Introduction

Herbal drugs have a long tradition as medicines in the European market and are recognised within the regulatory framework on medicinal products. Nonetheless their importance and economic impact varies from country to country [1]. Like all kinds of medicines, herbal drugs and the products made thereof have to prove their quality, efficacy and safety prior to gaining access to the market [2].

The quality parameters of herbal drugs are usually specified and implemented in the respective pharmacopoeias, either in national ones or in the European Pharmacopoeia (EP), which is currently published in the 7th edition. The EP arose out of the need for a transnational pharmacopoeia in Europe, in which different states could agree and mutually accept the best common standards for medicinal substances [3]. The European Pharmacopoeia Convention has been signed by 27 states and by the Commission of the European Communities. Moreover, 22 countries and WHO have observer status [4,5]. Therefore, the member states are exceeding the 27 countries of the European Union. The EP is elaborated and published by the European Directorate for the Quality of Medicines & Health Care in Strasbourg, which is an institution of the Council of Europe [4]. The monographs in the EP are addressed to the respective national authorities, manufacturers and also to public or community pharmacies.

In 1997, the European Parliament stated in document A4-0075/97 on the issue of incorporating nonconventional medical remedies to the European Pharmacopoeia: “The European Pharmacopoeia, as drawn up by the Council of Europe, needs to be opened up to other pharmacopoeiae particularly the medicinal plants used in Chinese medicine.” The activities of the EP to include traditional ethnic medicines started in 2005, when the respective commission published a statement as follows: “Monographs on herbal drugs used in traditional Chinese medicine (TCM) should be developed to give a modern quality standard according to European Pharmacopoeia in principles and to facilitate and encourage use by practitioners for safe, authorised products”.

In this initial phase, only TCM-herbal drugs were considered for an elaboration process. Others, such as products originating from Ayurvedic medicine or South American medicines were not considered in 2005 to establish TCM-herbal drug monographs for the most important medicinal plants imported from Far East. These new monographs had to be established and evaluated on the basis of existing monographs in the Chinese Pharmacopoeia (ChP), English edition 2005. Due to important differences in the overall features of EP and ChP, a simple adapt/adopt procedure was not feasible. Therefore, specialist groups were mandated with a corresponding working programme. Some results and actual problems related to this working programme will be presented and discussed.

Abstract

The actual concern about the safety and efficacy of herbal drugs originating from traditional Chinese medicine (TCM) is based on observations that these medicinal plants may have a high risk potential due to insufficient definitions, problems with identity, purity and falsifications. No uniform legal status for these groups of herbal drugs currently exists in the European Union. For quality control, monographs for TCM herbs can mainly be found in the Pharmacopoeia of the Peoples Republic of China. Based on these facts the Commission of the European Pharmacopoeia decided in 2005 to establish TCM-herbal drug monographs for the most important medicinal plants imported from Far East. These new monographs had to be established and evaluated on the basis of existing monographs in the Chinese Pharmacopoeia (ChP), English edition 2005. Due to important differences in the overall features of EP and ChP, a simple adapt/adopt procedure was not feasible. Therefore, specialist groups were mandated with a corresponding working programme. Some results and actual problems related to this working programme will be presented and discussed.
Traditional Chinese Medicines for the European Pharmacopoeia

The selection of items, i.e., herbal drugs originating from TCM, is not an easy task, since it is known that approximately 5000 herbal, animal and mineral drugs have been used in China [6]. ChP 2005 Vol. I contains 1145 monographs on drugs of herbal, animal and mineral origin. Among them are 538 monographs on herbal drugs. Detailed data for the utilisation of TCM medicines in Europe are not published. It was estimated that in the different EU member states between 75 and 125 herbal drugs of Chinese origin are most frequently used.

Thus, the selection of candidates to be included in the EP Working Programme, i.e., the priority setting, was based – after an inquiry at the respective national authorities – on the following criteria:

- Quality and completeness of existing monographs in the ChP 2005
- Extent of use in the different EU member states
- Risk potential (adulterations, toxicity, poor quality)

Apparent Differences between Herbal Drug Monographs in EP6 versus ChP 2005 (Table 2)

Definition

According to the current technical guide of the EP, in the “Definition” section the following information should be provided:

- State of the drug: whole, cut, peeled, fresh or dried
- Complete scientific name of the plant (genus, species, subspecies, variety, author)
- Whenever possible, the minimum content of quantified constituents should be specified

Since nomenclature is not yet harmonised in East Asia, there is an urgent need for a clear definition of the botanical source. For example, “Bianxu” obtained from China mainland is supposed to be Polygonum aviculare (Polygonaceae); obtained from Taiwan it is Euphorbia thymifolia (Euphorbiaceae), and from Hong Kong it may be Belamcanda chinensis (Iridaceae) [8].

A problem to be solved is the inclusion of the original Chinese name of the plant (herbal drug material) citing the Pinyin names in the “Definition” section. The Pinyin names are the originating names of the EP [7]. Unfortunately, this was not accepted by the EP Commission with the reasoning that in Chinese different spellings exist for the same herbal drug. However, they do not correspond with the Tongyong Pinyin used in Taiwan. When the first TCM herbal drug monographs were ready for publication in the EP, the Chinese titles, taken from the ChP, both, as sinograms and Pinyin, were included in the “Definition”. Unfortunately, this was not accepted by the EP Commission with the reasoning that in Chinese different spellings exist for the same herbal drug. However, it was agreed that the Chinese names are kept in the monographs until final publication. But since the Chinese names of the individual herbal drug are an essential piece of information for the user, a solution for this problem has to be found.

In TCM herbal drug monographs the specification of a minimum content of active constituents is not always obvious, because pharmacological data of therapeutically relevant compounds, as
Table 1  Initial working programme based on the proposals of the respective EP member states.

Acanthopanacis gracilistyli cortex  
Aconiti carmichaeli radix  
Aconiti Kusnezoffii radix praeparata  
Aconiti radix lateralis praeparata  
Aconiti radix praeparata  
Acori calami rhizoma  
Acori tatarinowii rhizoma  
Acebiae caulis  
Amomi villosi vel longiligularis fructus  
Amomi rotundi kravanh vel compacti fructus  
Andrographis herba  
Anemarrhenae rhizoma  
Angelicae dahuricae radix  
Angelicae pubescentis radix  
Angelicae sinensis radix  
Arnebiae radix  
Artemisiae scorpariae herba  
Asari radix et rhizoma  
Atractylodis macrocephalae rhizoma  
Atractylodis rhizoma  
Aucklandiae radix  
Belamcandae chinensis rhizoma  
Bupleuri radix  
Chaenomelis fructus  
Citri reticulatae epicarpium et mesocarpium  
Clematidis caulis  
Clematidis radix  
Codonopsis radix  
Cocis semen  
Coptidis rhizoma  
Daturaæ flos  
Dioscoreæ rhizoma  
Drynariae rhizoma  
Ecliptæ prostratae herba  
Eucommiae ulmoidis cortex  
Eupatorii herba  
Evodiae fructus  
Farfarae flos immaturas  
Forsythiae fructus  
Fraxini cortex  
Fritillariae cirrhosae bulbus  
Fritillariae thunbergii bulbus  
Gardeniae fructus  
Gastrodiae rhizoma  
Herba articulatae scapariae  
Houttuyniae herba  
Indigo naturalis  
Indigo plant leaf  
Isatidis radix  
Ligustici chuanxiong rhizoma  
Ligustici sinensis radix et rhizoma  
Lycii fructus  
Lycopi herba  
Magnoliae officinalis caulis cortex  
Magnoliae officinalis flos  
Notopterygii rhizoma et radix  
Paoniae radix alba  
Paoniae radix rubra  
Paoniae suffruticosae cortex  
Pinelliae rhizoma praeparatum  
Pinelliae rhizoma  
Pleioblastis radix  
Polygoni cuspisat  
Polygoni multiflori caulis  

Table 2  Apparent differences between herbal drug monographs in EP 2008 versus ChP 2005.

|--------|--------------------------|
| 1. Nomenclature:  
  Engl. title | 1. Chinese Title  
  Latin Title | (Translated Engl. Title) |
| 2. Source | 3. Formulary |
| 4. Definition:  
  state of the drug: whole, fragmented | 4. Processing  
  scientific botanical name | 5. Description |
| 6. part of the plant used | 6. Identification |
| 7. stage in the growth cycle when harvesting takes place | 7. Inspection |
| 8. minimum content of quantified constituents | 8. Extractives |
| 12. Usage and dosage  
  Macroscopic botanical characters | 13. Precautions  
  Microscopic botanical characters of powdered drug only |
| 14. Strength | 15. Storage |
| 16. Preparation and dosage form |

5. Tests:  
   classical tests (ash, loss on drying, etc.)  
   heavy metals  
   pesticides  
   aflatoxins  
   if necessary: aristolochic acids, pyrrolizidine alkaloids  
6. Assay  
7. Storage  
8. Reagents
Identification

The “Identification” section in the EP is a very important chapter for all herbal drugs including the new TCM materials. The combination of different methods such as microscopic and macroscopic examination of the botanical characters (Identification A and B), and TLC fingerprinting (Identification C) are typical features of EP monographs. Wagner and Bauer [11] have published 75 monographs with TLC and HPLC fingerprints of Chinese herbs so far, which are very useful for the elaboration of the pharmacopoeia monographs.

In community pharmacies, at least Identifications A and B have to be carried out. However, there are striking differences between EP and ChP in the identification part. Often ChP 2005 does not provide microscopic descriptions of the powder, and also no herbal drug powder illustrations, while TLC fingerprinting is also common [12]. However, EP is providing schematic chromatograms of reference substances in comparison to the sequence of compounds in the herbal drug extract (Fig. 1), while ChP is only describing the separation in words. In both cases, coloured photographs would be desirable. The question whether additional identification methods by molecular biological methods, i.e., CE and DNA fingerprinting [13–16], should be included into the EP, is currently under discussion.

Test

The “Test” section in the EP contains chapters for the classical test methods, such as “Foreign Matter” (2.8.2.), “Loss on Drying” (2.2.32.), “Water” (2.2.13.), “Pesticides residues” (2.8.13.), “Heavy metals” (2.4.27.), determination of “Total Ash” (2.4.16.), “Ash soluble in hydrochloric acid” (2.8.1.), “Extractable Matter” “Swelling Index” (2.8.4.), “Bitterness Value” (2.8.15.), “Aflatoxin B1” (2.8.18.), “Ochratoxin” (2.8.22.), and “Radioactive Contamination”. In addition, microbiological purity has to be tested according the monograph 2.6.31. Microbiological examination of herbal medicinal products for oral use. Recommendations on the microbiological quality of herbal medicinal products consisting solely of one or more herbal drugs are given in the EP chapter 5.1.4. Microbiological quality of pharmaceutical preparations and substances for pharmaceutical use. EP provides tolerance levels for the microbial load of medicinal plants, which are based on intended application and on preparation technique. The accepted microbial load is higher when a plant drug is intended to be treated with boiling water prior to use, as this leads to a decrease of microbial growth. The criteria of EP are not mandatory, but are used as a recommendation for target levels. The limits recommended have been intensively discussed because in some cases it is rather difficult...
to comply with them. Especially organically produced materials may be treated with natural fertilizers such as stinging nettle broth which contains considerably higher microbial levels, and they are also preferred by many insects which often carry contaminants [17, 18]. Another problem is insufficient drying of the material, which often leads to the growth of moulds. Therefore, according to EP, “Loss on Drying” should be limited to a low percentage [7].

Also the monograph on “Pesticide Residues” (2.8.13.) has recently been updated based on previous experience [19,20]. A new monograph on “Heavy metals in herbal drugs and fatty oils” (2.4.27.) has been established. For the EP monograph Herbal drugs the following maximum limits have been set with respect to dry matter: lead 5 mg/kg, cadmium 1.0 mg/kg, mercury 0.1 mg/kg, “unless otherwise stated in an individual monograph or unless otherwise justified and authorised”. These tolerance levels have been discussed for a long time [19,21–23].

A test method for aristolochic acids in herbal drugs has recently been developed and implemented in the EP. Aristolochic acids are liver and nephrotoxic, and herbal medicinal products containing these compounds are banned [24]. Nevertheless, there are several Chinese medicinal herbs still on the market, which contain aristolochic acids [25,26]. The “Test for Aristolochic Acids in Herbal Drugs” (2.8.21.) contains a Method A as a screening test for aristolochic acids by HPTLC, further Method B as a limit test for aristolochic acid A by HPLC, and finally a Method C as a confirmation test for aristolochic acid A by LC-MS. The urgent need for an elaboration and inclusion of these new test methods was based upon a series of intoxications because of adulterations. Currently, elaboration and validation of appropriate test methods for the determination of pyrrolizidine alkaloids are in progress and will be implemented in the “Test” programme. Pyrrolizidine alkaloids are highly liver toxic, and therefore limits are urgently needed [27,28]. Pyrrolizidine alkaloids occur predominantly in the Compositae family, in plants of the Senecioneae (24 genera, the genus Senecio is prevalent) and Eupatorieae subtribe (mainly in the genera Eupatorium and Ageratum), in virtually all plants of the Boraginaceae family, and in the Fabaceae family (Leguminosae) in the subtribe Crotalarieae, mainly in the genus Crotalaria, but also in the genera Chromolaena and Lotononis. In comparison, the “Test” section of the ChP 2005 has been restricted to items such as Foreign Matter, Water, Total Ash, Acid In-

Assay

The “Assay” is an important section of all herbal drug monographs, whereby the minimum content of quantified constituents provided in the “Definition” should be determined by appropriate methods. However, for many TCM herbal drugs no constituents with known therapeutic activity (active markers) are known which could be utilised as a standard. In these cases “analytical markers” have to be used and examined with the appropriate methods. In earlier monographs on herbal drugs, assays often have been carried out with global spectrophotometric or titrimetric methods (i.e., determination of flavonoids, or of total alkaloids). For modern monographs, specific determinations of single constituents by HPLC or GLC are widely preferred, although it is known that therapeutic efficacy of herbal drugs is based on several active compounds in most of the cases. Therefore modern concepts of fingerprint analyses are scientifically discussed for Chinese herbs [29,30]. However, such methods have not yet been implemented. Instead an assay of a polar and a nonpolar marker may be a surrogate, as it is practised for salvianolic acid B and tanshinone IIA in Salviae miltiorrhizae Radix et Rhizoma (Danshen) [31–33] (Fig. 2).

For the assays, reference standards (Chemical Reference Standards CRS or Herbal Reference Standards HRS) have to be established by EDQM. For example, for the assay of Schisandrae chinensis fructus Ph.Eur. 6.3, Schisandrin A (=Wuweizichun A) has been established as a Chemical Reference Standard Schisandrin CRS. Comparing the assay section in the ChP, it is obvious that in several monographs no minimum content for active or analytical markers is specified. In cases where appropriate methods are specified and minimum contents are provided, it is often a problem that reference compounds utilised for the assay of the ChP are not available at an acceptable price. In these cases, new analytical markers have to be selected, examined and validated by appropriate methods. In case pure compounds are not available, Herbal Reference Standards HRS will be used, like in Valerian root EP 6.8.

Current Status of the EP Working Party on TCM Herbal Drugs

In the initial phase, the experts of the Phytochemistry Groups (13 A, 13 B) of the EP started work with the elaboration of TCM monographs. As a consequence of the heavy load of work for both Expert Groups, the EP Commission installed a TCM Working Party in 2008 with the only task to continue with the elaboration, evaluation and implementation of the urgently needed quality TCM herbal drug monographs. It was obvious that there was still a growing interest in the EU Member States to elaborate these quality monographs, since the import of TCM herbal drugs had increased considerably. Legally binding quality standards for TCM herbal drugs were very few at the time. General knowledge
about herbal drugs from TCM practise was still rather limited. Finally, many quality problems had been observed during the past, indicating a high risk potential for the patient if quality control is omitted. Consequently, inauguration of a specialised Working Party seemed to be necessary.

The original working programme of this TCM Working Party consisted of 83 monographs. Again, the elaboration should be carried out based on monographs of ChP 2005 and other relevant literature, such as the Japanese Pharmacopoeia and the Hong Kong Chinese Materia Medica Standards (HKCMMS), or the Chinese Drug Monographs and Analysis [11]. A precondition for all elaborations on TCM herbal drugs was the availability of commercial samples from the European market. As a minimum condition it was essential to have at least 5 to 8 commercial drug samples at our disposal, typical of material supplied to the market. These samples should be used for the confirmation of identification parameters and determining numerical values to be given in “Tests” and “Assays”. Furthermore, authentic reference samples were needed to confirm that commercial samples are both genuine and of acceptable quality. In addition, reference samples of substitute/adulterant herbal drugs for exclusion tests should be available in sufficient quantity, to elaborate the respective methods for the “Test” section.

**Processed TCM Herbal Drugs**

The majority of herbal drugs used in traditional Chinese medicine appears to be subjected to some form of pretreatment (processing). In the context of the EP, these processed herbal drugs can be classified as “Herbal Drug Preparation”. The current methods of processing have the potential to alter the appearance, the texture or molecular structure in order to increase effectiveness and better stability; reduce toxic or undersized effects; modify the texture or molecular structure in order to increase solubility; prepare new herbal drugs by fermentation methods. Herbal drugs can be treated by: mechanical processing; water for moistening the herbal drug prior to cutting; heat for altering the therapeutic properties; heat and water, or other liquids, like honey, saline, vinegar, wine or ginger juice, done by frying, boiling, or steaming with the liquids in question.

Compared to these “Herbal Drug Preparations” of Western medicine, processed herbal drugs in TCM are quite different. Processing can be carried out in order to:
- obtain drugs of consistent size for better and constant effectiveness and better stability;
- reduce toxic or undersized effects;
- modify or increase the genuine effect of the herbal drug;
- modify the texture or molecular structure in order to increase solubility;
- prepare new herbal drugs by fermentation methods. Herbal drugs can be treated by:
  - mechanical processing;
  - water for moistening the herbal drug prior to cutting;
  - heat for altering the therapeutic properties;
  - heat and water, or other liquids, like honey, saline, vinegar, wine or ginger juice, done by frying, boiling, or steaming with the liquids in question.

Against the background of these complex processing methods, a detailed chapter for these techniques may be established in order to be included in the EP as a “General Chapter”. It will be important for the future implementation of TCM herbal drug monographs to be able to refer to the “Processing Methods” listed in this new “General Chapter”. However, not all of the analytical requirements for the elaboration of herbal drug monographs may be appropriate for the respective processed herbal drug. This may necessitate the inclusion of additional tests, for example, the absence of rancidity when the plant material has been processed by stir baking in the presence of a vegetable oil. When herbal drugs such as aconite have been processed in order to reduce the content of toxic constituents, appropriate analytical methods to determine the acceptable limit values of the toxic compounds must be included [34–36].
Table 5 Pharmacopoeia or standards of various countries or regions that have monographic standards for CMM [40].

<table>
<thead>
<tr>
<th>Pharmacopoeia and monograph</th>
<th>Authority</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Monographs on Selected Medicinal Plants</td>
<td>WHO</td>
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</tr>
<tr>
<td>Chinese Pharmacopoeia</td>
<td>SFDA China</td>
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<tr>
<td>Australian Regulatory Guidelines for Complementary Medicines</td>
<td>TGA Australia</td>
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<td>American Herbal Pharmacopoeia (AHP)</td>
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</table>

Conclusion

The development of Chinese medicine in Europe has reached a stage which requires precise studies and reliable quality control methods of the Materia Medica. Five years of intensive work of the Expert Groups resulted in a series of finalised and implemented monographs for the EP (Table 3), furthermore, in a large number of published drafts (Table 4), and many still pending working projects. Requirement is still the availability of sufficient samples, both commercial and authentic reference samples. Furthermore, the problems related to the pharmacological approach of appropriate assays to be included in the new concept of TCM herbal drug quality monographs should be resolved, since in most cases a defined pharmacological background requires precise studies of the Chinese Materia Medica and adaption to obtain reliable data on TCM drugs. Because of the differences between ChP and EP, all new TCM herbal drugs for the EP had to be examined with the whole range of test methods available. In order to reduce contaminations, GACP rules have been established by WHO [37]. Even though a Good Agricultural Practice (GAP) system for the cultivation of Chinese herbs has been established, most Chinese herbs are not yet cultivated under controlled conditions, but are collected from their natural habitat or harvested from small cultivation bases [38]. Until June 2004 only 13 TCM herbs were grown in agricultural sites complying with GAP [39]. However, in the meantime the authorities have implemented GAP for 80 species [40]. Various countries or regions are currently establishing monographic standards for Chinese herbs (see Table 5) [40]. Unfortunately, no harmonisation has been achieved so far. In order to reflect globalisation of TCM, a harmonised regulatory system would be desirable in order to improve quality and practicability.

References

30. Liang YZ, Xie PS, Chan K. Chromatographic fingerprinting and Metabolomics for Quality Control of TCM. Comb Chem High Throughput Screen, advance online publication 30 September 2010


40 Chan K, Leung KS, Zhao SS. Harmonization of monographic standards is needed to ensure the quality of Chinese medicinal materials. Chin Med 2009; 4: 18