HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Traditional Herbal Medicinal Products Registration Scheme

AUT-G0029-~~3~~4
~~**20 JANUARY 2012**~~
17 October 2018

This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

CONTENTS

1 SCOPE

This guideline concerns the traditional herbal medicinal products registration scheme, under which applications may be made for the granting of a certificate of traditional-use registration ~~to~~for relevant herbal medicines. It aims to provide information and guidance on the documents and particulars required to make such an application.
Applications for herbal medicinal products may also be submitted under Article 8(3) or Article 10(a) of Directive 2001/83/EC; however, this guideline does not cover these procedures. More detailed information about these procedures can be found on the HPRA and European Medicines Agency (EMA) websites.

2 INTRODUCTION

The Directive on Traditional Herbal Medicinal Products (2004/24/EC) ~~as published in the Official Journal of the European Union (Ref: OJ L 136, 30.04.2004, p. 85) has now been~~was transposed into Irish law ~~by~~with the ~~Department~~implementation of ~~Health and Children. The~~the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007) ~~were implemented~~ on 23 July 2007 ~~by the Minister for Health and Children~~.

~~This~~The legislation is designed to provide an appropriate legal framework for placing traditional herbal medicinal products (THMPs) on the market within the European ~~Community~~Union. It introduces a simplified registration procedure ~~that gives traditional herbal medicinal products recognition and enhanced status~~for THMPs, while ensuring protection of public health. The Directive and its related regulations were introduced to ensure that consumers will have assurance that the THMPs they buy in their local health-food store, pharmacy or shop:

- ~~The~~are produced to an appropriate quality standard,
- are safe under the proposed conditions of use,
- can be expected to act in accordance with an established tradition of use and
- are appropriately labelled.

In 2007 the Department of Health and Children designated the HPRA as the competent authority for implementation of this legislation ~~and~~; on this basis, the HPRA has established the ~~Traditional Herbal Medicinal Products Registration Scheme~~traditional herbal medicinal products registration scheme. Under this registration scheme an applicant can apply for a certificate of traditional-use registration for their ~~traditional herbal medicinal product.~~THMP. A THMP registration ~~will be~~is called a traditional-use registration and ~~will be~~each registered THMP is allocated a TR number.

~~The following~~All THMPs currently on the market in Ireland should be registered with the HPRA and have a TR number.

A traditional herbal medicinal product, as defined in Article 16(a)(1) of Directive 2004/24/EC:
- must be intended and designed for use without the intervention of a medical professional for diagnosis, prescription or monitoring of treatment,
- must be taken orally, or be for external use or inhalation,
- must be administered exclusively at a specified strength and dose and
- must have been on the market for a 'period of traditional use'.

Some herbal medicines may contain vitamins or minerals. Where there is well-documented evidence of the safety of these vitamins or minerals, the product will still be eligible for registration, provided that the action of the vitamins or minerals is ancillary to that of the herbal active ingredients regarding the specified claimed indication(s).

This document provides guidance ~~is for applicants to~~on the format and content of applications made under the traditional herbal medicinal products registration scheme ~~on the format and content of applications~~. Applicants also should ensure that they are familiar with the relevant EU legislation and guidelines published for human medicines including:
- Directive 2001/83/EC, ~~as amended by 2004/24/EC and 2004/27/EC~~ available on the European Commission website.
- EUDRALEX Volume ~~2~~2B - Pharmaceutical Legislation~~:~~: Notice to Applicants available on the European Commission website.
- Scientific guidelines for human medicinal products and specific herbal guidelines published by the EMA and available on their website

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Appendix I provides definitions relating to THMPs.

3 FORMAT AND CONTENT OF THE DOSSIER

The format of the dossier is based on the Common Technical Document (CTD). The CTD is an internationally agreed structure and format for an application dossier and is the format currently used for marketing authorisation applications. General guidance on the compilation of dossiers in CTD format is given by the European Commission and the. The Committee on Herbal Medicinal Products (HMPC) at the EMA has also prepared guidance inon submitting an application for a traditional herbal medicinal productTHMP in this format. These documents should be consulted,are available on the European Commission website and on the EMA website:

- Notice to Applicants-Volume 2B, incorporating the Common Technical Document (CTD) (June 2006)).
- Committee on Herbal Medicinal Products (HMPC) -HMPC Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products EMEA/HMPC/71049/2007 - EMA/HMPC/71049/2007. Appendix 2 of this guideline contains a mock-up of the module 3 quality information to help the applicant with their submissions.

Details of documents and particulars to be submitted as part of an application for a traditional-use registration are given in Article 16c16(c) of Directive 2004/24/EC. Therefore, applications to the HPRA in accordance with this article and in CTD format will consist ofshould include, but not be limited to, the following:

- Module 1
  - Administrative data including EU Part IA (application) form (Module 1)
  - Summary of Product Characteristics (SPC) (Module 1)SmPC)
  - Product label and package leaflet (Module 1)
- Module 2
  - Summaries of the dossier and/or required expert reports (Module 2)
- Module 3
  - Quality data (Module 3)
- Module 4
  - Supporting Safety Data (Module 4)non-clinical safety data
- TraditionalModule 5
  - Supporting traditional-use data (Module 5)and clinical safety data

Further information about the requirements can be found in the HMPC guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products, EMA/HMPC/71049/2007, available on the EMA website.

It should be noted that information relating to clinical trials is not required for THMP applications.

4 APPLICATION FORM

An application form must be submitted electronically as part of Module 1 of the application dossier. The EU electronic application form for all medicinal product applications (Medicinal Products for Human Use Volume 2B Module 1.2: Administrative information Application form) is required to apply for a certificate of traditional-use registration ~~is the EU application form required for all medicinal product applications, available on~~. Please see the European Commission website~~:~~
~~Application Form : Module 1.2 Application form February 2007 – pdf document~~ (https://ec.europa.eu/health/documents/eudralex/vol-
~~Application Form : Module 1.~~2 ~~Application form February 2007 – word document~~ en) or the EMA website (http://esubmission.ema.europa.eu/eaf/index.html).

5 PRODUCT INFORMATION

A Summary of Product Characteristics (~~SPC~~SmPC) is required as part of the product information in Module 1 of the application. The ~~SPC~~SmPC includes the name of the product~~, strength~~, pharmaceutical form, quantity of active ingredients, posology, method of administration, indications, contraindications, excipients, shelf life and any special warnings and precautions for use, etc. According to Article ~~16c~~16(c) of Directive 2004/24/EC, section 5 of the ~~SPC~~SmPC, which relates to pharmacodynamic, pharmacokinetic and pre-clinical data, is not required for ~~traditional herbal medicinal products~~THMPs.

In addition to the Notice to Applicants ~~SPC~~SmPC guideline~~,~~ (European Commission Guideline on Summary of Product Characteristics (SmPC)), the ~~Committee on Herbal Medicinal Products~~HMPC has ~~published~~prepared guidance on the quantitative and qualitative declaration of the active substance in section 2 of the ~~SPC~~SmPC for herbal medicinal products, 'Guideline on Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products EMA/HMPC/CHMP/CVMP/287539/2005', available on the ~~European Commission~~EMA website.

~~- Guideline on Summary of Product Characteristic, Revision 1, October 2005~~
~~- Guideline on Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products/Traditional Herbal Medicinal Products in the SPC~~

A THMP must be intended and designed for use without the intervention of a medical professional for diagnosis, prescription or monitoring of treatment. Therefore the indication proposed within the SmPC must be suitable for self-diagnosis and must include the statement *'exclusively based upon long-standing use'.*

The proposed product labelling and package leaflet must be submitted as part of the product information in Module 1. The proposed label information and the user package leaflet should be in English and meet the requirements of Articles 54 to 65 of Directive 2001/83/EC~~, as amended~~. It will be necessary to submit a mock-up of the label and package leaflet for each product ~~and strength.~~. Article ~~56a~~56(a) of Directive 2001/83/EC ~~as amended~~, requires certain information on the packaging and package leaflet to be in Braille for the blind and partially sighted. Please see information on these requirements in the Guide to Labels and Leaflets of Human Medicines on the 'Publications and Forms' section of ~~www.hpra.ie.~~www.hpra.ie.

In addition to this, Article 16(g)(2) of Directive 2004/24/EC requires the labelling and user package leaflet of any relevant product to contain a statement to the effect that:
…~~this~~ the product is a traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use; and the user should consult a doctor or a qualified health care practitioner if the symptoms persist during the use of the medicinal product or if adverse effects not mentioned in the package leaflet occur.
As the term 'health care practitioner' is not used in the Irish healthcare system the term 'qualified healthcare professional e.g. a doctor or pharmacist' should be used instead.

The following guidance ~~should also be consulted,~~documents are available on the European Commission ~~website~~ and the EMA ~~website~~websites:

- ~~Guidance concerning the Braille requirements for labelling and the package leaflet (Article 56a of Directive 2001/83/EC amended by Directive 2001/27/EC~~
- Volume ~~3B~~2C Guidelines~~-~~, Medicinal Product for human use~~-~~, Safety, environment and information~~-~~, Excipients in the ~~label~~labelling and package leaflet of medicinal products for human use, ~~July 2003~~March 2018 (SANTE-2017-11668)
- ~~A~~Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use (SANTE-2017-11668)', EMA/CHMP/302620/2017
- Guideline on the readability of the label and package leaflet of medicinal products for human use (European Commission, ENTR/F/2/SF/jr (2009)D/869)

6 QUALITY

The quality aspect of a medicinal product is independent of traditional use and so the normal quality requirements applicable to all authorised medicinal products, also apply to ~~traditional herbal medicinal products for human use~~THMPs.

In addition to the EU quality guidance on medicinal products for human use, specific guidance on the quality requirements for herbal medicinal products is available on the EMA website. Applicants should be familiar with all the relevant available guidance ~~on quality~~ when considering the quality aspects of their product.

The quality data are submitted in Module 3 of the dossier. A pharmaceutical expert is required to provide a Quality Overall Summary in Module 2.3 of the application.

A declaration of compliance with the EMA's 'Guideline on good agricultural and collection practice (GACP) for starting materials of herbal origin' is required to provide assurance that an adequate quality assurance system exists for the collection and/or cultivation, harvesting and primary processing of herbal starting materials.

Compliance with Good Manufacturing Practice (GMP) is required and there is also a requirement to hold a manufacturer's authorisation or a wholesaler's authorisation where appropriate~~.~~ (see section 13 below). For further information on obtaining a manufacturer's or wholesaler's authorisation please see the 'Publications and Forms' section of www.hpra.ie.

7 SAFETY

A long tradition does not exclude the possibility that there may be concerns with regard to the product's safety. According to Article ~~16c 1(d~~16(c)(1d) of Directive 2004/24/EC, a bibliographic review of safety data, together with an expert report, must be submitted with

each application. This review must be up-to-date, comprehensive and objective. It is in the interest of the applicant to ensure the expert compiling these reports has appropriate qualifications and experience. The HPRA, where justified, may request more data in order to assess the safety of the product. The applicant is reminded that products, including their indications must be intended and designed for use without the intervention of a medical practitionerprofessional for diagnosis, prescription or monitoring of treatment.

The bibliographic review of safety, together with the expert report, is submitted in Module 2.4 (non-clinical) and Module 2.5 (clinical) of the dossier and the supporting safety literature is submitted in Module 4. (non-clinical) and Module 5 (clinical).

If applicants can demonstrate that their THMP complies with an EU list entry (see section 10), no further evidence of the safe use is required.

8 TRADITIONAL USE

A traditional herbal medicinal product, as defined in Article 16a 1 of Directive 2004/24/EC must be:

- intended and designed for use without the intervention of a medical practitioner for diagnosis, prescription or monitoring of treatment
- taken orally, for external use or inhalation
- administered exclusively at a specified strength and dose
- on the market for a 'period of traditional use'

To demonstrate 'traditional use', the applicant will need to prove that the traditional herbal medicinal productTHMP or a 'corresponding productproduct' has been in medicinal use for at least 30 years at the time of application. At least 15 years of this period must have been within the European CommunityUnion. The efficacy of the product must be *'plausible on the basis of long-standing use and experience.*'

In accordance with Directive 2004/24/EC, a corresponding product refers to a product that has the same active ingredient (irrespective of excipients used), the same indication(s) for use, contains the same equivalent strength and dose, and has the same or similar route of administration.

Applicants are required to produce bibliographic or expert evidence documenting the traditional use of the product for the proposed indication. While a final EU herbal monograph (see section 9) can be used in an application as reference material, additional traditional use data should be provided. There is a wide range of possible sources which, taken together if necessary, can be usedcombined to provide the required evidence. The following are examples of the types of bibliographical and/or expert evidence which may be used:

- Information from handbooks of medicine, pharmacy, pharmacology, pharmacognosy, phytotherapy, herbal medicine, etc.

- Official expert committee reports or monographs from learned societies, such as WHO, Commission E, ESCOP and national formularies/compendia, etc.
- A monograph in the Ph. Eur. or an official national pharmacopoeia will be accepted as a general proof of medicinal use during the years the monograph has been valid. It may also provide relevant information on strength/type of extract.
- Product-related documentation, such as post-marketing studies, product information leaflets, sales catalogues, sales statistics, etc.

The bibliographic or expert evidence of traditional-use overview should be submitted in Module 2.1 of the dossier and the supporting evidence of traditional use should be submitted in Module 5.

If applicants can demonstrate that their THMP complies with an EU list entry (see section 10), no further evidence of traditional use is required.

9 EUROPEAN ~~LIST~~UNION HERBAL MONOGRAPHS

~~In accordance with~~ The Committee on Herbal Medicinal Products (HMPC) is a European scientific committee established by the EMA under Directive 2004/24/EC~~, a list of traditional~~. The HMPC has responsibility for the development of European Union (EU) herbal ~~medicinal 'substances/~~monographs (formerly known as Community herbal monographs). Each EU herbal monograph contains the HMPC's scientific opinion on safety and efficacy data about a herbal substance and its preparations intended for medicinal use. The HMPC evaluates all available information, including clinical and non-clinical data. The HMPC also considers documented long-standing use and experience in the EU. Monographs are published together with other documents, including an assessment report. The assessment report contains reviews of all available data relevant for the medicinal use of the herbal substance or ~~combinations thereof' will~~preparations.

EU herbal monographs are based on the format of an SmPC under either Article 10(a) for 'well-established' medicinal products (i.e. full marketing authorisations) or Article 16(a)(1) for THMPs.

EU herbal monographs may be ~~established by the~~ used to support an application to the registration scheme and are taken into account by each Member State when assessing an application. However HMPC monographs are not legally binding and national opinions can differ.

Further information and EU herbal monographs published by the HMPC are available from the EMA website.

10 EUROPEAN UNION LIST ENTRIES

The HMPC is continually developing the European Union list through 'list entries'. Draft list entries are developed by the HMPC and can be found on the HMPC website. However the final list entries are adopted and published by the European Commission ~~on the basis of scientific advice provided by the Committee on Herbal Medicinal Products. This list will state the therapeutic~~. To view all final EU list entries adopted by the European Commission, refer to the European Commission's webpage on herbal medicinal products.

Each list entry contains the indication, the specified strength, ~~dose,~~the posology, the route of administration and any ~~relevant safety~~other information ~~relating to each~~necessary for the safe use of the herbal substance~~/preparation or combination~~ as a THMP.

In contrast to EU herbal monographs, EU list entries are legally binding for applicants and national competent authorities in the Member States. An applicant seeking to register a product containing a substance/preparation or combination ~~on the~~with a list entry (in the form and for the indications specified ~~on~~in the list entry) can refer to ~~this~~the list entry rather than have to demonstrate traditional use and safety. The applicant must, however, still demonstrate quality.

The absence of a list entry for a substance/preparation or combination ~~from the positive list~~ will not prevent a successful traditional-use registration, subject to full quality, safety and traditional-use requirements being met.

~~10 COMMUNITY HERBAL MONOGRAPHS~~

~~The Committee on Herbal Medicinal Products also has responsibility for the development of Community herbal monographs. These are documents based on the format of a summary of product characteristics under either Article 10a for 'well-established' medicinal products (i.e. full marketing authorisations) or Article 16a(1) for traditional herbal medicinal products. Community herbal monographs may be used to support an application to the registration scheme.~~

~~Herbal monographs and list entries published by the HMPC are available from the EMA website.~~

11 PHARMACOVIGILANCE REQUIREMENTS FOR TRADITIONAL HERBAL MEDICINAL PRODUCTS

For herbal medicinal products the pharmacovigilance requirements provided in Title IX of Directive 2001/83/EC apply. In accordance with Article ~~16g~~16(g) of Directive 2004/24/EC, the pharmacovigilance requirements described in Articles 101-108 of Directive 2001/83 EC ~~as amended,~~ also apply in respect of ~~traditional herbal medicinal products.~~

~~It is important to note that revised legislation providing for strengthened and increased harmonisation of pharmacovigilance obligations will come into force in July 2012. These revisions will introduce extensive changes to all aspects~~THMPs. However, holders of registrations for traditional herbal medicinal products referred to in Article 16(a) of Directive 2001/83/EC are not required to submit PSURs, except when one of the cases provided for in Article 107b(3)(a) or (b) of Directive 2001/83/EC is applicable i.e. the requirement to submit a PSUR is laid down as a condition in the marketing authorisation or has been requested by a competent authority in a Member State on the basis of concerns relating to pharmacovigilance ~~including routine activities, such as adverse reaction reporting arrangements and requirements for periodic safety update reports (PSUR), as well as for the evaluation of new and emerging safety concerns. For further information, please see : Directive 2010/84/EU and Regulation (EU) No. 1235/2010, available on the European Commission website~~data or due to the lack of PSURs relating to an active substance.

Detailed guidance on arrangements for and reporting requirements are described in Good Pharmacovigilance Practices (GVP), a set of measures drawn up to facilitate the performance of pharmacovigilance in the European Union (EU). GVP applies to marketing-authorisation holders, the European Medicines Agency and medicines regulatory authorities in EU Member States. Further information relating to GVP, including the modules themselves, are available from the European Medicines Agency website, www.ema.europa.eu.

12 COMPLIANCE WITH REGULATIONS AND POST-REGISTRATION OBLIGATIONS

12.1 Regulatory action

The HPRA will monitor and, where appropriate, take regulatory action against unregistered THMPs found in breach of the requirements.

12.2 Defects and recalls

Registration holders, manufacturers, importers and wholesalers are required to notify the HPRA of any defect in a product or batch which may lead to an abnormal restriction on the supply of the THMP or to its recall. All notifications should be sent to qualitydefects@hpra.ie. Further information is available on the HPRA website.

12.3 Variations and Renewals

When new EU herbal monographs are established (see section 9), the registration holder shall consider whether it is necessary to modify the registration dossier accordingly. The registration holder shall notify any such modification to the competent authority of the Member State concerned by way of a variation.

THMP registrations are typically valid for five years from the date of first issue. For the registration to remain valid, it should be renewed at the end of this five year period. Following this renewal, the registration remains valid for an indefinite period (unless further renewals are deemed necessary by the HPRA on safety grounds). Renewal applications should be submitted to the HPRA at least nine months before the expiry of the registration.

Registration holders shall inform the competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product for human use is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product for human use concerned. In order that the risk-benefit balance may be continuously assessed, the competent authority may at any time ask the registration holder to forward data demonstrating that the risk-benefit balance remains favourable.

Further information in relation to variations and renewals of medicinal products, including additional situations for which variations are required, can be found on the HPRA website. Registration holders must also comply with all the conditions attaching to the registration, including any special conditions as may be specified in the Schedule to the registration.

13 LEGAL REQUIREMENTS FOR MANUFACTURERS AND IMPORTERS OF THMPS

A manufacturer of THMPs, or any other medicinal product, is required to hold a Manufacturer's Authorisation in accordance with the Medicinal Products (Control of Manufacture) Regulations 2007 (S.I. No 539 of 2007).

Application details can be obtained by contacting compliance@hpra.ie or on the relevant section of the HPRA website.

Importation of THMPs, or any other medicinal product, from countries outside the EEA is also classified as manufacture and, accordingly, requires that a Manufacturer's Authorisation be held by the importer.

14 SUBMISSION DETAILS AND FEES

~~11.1~~ Application ~~Submission of periodic safety update reports~~

~~At present, once a medicinal product is authorised in the EU, even if it is not marketed, the marketing authorisation holder is required to submit PSURs. PSURs are normally required to be prepared and submitted if requested by a national Competent Authority, at 6-monthly intervals for the first two years following the medicinal product's authorisation in the EU, annually for the following 2 years, and thereafter at 3-yearly intervals.~~

~~There may, however, be exceptions where the cycle may be re-started, or an exemption to the requirement for 6-monthly and annual PSURs is granted.~~

~~Where an amendment is proposed, the applicant should submit, as part of the application for a marketing authorisation, a reasoned request for the amendment which, if granted, becomes part of the conditions of authorisation. If an amendment is applied for after authorisation, such an application should follow the procedures for a type II variation. Refer to Volume 9A of The Rules Governing Medicinal Products in the European Union for further details regarding the current requirements.~~

~~The revised pharmacovigilance legislation introduces a number of new provisions, including changes to the current requirements for PSURs. In accordance with the provisions of this legislation, (specifically, Article 107b (3) of Directive 2010/84/EU) it is intended to provide a general exemption for the requirement for PSUR submission for Traditional Herbal Medicinal Products, unless:~~

- ~~the authorisation provides for the submission of PSURs as a condition~~
- ~~PSURs are requested by a Competent Authority on the basis of the grounds defined in legislation.~~
- ~~The active substance is included on the list of Union Reference Dates (URDs) and the requirement for submission of a PSUR according to the harmonised frequency is indicated on the list in accordance with Competent Authority consultation.~~

~~Supplementary legislation and guidance is currently being developed to facilitate implementation of the new requirements and additional information regarding these developments will be highlighted at EU and national level, with public consultation related to good vigilance practice activities, expected early in 2012. The HPRA advises checking in regularly with the EMA website as well as our own to keep up to date on this evolving area, particularly in relation to the publication of the list of URDs.~~

~~Specific queries in relation to the pharmacovigilance requirements for traditional herbal medicinal products can be sent by e-mail to herbals@hpra.ie.~~dossiers should be submitted via CESP, the Common European Submission Platform.

Alternatively, application dossiers will also be accepted on USB or in CD format and can be posted to the address below:

Receipts and Validation Section
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
D02 XP77
Ireland

The competent authority of each EU Member State is responsible for national fees for THMP registrations. For current information about fees in Ireland, please see the relevant section of the HPRA website.

General queries in respect of application requirements can be submitted to herbalmedicines@hpra.ie.

APPENDIX I DEFINITIONS

Corresponding product:
A corresponding product is characterised by having the same active ingredients, irrespective of the excipients used, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration as the medicinal product applied for.

Herbal medicinal product:
Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

Herbal preparations:
Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

Herbal substances:
All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

Traditional herbal medicinal product:
A herbal medicinal product that fulfils the conditions laid down in Article 16(a)(1) of Directive 2004/24/EC.