

EUROPEAN HERBAL TRADITIONS AND MONOGRAPHS*

Wykład na temat europejskiej dyrektywy 2004/24/EC, zwalniającej producentów tradycyjnych leków roślinnych z obowiązku przeprowadzania prób klinicznych, za to nakładającej obowiązek opracowania ich monografii

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Traditional herbal medicinal products have been officially recognized in the European legislative framework for medicines since 2004, when the Directive on traditional herbal medicinal products (2004/24/EC) was set into force which became part of the general European legislation as laid down in Directive 2001/83/EC. The reasons of Directive 2004/24/EC explain that the long tradition of a medicinal product makes it possible to reduce the need for clinical trials, in so far as the efficacy of the medicinal product is plausible on the basis of long-standing use and experience. Thus, besides the option of a marketing authorisation (well-established medicinal use with recognised efficacy and an acceptable level of safety), herbal medicinal products can be registered with a documented traditional use.

By end of 2015, altogether 1577 registrations were granted by Member States of the European Union, most of them in the United Kingdom (344), Germany (263), Poland (197) and Austria (195). Out of a total of 768 marketing authorisations, most of them were granted in Germany (278), followed by Austria (51), Poland (24) and the Czech Republic (33) [1].

DOCUMENTS PREPARED BY THE HMPC

The Herbal Medicinal Products Committee (HMPC) was established as a permanent Committee at the EMA, London, in 2004. It consists of one delegate and one deputy member per EU Member State representing national health authorities as well as observers and maximum five co-opted 5 additional experts. Besides the preparation of guidance documents quality, efficacy and safety of herbal medicinal products and traditional herbal medicinal products, one of the main tasks of the Committee is the elaboration of European Union Herbal Monographs in the fields of the well-established medicinal use (marketing authorisation) and the traditional use (registration) of herbal medicinal products in accordance with Directive 2001/83/EC. These monographs are published on the EMA website and represent important and helpful tools for applications submitted to the national health authorities and for their assessment prior to approval.

The minimum requirements for the „well-established medicinal use” are laid down in a respective HMPC guideline:

* This article is based on the presentation held at 16. Sejmik Zielarski – Herbal Jubilee Symposium, Stęszew, 17-18 June 2016. ➤

► „In general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy. In the absence of a controlled clinical trial a case-by-case assessment taking into account possible benefits, risks and types of disease may be acceptable, if clinical experience with the herbal medicinal product is well documented and supportive, conclusive (human) pharmacological data of good quality are available. Evidence of grade C/level IV supported only by pre-clinical data are not sufficient to make the clinical efficacy of a product recognised” [2].

As a consequence, available clinical studies should lead to allocation of the respective preparations to the „well-established medicinal use”. However, in case these studies are not assessed as being „of good quality” (a criterium that might be open for individual interpretation), and as far as the traditional use can be proven, a „traditional” indication is granted for these preparations.

HMPC MONOGRAPHS AND TRADITIONAL USE

The following examples of recently published monographs or drafts [3] shall illustrate which indications have been adopted by the HMPC.

Draft monograph *Silybum marianum* (milk thistle, owoc ostropestu plamistego)

This document describes both areas of use with different indications, depending on the preparation. A „well-established medicinal use” is proposed for a dry extract (DER 36-44:1), (extraction solvent: ethyl acetate) standardised to contain 40-65% silymarin, calculated as silibinin with the indication „herbal medicinal product for supportive treatment of alcoholic liver disease”. Further extracts are proposed to be suitable for a traditional use „... for the symptomatic relief of digestive disorders with a sensation of fullness, bloating and flatulence”. As compared to existing preparations in the European market, the proposed wording covers only part of their indications. Apparently the HMPC came to the conclusion that the minimum criterium for the „well-established medicinal use” was not fulfilled, and that

the existing data do not justify indications other than the mentioned ones.

Monograph *Serenoa repens* (sabal – saw palmetto, owoc palmy sabal)

This monograph as well contains both areas of use, a „well-established medicinal use” for a soft extract (DER 7-11:1, extraction solvent: hexane) with the indication „herbal medicinal product for the symptomatic treatment of benign prostatic hyperplasia”; a „traditional use” for soft extracts (DER 7.5-14.3:1, extraction solvent: ethanol 90% to 96% m/m) with the indication „traditional herbal medicinal product for the relief of lower urinary tract symptoms related to benign prostatic hyperplasia, after serious conditions have been excluded by a doctor”. Also the posology is almost identical: „320 mg once daily or 160 mg 2 times daily” as compared to „320 mg once daily”. Although this might sound strange at a first glance, the assessment is apparently based on a pure formalistic argument with respect to the minimum criterium for the „well-established medicinal use”, and existing clinical data for the ethanolic extracts have obviously not been considered sufficient.

Monograph *Epilobium angustifolium, parviflorum* (willow herb, ziele wierzbowki kiprzycy)

The same traditional indication like for sabal fruit has been granted for a herbal tea from willow herb: „traditional herbal medicinal product for the relief of lower urinary tract symptoms related to benign prostatic hyperplasia after serious conditions have been excluded by a medical doctor”. Compared to the amount of clinical studies existing for the ethanolic extracts of sabal described above and the availability of only pharmacological data for willow herb, this example shows the broad variety of evidence on which the traditional use can be based following the assessment within European Union herbal monographs.

Monograph *Rhodiola rosea* (arctic root, kłącze różeńca)

For products from arctic root so far not registered as medicines, this monograph offers an interesting option. It describes a dry extract

(DER 1.5-5:1), extraction solvent ethanol 67-70% with the indication „Traditional herbal medicinal product for temporary relief of symptoms of stress, such as fatigue and sensation of weakness”.

Draft monograph *Sideritis* (ironwort, ziele gojnika)

Another new project is a monograph on a herbal tea originating from the Greek mountains. Two indications are proposed: „traditional herbal medicinal product used for the relief of cough associated with cold” and „traditional herbal medicinal product used for the relief of mild gastrointestinal discomfort”.

Draft revision *Harpagophyti radix* (devil's claw root, korzeń hakorośli)

This monograph which was open for comments of interested parties by mid of May 2016, proposes to maintain the indications from the existing monograph on the same herbal drug: „traditional herbal medicinal product for relief of minor articular pain” and „traditional herbal medicinal product used for the relief of mild digestive disorders such as bloating and flatulence and where there is loss of appetite”. Like during consultation on the original monograph, the herbal industry submitted comments on the assessment of the available clinical studies which, from the HMPC's point of view, were not regarded sufficient to justify a „well-established medicinal use” in the area of rheumatic complaints.

Draft monograph *Origanum majorana* (majoram, ziele majeranku)

Interestingly, for this herbal drug and its preparations (herbal tea and semi-solid preparations), respectively, the following traditional indications were proposed: „symptomatic relief of mild spasmodic gastro-intestinal complaints such as bloating and flatulence” and „relief of irritated skin around the nostrils”, the latter one representing a traditional dosage form „majoram butter” and being recommended expressively for children 1-11 years of age.

These examples demonstrate that traditional use as well as experience is represented in

HMPC monographs, in accordance with the assessment criteria laid down in the European legislation for medicinal products. In this context, a rather high indication level for traditional herbal medicinal products is considered important in order to provide a distinction from food supplements for which to a certain extent health claims can be accepted if proven by specific data.

THE EUROPEAN SCIENTIFIC COOPERATIVE ON PHYTOTHERAPY (ESCOP)

ESCOP was founded in 1989 as a scientific organization consisting of national societies on phytotherapy. Its main objective is to establish harmonized criteria for the assessment of efficacy and safety of herbal medicinal products and to contribute to the acceptance of phytotherapy on a European level. As an important tool for European harmonization, ESCOP started to elaborate monographs on the medicinal use of plants and their preparations which was a unique task and a pioneer work at that time, long before the HMPC was founded in 2004.

Scientific societies from the following countries are members of ESCOP:

- Austria
- Denmark
- Germany
- France
- Ireland
- Italy
- The Netherlands
- Poland
- Portugal
- Romania
- Switzerland
- Spain
- Turkey
- United Kingdom

Currently, the ESCOP Board of Directors consists of the following persons:

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The preparation of monographs is performed in the Scientific Committee which works in two parallel subcommittees. The project leaders are responsible for performing literature searches, assessing the references for their relevance and scientific value, summarizing the relevant results and elaborating the draft monograph which is then presented to one of the subcommittees. In some cases, external experts are involved. During the discussions, the views, knowledge and experience are incorporated not only of different nationalities, but also of individuals from different scientific and professional backgrounds, such as medical doctors, pharmacists, practising phytotherapists, pharmacognosists, pharmacologists and regulatory affairs specialists.

The following scientists are members of the ESCOP Scientific Committee:

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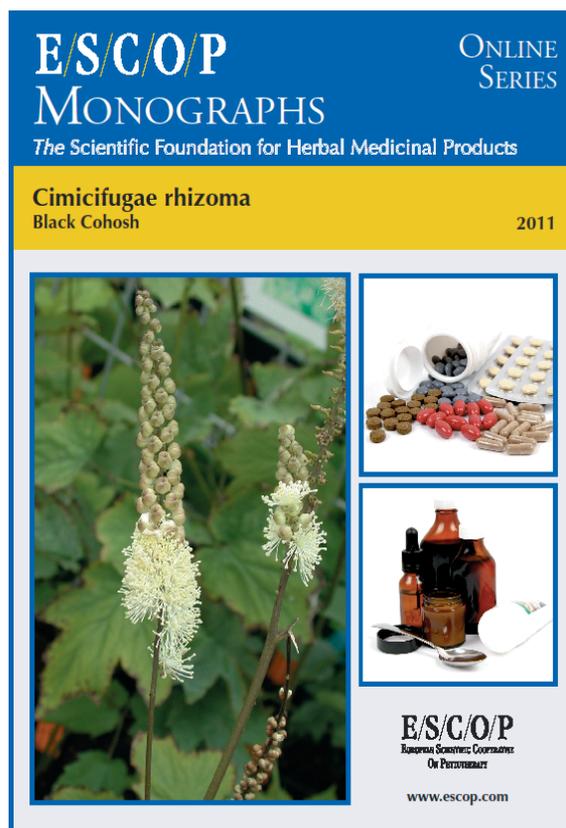


Fig. 1. Example for ESCOP online monographs

After finalisation of the discussion in the Scientific Committee, the drafts are circulated to an independent Board of Supervising Editors for appraisal. These academic experts in phytotherapy, pharmacology or medicinal plant research from all over Europe are invited to comment on and criticise each draft, and their comments are discussed and where appropriate incorporated into the final version.

Each monograph text represents an up-to-date review of scientific information on the therapeutic uses of herbal medicinal products, including indications, dosage, contra-indications, interactions and undesirable effects, together with detailed summaries of pharmacological, clinical and toxicological data, each statement being supported by literature references.

After publication of two books containing altogether 115 monographs (2003 and 2009), nowadays ESCOP monographs are published online and can be obtained through the ESCOP website [4]. They are freely available for members of the national societies of phytotherapy. The

first monograph published online has been the *Cimicifuga* monograph (see Fig. 1)

Moreover, an extract of most important information from ESCOP monographs can be obtained through the ESCOP Herb Reference Smartphone and Tablet App (see Fig. 2). These are currently available in English and in German, further languages will follow.

Currently, revision of existing monographs based on new literature data represents an important task of ESCOP. E.g., recently an extensive revision of *Hyperici herba* has been finalised, and further revision projects such as *Allii sativi bulbosus*, *Solidaginis herba*, *Agni casti fructus*, *Echinaceae purpureae/pallidae* root/herb and *Lini semen* are ongoing. New monographs are being established e.g. on *Equiseti herba* or *Rhodiolae roseae radix*. ESCOP is aware of the fact that the HMPC monographs that appeared approximately 15 years after ESCOP started its work, have the advantage of „official” monographs which are adopted by health authorities and which can serve as a basis for marketing authorization or registration procedures. ESCOP monographs can be regarded as a scientific publication which might in some cases come to conclusions different from an HMPC monograph. ESCOP's aims for the future consist in the further preparation and updating of monographs,

predominantly on medicinal plants with relevance in the European market, and with their focus on the medicinal use of these plants. Moreover, exchange with the views of the HMPC can take place by submission of comments on HMPC documents, e.g. monographs. With regard to building up a European network of scientists interested in the utilization of medicinal plants and the research in this field, an extension of the ESCOP website is planned which will also include detailed information from national societies. ■

References:

1. EMA. Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004/24/EC in EU Member States. Status: 31 December 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/05/WC500106706.pdf (checked 1 July 2016)
2. Guideline on the Assessment of Clinical Safety and Efficacy in the Preparation of Community Herbal Monographs for well-established and of Community Herbal Monographs / List Entries for Traditional Herbal Medicinal Products / Substances / Preparations (EMA/HMPC/104613/2005). 7 September 2006. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003644.pdf (checked 1 July 2016)
3. EMA. Herbal Medicines for Human Use. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp&mid=WC0b01ac058_001fa1d (checked 1 July 2016)
4. ESCOP. The European Scientific Cooperative on Phytotherapy. <http://escop.com/> (checked 1 July 2016)

ESCOP Herb Reference Smart Phone and Tablet Apps

ESCOP publishes an app for Apple and Android devices summarising over 100 ESCOP monograph conclusions on the uses, safety and quality standards of many European phytomedicines.

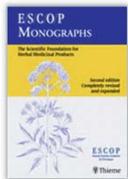
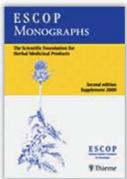
The app is currently available in English and German language and is **NOW** available for download from iTunes or Google Play stores. [Click here](#) for more information.







ESCOP Printed Publications

Hardback editions on the original ESCOP monograph (First and Second edition), published in collaboration with Thieme Verlag are classic references available to order. [read more](#)

Fig. 2. ESCOP's printed publications and Apps