



Regulatory Requirements for Registration of Herbal Medicinal Products in European Union and Australia

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ABSTRACT

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils, expressed juices and processed exudates of herbal materials. Increase in popularity of herbal medicines has brought concerns and fears over the professionalism of practitioners regarding to quality, efficacy and safety. As the side effects of herbal medicines are much less as compared to the allopathic drugs/medicines, the marketing of herbal medicinal products have gone beyond the expectations. The herbal preparations contain more than one constituents having distinct individual pharmacological/therapeutic effects hence it is necessary to check its safety and efficacy. Thus, study of regulatory requirements of herbal products is required so they do not adversely affect to the health of patients. Different countries have different regulatory requirements for herbal medicinal products. This article gives brief overview of herbal products and herbal preparation, Classification of herbal medicines, regulation of herbal medicines and types of documents required for the registration of herbal medicines in European Union and Australia. It mainly focuses on the preparation of documents required for registration of herbal dosages forms in European Union and Australia.

Keywords: Herbal preparations, The European Medicines Agency (EMA), Therapeutic Goods Administration (TGA), Pharmaceutical Regulatory Authority (PRA), common technical document, quality, safety, efficacy.

INTRODUCTION

Herbal Medicines

These include herbs, herbal materials, herbal preparations and finished herbal Products.

Herbs

Herbs include crude plant material such as leaves, flowers, fruit, seeds, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.¹

Herbal Materials

Herbal materials are either whole plants or parts of medicinal plants in the crude state. They include herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir baking with honey, alcoholic beverages or other materials.¹

Herbal Preparations

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils, expressed juices and processed exudates of herbal materials.

They are produced with the aid of extraction, distillation, expression, fractionation, purification, concentration, fermentation or other physical or biological processes. They also include preparations made by steeping or

heating herbal materials in alcoholic beverages and/or honey, or in other materials.¹

Finished Herbal Products or Herbal Medicinal Products

Medicinal products containing as active substances exclusively herbal drugs or herbal drug preparations. They may consist of herbal preparations made from one or more herbs. If more than one herb is used, the term **mixed herbal product** can also be used. They may contain excipients in addition to the active ingredients. In some countries herbal medicines may contain, by tradition, natural organic or inorganic active ingredients, which are not of plant origin (e.g. animal materials and mineral materials). Generally however, finished products or mixed products to which chemically defined active substances have been added, including synthetic compounds and/ or isolated constituents from herbal materials, are not considered to be herbal.

Classification of Herbal Medicines as per WHO Guidelines²

Category 1

Indigenous Herbal Medicines

This category of herbal medicines is historically used in a local community or region and is very well known through long usage by the local population in terms of its composition, treatment and dosage. Detailed information on this category of TM, which also includes folk medicines, may or may not be available. It can be used freely by the local community or in the local region.



Category 2***Herbal Medicines in Systems***

Medicines in this category have been used for a long time and are documented with their special theories and concepts, and accepted by the countries. For example, Ayurveda, Unani and Siddha would fall into this category of TM.

Category 3***Modified Herbal Medicines***

These are herbal medicines as described above in categories 1 and 2, except that they have been modified in some way—either shape, or form including dose, dosage form, mode of administration, herbal medicinal ingredients, methods of preparation and medical indications. They have to meet the national regulatory requirements of safety and efficacy of herbal medicines.

Category 4***Imported Products with a Herbal Medicine Base***

This category covers all imported herbal medicines including raw materials and products. Imported herbal medicines must be registered and marketed in the countries of origin. The safety and efficacy data have to be submitted to the national authority of the importing country and need to meet the requirements of safety and efficacy of regulation of herbal medicines in the recipient country.

Regulation in European Union³

The main regulatory body is the European Medicines Agency (EMA) but each Member State also has their own regulatory agency e.g. The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. To date, there is no separate regulation for the registration of TCMs.

Increasingly consumers have turned to plant-derived remedies in the belief that these 'natural' products are 'safer' than conventional medicines. The words "natural", "herbal" and "plant-derived" can be misleading and it is important for the public to be reminded that herbal remedies are medicines in their own right. Health Authorities have been concerned about the safety profile and quality of such medicines for a number of years now.³

Traditional Herbal Registration Scheme

In March 2004 the European Directive 2004/24/EC was adopted and so the term "traditional herbal medicinal product" (THMP) was established.

The word "traditional" is key: it is important to demonstrate that the herbal medicine or 'corresponding' (i.e. comparable) product(s) has been in traditional medicinal use for 30 years preceding the date of the application for the required medicinal indication. 15 years of this usage must have been within the European Union (EU). The latter is not absolutely essential and therefore,

if the 15 years of usage in the EU cannot be satisfied but the product(s) meets all the other requirements of the Directive, the Health Authority can refer the product(s) to the Committee on Herbal Medicinal Products (HMPC) who have the discretion to lower the requirement for 15 years' use (but there is no guarantee of this).

Registration Process in European Countries⁴

1. The applicant and registration holder shall be established in the Community.

2. For traditional-use registration, the applicant shall submit an application to the competent authority of the Member State concerned.

3. The application shall be accompanied by

(a) The particulars and documents

(i) The results of the pharmaceutical tests.

(ii) The summary of product characteristics.

(iii) In case of combinations, the information referred relating to the combination as such; if the individual active ingredients are not sufficiently known, the data shall also relate to the individual active ingredients.

(b) Any authorisation or registration obtained by the applicant in another Member State, or in a third country, to place the medicinal product on the market, and details of any decision to refuse to grant an authorisation or registration, whether in the Community or a third country, and the reasons for any such decision.⁴

(c) Bibliographical or expert evidence to the effect that the medicinal product in question or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community. At the request of the Member State where the application for traditional-use registration has been submitted, the Committee for Herbal Medicinal Products shall draw up an opinion on the adequacy of the evidence of the long-standing use of the product, or of the corresponding product.

The Member State shall submit relevant documentation supporting the referral;

(d) A bibliographic review of safety data together with an expert report, and where required by the competent authority, upon additional request, data necessary for assessing the safety of the medicinal product. Where the product has been used in the Community for less than 15 years, but is otherwise eligible for simplified registration, the Member State where the application for traditional-use registration has been submitted shall refer the product to the Committee for Herbal Medicinal Products. The Member State shall submit relevant documentation supporting the referral. The Committee shall consider whether the other criteria for a simplified registration are fully complied with. If the Committee considers it



possible, it shall establish a Community herbal monograph which shall be taken into account by the Member State when taking its final decision.

4. The competent authorities of the Member States shall notify the applicant, the Commission and any competent authority that requests it, of any decision they take to refuse traditional-use registration and the reasons for the refusal.

The list shall contain, with regard to each herbal substance, the indication, the specified strength and the posology, the route of administration and any other information necessary for the safe use of the herbal substance as a traditional medicinal product.

Regulation in Australia⁵

The Therapeutic Goods Administration (TGA) is the main regulator for Herbal Medicines product sponsors must register or list their products in the Australian Register of Therapeutic Goods (ARTG). The TGA maintains the ARTG, a database that includes details of all therapeutic goods that are imported into, supplied in, or exported from Australia. Once a product is successfully listed or registered, TGA will issue a certificate of listing/registering to sponsors who can then make the logistic arrangement for shipping these products.

TGA Regulatory Aspects of Complementary Medicines

Generally, the therapeutic goods whose supply is regulated by the TGA fall into three categories:

➤ **Registered Medicines**

Registered medicines are those assessed as having a higher level of risk. The degree of assessment and regulation they undergo is rigorous and detailed, with sponsors being required to provide comprehensive safety, quality and efficacy data. They include all prescription medicines, most ‘over the-counter’ medicines and a small number of complementary medicines.

➤ **Listed Medicines**

Listed medicines are considered to have a lower level of risk. They have established ingredients, usually with a long history of use, such as vitamin and mineral products or sunscreens. This category includes about 98% of complementary medicines.

Registration Process Flow Chart in Australia⁵

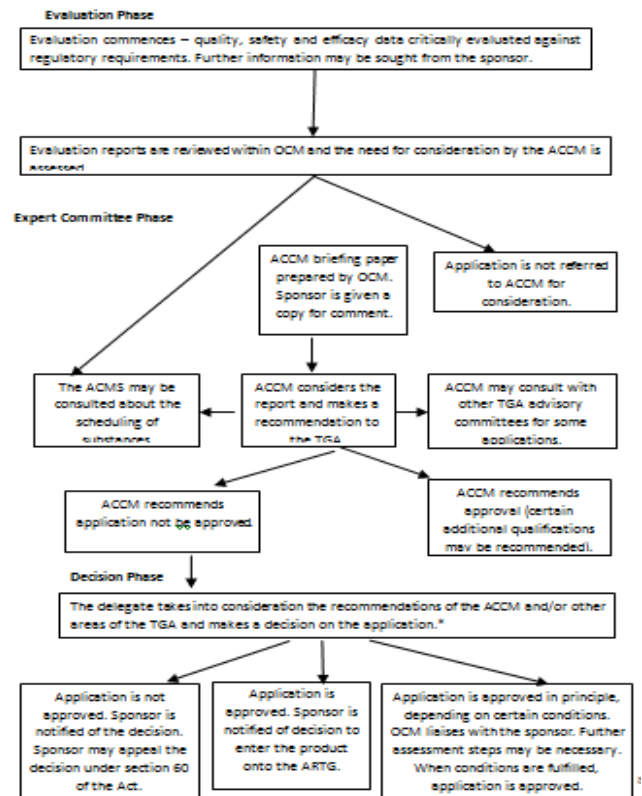
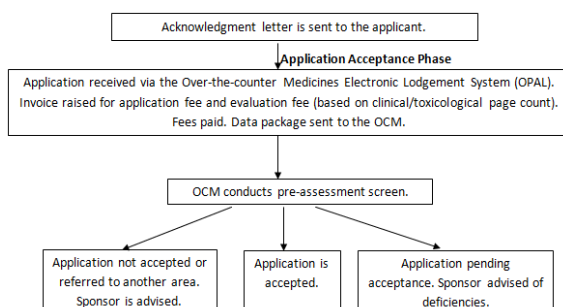


Figure 1: Flow chart for registration of Herbal Medicinal Products in Australia

The key responsibilities of the TGA are to:⁴

- Acknowledge receipt of the application;
- Check that fees are allocated correctly; and enter the application into the TGA tracking system

Applications for new Registered complementary medicines are lodged electronically using the online application system currently used for registered OTC medicines, the OTC Medicines Electronic Lodgement system (OPAL).

Pre-assessment of Registration Applications⁴

There are three possible outcomes of the pre-assessment process:

The TGA may **reject the application** if there are profound deficiencies, if no fees have been paid, if the medicine is not a complementary medicine or if the medicine is required to be in the part of the Register for Listed goods;

The TGA may grant **conditional acceptance** where additional fees or additional significant information is sought and the evaluation cannot proceed until the fees are paid or the information is supplied. This situation also applies where advice is being sought from the sponsor about whether or not they wish to amend the product indications to reflect the level of evidence available. When the additional fees are paid or the information is received, the application is referred back to the pre-assessment stage for a decision on whether it can then proceed to evaluation;



The TGA may **accept the application** where there are no obvious deficiencies, or only minor deficiencies that are not considered significant enough to prevent evaluation, and all fees are paid. The application then proceeds to the evaluation stage.

Evaluation

In the evaluation stage, the quality, safety and efficacy of the product are critically evaluated and an evaluation

report is produced. Details of how the TGA evaluates quality, safety and efficacy, and the related issues of labelling and product information, are found in later sections of these guidelines.⁵

Documents Required for Registration of Herbal Solid Dosages form in European Union and Australia⁵⁻⁷

In European Union and Australia Common Technical Documents (CTD) format used.

Table 1: Comparison of CTD format of EU and AUS

European Union (EU) ^{5,6}	Australia (AUS) ⁷
<p>Module 1: administrative information: It should contain documents specific to each region e.g. application forms or the proposed label for use in the region.</p> <p>1.1 Table of contents 1.1. Comprehensive Table of contents 1.2. Application form 1.3. Product Information 1.3.1. SPC, Labelling and package leaflet 1.3.2. Mock-up 1.3.3. Specimens 1.3.4. Consultation with Target Patients Groups 1.3.5. Product Information already approved in the Member States 1.3.6. Braille 1.4. Information about the experts 1.4.1. Quality Applicable (to be signed by the expert responsible for the information included in Module 2.3) 1.4.2. Non-Clinical Applicable (to be signed by the expert responsible for the information included in Module 2.4) 1.4.3. Clinical Applicable (to be signed by the expert responsible for the information included in Module 2.5) 1.5. Specific requirements for different types of applications</p>	<p>Administrative information (consistent with CTD Module 1) Application form Form submitted via the TGA's eBusiness services (eBS) portal Application covering letter Table of contents Identification of information that is commercially confidential Proposal for a new ingredient name Literature search Labelling and packaging Australian Product & Consumer Information Expert information Good manufacturing practice International regulatory status Pre-submission meetings Other information where available For example: patent certificates, summary of Biopharmaceutics studies or information relating to pharmacovigilance</p>
<p>Module 2: Common Technical Document Summaries</p> <p>2.1. CTD table of contents (Module 2-5) 2.2. Introduction 2.3. Quality Overall Summary 2.3. S. Quality Overall Summary Drug Substance 2.3. P. Quality Overall Summary Drug Product 2.3. A. Quality Overall Summary Appendixes 2.3. R. Quality Overall Summary Regional Information 2.4. Non-clinical overview 2.5. Clinical overview 2.6. Non-clinical written and tabulated summaries 2.7. Clinical Summaries</p>	<p>Overview and summaries of quality, safety and efficacy data for a new registered complementary medicine application (CTD module 2) Medicine details Name Proposed name of medicine Dosage Dosage form, range, frequency and duration of use and pack sizes Composition Route of administration Container type Proposed therapeutic use History of use Human exposure data, dietary, traditional and commercial use in Australia and internationally Expert summaries Summary of quality information Summary of safety information Summary of efficacy information Risk-benefit assessment</p>
<p>Module 3 Quality</p> <p>3.1. Table of contents of Module 3 3.2. Body of data 3.2. S. Drug substance (name, manufacturer) 3.2. S.1. General Information (name, manufacturer) 3.2. S.1.1. Nomenclature (name, manufacturer)</p>	<p>Quality information for a new registered complementary medicine application⁸ (CTD Module 3) Information on quality for each active ingredient of the medicine Nomenclature Using Australian approved name format</p>



Information on the nomenclature of the herbal substance should be provided
 Information on the nomenclature of the herbal preparation should be provided:
 3.2. S.1.2. Structure (name, manufacturer)
 The following information for herbal substance(s) and herbal preparation(s) where applicable, should be provided:

- Physical form
- Description of the constituents with known therapeutic activity or markers

3.2. S.1.3. General Properties (name, manufacturer)
 3.2. S.2. Manufacture (name, manufacturer)
 3.2. S.2.1. Manufacturer(s) (name, manufacturer)
 For herbal substances
 The name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved in production/collection and testing of the herbal substance should be provided, where appropriate.
 For herbal preparations
 The name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation should be provided, where appropriate.
 3.2. S.2.2. Description of Manufacturing Process and Process Controls (name, manufacturer)
 For herbal preparations
 3.2. S.2.3. Control of Materials (name, manufacturer)
 3.2. S.2.4. Controls of Critical Steps and Intermediates (name, manufacturer)
 3.2. S.2.5. Process Validation and/or Evaluation (name, manufacturer)
 3.2. S.2.6. Manufacturing Process Development (name, manufacturer)
 3.2. S.3. Characterization (name, manufacturer)
 3.2. S.3.1. Elucidation of Structure and other Characteristics (name, manufacturer)
 For herbal substances
 For herbal preparations.
 3.2. S.3.2. Impurities (name, manufacturer)
 For herbal substances
 For herbal preparations
 Residual solvents
 3.2. S.4. Control of Drug Substance (name, manufacturer)
 3.2. S.4.1. Specification (name, manufacturer)
 3.2. S.4.2. Analytical Procedures (name, manufacturer)
 3.2. S.4.3. Validation of Analytical Procedures (name, manufacturer)
 3.2. S.4.4. Batch Analyses (name, manufacturer)
 3.2. S.4.5. Justification of Specification (name, manufacturer)
 3.2. S.5. Reference Standards or Materials (name, manufacturer)
 3.2. S.6. Container Closure System (name, manufacturer)
 3.2. S.7. Stability (name, manufacturer)
 3.2. S.7.1. Stability Summary and Conclusions (name, manufacturer)
 3.2. S.7.2. Post-approval Stability Protocol and Stability Commitment (name, manufacturer)
 3.2. S.7.3. Stability Data (name, manufacturer)
 3.3. Literature References

Structural formula
 Structural formula of the ingredient and/or components e.g. herbal components

General properties
 Physicochemical and other relevant properties

Manufacturing details
 List of manufacturers
 Description of manufacturing process and process controls
 Control of materials
 Control of critical steps and intermediates
 Process validation and/or evaluation
 Manufacturing process development

Characterization
 Elucidation of structure and other characteristics of ingredient and/or components e.g. herbal components
 Impurities

Control of substances - specifications of raw materials^a
 Specifications providing set of tests and limits
 Analytical procedures and validation
 Batch certificate of analysis
 Justification of specifications

Reference standard
 Reference standards or materials

Stability of active ingredients
 Stability summary and conclusions
 Stability data

Information on quality for the medicine (finished product)

Description and composition
 Name, Dosage form, including any special characteristics, for example: modified release

Medicine development
 Formulation of the medicine - table of the active and Excipient ingredients and their purpose in the formulation
 Formulation development including a discussion of the studies that led to the proposed dosage form, formulation, method of manufacture and container
 Overages and batch to batch variation
 Physicochemical and biological properties
 Manufacturing process development
 Container closure system
 Microbiological attributes
 Compatibility

Manufacture of the medicine
 Manufacturer information
 Batch formula
 Description of manufacturing process and process controls
 Control of critical steps and intermediates
 Process validation and/or evaluation

Control of Excipient/s
 Specifications
 Analytical procedures
 Validation of analytical procedures
 Justification of specifications
 Excipients of human or animal origin
 Novel Excipients

Control of finished product
 Specifications
 Analytical procedures



	Validation of analytical procedures Batch analysis Characterization of impurities and requirements for non-pharmacopoeial products Justification of specifications Reference standards or materials Container closure system Finished product stability Stability summary and conclusion Stability data
CTD Module 4: Safety studies reports 4.1. Module 4 Table of Contents 4.2. Study Reports 4.3. Literature References	Nonclinical data (CTD Module 4) Pharmacology study Pharmacokinetics study Toxicology study
Module 5: Clinical study reports 5.1. Module 5 Table of Contents 5.2. Tabular Listing of All Clinical Studies 5.3. Clinical Study Reports 5.4. Literature References	Clinical data (CTD Module 5) Pharmacology studies Efficacy studies Safety studies

Comparison of Regulation of Herbal Products in EU and Australia

Table 2: Comparison of herbal products in EU and Australia

Contents	EU	Australia
Regulatory Agency	National agencies in each country (European Medicines Agency provides scientific opinion to assist national agencies in their decision making process)	Office of Complementary Medicines (OCM), Therapeutic Goods Administration (TGA)
Major legislation or guidance documents	European Union Directive 2004/24/EC	Australian regulatory guidelines for complementary medicines (ARGCM)
Category where herbal products can be registered	Traditional Herbal Medicinal Products, Prescription or OTC Drugs	Complementary Medicine
Pharmacopoeia	European Pharmacopoeia	British Pharmacopoeia
Mutual recognition	Yes (for EU Member States only)	Not stated
Uniqueness	30/15 years of traditional use; Benefit-risk Methodology. In this after giving of evidences of traditional use no further study required.	Level of evidence in supporting efficacy and safety; Early market access for low-risk complementary medicines through Listed medicine system (2 tier-system)
Period of marketing	7 years	5 years

CONCLUSION

Herbal medicine is the use of herbs and medicinal plants which provide a better quality of life.

Herbs are just as effective as drugs, but without the side effects. They create a more potent, effective and efficient treatment to ensure quicker therapeutic response.

They contain more than one constituent which have different pharmacological effects and so it is necessary to check its quality and safety. Hence study of the regulatory requirements of herbal medicinal products is essential to get quicker marketing approval.

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