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European regulation of herbal medicinal products on the border area to the food sector

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ABSTRACT

This article summarizes the regulation of herbal medicinal products in the EU with emphasis on traditional herbal medicinal products (THMP) and provides an evaluation of the borderline between medicine and food. Differences in the regulation of THMP with influence on the harmonization are revealed. With regard to the borderline between medicine and food, THMP may not be medicinal products by function but by presentation. The thesis is established that depending on the presentation, the product can be medicine (THMP) as well as food. To avoid shifting into the food sector the regulatory system of THMP is evaluated with regard to its attractiveness to applicants. Recommendations to achieve a better harmonization of THMP in the EU and to increase the attractiveness of the simplified registration procedure are given.

Introduction

The medicinal use of plants and preparations thereof has been passed on for centuries and is still the most common form of traditional medication worldwide (Keller et al. 2003; WHO 2005). However, for many plant products there is a lack of sufficient scientific data regarding safety and efficacy as required for marketing authorization (MA) in Europe (COM(2002) 1 final 2002/0008 (COD) 2002). Since herbal medicinal products (HMP) should be available on the market, member states established individual levels of evidence needed for registration purposes (AESGP 1998). With Directive 2004/24/EC a simplified registration procedure for traditional herbal medicinal products (THMP) was finally established, allowing conclusions on safety and efficacy on the basis of their traditional use (TU) (Directive 2004/24/EC). In some member states herbal preparations have been regulated under food law, although they have pharmacological properties (AESGP 1998). Unfortunately, the tendency remains to position typical medicinal plants on the market as food products (e.g. EFSA 2010). This has resulted in concerns being raised due to the following reasons: Firstly, the food law is not regulated as strictly as the drug law which contains additional regulatory provisions for protection of the consumer's health. Secondly, it is necessary to disclose the factual therapeutic properties of medicinal plants in form of disease related indications and not in form of masked health-related claims.

History and background of the regulation of HMP

Also for HMP the first pharmaceutical directive applied demanding analytical, pharmaco-toxicological tests as well as clinical trials (Directive 65/65/EEC 1965). Bibliographic references have been deemed acceptable if the constituents have a well-established medicinal use (WEU) with a recognized efficacy and an acceptable level of safety (Directive 65/65/EEC 1965 as amended by Directive 87/21/EEC 1987). The European Court of Justice (ECJ) clearly specified that the references have to include data on the pharmaco-toxicological tests and clinical trials in accordance with each of the requirements laid down in Parts 2 and 3 of Annex to Directive 75/318/EEC (ECJ 1995). The legislature further defined criteria for WEU. This included the period for which a constituent has to be used (at least ten years in the EU), the quantitative aspects on the use of that constituent, the degree of scientific interest on its use and the coherence of scientific assessment (Directive 1999/83/EC 1999). Unfortunately, many plant products lack of sufficient scientific data and therefore a WEU cannot be demonstrated without additional product-specific tests. Such tests are time and cost intensive and entail disadvantages for animals and humans (COM(2002) 1 final 2002/0008 (COD) 2002).

Some member states enacted different procedures and provisions for regulation of such products leading to different requirements for MA. Besides the resulting hindrance on the free movement of goods, this also raised concerns on the consumer's health as the required level of quality, safety and efficacy was not always given (Directive 2004/24/EC 2004). This situation was further enforced by different national systems classifying the constituent as medicine, as food or as dual-use-substances (AESGP 1998).

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Table 1
Recommendations for regulation of HMP in Europe (AESGP 1998).

Strengthening the Ad hoc Working Group on HMP:
– To further develop and update guidelines for the particular needs of HMP.
– To verify monographs proposed by ESCOP, WHO in order to achieve generally accepted Summary of Product Characteristics (SPC) for widely used medicinal plants.
Clarifying Council Directive 75/318/EEC:
– To consider regulations of those HMP which are safe, of appropriate quality and whose indications are exclusively based on adequate proof of efficacy by documented TU.

In the late 80s the principles of the further regulation of HMP were formulated (European Parliament 1987; Capasso et al. 2003). The Note for Guidance on "*Quality of Herbal Remedies*" (3AQ22, May 1989) came into force but specific precepts for the evidence of safety and efficacy were still missing. In order to enforce the regulatory particularities of HMP, the Ad hoc Working Group on HMP was established by the European Agency EMEA, now EMA in 1997. Calling for further information on the current regulatory situation of HMP in the member states, the Association of the European Self-Medication Industry (AESGP) was mandated in 1998 to initiate a study and to provide recommendations for future regulations (European Council 1996; European Commission 1996; European Council 1995; AESGP 1998) (Table 1).

Directive 2004/24/EC regarding traditional herbal medicinal products (THMP)

This directive provides a simplified registration procedure for HMP fulfilling specific provisions (Table 2).

The proof of efficacy and safety is facilitated for THMP taken their history of use into consideration, which can be demonstrated with product-specific-documentation (e.g. monographs (ESCOP, WHO), expert reports), community monographs, list entries. Whereas clinical evidence is needed for MA, the simplified registration procedure refers to the plausibility of the pharmacological effect or the efficacy.

Community monographs and list entries serve as preferred references which contain details for the Summary of Product Characteristics (SPC). Community monographs are published by the Committee of Herbal Medicinal Products (HMPC) whereas list entries are published by the European Commission and have therefore a broader legal status. List entries are legally binding and competent authorities will not request additional data to assess the safety and TU of the product, but Community monographs must not be followed and further data can be requested. Different grades for harmonisation of THMP result due to differences in the status for registration and mutual recognition of product-specific documentation, community monographs and list entries as referenced in Directive 2004/24/EC (Table 3).

Table 2
Provisions for THMP acc. to Directive 2004/24/EC.

– Being a HMP (Art. 1).
– MA provisions cannot be fulfilled (rec. 4).
– Indications appropriate to THMP which, by virtue of their composition and purpose, are intended and designed for use without supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment.
– Exclusively for administration in accordance with a specified strength and posology.
– Oral, external and/or inhalation preparation.
– Period of TU of at least 30 years, including at least 15 years within the EU.
– Data on the TU of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience (Art. 16a (1)).

Table 3
Grades of harmonization.

Type of reference	Status for national registration	Mutual recognition (MRP/DCP)
Product-specific documentation	No further status defined	Not possible (registrations granted by other Member States shall to be taken merely into account Art. 16d (2))
Community monograph	Not legally binding. (Shall be taken into account Art. 16h (3))	Possible (Art. 16d (a), rec. 11)
List entry	Legally binding (Art. 16f (2))	Possible (Art. 16d (1), rec.11)

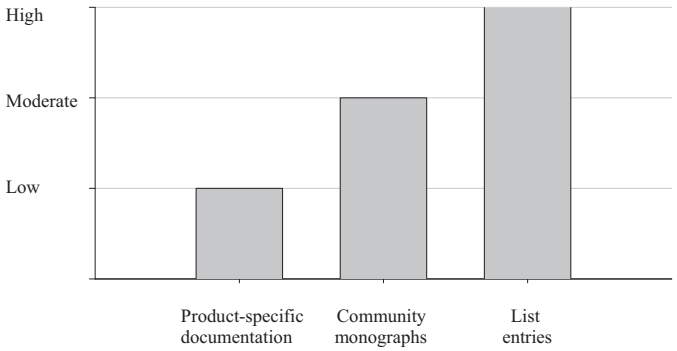

Fig. 1. Three-stage model.

A three-stage model, which is depicted in Fig. 1 results. The model shows three grades of harmonization (*y*-axis) for the different reference types (*x*-axis). It can be stated that the effectiveness of harmonization is low for product-specific documentation, moderate for community monographs and high for list entries.

Evaluation of the borderline between medicine and food

Directive 2004/24/EC established a regulatory framework for herbal products, which are medicinal products in terms of Art. 1 of Directive 2001/83/EC (Directive 2001/83/EC 2001 as amended). Classification is performed on basis of their presentation and/or function.

In legal meanings the function of a medicinal product is focused on the pharmacological effect, which is scientifically evaluated, in contrast to the (nutritional-) physiological effect of a food. For preparing Community monographs the HMPC has defined that at least one controlled clinical study or alternatively a well documented clinical experience with sufficient supportive (human-) pharmacological data is needed to substantiate efficacy for WEU (EMEA/HMPC/104613/2005). From a legal point of view, solely the plausibility of THMP may be insufficient to support a certain pharmacological effect as required by ECJ. Reliable scientific data are needed, i.e. not in vitro data or clinical studies not meeting current scientific criteria (BVerwG, 2007; OLG Cologne 2007; BVerwG, 2009). Based on these considerations, THMP may not be medicinal products by function, but by presentation. The thesis can be established that depending on the presentation, the product can be medicine (THMP) as well as food because of the ambivalent character of its constituents.

Table 4
Comparison of regulatory instruments for medicinal products and for food.

Parameter		Medicinal product	Food
Pre-market control	Proof of quality	Yes	No
	Proof of efficacy	Yes	Yes[a]
	Proof of safety	Yes	Different, depends on ingredients used[b]
Post-market control	Pharmacovigilance system	Yes	No

[a] Applies to: food with health-related claims acc. to Regulation 1924/2006 (2006).
[b] E.g. Pre-market safety assessment needed for herbals falling under the novel food Regulation No. 258/97 (1997).

Table 5
Evaluation of the simplified registration procedure in regard to its attractiveness.

Simplifications for THMP registration acc. to Directive 2004/24/EC	Product-specific documentation	Community monograph	List entry
Needed documentation for application (acc. to Art. 16c (1))	Full documentation needed	Full documentation needed	Reduced documentation needed (not evidence of the safety, TU – Art. 16c (1) (b) (c) (d))
Reasons for refusal (acc. to Article 16e (1))	Apply fully	Apply fully	Not relevant in regard to safety, TU
Possibility for using MRP/DCP (acc. to Art. 16d)	Not possible. (THMP registrations granted by other Member States shall be taken into account)	Possible	Possible

Plants and preparations thereof[1] are also available in the food sector for instance as food supplements, novel foods, dietary foods for special medical purposes or as functional foods. In the perception of the consumer such products become more and more drug-like because of marketing strategy by industry (Schweim & Schweim 2010). The products pose the risk of misleading consumers if they are assigned qualities that they do not have. The so-called Health-Claim-Regulation could help to avoid consumers being misled at least by claims made in commercial communications, whether in labelling, presentation or advertisement, because they have to pass an obligatory authorization procedure (Regulation 1924/2006 2006). Further instruments for consumer protection with regard to plants in food were provided recently by European guidance and regulation. The first includes criteria for safety assessments, the second foresees lists of constituents which are prohibited, restricted or under Community scrutiny (EFSA, 2009; Regulation 1925/2006 2006). Despite these recently implemented instruments, the food law is still not as stringently regulated as the drug law as detailed in Table 4.

On the one side the strict regulation of medicinal products result in a high level of consumer protection. On the other side, these contain major burdens for applicants often connected with high monetary costs. Shifting plants into the food sector means that they are no longer subject to the strict pre- and post-market control of the drug law.

Consequently the simplified registration procedure for THMP should be assessed with regard to its attractiveness for applicants as they consist of ambivalent substances due to the thesis established above. Simplifications are particularly attractive to applicants. For THMP these consist of the documentation needed for the application, any reasons for refusal and the possibility for using the MRP/DCP. Differences are noted for the already described types of references. The particular reasons for the attractiveness are evaluated for these three different reference types in Table 5.

It is noted that the attractiveness of the simplified registration procedure is different depending on the referenced source: low for product-specific documentation, moderate if a community monograph exists and high if a list entry can be referenced. Also a three-stage model results, as shown in Fig. 1.

Conclusion and recommendation/improvements for the future regulation of THMP

The three-stage model (Fig. 1) clearly points out the weakness of the regulatory system of THMP with regard to harmonization and attractiveness. The following is proposed to achieve a better harmonization of THMP in the EU and to increase the attractiveness of the simplified registration procedure:

- Community monographs should become better accepted by competent authorities.
- *Proposal*: the applicant has to submit product-specific testing only if there is a lack of safety information as noted in the Community monograph. Further community monographs should be revised solely with respect to findings in pharmacovigilance and product-specific testing.
- List entries should be created and adopted in a shorter period of time as they are the best instrument to achieve harmonization and to make the simplified registration procedure more attractive.
- Indications of community monographs and list entries should allow a clear separation from food. For THMP a clear disease-relationship should be established.

[1] According to the Guidance document of EFSA Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements plants are named as botanicals in the food sector (EFSA, 2009).

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