographs" for TCM products[14], and already 43 TCM herbal drug monographs adopted by the Ph Eur. The present article mainly focused on EDQM's herbal drug monographs, which will be the key for a quality standard for herbal drugs used in Europe. This quality standard can be applied to herbal raw materials that are

Table 5. Seventeen ancient processing methods (Zhang and Cai 1984)

No	Descriptions	No	Descriptions
1	**"Pao"** heat on fire till smoking comes out	10.	**"Du"** correcting the size of drugs
2	**"Yan"** heat till almost burnt:	11.	**"Fei"** prepare drugs in fine powders
3	**"Fu"** dry on fire	12.	**"Fu"** sop the drugs in water and then place in canister
4	**"Zhi"** Coated with otherness slightly heated by fire to dry	13.	**"Bang"** to prepare the drug in thin sliced
5	**"Wei"** simmer heat of drugs in ash	14.	**"Sha"** to reduce the drugs into small size till powders
6	**"Chao"** yellow fry, black fry, fry coke	15.	**"Shai"** Sundry the drugs
7	**"Duan"** Put the herbs into fired carbon till it becomes red	16.	**"Bao"** Exposure the drugs in direct sun shine
8	**"Lian"** heat on fire for a long time	17.	**"Lu"** keep the drug outside inducing night
9	**"Zhi"** correcting properties of drugs with various methods		

Table 6. Ten different type of excipients used in processing (Zhang and Cai 1984)

No.	Descriptions
1	Honey
2	Chinese yellow wine
3	Chinese vinegar
4	Concoctions, this can be derived from black bean, soybean, ginger, Licorice, pepper etc.
5	Salt
6	Soil
7	Rice
8	Wheat bran
9	Powders from clams
10	Others, this can be milk and fat etc.

used in pharmacy as well as to the preparation of the finished herbal medicinal product during the manufacturing process (e.g. under EU Good Manufacture Practice, GMP).

OUTLOOK FOR THE FUTURE DEVELOPMENT OF TCM PRODUCTS IN EUROPE

The classical therapeutic dosage form in TCM therapy is the hot water decoction of mostly a complex mixture of different TCM herbal drugs. In order to facilitate the compliance of these aqueous extracts, large scale decoctions at an industrial level are spray dried, mixed with excipients and formulated to the so called granules, which have recently been introduced in large amounts to the European market. The necessary quality parameters, however, of these TCM products is often not provided and sometimes rather doubtful, since the preparation methods for these solid forms of decoctions are not officially specified and hence, there are often considerable differences in the overall composition when comparing a classical decoction versus any granule preparation of the commerce.

A very promising step forward for the general acceptance of TCM products in the European Countries should be the industrial production of defined and specified extracts from single TCM herbs or even from complex mixtures of several herbal drugs. These, by Ph Eur monographs qualified extracts are the common basis for any legal registration by either the respective National Authorities or even by the EMA in London for all the European Member States. A first positive example in this direction was the production and registration of a defined saponin extract obtained from the TCM herbal drug *Dioscorea nipponica rhizome*, which now is the basis for the newly registered Phytomedicine DXXK in the Netherlands[15].

Consequently, the Ph Eur Commission inaugurated the elaboration of the respective quality monograph for this herbal drug (*Dioscorea nipponica rhizome*) to be implemented in the Ph Eur. The following step should be, to elaborate the corresponding quality monograph of the *Dioscorea nipponica rhizome* extract, and further to classify this new extract as a standardised-, quantified- or other extract according to the rules of the Ph Eur Monograph on Herbal Extracts. This adoption of a first TCM herbal drug as the basis of a registered European phytomedicine (DXXK) should be an important signal for the Pharmaceutical Industry in China, to follow a similar way, i.e., to produce defined herbal extracts with well-established pharmacological and clinical data as the basis for any registration in either individual countries of the EU or for all EU Member States by the centralised registration procedure via the EMA in London[16].

Following the future initiatives of the Chinese Pharmaceutical Industry, the Ph Eur will react accordingly by elaborating the respective Quality Monographs for both, the TCM herbal drug and the respective defined extract following the rules and guidelines specified for herbal drugs and herbal drug preparations (extracts). It can be hoped that in the near future intensified contacts and collaborations between Chinese and European Officials and between Chinese and European Pharmaceutical Industries can be inaugurated in order to create most efficient new TCM phytomedicines for the patients in Europe.

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