

The ESCOP Monographs

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The European marketing authorization system

For achievement of a free movement of medicines within the common market of the European Union, besides a centralized system of marketing authorization and the option for an application on a national level only, a system of mutual recognition of marketing authorization decisions has been installed, the so-called "decentralized procedure". It provides as a general rule that the assessment by one national authority (Reference Member State - RMS) should be sufficient for subsequent registration in other Member States (Concerned Member States - CMS).

Within the decentralized procedure, the so-called "Summary of Product Characteristics (SPC)" approached by the first authority is one of the basic elements. It represents the main characteristics of the product e.g. active ingredient, indication, dosage, contra-indications, side-effects, shelf-life, etc. If differences in evaluation occur between national authorities, a decision will be reached by a specific arbitration procedure. In accordance with the new legislation, this decision is binding and may have - in case of a negative result - a negative "rebound effect" on the first registration in a Member State. That means that under this system the first registration might be lost unless the applicant does not withdraw his application for recognition of the dossier.

In fact, by September 1998, only three applications have been successful, namely two products containing Ispaghula husk (*Plantago ovata*), and one containing Valerian. The decentralized procedure however is not mandatory in case of different SPCs in Member States. In July 1998 it has been clarified by the European Commission that in case of non-identical SPCs also national marketing authorizations can be applied for when the product is intended to be brought into the market in more than one Member State.

The option of bibliographic applications

As herbal medicinal products have in most cases well-known active ingredients for which a lot of experience exists, performance of new clinical and pharmacological/toxicological studies does not seem necessary. In these cases an option for a so-called "bibliographic application" is provided by Article 4.8 (a) (ii) of Directive 65/65/EEC.

"The applicant is not required to provide the results of pharmacological and toxicological tests or clinical trials if he can

demonstrate by detailed references to published scientific literature that the constituent(s) of the medicinal product have a well-established medicinal use, with recognized efficacy and an acceptable level of safety."

National assessment criteria for herbal medicinal products

As from the regulatory point of view uniform criteria on a European level regarding the assessment of safety and efficacy do not exist at present, only a guideline on the quality of herbal medicinal products, harmonization of scientific assessment is regarded to be a precondition for adjustment of different marketing authorization decisions, particularly in case of products for which different national viewpoints, traditions and assessment criteria exist in different Member States of the European Union. E.g. in France, a system for assessment of herbal medicinal products has been established by the "Avis aux fabricants". This is a list of about 200 medicinal plants and their indication fields. If the product is in line with the requirements of this guideline, there is no need to submit a pharmacological-toxicological or a clinical dossier. In Germany, the system of "Commission E-monographs" has been established since the beginning of the eighties. These monographs which have officially been published by the health authority describe more than 300 medicinal plants together with their indications, dosage recommendations, risk information, etc. Registration is in principle possible if the product is in line with such a monograph. Further countries have developed further systems, or - in several cases - no specific system at all to utilize bibliographic data as a basis for an application for marketing authorization.

The foundation of ESCOP as scientific umbrella organization

ESCOP was founded in 1989 by six national scientific associations, and during the past years a large number of further associations have joined ESCOP. The main objectives of this European scientific umbrella organization are

- to establish harmonized criteria for the assessment of herbal medicinal products,
- to give support to scientific research and
- to contribute to the acceptance of phytotherapy on a European level.

In order to provide harmonized criteria for the assessment of herbal medicinal products, proposals for monographs on medicinal plants and their medicinal use have been prepared.

The following national associations are members of ESCOP:

Österreichische Gesellschaft für Phytotherapie	Austria
Société Belge de Phytothérapie	Belgium
Dansk Selskab for Fytoterapi	Denmark
Association Française pour le Médicament de Phytothérapie	France
Gesellschaft für Phytotherapie	Germany
Irish Phytotherapy Association	Ireland
Società Italiana di Fitochimica	Italy
Nederlandse Vereniging voor Fytotherapie	Netherlands
Norwegian Society for Phytotherapy	Norway
Associação Nacional de Fitoterapia	Portugal
Svenska Sällskapet för Fytoterapi	Sweden
Schweizerische Medizinische Gesellschaft für Phytotherapie	Switzerland
British Herbal Medicine Association	United Kingdom
American Botanical Council	USA

How ESCOP monographs are prepared

The ESCOP Scientific Committee consisting of representatives of all ESCOP member countries, works on monographs, structured like SPCs, for individual plant drugs, primarily those for which European or national pharmacopoeial monographs exist. To be in line with the requirements laid down in European guidelines, the format of the Summary of Product Characteristics (SPC) was adopted for subsequent documentation as part of an application for marketing authorization. The sequence of topics in the SPC, as set out in the respective guideline, is designed to highlight clinical aspects and pharmacological properties in order to represent a statement on efficacy and safety of a medicinal plant and its preparations.

The ESCOP Scientific Committee incorporates the views, knowledge and experience of different nationalities as well as of individuals from different scientific and professional backgrounds, such as medical doctors, pharmacists, practising phytotherapists, pharmacognosists, pharmacologists and regulatory affairs specialists.

The Committee, which operates as two subcommittees, assesses information from scientific literature, mainly of pharmacological and clinical properties of each medicinal plant. Leading researchers on specific plants are invited to meetings of the Committee for discussion and evaluation of the literature. In the next step, drafts prepared by the subcommittees are circulated to an independent Board of Supervising Editors for appraisal. These academic experts in phytotherapy and medicinal plant research are asked to comment on the drafts and, where appropriate, their comments are incorporated into the final version of the monograph.

Thus each ESCOP monograph takes into account the available scientific literature as well as national viewpoints and the advice of many authorities on the subject.

The following experts are members of the Board of Supervising Editors:

Prof. R. Anton, Strasbourg (F)
 Prof. G. Balansard, Marseille (F)
 Prof. Dr. H. van Dijk, de Bilt (NL)
 Prof. P. Delaveau, Paris (F)
 Prof. Dr. med. F.H. Kemper, Münster (D)
 Prof. Dr. Dr. D. Loew, Wiesbaden (D)

Dr. med. F. Oelze, Hamburg (D)
Prof. J.D. Phillipson, London (UK)
Prof. Dr. H. Schilcher, Munich (D)
Prof. Dr. O. Sticher, Zürich (CH)
Prof. A.J. Vlietinck, Antwerpen (B)
 Dr. J.H. Zwaving, Groningen (NL)

In terms of structure and content, ESCOP monographs consist of the following elements, according to the European guideline on the Summary of Products Characteristics:

Definition

Constituents
 Clinical particulars
 Therapeutic indication
 Posology and method of administration
 Contra-indications
 Special warnings and special precautions for use
 Interaction with other medicaments and other forms of interaction
 Pregnancy and lactation
 Effects on ability to drive and use machines
 Undesirable effects
 Overdose

Pharmacological properties

Pharmacodynamic properties
 In vitro experiments
 In vivo experiments
 Pharmacological studies in humans
 Clinical studies
 Pharmacokinetic properties
 Preclinical safety data
 References

50 monographs are already available

In October 1990, the first five monographs were presented at a symposium in Brussels and were officially handed over to representatives of the European Community. After a thorough assessment the Committee on Proprietary Medicinal Products (CPMP) adopted four monographs on anthraquinone laxatives in May 1994. Unfortunately, assessment of further monographs was not performed at that date. Although this was disappointing for ESCOP, it was decided to continue preparing harmonized SPC proposals in order to fulfil an obligation to the European Union of 50 monographs by end of December 1996.

ESCOP has published its finalized monographs as a loose-leaf binder which today contains 50 monographs and which will be amended soon.

Fascicule 1:

Althaeae radix	Marshmallow Root
Betulae folium	Birch Leaf
Boldo folium	Boldo
Calendulae flos	Calendula Flower
Foeniculi fructus	Fennel
Hyperici herba	St. John's Wort
Lini semen	Linseed
Orthosiphonis folium	Java Tea
Thymi herba	Thyme
Zingiberis rhizoma	Ginger

Fascicule 2:

Harpagophyti radix	Devil's Claw
Melissae folium	Melissae Leaf
Plantaginis ovatae semen	Ispaghula
Plantaginis ovatae testa	Ispaghula Husk
Salviae folium	Sage Leaf
Solidaginis virgaureae herba	Golden Rod
Tanacetum parthenii herba/folium	Feverfew
Taraxaci folium	Dandelion Leaf
Taraxaci radix	Dandelion Root
Urticae radix	Nettle Root

Fascicule 3:

Allii sativi bulbus	Garlic Bulb
Anisi fructus	Aniseed
Carvi fructus	Caraway
Juniperi fructus	Juniper Berries
Lichen islandicus	Iceland Moss
Menthae piperitae aetheroleum	Peppermint Oil
Menthae piperitae folium	Peppermint Leaf
Polygalae radix	Senega Root
Primulae radix	Primula Root
Rosmarini folium cum flore	Rosemary

Fascicule 4:

Absinthii herba	Wormwood
Arnicae flos	Arnica Flower
Gentianae radix	Gentian Root
Lupuli flos	Hop Strobiles
Meliloti herba	Melilotus
Passiflorae herba	Passiflora
Ribis nigri folium	Blackcurrant Leaf
Salicis cortex	Willow Bark
Urticae folium/herba	Nettle Leaf and Herb
Valerianae radix	Valerian Root

Fascicule 5:

Aloe capensis	Cape Aloe
Frangulae cortex	Frangula Bark
Hamamelidis folium	Hamamelis Leaf
Ononidis radix	Restharrow Root
Psyllii semen	Psyllium Seed
Rhamni purshiani cortex	Cascara
Sennae folium	Senna Leaf
Sennae fructus acutifoliae	Alexandrian Senna Pods
Sennae fructus angustifoliae	Tinnevelly Senna Pods
Uvae ursi folium	Bearberry Leaf

These monographs have the same content as an SPC, the same wording and the same order of information. The only difference is that the numbering system has been left out, and those items which are formalistic and refer only to the information on the finished product have also been deleted. The next publication will probably include the following monographs:

Centaurii herba
Crataegi folium cum flore
Echinaceae pallidae radix
Echinaceae purpureae herba
Echinaceae purpureae radix
Eucalypti aetheroleum
Hamamelidis cortex
Hippocastani semen
Matricariae flos
Myrrha
Rhei radix

Further monographs are in discussion:

Cardui mariae fructus
 Chelidonii herba
 Cinnamomi ceylanici cortex
 Cynarae folium
 Eleutherococci radix
 Foenugraeci semen
 Ginseng radix
 Hamamelidis aqua
 Liquiritiae radix
 Piperis methystici rhizoma
 Serenoae repentis fructus
 Vaccinium myrtillus

Perspectives for the utilization of ESCOP monographs in the European regulatory assessment

In 1997, the Ad Hoc-Working Group on Herbal Medicinal Products was founded by the European Agency for the Evaluation of Medicines - EMEA. It consists of representatives of health authorities and further experts from each European Member State, furthermore of the European Commission, the European Parliament and the European Pharmacopoeia Commission. Under the chairmanship of Dr. Konstantin Keller, Germany, the group had considered in its November 1997 meeting that drafting so-called "Core-SPCs" would be the most appropriate way to develop general guidance on criteria to assess efficacy data based on bibliographic documentation. General agreement already was reached during the discussion on a core-SPC for Valerianae radix based upon a proposal submitted by ESCOP.

Furthermore the Working Group has proposed an amendment to Notice to Applicants, Vol. 2A of May 1996, stating that scientific monographs on certain substances e.g. those drafted by ESCOP and WHO offer a valuable and updated overview on published scientific literature, which together may be used in support of the demonstration of the safety and efficacy of a medicinal product in a bibliographical application in accord-

ance with Article 4.8 (a) (ii) of Directive 65/65/EEC. These monographs were regarded to be helpful in avoiding duplication of work and in bringing about gradual harmonisation in the evaluation of herbal medicinal products. Therefore it was suggested that the Commission and Member States recommend that both applicants and competent authorities should make use of these monographs.

In the meeting of June 1998, the Ad hoc Working Group finally adopted the above mentioned guidelines after discussing comments from interested parties. They also discussed a document on herbal combination products and checked the ESCOP monographs on Plantaginis ovatae semen and Plantaginis ovatae testa. Furthermore they asked ESCOP to submit the literature documentation on various medicinal plants such as Sennae fructus/folium, Aloes, Frangulae cortex, Rhamni purshiani cortex, Gentianae radix, Harpagophyti radix, Anisi fructus, Lupuli flos, Passiflorae herba, Orthosiphonis folium, Solidaginis herba, and it is supposed that a discussion on these ESCOP monographs will take place in the next meeting of the group.

Future perspectives for the utilization of ESCOP monographs

ESCOP monographs represent an overview on the current scientific data on a medicinal plant, but they cannot replace neither an expert report nor a documentation. They can be used as a "harmonized" scientific background for an application, whereas the questionnaire, i.e. the requirements of the expert report, has to be answered item by item by the applicant. After general agreement to "Valerianae radix" in November 1997 and the call for literature references on further medicinal plants, there is reason to hope that the Ad Hoc-Working Group on Herbal Medicinal Products will perform a positive assessment of further drafts in the near future. From the scientific as well as from the regulatory point of view these developments are highly appreciated, and maybe further steps towards a European-wide rational assessment of herbal medicinal products can be achieved.

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