HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Traditional Herbal Medicinal Products Registration Scheme

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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 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) was transposed into Irish law with the implementation of the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007) on 23 July 2007.

The legislation is designed to provide an appropriate legal framework for placing traditional herbal medicinal products (THMPs) on the market within the European Union. It introduces a simplified registration procedure 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 pharmacy, health-food store~~, pharmacy~~ or shop:

- 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; on this basis, the HPRA has established the traditional herbal medicinal products registration scheme. Under this registration scheme an applicant can apply for a certificate of traditional-use registration for ~~their THMP.~~a relevant product. A THMP registration is called a traditional-use registration and each registered THMP is allocated a TR number by the HPRA.

All THMPs currently on the market in Ireland should be registered with the HPRA and must 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~~supervision 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 as a THMP, 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 on the format and content of applications made under the ~~traditional herbal medicinal products~~THMP registration scheme. Applicants ~~also~~ should also ensure ~~that~~ they are familiar with the relevant EU legislation and guidelines published for human medicines including:

- Directive 2001/83/EC, available on the European Commission website.
- ~~EUDRALEX~~EudraLex Volume ~~2B -~~2 Pharmaceutical Legislation: Notice to Applicants Volume 2B presentation and content of the dossier, available on the European Commission website.
- Scientific guidelines for human medicinal products and specific ~~herbal~~ guidelines for herbal medicines published by the EMA and available on their website.

Appendix I of this guide provides definitions relating to THMPs.
Appendix II of this guide provides some useful references.

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. The Committee on Herbal Medicinal Products (HMPC) at the EMA has also prepared guidance on submitting an application for a THMP in this format. These documents are available on the European Commission website and on the EMA website:

- Notice to Applicants-Volume 2B, incorporating the Common Technical Document (CTD).
- 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. Appendix 2 of this guideline contains a mock-up of the module 3 quality information to help ~~the applicant~~applicants 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 16(c) of Directive 2004/24/EC. Therefore, applications to the HPRA in accordance with this article and in CTD format should include, but are not ~~be~~ limited to, the following:

- Module 1
  - Administrative data including EU Part IA (application) form
  - Summary of Product Characteristics (SmPC)
  - Product label and package leaflet

- Module 2
  - Summaries of the dossier and/or required expert reports
- Module 3
  - Quality data
- Module 4
  - Supporting ~~**non-clinical**~~nonclinical safety data
- Module 5
  - Supporting traditional-use data 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. ~~Please see~~This application form is available on the European Commission website ~~(https://ec.europa.eu/health/documents/eudralex/vol-2_en) or the EMA website (http://esubmission.ema.europa.eu/eaf/index.html).~~under 'Volume 2B Module 1.2 application form'.

5 PRODUCT INFORMATION

A Summary of Product Characteristics (SmPC) is required as part of the product information in Module 1 of the application. The SmPC includes the name of the product, 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~~In accordance with Article 16(c) of Directive 2004/24/EC, section 5 of the SmPC, which relates to pharmacodynamic, pharmacokinetic and pre-clinical data, is not required for THMPs.

In addition to the Notice to Applicants SmPC guideline (European Commission Guideline on Summary of Product Characteristics (SmPC)), the HMPC has prepared guidance on the quantitative and qualitative declaration of the active substance in section 2 of the SmPC for herbal medicinal products~~,~~. Refer to the 'Guideline on ~~Declaration~~declaration of ~~Herbal Substances~~herbal substances and ~~Herbal Preparations~~herbal preparations in ~~Herbal Medicinal~~

~~Products~~herbal medicinal products/traditional herbal medicinal products'
EMA/HMPC/CHMP/CVMP/287539/~~2005'~~2005, available on the EMA website.

In addition, in November 2022 the HMPC published specific guidance on the product information for a THMP, refer to CMDh/349/2016, Rev.1 (EMA/HMPC/770889/2014).

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~~Text versions of 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. ~~It will be necessary to submit a mock-up of the label and package leaflet for each product.~~ Article 56(a) of Directive 2001/83/EC~~,~~ requires certain information on the packaging and package leaflet to be in Braille for the blind and partially sighted. ~~Please see information~~Information on these requirements is included in the 'Guide to Labels and Leaflets of Human ~~Medicines on~~Medicines' in the '~~Publications and Forms'~~regulatory guidance documents' section of ~~www.hpra.ie~~the HPRA website. Prior to placing the THMP on the Irish market, it will be necessary to submit a mock-up of the label and package leaflet agreed during the registration procedure. This will require the submission of an Article 61(3) notification after the THMP licence has been granted.

~~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:
… 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~~phrase 'qualified healthcare professional, e.g. a doctor or pharmacist' should be used instead.

~~The~~ In addition to those already mentioned, the following guidance documents on the product information are available on the European Commission and ~~the~~ EMA websites:

- Volume 2C Guidelines, Medicinal Product for human use, Safety, environment and information, Excipients in the labelling and package leaflet of medicinal products for human use, March 2018 (SANTE-2017-11668)
- 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~~ ; use the most recent version
- Guideline on the readability of the ~~label~~labelling 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~~. The normal quality requirements applicable to all authorised medicinal products~~,~~ also apply to 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 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~~. 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~~section 13 of this guide and ~~Forms'~~the relevant section of ~~www.hpra.ie.~~the HPRA website.

7 SAFETY

A long tradition of use does not exclude the possibility that there may be concerns with regard to the product's safety. According to Article 16(c)(1d) of Directive 2004/24/EC, a bibliographic review of safety data, together with an expert report, must be submitted with ~~each~~the 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~~additional data ~~in order~~ to assess the safety of the product. The applicant is reminded that ~~products, including their~~the product and the proposed indications must be intended and designed for use without the intervention of a medical professional 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~~nonclinical) and Module 2.5 (clinical) of the dossier and the supporting safety literature is submitted in Module 4 (~~non-clinical~~nonclinical) and Module 5 (clinical).

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

8 TRADITIONAL USE

To demonstrate 'traditional use', the applicant will need to prove that the THMP or a 'corresponding product' 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 Union. 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 of this guide) 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 can be combined 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 the WHO, Commission E, ESCOP and national formularies/compendia, etc.
- A monograph in the Ph. Eur. or an official national pharmacopoeia. This monograph 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 the 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~~an applicant can demonstrate that ~~their~~the THMP complies with an EU list entry (see section 10 of this guide), no further evidence of traditional use is required.

9 EUROPEAN UNION HERBAL MONOGRAPHS

The Committee on Herbal Medicinal Products (HMPC) is a European scientific committee established by the EMA under Directive 2004/24/EC. The HMPC has responsibility for the

development of European Union (EU) herbal monographs (formerly known as Community herbal monographs). Each EU herbal monograph contains the HMPC's scientific opinion on the 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~~nonclinical data. The HMPC also considers documented long-standing use and experience of the herbal substance and its preparations in the EU. ~~Monographs~~These EU herbal monographs are published together with other documents, including an assessment report. The assessment report contains ~~reviews~~the review of all available data relevant for the medicinal use of the herbal substance ~~or~~and preparations.

EU herbal monographs are ~~based on~~written in the same format ~~of~~as an SmPC ~~under~~. They can be used as supporting documentation for either ~~Article 10(a) for~~ 'well-established' medicinal products submitted under Article 10(a) (i.e. full marketing authorisations) or THMPs submitted under Article 16(a)(1~~) for THMPs.~~).

EU herbal monographs ~~may be 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 the EU herbal monographs published by the HMPC are available ~~from~~on 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~~The final list entries are adopted and published by the European Commission~~. To view all final EU list entries adopted by the European~~ and are available on the Commission~~, refer to the European Commission's webpage on herbal medicinal products~~ website.

Each list entry contains the indication, the specified strength, the posology, the route of administration and any other information necessary for the safe use of the herbal substance 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 herbal substance~~/~~, a herbal preparation or combination with a list entry (~~in~~for the same dosage form and for the indications specified in the list entry) can refer to the list entry ~~rather than have~~and there is no requirement to demonstrate traditional use and safety. The applicant must, however, ~~still~~ demonstrate quality.

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

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 16(g) of Directive 2004/24/EC, the pharmacovigilance requirements described in Articles 101-108 of Directive 2001/83 EC also apply in respect of 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 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~~ is 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 by email 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 relating to the concerned medicinal product for human use 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.

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

14 SUBMISSION DETAILS AND FEES

Application 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.~~by email to info@hpra.ie.

~~APPENDIX I DEFINITIONS~~

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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~~that is the subject of the application.

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~~:~~ (herbal drug 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~~:~~ (herbal drugs):
All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed state, usually in 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.

APPENDIX II REFERENCES

The following references may be used when preparing an application for the THMP registration scheme. Links are not provided as they may change. However, the title of the document is unlikely to change and should be used in the search for the link.

- Directives:
  - Directive 2001/83/EC relating to medicinal products for human use.
  - Herbal Directive 2004/24/EC relating to traditional herbal medicinal products.

- HMPC guidelines relating to THMPs:
  - Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products, EMA/HMPC/71049/2007. Note that the Appendix 2 of this guideline contains a mock-up of the module 3 quality information to help applicants with submissions.
  - Addendum to the QRD template specific for THMPs: refer to CMDh/349/2016, Rev.1 (EMA/HMPC/770889/2014). This document is located on the Heads of Medicines Agencies (HMA) website under human medicines/CMDh/Templates/QRD.
  - Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products, EMA/HMPC/CHMP/CVMP/287539/2005 Rev.1
  - HMPC Guideline on Good agricultural and collection practice (GACP).

- HPRA useful references:
  - HPRA medicines authorisation: refer to the regulation section of the HPRA website: medicines for human use / MA holders / New applications / Herbal medicines

- General EMA/European Commission guidance documents:
  - Notice to Applicants (NTA):
    - Volume 2A Procedures for marketing authorisation Chapter 1 Marketing authorisation.
    - Volume 2B, Presentation and content of the dossier, incorporating the Common Technical Document (CTD) (May 2008).
  - EMA SmPC guidelines: How to prepare and review a summary of product characteristics.
  - EMA excipient guideline: Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'; use the most recent version.
  - European Commission guideline on readability.
  - EMA Product information QRD templates – Human.
  - European Commission herbal medicinal products.
  - European Union monographs and list entries.