ESCAMP
European Scientific Cooperative on Anthroposophic Medicinal Products

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1. Summary of the ESCAMP project (2014-2016)

Background: There is a need for a permanent regulatory frame work for anthroposophic medicinal products (AMPs) in Europe as to guarantee the future availability of these products for doctors and patients. In anthroposophic medicine, AMPs are essential to promote the inherent human ability of self-healing. The existing regulatory requirements for conventional medicinal products are not appropriate for AMPs. Special registration procedures exist in some EU countries for homeopathic and herbal products. However, these procedures only apply to a proportion of AMPs and the particular properties of AMPs are only in part accounted for.
Objective: The overall aim of ESCAMP is to develop the scientific basis for a permanent regulatory framework for AMPs in Europe. This includes the following tasks: 1. Development of methods and standards for the scientific assessment of efficacy/effectiveness, safety and cost-effectiveness of AMPs, 2. Elaboration of appropriate categories and criteria for regulatory assessment of AMPs, which could be implemented in a draft law for registration of AMPs in Europe, 3. Implementation of the these methods and regulatory criteria in registration documents and product monographs.
Methods: For monograph development a systematic literature review was carried out, using different sources (pharmacopoeias and codex, monographs, databases, books) to collect and analyse data on the pharmaceutical quality, safety and effectiveness of AMPs. Conceptual publications on anthroposophic medicine and AMPs were written based on the existing literature. For the empirical publications, a systematic evaluation of the safety of AMPs was carried out in the EvaMed pharmacovigilance database and a descriptive analyses of the Vademecum was carried out regarding its future use for scientific purposes.

Results: ESCAMP has drafted four example AMP monographs on Apis ex animale, Chamomilla Radix, Citrus/Cydonia and Phosphorus, which are currently under internal review. Four conceptual publications were published or submitted to demonstrate that anthroposophic medicine is a scientific system and that it can promote self-management of patients. In two of these conceptual publications, the characteristics and evaluation of anthroposophic medicine as part of a whole medical system were described. In an empirical analysis of the EvaMed pharmacovigilance database using data from 44,662 patients, it was demonstrated that adverse drug reactions to AMP therapy in outpatients are rare and that anthroposophic medication therapy was a safe treatment. In addition, a description of the Vademecum was published describing how this essential series of mini-reviews on AMP use can be used for scientific purposes.
Conclusions: ESCAMP has structurally and successfully worked to build the scientific basis for a permanent regulatory framework for AMPs. Continuation of ESCAMPs activities is needed in order to further build the scientific evidence, necessary to guarantee the future availability of AMPs for doctors and patients.

2. Introduction

There is a need for a permanent regulatory framework for anthroposophic medicinal products (AMPs) in Europe in order to guarantee the availability of these products for doctors and patients. In anthroposophic medicine, AMPs are essential to promote the inherent human ability of self-healing. The existing regulatory requirements for conventional medicinal products are not appropriate for AMPs. Special registration procedures exist in some countries for homeopathic products and in the European Union for herbal products. However, these procedures only apply to a proportion of AMPs and the particular properties of AMPs are only in part accounted for. Suitable registration procedures especially for AMPs exist only in Germany and Switzerland, but not in other EU countries. Moreover, in the context of international harmonisation of drug regulation and the upcoming Transatlantic Trade Investment Partnership (TTIP) between the USA and Europe, even these special procedures in individual states may become affected and possibly jeopardized in the future.

The European Commission has acknowledged the existence of whole therapy systems, whose medicinal products have no adequate regulation, and it has proposed that the suitability of a separate legal framework for products of certain traditions such as Anthroposophic Medicine (AM) should be assessed. With this background and at the behest of the international AMP stakeholders, an independent working group, the European Scientific Cooperative for Anthroposophic Medicinal Products (ESCAMP, http://www.escamp.org/) was established.

ESCAMP aims to develop the scientific basis for a permanent regulatory framework for anthroposophic medicinal products (AMPs) in Europe. AMPs are widely used in some EU states and relatively unknown in other states. Lack of knowledge about AMPs, anti-CAM bias and a recent international campaign against homeopathy can affect political and regulatory acceptance of the overall aim of ESCAMP. To overcome these challenges and justify the new regulatory provision for AMPs, maximum scientific "backing" is needed. In addition, scientific developments have to be accounted for: The paradigm of "double-blind randomised controlled trial is the only valid evidence for drug effects" is still widespread and is not suitable for the AMP therapy system, but EU drug legislation acknowledges that for some products such as herbs, other evidence can be valid. This position might become undermined by the old paradigm in the future, but in the frontline scientific discussion there is also more questioning of the old paradigm and openness to other forms of evidence, more suited to AMPs, such as observational studies and well-documented case reports. In order to secure this "open flank", scientific backing is needed. Another scientific challenge is the development of stricter requirements for

quality assurance and transparency in the conduct, analysis and publication of scientific studies and systematic reviews thereof. The regulatory world has been slow in absorbing these developments but is catching up, and ESCAMP shall follow current up-to-date standards. Moreover, regulatory authorities have detailed requirements for documentation and of pharmaceutical quality, safety, and efficacy of each medicinal product in order to obtain a licence ('simplified registration' or 'full marketing authorisation') for marketing in the EU. These procedures, combined with the very large number of AMPs in use (more than 2,000 in Germany), together entail an enormous workload in order to fully implement a regulatory framework for AMPs. In order to make this job feasible, much technical work is and will be pre-structured, and specific simplified licensing procedures and modified marketing authorisation procedures suitable for AMPs will be proposed by ESCAMP.

3. Objectives

The overall aim of ESCAMP is to develop the scientific basis for a permanent regulatory framework for anthroposophic medicinal products (AMPs) in Europe. This includes the following tasks:

1. Development of methods and standards for the scientific assessment of efficacy/effectiveness, safety and cost-effectiveness of AMPs.
2. Elaboration of appropriate categories and criteria for regulatory assessment of AMPs, which could be implemented in a draft law for registration of AMPs in Europe.
3. Implementation of the these methods and regulatory criteria in registration documents and product monographs.

4. Deliverables ESCAMP project 2014-2016

In the period 2014-2016, the following ESCAMP deliverables were achieved:

1. To develop a proposed template for regulatory AMP monographs.
2. To draft exemplary AMP monographs.
3. To write conceptual publications on anthroposophic medicine and AMPs.
4. To write publications on empirical analyses of AMPs.
5. Completion of ESCAMPs AMP database.

5. Methods and Results

5.1 Template for regulatory AMP monographs

Monographs are condensed reviews of medicinal products that provide information on their pharmaceutical quality, safety and effectiveness. Monographs give guidance to regulators and healthcare professionals. Since existing monographs for AMPs are not adequate according to current standards, new AMP monographs need to be developed. As templates for the ESCAMP AMP monographs, the structure of corresponding herbal monographs of the European Medicines Agency (1) was used, with some modifications (see Table 1).

5.2 Exemplary AMP monographs

The various types of AMPs and AMP use that are used in clinical practice were categorized in 18 subgroups for which exemplary monographs would be desirable. The first four exemplary AMP monographs that have been developed are Apis ex animale, Chamomilla Radix, Citrus/Cydonia and Phosphorus (see Table 2). These four AMPs were chosen because they cover a majority of the 18 subgroups. A systematic literature search was carried out to collect data from several sources on the quality, safety and effectiveness of Apis ex animale, Chamomilla Radix, Citrus/Cydonia and Phosphorus. The following sources were considered:

Pharmacopoeias and codex: European Pharmacopoeia (Ph. Eur. (2]), The Swiss Pharmacopoeia (Pharm. Helv. (3,)), The German Pharmacopoeia (Deutsches Arzneibuch, DAB (5)),The German Homoeopathic Pharmacopoeia (Homöopathishes Arzneibuch, HAB (6)),The Homœopathic

Pharmacopœia of the United States (HPUS (7, 8)),The Anthroposophic Pharmaceutical Codex, 3rd Edition, of the International Association of Anthroposophic Pharmacists (APC-III (9)). Monographs: Herbal monographs of the World Health Organisation (10-14], Herbal monographs of the European Scientific Cooperative on Phytotherapy (ESCOP (15, 16]), Herbal monographs and their assessment reports of the Committee for Herbal Medicinal Products (HMPC) at the European Medicines Agency (1), AMP or substance monographs of the Commission C at the Federal Institute for Drugs and Medical Devices (BfArM) in Germany (17, 18). Literature databases: The literature database PubMed, Embase, CAMbase (19), Anthromedlit, Toxline (20) and Livertox (21). In addition, several books on anthroposophic use and related topics were searched for monograph development. Other sources included: Google Scholar, the Vademecum project on indications and clinical use of AMPs (22), the EvaMed study of use and safety of AMPs and other Medicinal Products (MPs) (23,24), the Health Technology Assessment (HTA) report on Anthroposophic Medicine (AM) by Kienle et al (25) with the subsequent update of the systematic review of clinical studies (26) and other existing systematic reviews of pre-clinical and clinical studies of one (Cardiodoron (27)) or several (e.g. (28)) AMPs or specific AMP groups (e.g. mistletoe products (29-33).

The safety of the four AMPs as described above were analysed by calculating the number of Adverse Drug Reactions (ADRs) from studies found in the literature search as well as systematic analyses of the EvaMed database (23)and AMOS study (34).The effectiveness of the four AMPs were assessed using the methodology as described by Kienle et al (35).

Drafs of the four monographs, Apis ex animale, Chamomilla Radix, Citrus/Cydonia and Phosphorus, are currently under internal review. After internal review, they will be discussed with experts in the field. ESCAMP aims to publish the final AMP monographs in scientific peer-reviewed journals or to make them available in other publicly available sources.

ESCAMPs work on the development of AMP monographs was presented at the Integrative Medicine & Health Congress in Berlin, 2017 (36).

Table 1. Template for regulatory AMP monographs.

Table of Contents	
1. Name of the AMP	
2. Qualitative and quantitative composition	
3. Pharmaceutical form	
4. Clinical particulars	4.1 Therapeutic indications 4.2 Posology and method of administration 4.3 Contraindications 4.4 Special warnings and precautions for use 4.5 Interactions with other medicinal products and other forms of interaction 4.6 Fertility, pregnancy and lactation 4.7 Effects on ability to drive and use machines 4.8 Undesirable effects 4.9 Overdose
5. Pharmacological / pharmaceutical properties	5.1 Pharmacodynamic properties 5.2 Pharmacokinetic properties 5.3 Preclinical safety data
6. Date of compilation / last revision	
7. References monograph template	

Table 2. Selection of candidates for exemplary monographs

Typology	**No.**	**Subgroup**	**First four exemplary AMP monographs under development**			
			Apis ex animale (dil. >D5)	Chamomilla Radix (substance)	Citrus/Cydonia (substance)	Phosphorus (dil. >D5)
Type of starting materials	1.	Mineral				X
	2.	Botanical		X	X	
	3.	Zoological	X			
Number of starting materials	4.	One	X	X		X
	5.	Several			X	
Concentration of active substances in finished product	6.	"Concentrated" / "high"		X	X	
	7.	Potentized / "low"	X			X
Dosage forms	8.	Oral		X		X
	9.	External				
	10.	Mucosal			X	
	11.	Parenteral	X	X	X	
Use without or with indications	12.	Major indication	X		X	
	13.	Minor indication		X	X	
	14.	No indication				X
Potential safety issue	15.	No	X	X	X	X
	16.	Yes				
Use in special patient groups	17.	Children	X	X	X	X
	18.	Elderly				

5.3 Conceptual publications

A number of descriptions and introductory texts on anthroposophic medicine already exist, particularly in the German language. The publications written by ESCAMP are aimed at politicians, scientists and governmental representatives without prior knowledge of anthroposophic medicine. The conceptual publications are based on the existing literature, with particular emphasis on conceptual compatibility with the Anthroposophic Pharmaceutical Codex [3]. The scientific manuscripts written by ESCAMP included an assessment of anthroposophic medicine as a scientific system. The starting point for this assessment was the pluralist conception of science in the 20th century. This was followed by a description of some common features of scientific systems (theory, empiricism, discourse, stability, development) and the investigation into whether these features apply to anthroposophic medicine and, as a consequence, whether anthroposophic medicine can be considered a scientific system of medicine.

The following conceptual manuscripts and publications have been achieved by ESCAMP during the last 3 years:

- Baars EW et al. Anthroposophic Medicinal Products: A narrative review of features, similarities and differences to conventional medicinal products, utilization, scientific and regulatory assessment. Status: *for submission*
- Baars EW, Kiene H, Kienle GS, Heusser P, Hamre HJ. An assessment of the scientific status of anthroposophic medi-cine, applying criteria from the philosophy of science. Status: *submitted 2017-12-02*
- Baars EW, Koster EB, Verhoef J. The contribution of anthroposophic medicine to self-management: an exploration of concepts, evidence and patient perspectives. *Complement Med Res. 2017;24(4):225-231*. (see Appendix 1).
- Baars EW, Hamre HJ. Whole Medical Systems versus the System of Conventional Biomedicine: A Critical, Narrative Review of Similarities, Differences, and Factors That Promote the Integration Process. *Evid Based Complement Alternat Med. 2017;2017:4904930.* (see Appendix 2).
- Kienle GS, Hamre HJ, Kiene H, Ostermann T, Anderle L, Naussner N, Schuster R. Methodological aspects of integrative and person- oriented health care evaluation. *Complement Med Res 2017;24(suppl 1):23–8.* (see Appendix 3).

5.4 Empirical analyses with publications

In this part of ESCAMPs evaluations, data on the pharmaceutical quality, efficacy/effectiveness and safety of the entirety of AMPs will be compiled. Relevant data include data on the system level (e. g. system evaluation studies such as AMOS (34)) as well as data on single products, such as clinical studies, reports of physicians' clinical experience, and pharmacovigilance data from the EvaMed database (23).

The following publications on empirical analyses have been achieved by ESCAMP during the last 3 years:

- Hamre HJ, Glockmann A, Heckenbach K, Matthes H. Use and safety of anthroposophic medicinal products: An analysis of 44,662 patients from the EvaMed Pharmacovigilance Network. *Drugs Real World Outcomes 2017 Dec;4(4):199-213.*(see Appendix 4).
- Hamre HJ. Scientific relevance of the Vademecum of Anthroposophic Medicines. *Der Merkurstab, 2018 (2), in press.*(see Appendix 5).

5.5 Completion and validation of ESCAMPs AMP database

The ESCAMP database of AMPs currently contains detailed information on the composition of all AMPs manufactured in Germany in the period 2000-2015 (46 items for each of ca 2,300 different AMPs). During the period 2014-2016, the database has been build, updated both in general, and also for use in conjunction with development of monographs and empirical analyses of AMPs. It was achieved that the ESCAMP database is now linked to two other very large databases: EvaMed: use & safety of AMPs including ca 42,000 patients and >300,000 AMP prescriptions; Vademecum: structured documentation of physicians' clinical experience with AMP therapy, involving 274 physicians from 19 different countries, and covering 627 different AMPs or AMP groups.

Conclusions

During the project years 2014-2016, ESCAMP has structurally and successfully worked to build the scientific basis for a future permanent regulatory framework for AMPs. First of all, ESCAMPs has shown that it is possible to develop AMP monographs that reflect the specific characteristics of anthroposophic medicine and adhere to contemporary scientific standards for quality, safety and effectiveness documentation. Secondly, through three published conceptual peer-reviewed papers, and one conceptual paper being under submission, ESCAMP has been able to demonstrate that anthroposophic medicine is a scientific system and that it can promote self-management of patients. In two of these conceptual publications the characteristics and evaluation of anthroposophic medicine as part of a whole medical system were described. In an empirical analysis of the EvaMed pharmacovigilance database using data from 44,662 patients, it was demonstrated that adverse drug reactions to AMP therapy in outpatients are rare and that anthroposophic medication therapy was a safe treatment. A description of the Vademecum was published describing how this essential series of mini-reviews on AMP use can be used for scientific purposes. Continuation of ESCAMPs activities is needed in order to further build the scientific basis, necessary to guarantee the future availability of AMPs for doctors and patients.

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