The Registration of Herbal Medicinal Products

Part 1:

Traditional herbal medicinal products versus herbals with well-established medicinal use

Introduction

Although within the European Union, herbal medicines are considered as alternative medicines or are used in adjunct therapies; their use is considered as an important component of the European health care system. This is due to the fact that herbal medicine forms part of the European tradition. In spite of the diversity of opinions between Member States, herbal medicines used in different therapies should be made available to all European citizens. However, although the efficacy of certain medicines is rather disputable, the European Commission aims at safeguarding the European consumer by ensuring that these medicines are safe and of an adequate quality.

Is the product a medicine?

A medicine is defined as

(a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

If the effect occurs on a physiological basis, the product may fall under the Food Supplements Directive (CD 2002/46/EC) or the Cosmetics Directive (CD 76/768/EC). Following these criteria, products that are ingested are usually considered as food supplements, while topical applications are usually considered as cosmetics. Foods and cosmetics in Malta are regulated by the Malta Standards Authority.

If the product specifically treats or controls a medical condition or set of conditions, then the product is a medicinal product. Products that prevent diseases have been in great dispute and therefore such products, which may be classified as either medicinal products and/or food supplements, are usually subjected to a case by case assessment. These products are also called Borderline products, until they are classified as medicinal or non-medicinal products.

Is the applicant a registered importer or distributor?

Once the product is classified and authorised as a medicine, then the company placing the product on the market must be a wholesale dealer or importer. If the product is being brought into Malta from the EU/EEU it is considered as wholesale dealing but if it is being brought directly from a third country this is considered importation. Before being placed on the market, the product has to undergo batch release in

any EU/EEA country.

What types of medicines do exist?

There are different types of medicines, primarily depending on their nature and purpose of use. If the product is derived from one or more herbal substances, then the product may be considered as a herbal medicinal product. If this product is a synthetic chemical entity, a highly purified extract or single constituent from a natural source (plant, animal or mineral origin), the product should satisfy the criteria laid under Council Directive 2001/83/EC to be granted a marketing authorisation. Another category of herbal medicines that fall under Directive 2001/83/EC are homeopathic medicinal products, which however have to be presented as diluted (potentised) medicines.

Chemical entities[1] (modern medicines) are regulated under Council Directive 2001/83/EC and all following amendments. In the manufacture and marketing authorisation of herbal medicines, European manufacturers and wholesale distributors, faced several difficulties to fulfill the criteria laid in this Council Directive in order to market their products. Due to a long standing history of use, the requirement that a medicinal product should satisfy the proof of clinical efficacy could not be fulfilled with herbal medicines. This places herbal medicines in a different category from chemical entities. In fact, a parliament legislative resolution was issued in November 2002 as a proposal to amend Directive 2001/83/EC to take into consideration this important aspect which otherwise will put the herbal industry at a halt. There was the need to consider herbal medicines as a group of medicinal products of their own, which should satisfy the safety and quality requirements, but could be exempted from the efficacy requirements. As a matter of fact, a new Council Directive 2004/24/EC was issued dealing specifically with herbal medicinal products with known traditional uses. With this, herbal medicines were categorized into:

- Herbal medicines with a long-history of medicinal usage within the European Community, the so-called Traditional Herbal Medicinal Products (THMPs), and
- Herbal medicines which have been tested clinically and showed clinical efficacy, the so-called Herbal Medicines with a Well-Established medicinal Use (WEU).

In fact, these two categories fall explicitly under different Council Directives. The main differences between these two categories are outlined in table 1.

	THMPs	**Herbals with WEU**
Discovery of product	Long History of Usage	Discovered recently or use proven recently
Proof of Efficacy	No proof. Bibliographic traditional information.	Proof of efficacy by bibliographic clinical data
Proof of Safety	*In vitro* testing for genotoxicity and support by bibliographic data	*In vitro* and *in vivo* testing of product
Proof of Quality	Processed under pharmaceutical manufacturing procedures or as	Processed under pharmaceutical manufacturing procedures. Reference

1 These include chemical synthetics, homeopathic medicines and isolated chemicals derived from medicinal plants.

	stated by an official European or Community Monograph	to a Community Monograph can be made
Registration	**Simplified Registration (registered HMPs)**	**WEU Marketing Authorisation (licensed HMPs)**
Regulated by Council Directive	2004/24/EC	2001/83/EC

Table 1. The main differences and similarities for THMPs and herbals with a WEU

Herbal medicinal products are further categorized into:

- Herbal Substances. These mainly include unprocessed herbal materials and are defined by the binomial botanical name and plant part used. These include also algae, fungi, lichen and certain exudates, in their fresh or dried state.
- Herbal Preparations. These include processed or treated herbal substances, employing a certain degree of transformation, such as extraction, expression, fractionation, distillation, fermentation or concentration. Such preparations include comminuted or powdered herbal substances, essential oils, plant extracts, tinctures and other herbal formulations.

What type of herbal medicinal product is the applicant applying for?

This question takes us back to the introduction of this article, i.e. whether the product has a WEU or is a THMP. Apart from the criteria summarized in table 1, there are more specific conditions which should be satisfied for herbal medicinal products to fall under a specific category. These conditions are categorised into three sections as illustrated in figure 1.

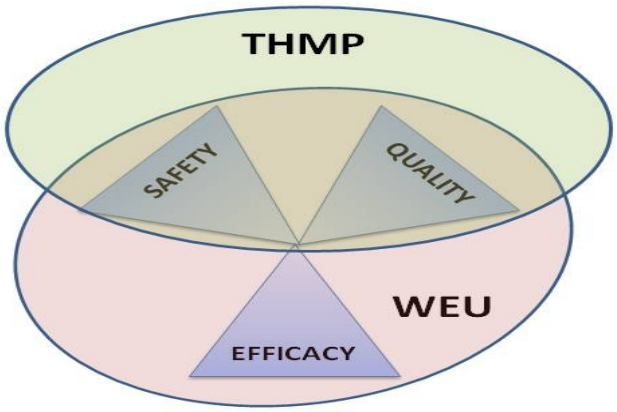

Figure 1. The relationship between safety, efficacy and quality for THMPs and herbals with a WEU

Is there proof of efficacy for the herbal medicinal product?

If the product efficacy has been proven scientifically, the HMP is probably a herbal with a WEU. Scientific proof should be well founded with appropriate *in vitro* and *in vivo* clinical trials, and with the relevant statistical backing. If no scientific efficacy is proven, the product may be a THMP. However, to qualify

under this category the medicinal product should have been used for more than 30 years, with at least 15 years within the European Union. If this is fulfilled the product may proceed along the THMP line, otherwise additional information is required for the product to reach the market, either as a THMP with more bibliographical data or as a herbal with WEU with more clinical data.

What are the routes of administration for the herbal medicinal product?

The route of administration has also an important implication on the categorizations of a HMP. A THMP should be administered orally, topically or by inhalation. In the case of herbals with WEU, these can be administered through any route of administration. This is because THMPs are intended to control or treat minor medical conditions that may be presented as over-the-counter (OTC) products for self treatment, while herbals with WEU require medical supervision and are usually intended to control or treat more serious medical conditions.

What are the doses and dosage regimens for the herbal medicinal product?

In spite of their medical intent, herbal medicinal products should contain specific herbal preparations or herbal substances with a specific dose range and frequency of administration. This is mandatory as a guide to the general public and healthcare professionals such as physicians and pharmacists. If the doses and dosing regimen are not included within the package leaflet (PL) and HMP packaging, the product will not be authorised. The contents of the HMP should be stated on the packaging. Since these HMPs are usually extracts, the extracts are adjusted according to a valuable reference substance. These substances may be active markers, i.e. compounds that exhibit the pharmacological activity stated, and analytical markers, i.e. compounds that indicate the strong presence of a class of compounds but do not necessarily contribute to the pharmacological activity. These categorise HMPs into standardised and quantified extracts, respectively. However, there are other HMPs that cannot be standardised or quantified, and in most cases, such extracts are not granted registration or marketing authorisation. Further classification of HMPs within these categories, is beyond the scope of this article.

Are there additional active constituents to the herbal medicinal product?

If there are no additional active constituents then the product is likely to be classified either as a THMP or a herbal with a WEU. However, additional active constituents that are allowed in herbal preparations are vitamins and minerals. If these do not have a pharmacological role, vitamins and minerals may be omitted from the herbal medicinal product. On the other hand, if these are retained in the product, the quantities should be according to or less than the daily maximum requirements, depending on the frequency of daily administration. If there are other active constituents other than vitamins and minerals, the product may be either modified to eliminate these constituents, particularly if the constituents are toxic, or else considered as a herbal combination product. Combination products that are not supported by a traditional use may only be considered as herbals with WEU as long as there is proof of clinical efficacy data.

Is the herbal medicinal product safe?

The primary aim of the European Union, with the registration of medicinal products, is the protection of the European citizens from fraudulent and unsafe products. In fact, the EU is rather rigorous on this issue and therefore manufacturers are urged to comply with safety issues. Although a THMP has been in circulation for centuries, it is possible that with time, research proves the presence of toxic substances within the product. In some cases, the THMP is either:

- withdrawn from the market, if it is already established within the Community, or
- not allowed to reach the market, if it is a new product, or
- modified to meet the required safety standards.

In the latter case, the product may be considered as a 'minus variant' which might require a slight modification. However, this modification should justify the safer profile of the HMP.

Conclusion

Once a product fulfils these conditions, the HMP can be identified as a THMP or a herbal with a WEU. A decision tree has been prepared to facilitate classification. In most cases, there is no clear distinction as at what dose one should consider the product to be a HMP or a food supplement. Although there is a list of herbal substances that are exclusively found in HMP, in other cases, assessment should be carried out on a case per case basis.

Part II:
Compiling the Dossier

Summary

This article is intended to help the applicant to understand the requirements to compile a dossier for the registration of a traditional herbal medicinal product (THMP). Therefore it is advisable that the applicant distinguishes between a traditional herbal medicinal product and a herbal with a well-established medicinal use (WEU).

Introduction

Since traditional herbal medicinal products should meet the quality and safety requirements, but are exempted from scientific efficacy (clinical) requirements, they should be registered through a simplified, though not simple, procedure. If an applicant is submitting an application for the first time, it is advisable that a single herbal substance/herbal preparation is presented.
The International Conference on Harmonisation (ICH) brings together three regions, Europe, the USA and Japan, reaching a harmonization on the presentation of medicinal products for human use. The information is presented in a series of documents collectively called the Common Technical Document (CTD) (Figure 1)

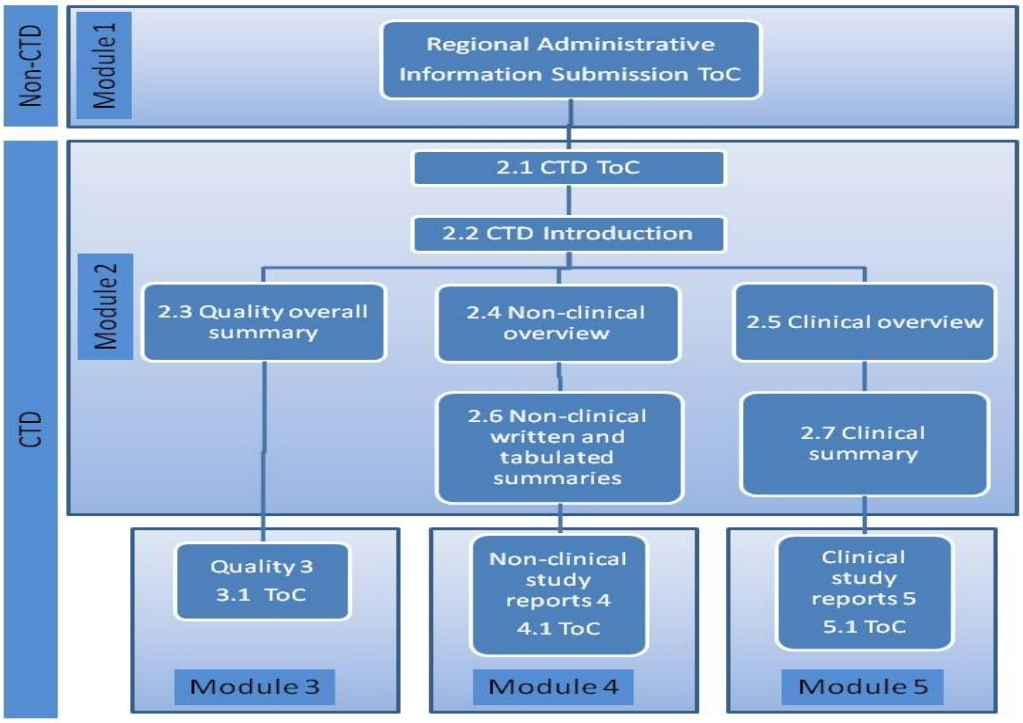

Figure 1. Diagrammatic Representation of the Organization of the ICH

In principle, there are five modules. However, not all modules and subsequent sections, are applicable to THMPs**.**

Module 1

Module 1 lies on top of all the modules. This module deals with administrative and prescribing information. It is region specific and therefore does not fall under the CTD, in this case EU specific as laid in the Notice to Applicants Volume 2B. Module 1 also represents a summary of Module 2.

1.0 Covering letter

The applicant should indicate what has been compiled in the dossier and for what reason. If the applicant decides to submit a detailed overview of the dossier, an appendix may be referred to in this section.

1.1 Comprehensive table of contents

This should provide a list of headings, for all the modules, with the corresponding page numbers for ease of reference. The M4 ICH guideline should be taken into account to compile the table of contents and the organization of the whole dossier.

1.2 Application form

Several application templates exist for the compilation of the dossier. Primarily, it has to be established whether the medicinal product is a herbal with well established use (WEU), or a homeopathic medicine, thus falling under Council Directive 2001/83/EC or else a THMP falling under Council Directive 2004/24/EC. The application forms depend on the legal basis of the application and includes information on the company, whether the product is a herbal or a homeopathic medicinal product, particular information on the product (such as route of administration], container type, closure type, storage and shelf life, company contact details, responsible person contact details, manufacturer's contact details, qualitative and quantitative composition) and whether there are variations to a product. The application forms for WEU and homeopathic products may be found in Volume 2B of Eudralex. A specific national application for THMPs will be published shortly.

1.3 Product information

1.3.1 Summary of product characteristics (SmPC), labelling and package leaflet

A detailed breakdown of the SmPC is provided in the EC guideline on Summary of Product Characteristics. The guideline on the labelling and packaging leaflet and guideline on readability are also provided by the EC. The SmPC should give a summary of the name, qualitative and quantitative composition of the medicinal product, the pharmaceutical form, clinical particulars (e.g. therapeutic indications, posology, method of administration, warnings, precautions, contraindications, interactions, side effects, overdosage and inability to perform certain skills), pharmacological properties, pharmaceutical particulars (excipients, incompatibilities, shelf-life, storage conditions and disposal instructions), and marketing authorization holder, number and date of authorization.

1.3.2 Mock –up

According to article 8 of Council Directive 2001/83/EC, a mock-up of the outer and immediate packaging of the product should be provided with the application. A guideline on the packaging and leaflet mock-up was published by the European Medicines Agency.

1.3.3 Specimen

An actual print out of the outer and immediate packaging materials and package leaflet should accompany the dossier. The information is provided by the European Medicines Agency in the guideline as for the mock-up material. In electronic submissions, the actual specimens should be provided separately from this section.

1.3.4 Consultation with target patient groups

The material provided to the patient, particularly the packaging leaflet, should be clear, legible, simple and easy to follow by the group of patients using the medicinal product. This is stated in articles 59(3) and 61(1) of Council Directive 2001/83/EC. Chapter 3 of the Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use deals specifically with this issue.

1.3.5 Product information already approved in the member states

In some cases, a product has already obtained a registration within another member state. The information should be provided in this section.

1.3.6 Braille

The name of the medicinal product must be presented in Braille format on the packaging, in accordance with Article 56a of Council Directive 2001/83/EC. Chapter 2 of the Guideline On The Readability of The Labelling and Package Leaflet of Medicinal Products for Human Use deals with this issue. The type of Braille letter (size of Braille cell), is also mentioned for standardization.

1.4 Information about the experts

Due to the scientific nature of the dossier, the applicant should involve experts in different fields to compile details in particular for Modules 3, 4 and 5. Three main experts are involved for quality, non-clinical and clinical competences, as set out in the duties in Article 12 and in accordance with Annex I, Part I 1.4 of Council Directive 2001/83/EC.

1.5 Specific Requirements for Different Types of Applications

In the case of THMPs, the issue of long-term use should be clearly stated and described in this section. This will justify the classification of the herbal medicinal product for simplified registration.

1.6 Environmental risk assessment (ERA)

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMA), ERA is not required.

1.7 Information relating to Orphan-market exclusivity

Not applicable to traditional herbal medicinal products.

1.8 Information relating to Pharmacovigilance

Not applicable to traditional herbal medicinal products.

1.9 Information related to Clinical Trials

Not applicable to traditional herbal medicinal products.

Module 2

Module 2 is a summary of Modules 3, 4 and 5. Briefly, it comprises the quality overview summary, the non-clinical overview and summaries (pharmacological, pharmacokinetics and toxicology) and the clinical overview. The clinical summary does not apply for THMPs. The organization of the summaries is described in the ICH guidelines:

- M4Q, for the quality issues in Module 3;
- M4S, for safety issues in Module 4; and
- M4E, for efficacy issue in Module 5.

2.1 Common Technical Document table of contents (Modules 2-5)

This section is only applicable if the dossier is submitted as a hardcopy. The CTD table of contents is omitted in Electronic submissions (eCTD). It is desirable that applications are submitted in electronic format and not as paper copies. Only the application form is to be submitted in paper.

2.2 CTD introduction

The introduction should include the pharmacological class, mode of action and the proposed clinical use for the THMP.

2.3 Quality overall summary

This is a summary of the scope and the outline of the Body of Data in Module 3, section 3.2. The information submitted here, should be sufficient to provide the Quality review a comprehensive overview of Module 3. In cases, where the guidelines were not followed, the applicant should provided justification in this section. It is also necessary to include information on potential contaminants (arising during the cultivation or wild stock production process and during the manufacturing process, as for example, pesticides, heavy metals, post-harvest spoilage, etc.). Some support information may be imported from Module 3 as indicated below with an "*".
This section is divided into four sections designated as 2.3.X where X stands for S (drug substance), P (drug product), A (Appendices), R (regional information). For a herbal medicinal product containing more than one drug substance, the information requested for part S should be provided separately for each drug substance present. Likewise, for a drug product supplied with one or more reconstitution diluents, the information requested for part P should be provided separately for each diluent present.

INTRODUCTION
The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s), usually in accordance with the *European Pharmacopoeia*.

2.3.S Drug Substance (Name, Manufacturer)

2.3.S.1 General Information (name, manufacturer)* including information from section 3.2.S.1

2.3.S.2 Manufacture (name, manufacturer)* including information from section 3.2.S.2. This should include information on the manufacturer, a brief description of the manufacturing process and adequate controls implemented, a process flow diagram* (3.2.S.2.2), a description of the source and starting materials (3.2.S.2.3), a discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria (3.2.S.2.4), a description of process validation and/or evaluation (3.2.S.2.5), a brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency (3.2.S.2.6). In case that a manufacturing process affects the quality of one or more batches, cross-referencing with modules 4 and 5 should be done.

2.3.S.3 Characterisation (name, manufacturer). A summary of data on potential or actual impurities arising from the manufacturing and/or degradation should be included under this section. Acceptance criteria should be set up and justified in this section. Tabulated data* provided in section 3.2.S.3.2, should be included in a graphical form, where appropriate.

2.3.S.4 Control of Drug Substance (name, manufacturer).
A brief summary of the justification of the specification(s)* (3.2.S.4.1), the analytical procedures* (3.2.S.4.4), and validation should be included.

2.3.S.5 Reference Standards or Materials (name, manufacturer). Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

2.3.S.6 Container Closure System (name, manufacturer). A brief description and discussion of the information, from 3.2.S.6 should be included.

2.3.S.7 Stability (name, manufacturer). This should include a summary of the stability test method, results and conclusions, proposed storage conditions, retest data or shelf-life (3.2.S.7.1). The post-approval stability protocol, as described in 3.2.S.7.2, should be included. A tabulated summary* of the stability results (3.2.S.7.3), with graphical representation where appropriate, should be provided.

2.3.P Drug Product (Name, Dosage Form)

2.3.P.1 Description and Composition of the Drug Product (name, dosage form). Information and composition* from 3.2.P.1 should be provided.

2.3.P.2 Pharmaceutical Development (name, dosage form). A discussion of the information and data from 3.2.P.2 should be presented. A table with the composition of formulations used in pharmacological experiments and dissolution profiles may be included.

2.3.P.3 Manufacture (name, dosage form). Information from 3.2.P.3 should include manufacturer information, a brief description of the manufacturing process and the controls , including a flow diagram, as prepared in 3.2.P.3.3*, and a brief description of the process validation and/or evaluation, as described in 3.2.P.3.5.
2.3.P.4 Control of Excipients (name, dosage form). A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.
2.3.P.5 Control of Drug Product (name, dosage form). A brief summary of the justification of the specification(s)* from 3.2.P.5.1, a tabulated summary (where appropriate) of the analytical procedures* and validation from 3.2.P.5.4, and characterisation of impurities should be provided.
2.3.P.6 Reference Standards or Materials (name, dosage form). Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.
2.3.P.7 Container Closure System (name, dosage form). A brief description and discussion of the information in 3.2.P.7 should be included.
2.3.P.8 Stability (name, dosage form). This includes a summary of the methodology, results* (3.2.P.8.3, tabulated summary) and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions, shelf-life and post-approval stability protocol (3.2.P.8.2) should be given.

2.3.A Appendices

2.3.A.1 Facilities and Equipment (name, manufacturer). This is a summary of facility information described under 3.2.A.1.
2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer). A discussion on measures implemented to control endogenous and adventitious agents (particularly fungi, bacteria and viruses) (3.2.A.2) during production process should be included. This indicates how an applicant can control and maintain the quality of the product throughout the manufacturing process.

2.3.R Regional Information

A brief description of the information specific for the region, as provided under "3.2.R" should be included, where appropriate.

2.4 Non-clinical overview (approx. 30 pages)

This section covers a critical assessment of the pharmacological, pharmacokinetic and toxicological profile of the herbal medicinal product. Apart from the quality determination of the plant product, vis-à-vis any impurities or degraded substance, the non-clinical effects of these compounds should be evaluated. Any relationships between quality, efficacy and safety with related products should be indicated, as appropriate. For THMPs, detailed references to published scientific literature are to be used in place of studies conducted by the applicant. Citations for the references should be clearly tabulated.

The expert report for this section should take into consideration the organization of the non-clinical overview in the CTD. This includes the following sequence: overview of the testing strategy, pharmacology, pharmacokinetics, toxicology, integrated overview and conclusions, and list of literature references. Inconsistencies in the data should be discussed. Inter-species comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, C_{max}, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted. Detail to be added regarding the onset, severity and duration of toxic effects, dose dependency, the extent of reversibility and interspecies/intergender differences should be discussed taking into account the ICH guideline on safety.

If alternatives to whole-animal experiments are employed, their scientific validity should be discussed.

The Integrated Overview and Conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labelling).

2.5 Clinical overview

Although the clinical overview is rather detailed for chemical entities and herbals with WEU, in the case of THMPs, this section refers specifically to Article 16c (1)(c) of Council Directive 2004/24/EC:
"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." However, any relevant information on clinical pharmacology, efficacy and safety of the medicinal products should be included too in this section. It is not intended that material presented fully elsewhere be repeated in the Clinical Overview; cross-referencing to more detailed presentations provided in the Clinical Summary or in Module 5 is encouraged.

2.6 Non-clinical summary (100-150 pages)

The non-clinical summary includes both written and tabulated information. When available, *in vitro* studies should precede *in vivo* studies. There are three main subsections pharmacological, pharmacokinetic and toxicological written summaries. These will be explained in detail later on in the text. In these subsections, particularly the pharmacokinetics and the toxicology sections any multiple studies of the same type need to be summarised and ordered by species, by route, and then by duration (shortest duration first). Species should be ordered as follows mouse, rat, hamster, other rodents, rabbit, dog, non-human primates, other non-rodent mammals, non-mammals. The routes of administration for these studies should also be considered in the following specific order, i.e. the intended route for human use, oral, intravenous, intramuscular, intraperitoneal, subcutaneous, inhalation, topical and other.

2.6.1 Introduction

The aim of this section is to introduce the reviewer to the pharmaceutical and to its proposed clinical use of the product.

2.6.2 Pharmacology Written Summary

Within this subsection, the data is presented in the following sequence: brief summary, primary pharmacodynamics, secondary pharmacodynamics, safety pharmacology, pharmacodynamic drug interactions, discussion and conclusions, and tables and figures. These should be presented in separate subsections. The difference between primary and secondary pharmacodynamics is described in ICH Guideline S7, Safety Pharmacology Studies for Human Pharmaceuticals. "Studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target are primary pharmacodynamic studies. Studies on the mode of action and/or effects of a substance not related to its desired therapeutic target are secondary pharmacodynamic studies (these have sometimes been referred to as part of general pharmacology studies)."

2.6.3 Pharmacology Tabulated Summary

The results presented in the written summary are tabulated in a similar format to the subsections presented in subsection 2.6.2.

2.6.4 Pharmacokinetics Written Summary

Within this subsection, the data should be presented in the following sequence: Brief Summary, Methods of Analysis, Absorption, Distribution, Metabolism, Excretion, Pharmacokinetic Drug Interactions, Other Pharmacokinetic Studies, Discussion and Conclusions and Tables and Figures (either here or included in text).

2.6.5 Pharmacokinetics Tabulated Summary

The results presented in the written summary are tabulated in a similar format to the subsections presented in subsection 2.6.4.

2.6.6 Toxicology Written Summary

Within this subsection, the data should be presented in the following sequence: brief summary, single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, studies in juvenile animals, local tolerance, other toxicity studies, discussion and conclusions and tables and figures.

2.7 Clinical Summary

Since the medicinal product in question is a THMP, no clinical proof is necessary. Therefore this section is not applicable.

Module 3

Module 3 is a detailed report on the chemical, pharmaceutical and biological documentation of a registration application for a herbal medicinal product. The activities related to the manufacturing of the medicinal product should be in accordance with Article 40 of Council Directive 2001/83/EC. Apart from the general guideline issued by the ICH, two other regional guidelines issued by the European Medicines Agency are the "Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products" and the "Guideline on Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products". There is also a specific guideline for Module 3 on herbals in the Notice to Applicants – Medicinal Products for Human Use, Volume 2.

Finally, relevant information can be extracted from the European Pharmacopoeia including specific monographs, general monographs and general chapters.
This section is divided into three sections designated as 3.2.X where X stands for S (drug substance), P (drug product) and A (Appendices). For a herbal medicinal product containing more than one drug substance, the information requested for part S should be provided separately for each drug substance present. Likewise, for a drug product supplied with one or more reconstitution diluents, the information requested for part P should be provided separately for each diluent present.

3.1. Table of Contents of Module 3
The CTD table of contents is omitted in Electronic submissions (eCTD). In fact, this section is only applicable if the dossier is submitted as a hardcopy.

3.2. Body of Data
3.2.S Drug Substance (Name, Manufacturer)

3.2.S.1 General Information (name, manufacturer). These include the nomenclature of the drug substance, structure (physical form, constituents with known markers and other constituents) and general properties (physicochemical and other relevant properties).
For herbal substances the nomenclature is mainly based on the binomial scientific name, plant part(s) used, and other names, while for herbal preparations, the information is mainly based on the characteristics of the herbal substance, the ratio of herbal substance to the herbal preparation, extraction solvent(s).
3.2.S.2 Manufacture (name, manufacturer). The information requested in this section include the details on the manufacturer(s), the description of manufacturing process and process controls (geographical source of medicinal plant, cultivation, harvesting, drying, storage, batch size; process flow diagram, solvents, purification stage, standardization), control of materials (for biologically-sourced materials, this can include information regarding the source, manufacture, and characterization), controls of critical steps and intermediates (tests and acceptance criteria), process validation and/or evaluation, manufacturing process development.
3.2.S.3 Characterisation (name, manufacturer). These include elucidation of structure and other characteristics (botanical, microscopic, macroscopic, phytochemical characterization and biological activity; phytochemical and physicochemical characterization, biological activity) and impurities (information should be provided).
3.2.S.4 Control of drug substance (name, manufacturer). Information on the drug substance is requested in this section, such as specification, analytical procedures, validation of analytical procedures, batch analyses and justification of specification.
3.2.S.5 Reference Standards or Materials (name, manufacturer). Information on the reference

standards or reference materials used for testing of the drug substance should be provided.

3.2.S.6 Container Closure System (name, manufacturer). This includes the identity of materials of construction of each primary packaging component, and their specifications.

3.2.S.7 Stability (name, manufacturer). The stability studies in two guidelines Q1A and Q1B, with appropriate validation tools (Q1C), carried out prior to application and post–approval periods (Q5C) are presented in this section. The headings include stability summary and conclusions, post-approval stability protocol and stability commitment, and stability data (including tabular, graphical, or narrative formats). The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency added information to certain sections and provided clarification to other sections of the ICH guideline Q1A.

3.2.P Drug Product (Name, Dosage Form)

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)(Q6B). These include a description of the dosage form and composition (list of all components of the dosage form, description of accompanying reconstitution diluent(s) and type of container and closure used for the dosage.

3.2.P.2 Pharmaceutical Development (name, dosage form) (Q6B). Information on the drug product (including compatibility with the excipients and important physicochemical characteristics) and development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

3.2.P.3 Manufacture (name, dosage form)(Q1C, Q6B) . This section requires the listing of the name, address, and responsibility of each manufacturer, batch formula, description of the manufacturing process controls, controls of critical steps and intermediate, process validation and/or evaluation.

3.2.P.4 Control of Excipients (name, dosage form)(Q1C, Q6B) . The following details should be presented for the excipients, such as the specifications, analytical procedures, validation of analytical procedures, justification of specifications (i.e., for the proposed excipient), excipients of human or animal origin, novel excipients (used for the first time in drug product or new route of administration).

3.2.P.5 Control of Drug Product (name, dosage form)(Q3BR). The European Medicines Agency guideline for impurities in new drug products (Q3BR2), also suggest referral to the ICH guideline on residual solvents (Q3CR4). The specification(s) for the drug product, analytical procedures (Q1C, Q6B), validation of analytical procedures (including experimental data), batch characterisation of impurities, and justification of Specification should be provided.

3.2.P.6 Reference Standards or Materials (name, dosage form). Information on the reference standards or reference materials used for testing of the drug product should be provided.

3.2.P.7 Container Closure System (name, dosage form). This includes the description and identification of the type of closure system used.

3.2.P.8 Stability (name, dosage form)(Q1A, Q1B, Q5C, Q3BR) .The information includes the stability summary and conclusion (highlighting important results such as the storage conditions and shelf-life), post-approval stability protocol and stability commitment, and stability data (in an appropriate format such as graphical, tabular or narrative).

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment (name, manufacturer). A diagram should be provided to illustrate the steps in the manufacturing process of the drug product. This should include elements of good manufacturing practices.

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer). If a conventional manufacturing process does not include any biotechnological steps (involving human

or animal materials), then this section does not apply to the THMP.
3.2.A.3 Excipients. Not applicable, if all details on excipients are listed under section 3.2.P.4.

3.3 LITERATURE REFERENCES
Key literature referenced should be provided, if applicable.

Module 4

Module 4 Information on the toxicological and pharmacological tests carried out on the drug/active substance and a drug/medicinal product, is documented in the non-clinical written summaries (Module 2) and the non-clinical study reports (Module 4). In this module, the reports have to be presented as outlined in the ICH guideline M4S.

4.1 Table of Contents of Module 4
This section is only applicable if the dossier is submitted as a hardcopy. The CTD table of contents is omitted in Electronic submissions (eCTD). It is desirable that applications are submitted in electronic format and not as paper copies. Only the application form is to be submitted in paper.

4.2 Study Reports
If applicable, the study reports should include pharmacology, pharmacokinetics, toxicology (genotoxicity, amongst others), carcinogenicity, reproductive and developmental toxicity, local tolerance, immunotoxicity and other toxicity studies. However, proof of pharmacological activities will lead to the scientific assessment of the herbal medicinal product and hence demonstrating a well-established use for the herbal, following out of the remits of Council Directive 2004/24/EC.

For THMPs, the pharmacological section should be represented by bibliographical references, regarding particularly safety data, in accordance with Article 16c(1)(d) of Council Directive 2004/24/EC.

Module 5

Module 5 Information on the clinical trials performed on the drug/active substance and a drug/medicinal product, is documented in the clinical written summaries (Module 2) and by the clinical study reports (Module 5).

5.1 Table of Contents of Module 5
This section is only applicable if the dossier is submitted as a hardcopy. The CTD table of contents is omitted in Electronic submissions (eCTD).

5.2 Tabular Listing of All Clinical Studies
If applicable, the clinical study reports mentioned in section 5.3, should be tabulated in this section. However, proof of clinical efficacy will lead to the scientific assessment of the herbal medicinal product and hence demonstrating a well-established use for the herbal, following out of the remits of Council Directive 2004/24/EC.

5.3 Clinical Study Reports
If applicable, the clinical study reports should include reports of biopharmaceutical studies, reports of

studies pertinent to pharmacokinetics using Human Biomaterials, reports of human pharmacokinetic (PK) studies, reports of human pharmacodynamic (PD) studies, reports of efficacy and safety studies, reports of post-marketing experience, and case report forms and individual patient listings.

5.4 Literature References

The references should be presented in the agreed ICH format (M4E) for the organisation of Module 5. For THMPs, since clinical data is missing, the CTD clinical report format is not applicable. However, any clinical observation studies that may be relevant to pharmacological effects or efficacy of the THMP, should be presented. An explanation such as "not applicable" or "no study conducted" should be provided when no report or information is available for a section or subsection.

Appendices

The applicant should consider the attachment of appendices only if the documentation does not fit directly into one of the specific module or the subsections there in, or else there are multiple documents falling under one specific subsection.

Although this article attempted to cover all the modules to be presented in a dossier, this was merely a brief summary. Reference to the mentioned guidelines is necessary for the registration of the traditional herbal medicinal product.