Globalization of Traditional Chinese Medicinal products And New Regulatory Structures in the European Union

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Traditional Chinese Medicine (TCM), Registration, EU pharmaceutical legislation, Traditional Herbal Medicinal Products, tHMP, quality, safety, efficacy, traditional use, EMEA, European Medicines Agency, European Pharmacopoeia, Herbal Medicinal Products Committee, HMPC, Community Monographs, Community List.

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In the European Union he was member of the Herbal Medicinal Products Working Party from 1997 till 2004, which at that time changed into the Herbal Medicinal Products Committee at the EMEA in London. Since 2004 he has been member of the Herbal Medicinal Products Committee, and is chair of its subgroup for Organisational Matters (ORGAM). During the past years several procedural guidance documents were established, also concerning traditional herbal medicinal products, all published at the EMEA website.

In November 2007, van Galen was elected as Chairman of the Homeopathic Medicinal Products Working Group (HMPWG), which is an EU working group in which all Member States participate with a focus on mutual recognition for homeopathic medicines.

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1. Introduction

The rationale behind the simplified registration procedure, which is discussed in this article, is to enable products that have been in long-standing (=traditional) medicinal use to be registered under a simplified regulatory procedure in the Member States of the European Union, because their safety and efficacy can be deduced from that long-standing use under the specified conditions of use. The majority of medicinal products with such a sufficiently long and coherent tradition are based on herbal substances and herbal preparations.

2. Registration of Herbal Medicinal Products in the European Union

2.1 Basic Introduction into regulations and procedures.

In the European Union a specific procedure has been introduced with respect to "traditional use" not only for herbal medicines with an European tradition, but in principle also for herbal medicinal products in the Chinese tradition. To gain access to the European market for medicines TCM products first of all will have to fulfil the European standards for quality, safety and efficacy. Regarding the globalization of TCM medicines, this is a real challenge but it will benefit both manufacturers and users of TCM medicines in Member states of the European Union.[1] Here a basic introduction in the complex European framework for the assessment of medicines is presented, with a role for national competent authorities of all 27 Member States of the EU, but also with a growing centralized influence on the market for herbal medicines by the work of the Herbal Medicinal Products Committee (HMPC), at the European Medicines Agency in London, United Kingdom.

Herbal medicinal products [2], also known as phytotherapeutic medicines, are medicinal products whose active ingredients are exclusively based on plants. Like all other medicinal products, herbal medicinal products require marketing authorization. This means that they can only be placed on the market after receiving marketing authorization by a competent authority. For example, in the Netherlands the marketing authorization is granted by the Medicines Evaluation Board (MEB) as competent authority. The legal criteria that the MEB uses in order to come to a decision are quality, efficacy and safety. As far as efficacy is concerned, an exception is made for herbal medicinal products with a long tradition of use in the European Union: these products are known as traditional herbal medicinal products (tHMP). The efficacy of these products has to be made plausible based on pharmacological explanation but also apart from use in patients mainly on the basis of a documented long history of use and experience. All other medicinal products, including non-traditional herbal medicinal products, have to be proven to be effective before they can be authorized.

2.2 The legal basis for the authorization of traditional herbal medicinal products

The simplified authorization procedure for traditional herbal medicinal products in the EU came into effect on 1 November 2005. The procedure implies that a condition for acquiring a marketing authorization under this procedure is that the (traditional) herbal medicinal product must have been used in medical practice for at least 30 years prior to the application date, and it must have been used in the European Union for at least 15 of those years. Furthermore, the product should only be administered orally (by mouth), externally (by the skin) or by inhalation, with an indication for use in conditions where a doctor is not required to establish the diagnosis, prescribe treatment or monitor the patient: in other words, exclusively for Over The Counter (OTC) indications.

The active ingredients of traditional herbal medicinal products should exclusively consist of one or more herbal substances [3] and/or herbal preparations [4]. Herbal substances are whole, broken or cut plants, parts of plants, algae, fungi and lichens. A herbal preparation is a preparation that is obtained by subjecting herbal substances to treatments such as extraction, distillation, pressing, fractionation, purification, concentration or fermentation. However, it should be noted that not all levels of purification/concentration of herbal substances are considered to be a "herbal preparation". Very high levels of purifications, containing high levels of a (limited number of) plant constituent(s) are not classified as a herbal preparation but as a (mixture of) isolated chemical constituent(s). The Herbal Medicinal Products Committee is currently drafting a guideline to clarify which level of purification can still be

classified as a herbal preparation.

Combinations with vitamins and minerals are permitted (for traditional herbal medicinal products) provided that the action of the vitamins and/or minerals can be shown to be ancillary to that of the herbal active ingredients regarding the specified indication. Ingredients of animal origin are not allowed in traditional herbal medicinal products.

2.3 Supporting evidence for traditional use

Traditional use must be demonstrated with bibliographic or expert evidence; the supporting evidence must show that the product or a corresponding product has been used in global medical practice for at least 30 years. Reference to a source published 30 years ago is not sufficient, as this simply demonstrates that the product was in use 30 years ago. There must also be a connection between the duration of use and the claimed use. A corresponding herbal medicinal product may also be referred to in order to support the length of use claim. Here, 'corresponding' means that it has the same active ingredients (regardless of the excipients used), an equivalent concentration and posology, an identical or comparable intended effect and an identical or comparable method of administration. If the composition of the product has changed, removal of substances is acceptable, but additions are not. Furthermore, in general, new extraction procedures or purification procedures are also not accepted for the simplified procedure, without a proper justification.

2.4 Dossier requirements for traditional herbal medicinal products

Applications for traditional herbal medicinal products must be supplied in European Notice to Applicants dossier format [5]. More information about this can be found on the European Commission website.

Quality

Herbal medicinal products are by nature very complex products. In addition because they are natural products their content varies. Due to this complexity and variability special quality requirements were developed in the European Union for herbal medicinal products. These highly technical guidelines are published at the internet at the EMEA website [6]. The quality requirements for herbal medicinal products are independent from the authorization procedure, Therefore identical quality requirements apply to herbal medicinal products registered via the simplified procedure based on traditional use and those authorized via the "regular" procedure, which requires clinical evidence.

In addition to the herbal specific requirements, other requirements related to the pharmaceutical dosage form also apply to traditional herbal medicinal products. Information on these quality requirements can be found in the European Pharmacopoeia[7] (Ph.Eur). In general the quality of all traditional herbal medicinal products must comply with the standards of the European Pharmacopoeia.

Pharmacopoeia monographs

Regarding herbal medicinal products based on traditional use in Chinese medicine, two official pharmacopoeias can play a role: In the European Union all medicinal products have to comply with standards of the European Pharmacopoeia. But several herbal substances and even herbal patent formulas, have monographs in the Pharmacopoeia of the People's Republic of China[8] (PPRC). Recognition and exchange of monographs between both official pharmacopoeias in a complex issue. The European Pharmacopoeia (published by the European Pharmacopoeia Commission in Strasbourg, France) is recognized as official standard for pharmaceutical quality not only in the European Union, but also by Switserland, Turkey, Ukraine and the Russian Federation. In the European Pharmacopoeia several monographs are included for herbal drugs[9] used in the European tradition; in the Chinese Pharmacopoeia even more herbal monographs are published, focussing on the use in Chinese tradition. Although these Chinese Pharmacopoeia monographs can contribute to the registration process, these monographs have not quite the same status as comparable

ones in the European pharmacopoeia. Moreover the general monographs for herbal medicines in Ph.Eur. have to be respected.

Recently an initiative started [10] to adapt existing herbal monographs in the Chinese Pharmacopoeia to the format and requirements of the European Pharmacopoeia. When these adapted monographs officially will be included in the European Pharmacopoeia (clarifying in the title of the monograph " for use in Chinese Medicine") this will be an important step in harmonisation between the two Pharmacopoeias. From a regulatory point of view, official pharmacopoeia monographs in the Ph.Eur. which are suitable for the herbal substance/-preparation in the registration, are considered already validated.

Draft monographs for Herbal drugs used in traditional Chinese medicine have been published in the official Publication Journal of the European Pharmacopoeia, called PharmEuropa[11]. Publication is the main step before inclusion to the Official Pharmacopoeia. Reference to European Pharmacopoeia monographs is compulsory(见表).

Draft monograph published in PharmEuropa	Chinese name
Ephedrae herba	Ma Huang
Polygoni multiflora radix	He Shou Wu
Stephaniae tetrandrae radix	Fang Ji
Puerariae lobatae radix	Ge Gen
Polygoni multiflora radix immutata	Zhi he Shou Wu
Puerariae thomsonii radix	Fen Ge
Arnebiae radix immutata	Zi Cao
Citri reticulatae epicarpium mesocarpiumque	Zi Cao
Schisandra chinense fructus	Wu Wei Zi
Sophorae japonicae calix	Huai Mi
Astragali mongholici radix	Huang Qi
Eucommiae ulmoidis cortex	Du Zhong
Sinomenii acuti caulis	Qing feng Teng

But even more important are the General pharmacopoeia monographs, which apply to all specific monographs. The European Pharmacopoeia does not have a separate part for Herbal drugs but relevant general monographs are published on: Extracts, Herbal drug preparations, Herbal drugs, Heavy metals in herbal drugs and fatty oils, Determination of essential oils in herbal drugs, Pesticide residues, and a monograph on Determination of Aflatoxin B_1 in herbal drugs.

Besides the quality requirements in the European Pharmacopoeia, applicants have also to pay due account to the guidelines established by the HMPC/EMEA, concerning quality of herbal medicinal products. [12] Quality is strongly related to the safety of the products. In the past, some incidents with Chinese medicines on the European market got much attention and lead to enforcement measures.[13]

Safety

Safety has to be demonstrated with a bibliography of data relating to safety (literature) together with an expert report. The report must show that the literature data is applicable. Additionally, data from experimental studies may be provided. Criteria for evidence of safety can be found in the HMPC guideline on 'Non-clinical documentation for herbal medicinal products in applications for marketing authorisation (bibliographical and mixed applications) and in applications for simplified registration'[14].

If the herbal substances or herbal preparations are included in the Community list[15] and if the preparation plus recommended doses for the product to be authorized match the product on the list, then a bibliography does not have to be provided. A reference to the list will then be sufficient.

It should be noted that because the efficacy of traditional herbal medicinal products is not demonstrated with clinical data, permitted contra-indications or adverse reactions are restricted. Hence contra-indications and adverse reactions which are accepted for other OTC medicinal products of proven efficacy are not necessarily acceptable for traditional herbal medicinal products.

Evidence of efficacy

The efficacy of traditional herbal medicinal products does not have to be supported using clinical tests. The pharmacological effects and efficacy must be shown to be plausible on the basis of long-standing use and experience. Clinical data, if available, can be supportive.

In the case of traditional herbal medicinal products that appear on the Community list, a reference to this list will be sufficient. If an established Community monograph for traditional use exists for the product, additional data may be requested to support the product's efficacy. To support its traditional use, applicants may refer to the section in the established Community monograph dealing with traditional use. Efficacy can be shown by, inter alia:

- data from experience;
- manuals;
- results of pharmacological studies;
- case studies.

Traditional herbal medicinal products may only be recommended for use with conditions that do not require a doctor to establish the diagnosis, prescribe treatment, or monitor the patient. In other words: only OTC (over-the-counter) indications are permissible.

2.5 How are traditional herbal medicinal products brought to the market?

Applicants can ask the competent regulatory authority for advice on dossier requirements prior to submitting a dossier. They then submit a dossier containing all the necessary information for assessment. Applications are only accepted after a validation of the dossier content. During this validation process it is checked if the application complies with all legal requirements, in particular if the manufacturer of the medicinal product has a EU certified manufacturing license and if batch release takes places in the European Union

In the Netherlands the Medicines Evaluation Board (MEB) evaluates and monitors the efficacy, risks and quality of human medicinal products. The Botanicals department of the MEB assesses the application on the basis of criteria laid down in the Dutch Medicines Act (Geneesmiddelenwet) and establishes the conditions under which the product can be allowed onto the Dutch market. Safety and quality are the key criteria. Once the MEB has given a positive assessment of the medicinal product, the manufacturer receives his registration. The medicinal product is then added to the Register of Medicinal Products and given a registrationnumber. The "Summary of Product Characteristics" or product information is part of the registration . This is the scientific text which contains all the key data about the product. Package leaflets are based on this text. Manufacturers submit a draft for these texts but the final version is drawn up by the MEB.

Applicants have the choice between two forms of marketing authorization for a medicinal product: a national marketing authorization and a European marketing authorization.

After registration or marketing authorization has been granted, any adverse events must be recorded. Pharmacovigilance is the process by which unwanted side-effects are detected, evaluated and wherever possible prevented. The MEB is responsible for pharmacovigilance with regard to registered/authorized medicinal products.

2.6 The Centralized procedure

Groups of medicinal products which are excluded from the simplified procedure, in which the aspect of "Traditional Use" is taken into account in the evaluation:

Assessment of medicinal products, also herbal medicinal products is still carried out in the different European Member States. However based on the following criteria, an authorization of a medicine is exclusively the responsibility of the EMEA, were in the so-called Centralized Procedure the safety and efficacy is evaluated on the purely scientific bases (= normal assessment procedure) in case of:

- medicinal products derived from biotechnology

- orphan medicines
- new (chemical) active substances (not known so far in the European Union) in particular with indications in the area of
- Acquired Immune Deficiency Syndrome (HIV)
- Cancer
- Diabetes
- Dementia (Alzheimers disease)
- Neuro-degenerative disorders (Multiple sclerosis, Parkinsons disease)

2.7 Herbal Medicinal Products Committee (HMPC)[16]:

The EMeA (European Medicines Agency) is located in London, and hosts different scientific committees, each of them is compiled of independent scientific experts in aspecific field, representing one Member State. In 2004 the Herbal Medicinal Products Committee (HMPC) was established, especially responsible for herbal medicines in the European Union. The HMPC is not dealing with direct assessment of herbal products to get a registration or marketing authorization , but their main task is establishing Community Monographs and List Entries for herbal substances. These monographs are a kind of mutual understanding between all members of the Committee (and thus a kind of agreement between Member States), under which conditions specific products, which comply with the monograph, would be accepted by national authorities. More than 50 monographs are already published on the website of the EMEA:

http://www.emea.europa.eu/htms/human/hmpc/hmpcmonographs.htm.

In the next years more and more monographs will appear, based on mutual assessment. Until now, these monographs are related to herbal substances of the European tradition. Extension to monographs which describe herbal substances used in Chinese or Indian tradition is currently under discussion in the European Union.

Recently, the European Commission issued an evaluation report in which this aspect is addressed. This Report offers a careful evaluation but pays attention also to traditional medicines used according to the Chinese tradition. It is acknowledged that many of these products are present on the market of the European Member States, and that inclusion of these products under the simplified registration procedure will bring more harmonisation in a sector where differences currently exist between different Member States. The European Commission is prepared to consider extending the simplified registration procedure to products other than herbal substances with a long tradition of safe use. But in the Report it is once more emphasized that European pharmaceutical legislation follows a product-specific approach and does not provide a framework for the regulation of several traditions of medical practice. The focus is on protection of public health and the quality, safety and efficacy of the products concerned will be evaluated also during the simplified registration procedure.

The HMPC can become important for applicants of-Traditional Chinese Medicines, especially for those products which have a very long medicinal use in China, but not yet 15 years on the European market. This special Herbal Committee procedure is the "referral-procedure" which means that the possibility exists for individual Member States to "refer" difficult cases in assessment in which no conclusion can be made, to a higher level, the Herbal Committee in London, in order to get their advisory opinion. Especially this Referral procedure can become of great importance in the future for manufacturers of Chinese herbal medicine, in cases where less than 15 years on the European Union market can not be justified.

The HMPC is also responsible for establishing a 'Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products'. The list is being gradually developed through entries of structured information relating to individual herbal substances or preparations. The List shall contain, for each herbal substance or preparation, the indication, the specified strength and the posology, the route of ad-

ministration and any other information necessary for the safe use of the herbal substance or preparation used as an ingredient of a traditional medicinal product. The Community list harmonises at EU level the above-mentioned information on substance(s) or preparation(s) that constitute traditional herbal medicinal products. The list covers substances and preparations that have been in medicinal use for a sufficiently long time, and therefore considered not to be harmful under normal conditions of use. The HMPC has published several documents which clarify in detail the structure of the List, as well as the documentation which has to be submitted for inclusion into the List of Herbal substances . To establish an inclusion into the List, for justifying the traditional use (period of medicinal use /within the European Community, bibliographical or expert evidence of medicinal use in specified indication and bibliographical review of safety data), information on the background of the specific type of tradition can be provided. When the long-standing medicinal use is found in the Traditional Chinese tradition, additonal documentation regarding TCM can find its place, and can be taken into account. An harmonized view on indicating the type of tradition on the registered medicinal product is on this moment under discussion.

When a draft entry for a given herbal substance or preparation has been produced by the Committee it is released for public consultation on this website, usually for a period of 3 months. The draft entry is then finalised by the Committee from a scientific point of view, before being submitted for approval by the European Commission. Following this approval, the final version of the Community list entry is published.

2.8 A way for Traditional Chinese herbal medicines in the European Union:

A herbal medicinal product in the European Union, is always a "finished medicinal product"; a medicine in an approved package, with a label which specifies the use of the medicine, how much has to be taken, at what time etc. The medicinal plant (or a part of that plant) is processed into an herbal preparation, and that herbal preparation is considered as the active substance. Taking into account the "globalization of TCM" it is self-evident that for all TCM herbal medicines herbal substances have to be declared not only with the Chinese name, but also with the scientific botanical name (according to the binomial system (genus, species, variety, author) with the plant part in Latin. Example: Curcuma longae L., rhizoma (JiangHuang). A link between the scientific name, and the traditional name in Chinese (both in Pinyin and in original Chinese character) can contribute to a safe use. In the case where more than one plant is used, all plant names should be mentioned, completed by the traditional formula name, if appropriate. Details on how to declare the herbal substance/preparations can be found in a specific guideline. in the guideline on the declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products.

TCM Modernization and the current simplified procedure in the European Union based on "traditional use" have its frontier. This simplified way of evaluation of a medicine is not designed for "innovations" of existing TCM herbal medicines. When evidence for a safe use is build on traditional sources, the herbal medicine itself must remain really traditional. New innovations in the manufacturing of Chinese herbal medicines should be in compliance with the existing regulatory and scientific framework which covers all pharmaceutical developments, including herbal medicinal products.

3. Conclusions and perspectives for TCM in the EU market

Traditional Chinese medicines, which have a long and consistent history of use in TCM and have been on the European market for some time should be submitted for evaluation under the simplified procedure based on traditional use, in order to acquire a registration as "traditional

herbal medicinal product" The regulatory procedure is applicable, and pays respect in different ways also to TCM. A more cooperative approach to make proper use of the system of Pharmacopoeia monographs, Community monographs, and of specific regulatory ways to improve harmonisation among Member States, can grant Chinese medicines a more recognized position on the European pharmaceutical market. This will improve the quality and the safety of use and will really contribute to TCM modernization.

References

1 Members of the European Union: Netherlands, Belgium, Luxembourg, France, Spain, Portugal, Ireland, United Kingdom, Italy, Malta, Greece, Cyprus, Germany, Danmark, Sweden, Finland, Poland, Austria, Hungary, Slovenia, Estonia, Letland, Lituania, Rumania en Bulgaria. Switserland is and European country not a member of the European Union. Croatia and Turkey are candidate-member. Norway and Iceland are members of the common economic area.

2 Herbal medicinal product: any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or ons or more such herbal subtances in combination with one of more such herbal preparations (Directive 2001/83/EC, article 1)

3 Herbal substances: all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to tbe herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system. (genus, species, variety and author) (Directive 2001/83/EC, article 1)

4 Herbal preparations: preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates. (Directive 2001/83/EC, article 1)

5 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol2_en.htm.

6 http://www.emea.europa.eu/htms/human/hmpc/hmpcguide.htm

7 EUROPEAN PHARMACOPOEIA, 6th edition, published in accordance with the Convention on the Elaboration of a European Pharmacopoeia (European Treaty Series no. 50), Council of Europe, Strasbourg, 2007.

8 Pharmacopoeia of the People's Republic of China, 8th edition, 2005. Chinese Pharmacopoeia Commission.

9 In the European Pharmacopoeia the term herbal drug is used instead of herbal substance.

10 TCM Working Group of the Pharmacopoeia Commission, European Directorate for the Quality of Medicines and Healthcare (EDQM), Strasbourg France.

11 Pharmeuropa - The European Pharmacopoeia forum published by the European Directorate for the Quality of Medicines & Healthcare (EDQM), Strasbourg France. http://www.edqm.eu

12 Guideline on the quality of herbal medicinal products / traditional herbal medicinal products.
Committee on Herbal Medicinal Products EMEA/CPMP/QWP/281900 rev.1, 2006
-Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products / traditional herbal medicinal products.
Committee on Herbal Medicinal Products EMEA/CPMP/QWP/2820/00 rev.1 2006
- Guideline on the quality of combination herbal medicinal products / traditional herbal medicinal products. Committee on Herbal Medicinal Products EMEA/HMPC/214869/2006.
-Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products.
Committee on Herbal Medicinal Products EMEA/HMPC/253629/2007.

13 Martena MJ, van der Wielen JC, van der Laak, LF, Konings EJ, de Groot, HN, Rietjens, IM.
Enforcement of the ban on aristolochic acids in Chinese traditional herbal preparations on the Dutch market. Anal Bioanl Chem 2007 Sep; 389 (1): 263~275.

14 http://www.emea.europa.eu/htms/human/hmpc/hmpcguide.htm, document reference: EMEA/HMPC/132154/06

15 http://www.emea.europa.eu/htms/human/hmpc/hmpclist.htm

16 In the Herbal Medicinal Products Committee all members of the European Union are represented: Netherlands, Belgium, Luxembourg, France, Spain, Portugal, Ireland, United Kingdom (England), Italy, Malta, Greece, Cyprus, Germany, Danmark, Sweden, Finland, Poland, Czech Republic, Slowakia, Hungary, Slovenia, Estland, Lituania, Letland, Romania, and Bulgaria. Croatia, Turkey and the republic of Macedonia have observers in the committee, and also Iceland and Norway are represented. the European Commission (from Brussels) and the European Pharmacopoeia Commission (from Strasbourg) are also present in the meetings.

17 Communication from the Commission to the Council and the European

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