ESCOP MONOGRAPHS – A SCIENTIFIC BASIS FOR HERBAL MEDICINAL PRODUCTS IN EUROPE UNDER SPECIFIC ASPECTS OF THE REGULATORY SITUATION

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Abstract

Following Directives 65/65/EEC and 75/318/EEC pharmaceutical products require pre-marketing approval. Requirements for quality, safety and efficacy are given in Directives91/507/EEC and 75/319/EEC. A system of mutual recognition of marketing authorization, the "decentralized procedure" has started taking into account the "Summary of Product Characteristics(SPC) of the first member state authority.

For well-known active ingredients a "bibliographic procedure" can be applied.

Since 1990 ESCOP, the European Scientific Cooperative on Phytotherapy is establishing criteria for the assessment of medicinal herbal products by publishing 50 monographs including a Summary of Product Characteristics(SPC).In future there will be cooperation with the EMEA in London.

1. Introduction

The European Union has developed a comprehensive legislative network in order to facilitate the free movement of goods, capital, services and persons in the community. According to the Directives 65/65/EEC and 75/318/EEC, pharmaceutical products require pre-marketing approval before gaining access to the market. Requirements for the documentation of quality, safety, and efficacy, the dossier and the expert reports are laid down in Directive 91/507/EEC. Article 39 para 2 of Directive 75/319/EEC obliged the European Member States to check all products in the market within a deadline of 12 years whether they met the requirements of the European directives. Different countries have made different approaches to review herbal medicinal products in the market in order to fulfil the requirements of these European directives. In case of herbal medicinal products, different ways of assessment are thus existing as well as different traditions in different countries. As an example, the medicinal use of garlic (Allium sativum) may serve which is used for common colds in the United Kingdom and for prophylaxis of arteriosclerosis in Germany.

In France, a system for assessment of herbal medicinal products has been established, the so-called "Avis aux fabricants". This is a list of 174 medicinal plants together with their indication fields and permitted combinations. If the product is in line with the requirements of the Avis aux fabricants, 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. Unfortunately, with the 5th amendment of the German Drug Law in 1994, the

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legal basis for the preparation of these monographs was abolished so that no further preparation of monographs or updates are possible. The Commission E has received new tasks within the assessment of individual applications.

For achievement of a free movement of medicines within the common market of the European Union, besides a centralized system of marketing authorization e.g. for new chemical entities on one side and the possibility for an application on a national level only on the other side, 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 should be sufficient for subsequent registration in other Member States. Within this decentralized procedure, the so-called "Summary of Product Characteristics (SPC)" approached by the first authority must be taken into account. It represents the main characteristics of the product e.g. active ingredient, indication, dosage, contra-indications, side effects, shelf life, etc. The SPC is one of the basic elements of the application procedure.

In the optimum case, the approval granted the First Member State is adopted by the Concerned Member States. If differences in evaluation occur between national authorities, a decision will be made 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 decentralized system of application the first registration might be lost unless the applicant does not withdraw his application for recognition of the dossier. This situation is rather dangerous for herbal medicinal products because of different assessment criteria and different traditions. In fact, up to now (November 1997), only one application has been successful, namely a product containing Ispaghula husk (Plantago ovata) from a French company in 1996.

As herbal medicinal products have in most cases well-known active ingredients for which a lot of experience is existing in several countries, performance of new clinical and pharmacological/toxicological studies do 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 no 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." That means that in principle data from literature can be used to answer the questions on safety and efficacy in order to prepare the expert report and the dossier.

As however 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 for quality of herbal remedies, the harmonization of scientific assessment is regarded to be a precondition for adjustment of different marketing authorization decisions, particularly in the field of herbal medicinal products for which different national viewpoints and traditions are existing in different Member States of the European Union.

In order to provide scientifically based assistance for a harmonized assessment of herbal medicinal products, ESCOP, the European Scientific Cooperative on Phytotherapy, had been founded in 1989. The main objectives 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 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, whilst no decision was made in case of Matricariae flos and Valerianae radix. 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. To be in line with the requirements laid down in European guidelines, the drafts, which are planned to be submitted to the CPMP, have the format of a Summary of Product Characteristics (SPC). An SPC describing a medicinal plant and its preparations refers to a Pharmacopoeia monograph with respect to quality, and the most important constituents are listed that are possibly able to contribute to the claimed effect. The most important parts of an SPC are the therapeutic indications, the dosage and the pharmacological properties. The latter paragraph gives as many details as possible on pharmacodynamic properties, pharmacokinetic properties and preclinical safety data, each statement supported by references. The SPC text is followed by a detailed reference list including all the papers that have been used for the evaluation of safety and efficacy of the respective medicinal plant and its preparations.

ESCOP hopes that the Ad Hoc-Working Group on Herbal Medicinal Products that has recently been founded by the European Medicines Evaluation Agency - EMEA - in London will perform an assessment of further drafts in the near future, and ESCOP is optimistic that they will be accepted.

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.

Parallel to submission to European Authorities, 20 monographs had already been published as loose-leaf binder at the ESCOP Symposium in Cologne 15 March 1996. During the past months ESCOP has continued its work on the preparation of monographs, and a further bundle of 30 new monographs has been published in summer 1997, so that 50 published monographs all together are available, which can be ordered at the ESCOP Secretariat in Exeter, United Kingdom.

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
Tanaceti 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 Aloes
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