Journal of Ethnopharmacology 158 (2014) 471–486

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

The use of community herbal monographs to facilitate registrations and authorisations of herbal medicinal products in the European Union 2004–2012 ☆

Wieland Peschel *

HMPC Secretariat, European Medicines Agency, 7 Westferry Circus, Canary Wharf, London E14 4HB - United Kingdom

ARTICLE INFO

Article history:
Received 23 March 2014
Received in revised form
11 June 2014
Accepted 8 July 2014
Available online 17 July 2014

Keywords:
Directive 2004/24/EC
European herbal medicines regulation
Traditional use registration
Community herbal monographs

ABSTRACT

The provisions for the simplified registration of traditional herbal medicinal products in the European Union were introduced by Directive 2004/24/EC amending Directive 2001/83/EC (Chapter 2a) in 2004. Since implementation in the European member states until December 2012 a total of 1015 registrations (traditional use) and 514 authorisations (well-established use) have been granted for products containing substances/ preparations from about 200 different herbal drugs. The overall number of received applications with more than one third still under assessment suggests a further increase for the next years. This review summarises the main features of registered and authorised herbal medicinal products in the EU and evaluates available data against provisions of Directive 2004/24/EC and European standards established by the Committee on Herbal Medicinal Products at the European Medicines Agency. The supportive function of Community herbal monographs is described as regards availability and their use in national procedures, which is complemented by an analysis of specific future challenges from experiences made with the implementation of Directive 2004/24/EC so far.

1. Introduction

The provisions for the simplified registration of traditional herbal medicinal products (THMP) in the European Union (EU) can be found in Chapter 2a of Directive 2001/83/EC as amended by Directive 2004/24/EC in April 2004. Objectives are (I) to protect public health by guaranteeing public access to safe and high quality medicinal products containing herbal active ingredients, (II) to allow European citizens access to medicines of their choice, including herbal medicines of a long tradition when their medicinal use has not been substantiated by clinical efficacy data according to modern requirements for the development of innovative medicines for human use, and (III) to facilitate the movement of products on the European market[1]. Directive 2004/24/EC has two dimensions: the evaluation by national competent authorities (NCA) of applications submitted by companies to put products on the market in the EU member states (MS) and, at the European Medicines Agency (EMA), the establishment of advisory scientific opinions on the medicinal use of herbal substances/preparations as active substances in such products. End of 2007, early experiences with both dimensions in their complementary functions

Abbreviations: DCP, decentralised procedure; Eur. Com., European Commission; EDQM, European Directorate for Quality of Medicines; EFTA, The European Free Trade Association; EMA, European Medicines Agency; EU, European Union; HMP, herbal medicinal product(s); HMPC, Committee on Herbal Medicinal Products; ICH, International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use; IP, interested party(ies); MRP, mutual recognition procedure; MS, Member State(s) of the European Union; NCA, national competent authority(ies); Ph. Eur., European Pharmacopoeia; SmPC, summary of product characteristics; TCM, traditional Chinese medicine; THMP, traditional herbal medicinal product(s); TU, traditional use; TUR, traditional use registration (s); WEU, well-established use; WEU-MA, well-established use marketing authorisation(s)

☆ The views expressed in this article are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

* Tel.: +44 20 7523 7742; fax: +44 20 7523 7051.
E-mail address: wieland.peschel@ema.europa.eu

http://dx.doi.org/10.1016/j.jep.2014.07.015
0378-8741/

[1] Directive 2004/24/EC Preamble (3): 'A significant number of medicinal products, despite their long tradition, do not fulfil the requirements of a well-established medicinal use with recognised efficacy and an acceptable level of safety and are not eligible for a marketing authorisation. To maintain these products on the market, the Member States have enacted differing procedures and provisions. The differences that currently exist between the provisions laid down in the Member States may hinder trade in traditional medicinal products within the Community and lead to discrimination and distortion of competition between manufacturers of these products. They may also have an impact on the protection of public health since the necessary guarantees of quality, safety and efficacy are not always provided at present.'

have already been summarised[2] (COM (2008) 584 final). On 30 April 2011 ended a 7-year transition period for the MS to apply the provisions of the Directive to THMP already on their market. As a result of an 'Action plan for herbal medicines 2010–2011' by the management board of the EMA and the Heads of Agencies (HMA) regularly a status report on the implementation of the Directive in the MS is compiled and published at the EMA website. Here we refer to the survey carried out at the beginning of 2013 to report on the end of year 2012 situation in 27MS and two EFTA states (Norway and Iceland) (EMA/322570/2011 Rev. 3). NCA informed on the numbers of applications for traditional use registrations (TUR) received and the number of TUR granted for THMP. The survey included also data on marketing authorisations (MA) for herbal medicinal products (HMP) on the basis of 'well-established use' (WEU) provisions of Article 10a of Directive 2001/83/EC. NCA provided also the date of registration/authorisation, the active substance(s), the therapeutic indication(s). The summarised figures published on the EMA website in May 2013 (EMA/322570/2011 Rev. 3.) as well as information on the use of Community herbal monographs presented at the TradReg conference (Bonn, October 2013) form the basis of a more detailed analysis in this review.

An essential element for national TUR and WEU-MA (well-established use marketing authorisation) is the use of Community herbal monographs generated by the Committee on Herbal Medicinal Products (HMPC). Since a very first 'European' group of experts in the field was created in the 1980s in Brussels the establishment of the HMPC in 2004 at the EMA (replacing the previous CPMP Working Party on Herbal Medicinal Products) has been a substantial milestone for the European harmonisation process in accordance with Regulation (EC) No 726/2004 and Directive 2004/24/EC. The HMPC's activities aim at assisting the harmonisation of procedures and provisions concerning HMP and further integrating them in the European regulatory framework, whereby Community herbal monographs have a fundamental role. Therefore the status of TUR and WEU-MA for HMP in the MS is presented and evaluated against European standards to facilitate the implementation of Directive 2004/24/EC. Based on registration / authorisation numbers and main characteristics of licensed products on the EU market so far, the advisory supportive function of HMPC monographs is described as regards availability and their use in national procedures, which is complemented by an analysis of specific challenges already addressed in the aforementioned 2008 EUR. COM. communication (COM (2008) 584 final). This review uses many abbreviations from the regulatory terminology based on 'The Rules Governing Medicinal Products in the European Union'.

2. Registration and authorisation of HMP in the EU

2.1. Traditional herbal medicinal products registered in EU member states

2.1.1. Number of registrations

Following a slow uptake of the registration scheme after implementation of the Directive in EU member states mainly in 2005/2006, a major increase happened towards the end of the transition period in April 2011 (Fig. 1A). By 31 December 2012, a total of 1015 TUR were granted in the EU. Around one third of registrations were granted for combination products. UK, Poland, Germany, Austria showed the highest numbers followed by Spain, Sweden, the Czech Republic and Hungary, while 17 MS (including Norway) registered 1–19 products (Table 1). The overall number of received applications (2109, 813 still under assessment) suggests a further increase for the next years. Most applications have been received in Germany, UK, Poland, and France, while the only country without any application is Malta. Liechtenstein and Luxemburg accept registrations from specified other countries (Table 1).

A relatively high percentage of refused (overall 8%) and withdrawn (overall 6%) applications may be caused by the new requirements to previously non-regulated (e.g. exemption rules) or differently regulated products (e.g. based on the 'traditional use' concept or categories such as 'healing products'). The diverse refusal/withdrawal rate across MS may be caused by different practice with regard to offering scientific/regulatory advice and/or pre-submission meetings to applicants beside divergent starting points in regulating HMP. In MS without comparable previous regulation it may indicate that many smaller companies not yet familiar with pharmaceutical requirements submitted dossiers for the first time. In MS with comparable previous legislation companies may initially test the new system with old dossiers of existing products on the market and adapt to new European standards upon specific request only.

The overall figures include products' transfers into the new THMP scheme from old licensing schemes existing on a national level as well as old well-established use products reaching the licence renewal deadline. In most MS, deadlines had been set for applications 'for transfer' before the end of the transition period (usually until 2010). Data still have to be read cautiously when estimating the THMP market. In some MS products under old categories had persisted in parallel and are now gradually registered or authorised in line with the new legislation according to specific national implementation provisions.

2.1.2. Main features of registered traditional herbal medicinal products

Overall 132 different herbal substances (or herbal preparations thereof) as single active substance appeared in registered mono-component products. Most registrations were obtained for products containing Harpagophyti radix, Hyperici herba, Pelargonii radix and Valerianae radix (Table 2). The listing order does not necessarily reflect the substances with the most variety of products, as sometimes the same product of the same original manufacturer received different national registrations. Registrations so far are not limited to a few main substances, instead there is a huge variety even for mono products (26 substances with 2 registrations, 52 substances with only one registration). Given that a number of other herbal substances appear additionally in combination products, the total number of herbal substances in all registered products gets close to 200.

Combination products form an important part of registered THMP (342 out of 1015). Combinations containing 2–3 herbal substances/preparations dominate (Fig. 2). Products with more components are not unusual (51 registrations with 5–9 components, 11 registrations with >10), with a maximum of 27 components. In addition, 12 combination products have been registered that contain ancillary vitamins/minerals beside herbal substances/preparations according to Art. 16a(2) of Directive 2001/83/EC. Another characteristic feature of traditionally used products is the relatively high number of liquid dosage forms and herbal teas beside the typical solid dosage forms (Fig. 3).

The self-medication character for minor but repeating disorders is reflected by the five main therapeutic areas for which THMP are indicated: cough & cold, mental stress & mood disorders, gastrointestinal disorders, urinary tract & gynaecology disorders and sleep disorders & temporary insomnia (Fig. 4**A**). There are a number of products registered with indications for which the HMPC could so far not find consensus on their appropriateness for self-medication

[2] COM(2008) 584 final: 'Communication from the Commission to the Council and the European Parliament concerning the Report on the experience acquired as a result of the application of the provisions of Chapter 2a of Directive 2001/83/EC, as amended by Directive 2004/24/EC, on specific provisions applicable to traditional herbal medicinal products'