Doc. No.: TMDA/DMC/MRE/G/013
Revision No. 01

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR MARKETING AUTHORIZATION OF HERBAL MEDICINAL PRODUCTS

Made under the Regulation 4 (1) of the Tanzania, Medicines and Medical Devices (Registration of Medicinal Products) Regulations, 2015

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ABBREVIATIONS

API	-	Active Pharmaceutical Ingredients
BSE	-	Bovine spongiform encephalopathy
BP	-	British Pharmacopoeia
CEP	-	Certificate of Suitability
CHMP	-	Committee for Medicinal Products for Human Use
CPP	-	Certificate of Pharmaceutical Product
CTD	-	Common Technical Document
DMF	-	Drug Master File
EDQM	-	European Directorate for the Quality of Medicines
FDA	-	US Food and Drug Administration
FHP	-	Finished Herbal Product
FIFO	-	First in First Out
FPP	-	Finished Pharmaceutical Product
EMA	-	European Medicines Agency
GACP	-	Good Agricultural and Collection Practices
GCP	-	Good Clinical Practices
GLP	-	Good Laboratory Practices
GMP	-	Good Manufacturing Practices
HPLC	-	High Performance Liquid Chromatography
ICH	-	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical Products
IR	-	Infrared radiation
PD	-	Pharmacodynamics
Ph.Eur	-	European Pharmacopoeia
Ph.Int	-	International Pharmacopoeia
PIL	-	Patient Information Leaflet
PK	-	Pharmacokinetics
QOS	-	Quality Overall Summary
RH	-	Relative Humidity
SPC	-	Summary of Product Characteristics
TLC	-	Thin Layer Chromatography
TMDA	-	Tanzania Medicines and Medical Devices Authority
TMDA	-	Tanzania Medicines and Medical Devices Act, Cap 219
TSE	-	Transmissible Spongiform Encephalopathy
USP	-	United States Pharmacopoeia
UV	-	Ultraviolet radiation
WHO	-	World Health Organization

ACKNOWLEDGEMENTS

This is the third revision of the Guidelines on Submission of Documentation for Marketing Authorization of Herbal Medicinal Products. The revision has been done to in order to align with the CTD format requirements and embrace new knowledge which have been gathered during implementation of the second edition.

I would like to acknowledge the contribution of individuals and organizations involved in the development of these guidelines. I thank the World Health Organization (WHO), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (*ICH*), Health Canada, Therapeutic good of Australia (TGA), US food and Drug Administration and the European Medicinal Products Agency (EMA) whose documents saved as important references in drafting these guidelines.

I would also like to thank all who worked tirelessly and incessantly in the development of this edition particularly Mr. Felchism Apolnary, Mr. Denis Mwangomo and Mr. Alex Juma for reviewing this guidelines and laws governing herbal medicines in the country.

Hmsallah
Akida M. Khea
Acting Director, Medical Products Control

FOREWORD

The Tanzania Medicines and Medical Devices (TMDA) was established under the Tanzania Medicines and Medical Devices Act, Cap 219 with the mission of protecting and promoting public health by ensuring quality, safety and effectiveness of medicines, medical devices and diagnostics. One of the TMDA functions is to conduct pre-marketing assessment of the regulated products to ensure that they meet quality, safety and efficacy standards before they are registered and allowed to circulate into the market.

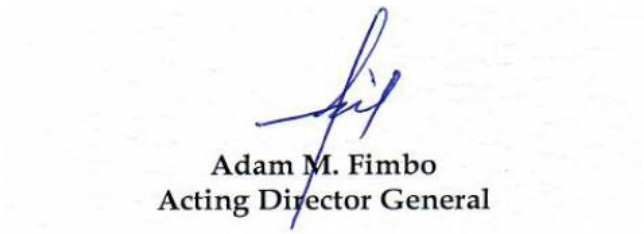
In trying to streamline and effectively control herbal medicinal products, TMDA developed the first Guidelines for Registration of Herbal Drugs in the year 2004 and revised it in 2017. The previous edition of the guidelines is therefore reviewed since the use of herbal medicinal products has expanded in recent times and gained popularity globally as a result of technological advancements.

The reviewed guidelines currently entitled as Guidelines for Submission of Documentation for Marketing Authorization of Herbal Medicinal Products outlines the minimum requirements for registration of herbal medicinal products in Tanzania. Applicants are required to demonstrate that the products they intend to register in Tanzania comply with the acceptable standards of quality, safety and efficacy.

It should be noted that the guidelines are applicable only to herbal medicinal products that meet quality, safety and efficacy requirements and manufactured in facilities that complies with the requirements of Good Manufacturing Practices (GMP). The Guidelines will not be applicable to local traditional medicines that are regulated under the Traditional and Alternative Health Practices Act, 2002.

All applicants are therefore encouraged to familiarize with the Guidelines and follow them strictly when preparing and submitting applications for registration of herbal medicinal products. Adherence to these Guidelines will ensure that all relevant information are provided in the applications submitted for registration. This will facilitate efficient and effective evaluation as well as approval process.

It is anticipated that the guidelines will continue to be revised regularly in response to the experiences gathered from their utilization. Marketing Authorization Holders as well as other stakeholders are encouraged to provide comments for improvement based on their experience on the use of the Guidelines. We therefore welcome comments and views at any time for improvement and update of these Guidelines.



Adam M. Fimbo
Acting Director General

INTRODUCTION

Of recent, the use of herbal medicinal products has expanded and gained popularity globally. They have not only been used for primary healthcare in the developing countries but also have been used in countries where conventional medicines are predominantly used in the national health care systems. With the expansion in the use of these products worldwide, quality and safety have become a challenge to National Medicines Regulatory Authorities.

Registration of herbal medicinal products is a legal requirement intended to protect the public against health hazards that may be associated with unsafe use of the products. In Tanzania there is notable increase in the use and demand for herbal medicinal products. Thus the Tanzanian population needs to be protected against the possible hazards that may be associated with consumption of these products.

Risks of herbal medicinal products may arise from exogenous contaminants such as pesticides or from the chemical properties of constituents and/or ingredients used to formulate the products. They may also arise from quality defects which are likely to occur during preparation and deterioration or contamination during transport or storage.

These guidelines have been developed to provide requirements in support of quality safety and efficacy for those who wish to register herbal medicinal products in Tanzania. They are intended to assist applicants in the preparation of documentation (product dossiers) for marketing authorization of herbal medicines.

It is expected that the guidelines will assist applicants to fulfill the legal requirements for registration as provided in Section 22 of the Tanzania Medicines and Medical Devices Act, Cap 219. Applicants are requested to carefully read these guidelines, prepare dossiers and submit them in hard and soft copy. This guidance document should be read in conjunction with other relevant and applicable guidance documents such as the Tanzania Medicines and Medical Devices (Registration of Medicinal Products) Regulations, 2015, Application Guidelines for Variation of Registered Medicinal Products and other internationally accepted guidelines.

The Guidelines have been divided into five modules. Module I provides Regional administrative information like how to file an application, payment of relevant fees and processing of applications. Module II provides for overview and summaries and overview of module III, IV and V, Module III provides for quality requirements like chemistry, manufacturing and quality controls part while Module IV and V provides for requirements of non-clinical and clinical documents respectively.

GLOSSARY OF TERMS

The terms listed below are defined specifically for the purpose of these guidelines:-

"Active pharmaceutical ingredient or active herbal ingredient or Active chemical ingredient" means herbal material or herbal preparation or herbal ingredient with required therapeutic activity.

"**Applicant**" means a person who submits an application for registration of herbal medicinal product, an update or amendment to an existing registration to the Authority who may be a manufacturer or a person to whose order and specifications, the product is manufactured. After the product is registered the applicant shall be "marketing authorization holder or registrant".

"**Batch**" or "**lot**" in relation to herbal medicinal product means a defined quantity of herbal medicinal product manufactured in a single manufacturing cycle and which has homogeneous properties.

"**Composition**" means the ingredients of which the herbal medicinal product consists, proportions, degree of strength, quality and purity in which those ingredients are contained.

"**Container**" means bottle, jar, box, packet, sachet or other receptacle which contain or is to contain herbal medicinal product, not being a capsule or other article in which the product is or is to be administered or consumed, and where any such receptacle is or is to be contained in another such receptacle, includes the former but does not include the latter receptacle.

"Country of origin" means a country in which the herbal medicinal product has been manufactured.

"Dosage form" means the form in which herbal medicinal product is presented, e.g tablet, capsule, elixir, powder etc.

"Dossier" means file(s) containing detailed technical information of a particular herbal medicinal product.

"Excipient" means any component of a finished dosage form other than active ingredient which has no therapeutic value.

"Finished herbal product" means 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

''Good Clinical Practice (GCP)'' is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects

"Good manufacturing practices (GMP)" means that part of quality assurance which ensures that herbal medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

''**Herbal materials'** means whole, fragmented or cut (including chopped), plants, parts of plants (including leaves, roots, flowers, seeds, bark, fresh juices, gums etc), in an unprocessed state, usually in dried form. For the purposes of this guidance document, herbal powders (herbal materials that are dried and ground to powders) are also included in this definition

"Herbal medicinal product" means any labeled preparation in pharmaceutical dosage form that contains as active ingredients one or more substances of natural origin that are derived from plants. It includes products which are standardized in terms of constituents with known therapeutic activity and whose safety and efficacy are well established.

''**Herbal preparations''** include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials.

"Label" means any tag, brand, mark, pictorial or other descriptive matter, written, printed, stenciled, marked, embossed or impressed on or attached to a container of any herbal medicinal product.

"Manufacture" means and includes all operations involved in the production, preparation, processing, extraction, compounding, formulating, filling, refining, transforming, packing, packaging, re-packaging and labeling of herbal medicinal product.

"Manufacturer" means a person or firm that is engaged in the manufacture of herbal medicinal product.

"Markers" means chemically defined constituents of herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity or not, serve to calculate the quantity of herbal medicinal product or preparation in the finished product if that marker has been quantitatively determined in the herbal medicinal product when the starting materials were tested.

"Pharmacopoeia" means the current version of British Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia, Japanese Pharmacopoeia, International Pharmacopoeia or any other approved Pharmacopoeia.

''Pharmacovigilance'' means the practice of monitoring the effects of medical drugs after they have been licensed for use, especially in order to identify and evaluate previously unreported adverse reactions

"Shelf life" means that length of time in which the herbal medicinal product is given before it is considered unsuitable for sale or consumption or it is amount of time that a properly packaged and stored product will last before undergoing chemical or physical changes, remaining within the specified uncertainty.

"Specification" means list of tests, references to analytical procedures and appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described.

''Traditional Medicine'' means the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.

''Traditional Medicine Remedy'' means and includes any method, process, practice or medicine consisting of a substance or a mixture of substances produced by drying, extracting, crushing or comminuting, compressing natural substance of a plant, animal or mineral origin or any part of such substances.

MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

Module 1 should contain all administrative documents (for example, application forms and certifications), labelling, general correspondence and annexes (environmental assessments, and overseas evaluation reports), as needed. Documents should be organized in the order listed below. Generally, all of the documents in Module 1, other than the annexes, can be provided in a single volume.

The annexes to the module should be submitted in separate volumes. Official language is English and/or Swahili as a mandatory languages for all medicines in Tanzania. However, where certificates are in another language, copies shall be presented together with certified Kiswahili or English translations. Products shall be evaluated on a First in First out (FIFO) basis and the timeline for review and communication to applicant shall be as stipulated in the current TMDA customer service charter.

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1.1 Comprehensive table of contents for all modules

1.2 Cover letter

Applicants shall include a cover letter for each submission. The cover letter shall be signed by the applicant and stamped.

1.3 Comprehensive table of content

The comprehensive table of contents should include a complete list of all documents provided in all modules. Where necessary, the location of each document should be identified by referring to the volume numbers that contain the relevant documents and any tab identifiers. In general, the name for the tab identifier should be the name of the document.

1.4 Application form

The submission must be accompanied by a completed, signed, dated and stamped application form. Appropriate application form must be used for first time and renewal applications as provided in **Annex II** and **III** of these guidelines.

1.5 Product information

This includes summary of product characteristics (SPC), labeling, patient information leaflet (PIL), artwork and samples. Applicant must provide copies of all package inserts, labels, artwork and any information intended for distribution with the product.

1.5.1 Summary of product characteristics

All prescription medicines should be accompanied by SmPC. Refer Guidelines on Format and Content of Summary of Product Characteristics for Pharmaceutical Products. The format of the SMPC should not be modified or rearranged. When a certain content is not available or applicant it should be stated.

1.5.2 Labeling

Product should be labelled as prescribed in the Guidelines on Format and Content of Labelsfor Pharmaceutical Products.

1.5.3 Patient information leaflet

All herbal preparations with potential for longterm use and and Over the Counter (OTC) must contain a patient information leaflet. Languages used for PIL and labelling should be clearly expressed in English and/or Swahili. Refer Guidelines on Format and Content of Patient Information Leaflet for Pharmaceutical Products.

1.5.4 Artwork (Mock-ups and specimens)

If the product applicant has a specimen or mockup of the sample(s) presentation of the medicine available at the time of initial application, it should be included in Module1.5.2.If there are multiple strengths and/or pack sizes, one representative specimen or mockup for each will be sufficient. If batch number and expiry date are to be printed on the label during packaging, a statement to this effect should accompany the labels. If mockups or specimens are not available at the time of initial application, a text version may be submitted, however, mockups or specimens must be submitted to the TMDA, during the evaluation process and prior to finalization of the application.

In addition to guidance provided for preparation of summary of product characteristics and patient information leaflet by the respective guidelines, applicant should also include the following in product information:

Formulation/indication	Guidance on product information (SMPC, PIL and Labels)
For products containing Camphor, the following warning should be stated on the label:-	"Can cause convulsion, contraindicated in children below 2 years of age. Caution must be exercised when older children are treated. Avoid direct application into nostrils. Precaution: 'It is dangerous to place any camphor – containing product into the nostril of children. A small amount applied this way may cause immediate collapse' - Avoid contact with the eyes - Do not apply to wounds or damaged skin
For products containing Ginseng (including all *Panax*genus) state:	• Safe use of ginseng in pregnant women and children has not been established. • Safety on long term use has not been established
For products containing Flower parts, state:	• This product may contain pollen which may cause severe allergic reactions, including fatal anaphylactic reactions in susceptible individuals. • Asthma and allergy sufferers may be at greater risks.
For product containing *chelidonium majus*, state	• Warning: This Product may cause adverse reaction to the liver.
For product containing Senna Leaf (*Cassia*) and Rhubarb/Radix et, Rhizoma Rhei, state:	a) Do not use when abdominal pain, nausea or vomiting is present. b) Frequent or prolonged used of this preparation may result independence towards the product and 'imbalanced electrolytes'.
For product containing	• Text Box: This product contains Alfalfa (*Medicago sativa*).

Alfalfa (*Medicago sativa*), state:	Individuals with a predisposition to systemic lupus erythematosus should consult their physician before consuming this product.
For product containing St. John's Wort,	State: The product may interact with other medicines. Please consult a doctor / pharmacist before using it.
For product containing *Pelargonium sidoides*,	State: In very rare cases, pelargonium sidoides may cause hypersensitivity reactions.
For product containing Benzyl Alcohol/ Phenylmethanol (as preservative)	State: As this preparation containing Benzyl Alcohol, its use should be avoided in children under 2 years of age. Not to be used in neonates.
For product containing *Ginkgo biloba* / Ginkgo extract	State: 'Please consult your physician/ pharmacist if you are on or intend to start using any other medicines and before you undergo any surgical/dental procedure' as the use of Ginkgo may increase the tendency of bleeding.
For product containing royal jelly	State: - This product contains royal jelly and may cause severe allergic reactions including fatal anaphylactic reactions insusceptible individuals. Asthma and allergy sufferers may be at the greater risk.
For product containing *Propolis* (topical preparation)	State: Propolis may cause allergic skin reaction.
For product containing 'Anti-diarrhoea'	State: Contraindicated in children below 1 year old.
For product with indication 'To regulate menstruation / to improve menstrual flow'	State: Contraindicated in pregnant women.
For product with indication 'To reduce body weight'	state: Balanced diet and regular exercise are essential

1.5.5 Sample

A sufficient number of samples should be provided in order to perform complete testing. A minimum of three (2) samples of the smallest commercial pack must be submitted during application. The samples must be in the form and container in which they will be marketed.

1.6 Information on the experts

It is important to emphasize that well prepared expert reports greatly facilitate the evaluation of dossier and contribute towards the speedy processing of applications.

Authors of expert reports must be chosen on the basis of their relevant qualifications and their recognized expertise in the respective field. The experts should preferably not have been personally involved in the conduct of the tests included in the dossier. Each expert report should contain:-

a) An abbreviated product profile;
b) A critical evaluation of the dossier;
c) The opinion of the expert as to whether sufficient guarantees have been provided as to the suitability of the product for its proposed use;
d) A summary of all the important data;
e) The signature of the expert and the place and date of the report's issue;
f) The expert's *curriculum vitae* and a declaration of the expert's professional relationship to the applicant.

It is essential to note that the expert reports must include a critical discussion of the properties of the product as demonstrated by the contents of the dossier. The expert is expected to take and defend a clear position on the final product, in the light of current scientific knowledge. A simple factual summary of the information contained in the application is not sufficient and the expert reports must not be a repetition of other parts of the dossier, although important data will need to be summarized in the expert report in some form. Both expert reports and summaries must contain precise references to the information contained in the main documentation. If experts wish to supplement their report by reference to additional literature, they must indicate clearly that the applicant has not included this information in the relevant part of the dossier.

1.7 Environmental Risk Assessment

The applicant must include an evaluation for any potential risks of the product to the environment. This should include risks to the environment arising from use, storage and disposal of products and not for risks arising from the synthesis or manufacture of products.

1.8 Pharmacovigilance

a. Pharmacovigilance System

It shall contain a detailed description of the pharmacovigilance system including the proof that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction.

b. Risk Management Plan

A detailed description of the risk management system which the applicant will introduce should be provided, where appropriate.

1.9 Certificates and documents

a. Good Manufacturing Practice (GMP) certificate

For all herbal medicinal products irrespective of the country of origin, all key manufacturing and/or processing steps in the production of finished pharmaceutical products must be performed in plants that comply with GMP standards. The Applicant must submit a valid GMP Certificate issued by competent Authority in the country of origin of the product.

b. CPP or Free sale

The CPP must be in accordance with WHO guidelines. However if the CPP is not available, a marketing authorization or free sales certificate from the country of origin should be submitted. Marketing authorization or free sales certificate should include the following:-

i. Product trade name in the country of origin.
ii. Number and date of marketing authorization in the country of origin.
iii. Name of active and inactive substances with their concentrations.
iv. A statement that certifies the product is marketed in the country of origin.
v. Provide the Summary of Product Characteristics (SPC).
vi. Provide a copy of the patient information leaflet (PIL).

c. Certificates of analysis - active ingredient and finished product

The Applicant must submit:-

i. Certificates of analysis for more than one batch of the active ingredient(s) from the supplier/manufacturer,
ii. Certificates of analysis for more than one batch of the active ingredient(s) from the manufacturer of finished product.
iii. Certificates of analysis for more than one batch of the finished product from the manufacturer.

d. Certificate of analysis – Excipients

Specifications sheet from either supplier or finished product manufacturer should be submitted. In case of having a pharmacopoeia excipient, the specifications sheet must cover all the pharmacopoeia parameters.

e. Bovine Spongiform Encephalopathy (BSE) certificate

BSE certificate must be submitted for materials originating from animals.

f. Certificate of suitability of monographs of the European pharmacopoeia (CEP)

If available, applicant should present copy of CEP.

g. Certificate of suitability for Transmissible Spongiform Encephalopathy (TSE)

A valid TSE certificate issued by the competent authority must be submitted

h. Diluents and coloring agents in the product formula

A declaration letter in an official company letter head stating the diluents and coloring agents used in the product formula must be submitted.

i. Patent information

A declaration letter in an official company letterhead stating the patent status of the product must be submitted.

j. Letter of access or acknowledgment to DMF

If applicable, a letter written by the DMF owner or authorized agent to permit the Authority to make reference to the information in the DMF on behalf of the applicant must be submitted.

k. Good Clinical Practice (GCP) or Good Laboratory Practice (GLP)

If available provide evidence such as accredited certificate for GCP or GLP for the sites participating in the clinical and nonclinical studies.

l. List of countries in which a similar product is registered

The Applicant should provide a list of countries in which a similar product has been registered, registration dates and validity.

MODULE 2: OVERVIEW & SUMMARIES

2.1 Table of contents of Module 2-5

There should be table of content that list all documents included in Modules 2 to 5.

2.2 Introduction

A description of the product and its composition should be provided. The information provided should include for example:-
Description of the dosage form;

a) Composition, i.e.:
    - list of all components of the dosage form,
    - their amount on a per-unit basis *(including overages, if any)*,
    - the function of the components, and
    - a reference to their quality standards *(e.g., compendial monographs or manufacturer's specifications)*;
b) Description of accompanying reconstitution diluent(s); and
c) Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

2.3 Quality Overall Summary (QOS)

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the body of data in Module 3. The QOS should not include information, data or justifications that are not included in Module 3 or in other parts of the CTD. The QOS should include sufficient information from each section to provide the quality reviewer with an overview of Module 3. The QOS should include a discussion of key issues that integrate information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies discussed under Module 4), including cross- referencing to volume and page number in other Modules. The use of tables to summarize the information is encouraged, *where possible*. The QOS should be arranged in the following order

2.3. Quality overall summary
2.3.S. Quality Overall Summary of the herbal Substance/Preparation
2.3.P. Quality Overall Summary of the finished herbal Product

2.3.A. Quality Overall Summary Appendixes
2.3.R. Quality Overall Summary Regional Information

2.4 Non-Clinical overview

A bibliographic review of the safety data and (upon additional request by the Authority) data necessary for assessing the safety of the product should be provided. The review must be up-to-date, comprehensive and objective. The list of relevant references for non-clinical data can be included at the end. In general, the non-clinical overview should not exceed about 30 pages.

The non-clinical overview should be presented in the following sequence:-

a) Overview of the non-clinical testing strategy
b) Pharmacology
c) Pharmacokinetics
d) Toxicology
e) Integrated overview and conclusions
f) List of literature references

Refer ICH Guidance on the CTD for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part.

2.5 Clinical overview

The clinical overview should generally be a relatively short document (about 30 pages). The length, however, will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged for brevity and to facilitate understanding. 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.

The clinical overview should be presented in the following sequence:-

a) Product Development Rationale
b) Overview of Biopharmaceutics
c) Overview of Clinical Pharmacology
d) Overview of Efficacy
e) Overview of Safety
f) Benefits and Risks Conclusions
g) Literature References

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy (M4E) for guidance on the format and the content of this part.

***2.6* Non clinical summary**

The clinical overview is intended to provide a critical analysis of the clinical data in the CTD. Tabulated non-clinical summaries should be provided. However, tables may not be necessary for well known substances, but a proper justification for not providing them will be required.

The length of the non-clinical summaries will vary substantially according to the information to be conveyed, but it is recommended that the total length of the Non-Clinical Summaries in general not exceed 100-150 pages.

2.7 Clinical summary

The Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the CTD. A tabulated Clinical Summaries should be provided. However, tables may not be necessary for well known substances, but a proper justification for not providing them will be required.
Clinical Summary includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and post-marketing data for products that have been marketed in other regions.

The length of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will usually be in the range of 50 to 400 pages.

MODULE 3: QUALITY

3.1 Table of contents of Module 3

The table of content should list all documents included in Module 3.

3.2 Body of data

3.2.S Active Herbal Ingredient (AHI)

The information on API can be submitted in one of the following options:

a) Certificate of suitability (CEP),
b) Drug Master File (DMF), or
c) Complete information on the "*3.2.S active ingredient*" sections.

The API information submitted should include the following for each of the options used.

a) Certificate of Suitability (CEP)

A complete copy of the CEP (including any annexes) should be provided in *Module 1.* Along with the CEP, the applicant should submit the following:

(i) 3.2.S.1.3 General properties

Discussion on any additional applicable physicochemical and other relevant properties of the API that are not controlled by the CEP and Ph. Eur monograph, *e.g. solubility*

(ii) 3.2.S.4.1 Specifications

The specifications of the finished product manufacturer including all tests and limits of the CEP and Ph. Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph. Eur. monograph, such as -solubility and/or particle size distribution.

(iii) 3.2.S.4.2 / 2.3.2.S.4.3 Analytical procedures and validation

For any tests in addition to those in the CEP and Ph. Eur. Monograph.

(iv) 3.2.S.4.4 Batch analysis

Results from three batches of at least pilot scale, demonstrating compliance with the finished product manufacturer's API specifications.

(v) 3.2.S.5 Reference standards or materials

Information on reference standards used to analyse the active herbal ingredient product should be provided.

(vi) 3.2.S.6 Container closure system

The specifications including descriptions and identification of primary packaging components should be included in this section, except where the CEP specifies a re-test period.

(vii) 3.2.S.7 Stability

The stability can be included in this section, except where the CEP specifies a re-test period that is the same as or of longer duration than the re-test period proposed by the applicant.

b) Drug Master File (DMF)

Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the AHI may be submitted as DMF. In such cases, the *Open part* needs to be included *in its entirety* in the dossier as an annex to 2.3.2.S. In addition, the applicant/finished product manufacturer can complete the following sections:

(i) 3.2.S.1 General information 2.3.2.S.1.1 through 2.3.2.S.1.3
(ii) 3.2.S.2 Manufacture
- 3.2.S.2.1 Manufacturer(s)
- 3.2.S.2.2 Description of manufacturing process and process controls
- 3.2.S.2.4 Controls of critical steps and intermediates

(iii) 3.2.S.3.1 Elucidation of structure and other characteristics
(iv) 3.2.S.3.2 Impurities
(v) 3.2.S.4 Control of Drug Substance 3.2.S.4.1 through 3.2.S.4.5
(vi) 3.2.S.5 Reference standards or materials
(vii) 3.2.S.6 Container closure system
(viii) 3.2.S.7 Stability 3.2.S.7.1 through 3.2.S.7.1

c) Complete Information on the "3.2.S Drug Substance" Sections.

Information on the *3.2.S active ingredient* sections, including full details of chemistry, manufacturing process, quality controls during manufacturing for the drug substance, should be submitted in the dossier as outlined in the subsequent sections of these guidelines.

3.2.S.1 General information

The qualitative and quantitative composition of all the constituents of the product should be described as follows:-

Active substance(s)

Name(s)	Quantity and/or percentage	Reference

Excipient(s)

Name(s)	Quantity and/or percentage	Function	Reference

3.2.S.1.1 Nomenclature

For Active herbal Ingredient which is used in the finished herbal product in the form of **herbal material (s),** the following information should be provided:

a) Binomial scientific name of plant (genus, species, variety and author), and chemotype where applicable,
b) Other names (synonyms mentioned in Pharmacopoeias),
c) Parts of the plants,
d) Laboratory code.

For Active herbal Ingredient which is used in the finished herbal product in the form of **herbal preparation,** the following information should be provided:

a) Binomial scientific name of plant (genus, species, variety), and chemotype where applicable,
b) Other names (synonyms mentioned in Pharmacopoeias),
c) Parts of the plants,
d) Laboratory code,
e) Definition of the herbal preparation,
f) Ratio of the herbal substance to the herbal preparation,
g) solvent(s) of Extraction,
h) Possible added excipients *(e.g. preservatives, carrier)*.

3.2.S.1.2 Structure

The following information where applicable, should be provided:

a) Physical form,
b) Description of the constituents with known therapeutic activity or markers *(molecular formula, relative molecular mass, structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass) If appricable*,
c) Other constituent(s)
d) If relevant, toxic constituents.

3.2.S.1.3 General properties

A list should be provided of physicochemical and other relevant properties of API(s). This includes the physical description such as appearance and colour, density, particle size, flowability, solubility in common solvents, pH values, UV absorption, refractive index (for liquids), hygroscopicity, partition coefficient etc.

3.2. S.2 Manufacture

3.2. S.2.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer/supplier, including contractors, and each proposed production site or facility involved in production/collection and testing of the active herbal ingredient(s) should be provided. In addition, a valid manufacturing authorization for the production of active ingredient(s) and a certificate of GMP compliance or where appropriate commitment letters on adherence to GACP should be provided.

3.2. S.2.2 Description of manufacturing process and process controls

For **herbal material (s)**, information should be provided to adequately describe the plant production and plant collection for herbal products, including:

a) Geographical source of medicinal plant,
b) Cultivation, time of harvesting, collection procedure (according to the Good agricultural and collection practice for raw herbal materials) and storage conditions,
c) Batch size.

For **herbal preparation**, information should be provided to adequately describe the manufacturing process and in process controls of the herbal preparation including data on the herbal substance as described above. The following information on herbal preparation should be provided:

a) Description of processing (including flow diagram),
- Such as extraction, distillation, purification, concentration, fractionation or fermentation including information on preliminary treatment e.g inactivation of enzymes, grinding or defatting and microbial decontamination treatment.
- Where alternative extraction processes are proposed each should be clearly defined and described.

b) Solvents and reagents,
c) Purification stages: on intermediates and on herbal preparation,
d) Standardization: if preparations from herbal substances with constituents of known therapeutic activity are standardised (i.e. adjusted to a defined content of constituents with known therapeutic activity), it must be stated how such standardisation is achieved. If another substance is used for these purposes, it is necessary to specify as a range the quantity that can be added,
e) Batch size: a maximum batch size should be stipulated corresponding to batches already manufactured
f) Filling, storage and transportation (shipping): a description of the filling procedure, process controls (including in-process tests and operational parameters) and acceptance criteria should be provided. The container closure system(s) used for storage as well as storage and shipping should be described.

3.2. S.2.3 Control of materials

This is only applicable to herbal preparations. Materials used in the manufacture of the active ingredient(s) *(*e.g., raw materials, starting materials, solvents, reagents, catalysts*)* should be listed identifying where each material is used in the process. Information on the quality and control of each of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided as appropriate.

3.2. S.2.4 Controls of critical steps and intermediates

Applicable to herbal preparation where;
Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at the critical steps identified in 2.3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

3.2. S.2.5 Process validation and/or evaluation

Process validation and/or evaluation studies (based on historical data) should be provided, especially if it is a non-standard process (e.g. spray dried products). The decontamination process validation should be included if necessary.

3.2. S.2.6 Manufacturing Process Development

A brief summary describing the development of the herbal material(s) and herbal preparation(s) where applicable should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phytochemical composition of the herbal material(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s) where applicable described in S1 should be provided where appropriate.

3.2. S.3 Characterization

3.2. S.3.1 Elucidation of structure and other characteristics

For **herbal material(s)**, information on the botanical, macroscopical, microscopical, phytochemical characterisation and biological activity, if necessary, should be provided. For a non-compendia herbal substance iconography of the plant, the part of the plant and of the microscopical characters should be provided.

For **herbal preparation(s)**, information on the phytochemical and physicochemical characterisation and biological activity, if necessary, should be provided.

3.2. S.3.2 Impurities

For **herbal material(s)**, potential contaminants originating from the herbal substance production and post-harvesting treatments such as pesticides and fumigants residues, toxic metals, mycotoxins (aflatoxins, ochratoxin A), microbial contamination and radioactive contamination as well as potential adulterants should be discussed. Degradation products

should be studied if relevant, e.g. the study of the possible modifications occurring with decontamination treatments such as ionizing radiation.

For **herbal preparation(s)**, potential contaminants originating from the herbal substance production and post-harvesting treatments such as pesticides and fumigants residues, toxic metals, mycotoxins (aflatoxins, ochratoxin A), microbial contamination and radioactive contamination as well as potential adulterants should be discussed. Possible impurities originating from the process or from degradation should be listed and discussed with an indication of their origin (e.g. the study of the possible modifications occurring with decontamination treatments as ionizing radiation).The presence of potential residual solvents should be discussed.

3.2. S.4 Control of active ingredients

3.2. S.4.1 Specification

A specification is a list of tests, references to analytical procedures, appropriate acceptance criteria and reference of each tested parameter (e.g., USP, BP, in-house… etc). Copies of the API(s) specifications, dated and signed by the concerned individual(s) should be provided, including specifications for each API manufacturer as well as those of the finished product manufacturer.

In the case of herbal substance(s) described in a pharmacopoeia, applicant is expected to follow pharmacopoeia specifications. Otherwise, the following specifications should be submitted for non-pharmacopoeia herbal substance(s):

a) Characteristics.
b) Identification tests.
c) Purity tests:
    (i) Potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, radioactivity, fumigants,etc.
    (ii) Physical.
    (iii) Chemical.
d) Other tests.
e) Assay(s) of constituents with known therapeutic activity or of markers, or other justified determination.

For standardized herbal preparation, the content of constituents with known therapeutic activity must be indicated with the lowest possible tolerance (with both upper and lower limits). In the case of active markers used for quantified extracts the content of the markers has to be given as a defined range. In the case of an analytical marker of an extract for which neither constituents of known therapeutic activity, nor active markers are known, the specified minimum and maximum content is related to the validated analytical range as a base for analytical suitability within the frame of batch related control. The test methods should be described in detail.

If preparations from herbal substances with constituents of known therapeutic activity are standardized (i.e. adjusted to a defined content of constituents with known therapeutic activity) it should be stated how such standardization is achieved. If another substance is used for these purposes, it is necessary to specify as a range the quantity that can be added.

3.2. S.4.2 Analytical procedures

All analytical procedures used for testing of API(s) should be provided. Copies of the in-house analytical procedures used to generate testing results provided in the dossier, as well as those proposed for routine testing of the drug substance by the finished product manufacturer, should be provided. Unless modified, it is not necessary to provide copies of the compendia analytical procedures.

3.2. S.4.3 Validation of analytical procedures

Copies of the validation reports for the analytical procedures used to generate testing results provided in the dossier, as well as those proposed for routine testing of the API by the finished product manufacturer, should be provided. Validation data are not required for methods described in the Pharmacopeias.

3.2. S.4.4 Batch analyses

Description of batches and results of batch analyses should be provided. This would include information such as batch number, batch size, dates of production and analysis, site of production etc.

Certificates of analysis for at least two recent commercial-scale production batches should be provided. If data on commercial-scale batches are not available, certificates of analysis should be provided for pilot-scale batches manufactured using the same process as intended for commercial-scale batches. When alternatives / different production sites are described in the dossier, the results of the analysis of the batches shall be provided for each.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as *"all tests meet specifications"*. For quantitative tests *(e.g. assay test, individual and total impurity tests)* it should be ensured that actual numerical results are provided rather than vague statements such as *"within limits" "conforms"* or "*complies*". In cases of use of TLC, a coloured photographic picture should illustrate the results.

3.2. S.4.5 Justification of specification (s)

Justification for the proposed specification(s) should be provided unless it is based on a recognized pharmacopoeia monograph. This should include a discussion on the inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria. If the pharmacopoeia methods have been modified or replaced, a discussion should as well be included. The justification for certain tests, analytical procedures and acceptance criteria may have been discussed in other sections *(e.g. impurities)* and does not need to be repeated here, although a cross-reference to their location should be provided.

3.2.S.5 Reference standards or materials

If applicable Information on the reference standards or reference materials used for testing the API *(including their source(s))* should be provided. The composition of non-pharmacopoeia reference standards intended for use in assays should be adequately controlled and the purity should be measured by validated quantitative procedures. For non-pharmacopoeia standards, the supplier's name and the standard reference number should be provided and storage conditions should be stated.

3.2.S.6 Container closer system

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications.

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description, identification and critical dimensions with drawings, where appropriate. For non-functional secondary packaging components (*e.g., those that do not provide additional protection*), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with API(s), including sorption to container and leaching, and/or safety of materials of construction.

3.2. S.7 Stability

Herbal materials or preparations, shall comply with specifications before use (e.g. before extraction) if data are available.
Storage conditions and shelf life/retest period should be stated based on the data submitted.

3.2. S.7.1 Stability summary and conclusions

The ICH guidelines for "*Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products (FPPs)*" should be consulted for recommendations on the stability data required for the API(s) and finished product(s).

The types of studies conducted, protocols used and the results of the studies should be summarized. The summary should include information on storage conditions, batch number, batch size, container closure system and completed (and proposed) test intervals, results and conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

The discussion of results focuses on observations noted for the various tests, rather than reporting comments such as *"all tests meet specifications"*. Where the methods used in the stability studies are different from those described in S.4.2, descriptions and validation of the methodology used in stability studies should be provided.

3.2. S.7.2 Post-approval Stability Protocol and Commitment

The post-approval stability protocol and stability commitment should be provided. When available long-term stability data do not cover the proposed re-test period granted at the time of assessment of the dossier, a commitment should be made to continue the stability studies in order to firmly establish the re-test period. A written commitment (signed and dated) to continue long- term testing over the re-test period should be included in the dossier when relevant.

If the submission includes:

a) Long-term stability data on primary batches that do not cover the proposed re-test period, a written commitment (signed and dated) should be made to continue the stability studies through the proposed re-test period.

b) Long-term stability data on three production batches that do not cover the proposed re-test period, a written commitment (signed and dated) should be made to continue these studies through the proposed re-test period.
c) Long-term stability data on less than three production batches, a written commitment (signed and dated) should be made to continue these studies through the proposed re-test period and to place additional production batches, to a total of at least three, in long-term stability studies through the proposed re-test period.
d) Long-term stability data on pilot batches, a written commitment (signed and dated) should be made to place the first three production batches on long term stability studies through the proposed re-test period.

The stability protocol for the *commitment batches* should be provided and should include, but not be limited to, the following parameters:

(i) Number of batch(es) and different batch sizes, if applicable;
(ii) Relevant physical, chemical, microbiological and biological test methods;
(iii) Acceptance criteria;
(iv) Reference to test methods;
(v) Description of the container closure system(s);
(vi) Testing frequency;
(vii) Description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines and consistent with the drug substance labeling, should be used); and
(viii) Other applicable parameters specific to the drug substance.

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue *(e.g. changes in levels of degradation products)*. For this purpose, the ongoing stability programme should include at least one production batch per year of API *(unless none is produced during that year)*. In certain situations, additional batches should be included. Therefore, a written commitment *(signed and dated)* for ongoing stability studies should be included in the dossier.

Any differences in the stability protocols used for the primary batches and those proposed for the *commitment batches* or *ongoing batches* should be scientifically justified.

3.2. S.7.3 Stability Data

Results of the stability studies should be presented in an appropriate format such as tabular, graphical, or narrative and data for all testing parameters per each batch should be presented in one summary. The description of batches (batch size, date of production, date of analysis) should be provided. For quantitative tests *(e.g. individual and total degradation product tests and assay tests)*, it should be ensured that actual numerical results are provided rather than vague statements such as "*within limits*" or "*conforms*". Information on the analytical procedures used to generate the data and validation of these procedures should be included.

3.2.P Finished product

3.2.P.1 Description and composition of the finished product

A description of the herbal medicinal product and its composition should be provided. The information provided should include, for example:

a) Description of the dosage form.
b) Composition, i.e.:
    (i) list of all components of the dosage form,
    (ii) their amount on a per-unit basis (including overages, if any),
    (iii) the function of the components, and
    (iv) a reference to their quality standards (e.g. compendial monographs or manufacturer's specifications)
c) Description of accompanying reconstitution diluent(s)
d) Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

3.2.P.2 Pharmaceutical development

3.2.P.2.1 Components of the finished product

3.2.P.2.1.1 Active ingredient(s)

Key physicochemical characteristics *(e.g., water content, solubility, particle size distribution, ash value)* of the API(s) that can influence the performance of the herbal medicinal product should be discussed. For combination products, the compatibility of API with each other should be discussed.

3.2.P.2.1.2 Excipients

The choice of excipients listed in 2.3.2.P.1, their concentration and their characteristics that can influence the performance of the herbal medicinal product should be discussed relative to their respective functions. Where relevant, compatibility study results *(e.g. compatibility of a primary or secondary amine API with lactose)* should be included to justify the choice of excipients. Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies. Where relevant, the Antimicrobial preservatives are discussed in 2.3.2.P.2.5.

3.2.P.2.2 Finished product

3.2.P.2.2.1 Formulation development

A brief summary describing the development of the herbal medicinal product taking into consideration the proposed route of administration and usage should be provided. Results comparing the phytochemical composition of the products used in supporting bibliographic data and the product described in 3.2.P.1 should be discussed, where appropriate.

3.2.P.2.2.2 Overages

In general, use of an overage of API to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged. Any overages in the manufacture of the finished product whether they appear in the final formulated product or not, should be justified considering the safety and efficacy of the product. Information should be provided on the 1) amount of overage, 2) reason for the overage (e.g., to compensate for expected and documented manufacturing losses), and 3) justification for the amount of overage. The justification of an overage to compensate for loss during manufacture should be provided, including the step(s) where the loss occurs, the reasons for the loss and batch analysis (assay results). The overage should be included in the amount of API listed in the batch formula (3.2.P.3.2).

3.2.P.2.2.3 Physicochemical and biological properties

If possible parameters relevant to the performance of the herbal medicinal product such as pH, ionic strength, dissolution, re-dispersion, re-constitution, particle size distribution, aggregation, polymorphism, rheological properties, potency, biological and/or immunological activity should be discussed.

3.2.P.2.3 Manufacturing process development

The selection and optimization of the manufacturing process described in 3.2.P.3.3 and, in particular its critical aspects, should be discussed. The scientific rationale for the choice of the manufacturing, filling, and packaging processes that can influence finished product quality and performance should be discussed. The equipment should be identified by type and working capacity. Differences between the manufacturing processes used to produce pilot scale batches and the process used for commercial batches that can influence the performance of the product should be also discussed.

3.2.P.2.4 Container Closer system

The suitability of the container closure system (described in 2.3.2.P.7) used for the storage, transportation (shipping) and use of the herbal medicinal product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form *(including sorption to container and leaching)*, safety of materials of construction and performance. In case of using new packaging materials, the discussion should include the safety of those materials, in addition to the above mentioned requirements.

3.2. P.2.5 Microbiological attributes

Where appropriate the microbiological attributes of the dosage form should be discussed, including for example the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. A single primary stability batch of the finished product should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

3.2. P.2.6 Compatibility

If relevant, information on compatibility of the herbal medicinal product with reconstitution diluent(s) or dosage device (e.g. precipitation of API in solution stability) should be provided to provide appropriate and supportive information for the labeling.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The name, address and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of finished product should be provided. Evidence of GMP compliancy from each site should be submitted when applicable.

3.2.P.3.2 Batch formula

A batch formula for the intended batch size (an application for variable and/or alternative batch size should be justified) should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overage, and a reference to their quality standards. The components used in the manufacturing process should be declared by their proper or common names and a reference to their quality standards *(e.g. BP, USP)*.

3.2.P.3.3 Description of manufacturing process and process controls

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be well described with a greater level of detail.

Equipment should, at least, be identified by type (e.g. tumble blender, in-line homogeniser) and working capacity, where relevant. Executed batch manufacturing record should be submitted.

Steps in the process should have the appropriate process parameters identified, such as time, temperature or pH, hardness and friability of tablet cores, which will be coated. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 2.3.2.P.3.4. In certain cases, environmental conditions *(e.g., low humidity for an effervescent product)* should be stated.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section.

3.2.P.3.4 Controls of critical steps and intermediates

Appropriate tests and acceptance criteria *(with justification, including experimental data)* for critical steps identified in 3.2.P.3.3 of the manufacturing process to ensure that the process is controlled. Information on the quality and control of intermediates isolated during the process should be provided.

The following are examples for applicable in-process controls:

a) *Granulations:* Moisture (limits expressed as a range), blend uniformity *(e.g. low dose tablets)*, bulk and tapped densities, particle size distribution etc.
b) *Solid oral products:* Average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating etc.
c) *Semi-solids:* Viscosity, homogeneity, pH etc.
d) *Liquids:* Specific gravity, pH, clarity of solutions etc.

3.2.P.3.5 Process validation and/or evaluation

Copy of process validation protocol and report for at least three consecutive commercial batches should be provided for verification.

3.2.P.4 Control of excipients

3.2.P.4.1 Specifications

The specifications should be provided for all excipients, including those that may not be added to every batch *(e.g. acid and alkali)*, those that do not appear in the finished product *(e.g. solvents)* and any others used in the manufacturing process *(e.g. nitrogen, silicon for stoppers)*. For excipients of natural origin, microbial limit testing should be included in the specifications. For oils of plant origin *(e.g. soy bean oil, peanut oil)* the absence of aflatoxins or biocides should be demonstrated.

The colors permitted for use are limited to those listed in the EU "List of permitted food colors" and the FDA "Inactive ingredient guide". For proprietary mixtures, the supplier's product sheet with the qualitative formulation should be submitted, in addition to the finished product manufacturer's specifications for the product including identification testing.

3.2.P.4.2 Analytical procedures

The analytical procedures used for testing the excipients should be provided, where appropriate. Copies of the in-house analytical procedures used to generate testing results should be provided. Unless modified, it is not necessary to provide copies of the compendia analytical procedures.

3.2.P.4.3 Validation of analytical procedures

If possible analytical validation information for in house methods, including experimental data, for the analytical procedures used for testing the excipients should be provided

2.3.2.P.4.4 Justification of specifications

Justification for the proposed excipient specifications should be provided, where appropriate. For herbal excipients (e.g. in herbal teas combinations) full details of manufacture, characterization and control should be provided in order to justify the specification and at least one certificate of analysis of each excipients should be provided.

3.2.P.4.5 Excipients of human or animal origin

For excipients of human or animal origin (e.g. magnesium stearate, lactose, gelatin…) information should be provided regarding adventitious agents (e.g. sources, specifications, description of the testing performed, viral safety data etc). For excipients obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents *(e.g., ruminant origin)*, a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a BSE/TSE affected country/area. When available, a CEP demonstrating TSE-compliance should be submitted. A complete copy of the CEP (including any annexes) should be provided in Module 1.

3.2.P.4.6 Novel excipients

For excipient(s) used for the first time in a herbal medicinal product or by a new route of administration, full details of manufacture, characterization and controls, with cross references to supporting safety data (non clinical and/or clinical) should be provided.

3.2.P.5 Control of finished product

3.2.P.5.1 Specification(s)

The specification(s) for the herbal medicinal product should be provided. A copy of the finished product specification(s) (release and shelf-life specifications), dated and signed by authorized personnel (i.e. the person in charge of the quality control or quality assurance department), should be provided.
The specification(s) sheet should include:

(i) The tests;
(ii) Acceptance criteria;
(iii) The standard declared by the applicant (e.g. compendia or a in-house standard);
(iv) The specification reference number and version *(e.g. revision number and/or date)*;
(v) Analytical procedures, including their type *(e.g. visual, IR, HPLC …)*, source *(e.g. Ph.Eur., BP, USP, in-house)* and version *(e.g. code number/version/date)*.

Specifications should include at minimum, tests for appearance, identification, assay, purity, pharmaceutical tests *(e.g. dissolution)*, physical tests *(e.g. loss on drying, hardness, friability, particle size, apparent density)*, uniformity of dosage units, identification of coloring materials, identification and assay of antimicrobial or chemical preservatives *(e.g. antioxidants)* and microbial limit tests. *(refer to ICH's Q6A).*

Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified. Note that such differences for parameters such as dissolution are normally not accepted.

3.2.P.5.2 Analytical procedures

The analytical procedures used for testing the herbal medicinal product should be provided. Copies of the non-compendia analytical procedures used during pharmaceutical development (if used to generate testing results provided in the dossier) as well as those proposed for routine testing should be provided. Unless modified, it is not necessary to provide copies of the compendia analytical procedures.

3.2.P.5.3 Validation of analytical procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the herbal medicinal product, should be provided *(in accordance with ICH Q2(R1) and Q6B)*. Copies of the validation reports for the in-house analytical procedures used during pharmaceutical development (if used to support testing results provided in the dossier) as well as those proposed for routine testing should be provided.

Verification of compendia methods should be necessary. The compendia methods as published are typically validated based on API or a finished product originating from a specific manufacturer. Different sources of the same API or finished product can contain impurities and/or degradation products or excipients that were not considered during the development of

the monograph. Therefore the monograph and compendia method(s) should be demonstrated suitable for the control of the proposed finished product.

For compendia assay methods, verification should include a demonstration of specificity, accuracy and repeatability (method precision). If a compendia method is used to control related substances that are not specified in the monograph, full validation of the method is expected with respect to those related substances.

If a compendia standard is claimed and an in-house method is used in lieu of the compendia method *(e.g. for assay or related substance)*, equivalency of the in-house and compendia methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For related substance methods, the sample analyzed should be the placebo spiked with related substances at concentrations equivalent to their specification limits.

3.2.P.5.4 Batch analyses

A description of batches (strength, batch number, batch size, batch type, date and site of production, date of analysis) and results of at least three batches analyses should be provided. When different alternatives / different sites are described in the dossier, the results of the analysis of the batches shall be provided from each site.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". For quantitative tests it should be ensured that actual numerical results are provided rather than vague statements such as *"within limits"* or *"conforms"*. Dissolution results should be expressed at minimum as both the average and range of individual results.

A discussion and justification should be provided for any incomplete analyses *(e.g. results not tested according to the proposed specification)*.

3.2.P.5.5 Characterization of impurities

Information on the characterization of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities". The discussion should be provided for all impurities that are potential degradation products and finished product process-related impurities.

3.2.P.5.6 Justification of specification(s)

Justification for the proposed herbal medicinal product specification(s) should be provided. The discussion should be provided on the omission or inclusion of certain tests, evolution of tests, analytical procedures, and acceptance criteria, differences from compendia standard(s) etc. If the compendia methods have been modified or replaced, a discussion should be included.
The justification for certain tests, analytical procedures and acceptance criteria *(e.g. degradation products)* may have been discussed in other sections of the dossier and does not need to be repeated here, although a cross-reference to their location should be provided.

3.2.P.6 Reference standards or materials

Information on the reference standards or reference materials used for testing of the herbal medicinal product should include the following, if not previously provided in "3.2.S.5 Reference Standards or Materials":

a) The source of reference standards or reference materials (e.g., House, USP, BP, Ph. Eur.).
b) Certificate of analysis for reference standards or reference materials.
c) Characterization and evaluation of non-official (e.g., non-compendia) reference standards or reference materials (e.g., method of manufacture, elucidation of structure, certificate of analysis, calibration against an official standard).

3.2.P.7 Container Closer system

A description of the container closure systems should be provided including unit count or fill size, container size or volume, the identity of materials of construction of each primary packaging component, its specification and the supplier's name and address. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). The specifications for the primary packaging components should include a specific test for identification *(e.g. IR)*. Specifications for film and foil materials should include limits for thickness or area weight. Non-compendia methods (with validation) should be included where appropriate.
For non-functional secondary packaging components *(e.g., those that do not provide additional protection nor serve to deliver the product)*, only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be located in 2.3.2.P.2.4. Information to establish the suitability (e.g. qualification) of the container closure system should be discussed in Section 2.3.2.P.2.4. Comparative studies may be provided for certain changes in packaging components (e.g. comparative delivery study "droplet size" for a change in manufacturer of dropper tips).

3.2.P.8 Stability

3.2.P.8.1 Stability summary and conclusions

The guidelines on *"Stability Testing Requirements for Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs)"* should be followed for recommendations on the stability data required for the finished product(s).

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include information on storage conditions, strength, batch number *(including the API batch number(s) and manufacturer(s)), batch size, batch type, batch manufacturing date, container closure system (including where applicable the orientation e.g. inverted)* and completed (and proposed) testing intervals, results, as well as conclusions with respect to storage conditions and shelf-life and if applicable, in-use storage conditions and shelf-life.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". For quantitative tests *(e.g. individual and total degradation product tests and assay tests)*, it should be ensured that actual numerical results are provided rather than vague statements such as *"within limits" or "conforms"*. Dissolution results should be expressed at minimum as both the average and range of individual results.

Where the methods used in the stability studies are different from those described in 3.2.P.5.2, descriptions and validation of the methodology used in stability studies should be provided.

3.2.P.8.2 Post-approval stability protocol and stability commitment

Post-approval stability protocol and if applicable, stability commitment should be provided. When the available long-term stability data on primary batches do not cover the proposed shelf-life period granted at the time of assessment of the dossier, a commitment should be made to continue the stability studies in order to firmly establish the shelf-life period. A written commitment (signed and dated) to continue long-term testing over the shelf-life period should be included in the dossier.

Where the submission includes long-term stability data on three production batches covering the proposed shelf-life period, a post-approval commitment is considered unnecessary. Otherwise one of the following commitments should be made:

a) If the submission includes data from stability studies on three production batches, a written commitment (signed and dated) should be made to continue these studies through the proposed shelf-life period.
b) If the submission includes data from stability studies on less than three production batches, a written commitment (signed and dated) should be made to continue these studies through the proposed shelf-life period and to place additional production batches, to a total of at least three, in long-term stability studies through the proposed shelf-life period.
c) If the submission does not include stability data on production batches, a written commitment (signed and dated) should be made to place the first three production batches on long term stability studies through the proposed shelf-life period.

The stability protocol for the *commitment batches* should be provided and should include, but not be limited to the following parameters:

a) Number of batch(es) and different batch sizes, if applicable;
b) Relevant physical, chemical, microbiological and biological test methods;
c) Acceptance criteria;
d) Reference to test methods;
e) Description of the container closure system(s);
f) Testing frequency; and
g) Description of the conditions of storage

The stability of the drug product should be monitored over its shelf-life to determine that the product remains within its specifications and to detect any stability issue *(e.g. changes in levels of degradation products)*. For this purpose, the ongoing stability programme should include at least one production batch per year of product manufactured in every strength and container closure system *(unless none is produced during that year)*. Therefore, a written commitment *(signed and dated)* for ongoing stability studies should be included in the dossier.

Any differences in the stability protocols used for the primary batches and those proposed for the commitment *batches* or *ongoing batches* should be scientifically justified.

3.2.S.8.3 Stability Data

Results of the stability studies should be presented in a tabular format. The results of all testing parameters related to each batch for the entire testing period should be presented in one table *(i.e. presenting the results of one parameter of all batches in one table is not acceptable)*.

The actual stability results/reports used to support the proposed shelf-life should be provided in the dossier. For quantitative tests *(e.g. individual and total degradation product tests and assay tests)*, it should be ensured that actual numerical results are provided rather than vague statements such as *"within limits"* or *"conforms"*. Dissolution results should be expressed at minimum as both the average and range of individual results. Information on the analytical procedures used to generate the data and validation of these procedures should be included. Information on characterization of impurities is located in 3.2.P.5.5.

3.1.1 Literature References

A list and copies of all bibliographical references cited in support of this application should be provided. References that have not been provided should be available upon request.

MODULE 4: NON CLINICAL

4.1 Table of Contents of Module 4

A table of contents should be provided that lists all of the non-clinical study reports and indicate the location of each study report in the dossier.

4.2 Study Reports

A bibliographic review of the safety data and data necessary for assessing the safety of the product should be provided. The study report must clearly indicate the following information:

i. Route of administration
ii. Dose levels
iii. Number of animals or subjects per dose level
iv. Animals' or subjects' origin, gender, weight range and age
v. frequency at which observations were made
vi. Duration of each study
vii. The relationship between the time of administration and the onset of the effects observed; and
viii. All measurements made.

4.3 Pharmacology

i. Primary Pharmacodynamics. Studies on primary pharmacodynamics should be provided and evaluated.
ii. Secondary Pharmacodynamics
iii. Safety Pharmacology
iv. Pharmacodynamic Drug Interactions

Refer ICH Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and marketing authorization for Pharmaceuticals (M3) for the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals.

Refer ICH Guideline on Safety Pharmacology Studies for Human Pharmaceuticals (S7A) for the definition, objectives and scope of safety pharmacology studies. It also addresses which studies are needed before initiation of Phase 1 clinical studies as well as information needed for marketing.

Refer ICH Guideline on The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (S7B) for a non-clinical testing strategy for assessing the potential of a test substance to delay ventricular repolarization. This Guideline includes information concerning non-clinical assays and integrated risk assessments.

4.4 Pharmacokinetics

Refer ICH Guideline on Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies (S3B) for guidance on circumstances when repeated dose tissue distribution studies should be considered (i.e., when appropriate data cannot be derived from other sources). It also gives recommendations on the conduct of such studies.

4.5 Toxicology

Refer ICH Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies (S3A) for guidance on developing test strategies in toxicokinetics and the need to integrate pharmacokinetics into toxicity testing, in order to aid in the interpretation of the toxicology findings and promote rational study design development.

4.5.1 Single-Dose Toxicity (in order by species by route)

Reports of acute oral toxicity studies on at least one mammalian species should be provided, if available. The inclusion of the results of LD50 testing for each species and route of administration is not mandatory

If acute toxicity studies could not be performed due to presence of studies from similar herbal substance or preparation, it should be documented in the application.

4.5.2 Repeat-Dose Toxicity

Repeat-dose studies (short-term, sub-chronic and chronic toxicity) allow proper, long-term assessment of the substance or its metabolites, which may accumulate in the body. The length of the repeat-dose study should be related to the duration of the proposed therapeutic use of the substance

Generally, short-term use (up to a week) would need to be supported by a short-term, 28-day toxicity study; longer therapeutic use would require a sub-chronic (90 days) study; and prolonged use must be supported by long-term, chronic-exposure studies.

Refer The Committee for Human Medicinal Products (CHMP) Guidelines on repeated dose toxicity for guidance on the conduct of repeated dose toxicity studies of active substances intended for human use.

Refer ICH Guideline on Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing) (S4) for the considerations that apply to chronic toxicity testing in rodents and non-rodents as part of the safety evaluation of a medicinal product. The text incorporates the guidance for repeat-dose toxicity tests.

4.5.3 Genotoxicity

Mutagenicity studies are aiming to determine the potential for a substance to contribute to genetic damage in humans. Principally genotoxicity studies will generally comprise of:

a) an investigation of the potential to induce point mutations (base-pair substitution and frame shift) using Ames assays, with and without appropriate metabolic activation systems; and
b) an investigation of the potential to induce chromosome damage using mammalian cells *in vitro*, such as the chromosomal aberration assay, with and without appropriate metabolic activation systems.

If positive correlation is observed in either of the above two assays, the following two *in vivo* or *in vitro* tests shall be studied:

a) Studies aiming at investigation of the potential to induce cytogenetic damage, such as the micronucleus test in the bone marrow or other proliferative cells of intact animals;
b) Studies aiming at investigation of the potential to induce genotoxic damage involving other than cytogenetic damage (for example: unscheduled DNA synthesis (UDS) or P32 post-labelling adduct formation) and preferably using a tissue known or suspected to be a toxicity target for the substance.

Supplementary tests (for example: sister chromatid exchange) can also be used to provide clarification of unexpected or equivocal results in the basic test package, or to provide additional evidence. *In vivo* germ cell tests using laboratory animals (for example: mouse specific locus tests, heritable translocation assay) could also be considered for the evaluation of a suspected mammalian mutagen.

For more guidance refer ICH Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (S2) for specific guidance and recommendations for in vitro and in vivo tests and on the evaluation of test results.

4.5.4 Carcinogenicity

Where the conditions suggest the need for carcinogenicity study, data should be submitted. Refer ICH Guideline on Need for Carcinogenicity Studies of Pharmaceuticals (S1A, S1B & S1C) for a consistent definition of the circumstances under which it is necessary to undertake carcinogenicity studies on new drugs and methodology. . The use of other pharmacodynamic-, pharmacokinetic-, or toxicity-based endpoints in study design should be considered based on scientific rationale and individual merits.

a) Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
b) Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

c) Other studies

4.5.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly)

Refer ICH Guidance on Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility (S5) for guidance on tests for reproductive toxicity.
Refer Committee for Medicinal Products for Human use (CHMP) guidelines on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications for guidance on the need for, role and timing of studies in juvenile animals in the non-clinical safety evaluation of medicinal products for paediatric use.

a) Fertility and early embryonic development
b) Embryo-foetal development
c) Prenatal and postnatal development, including maternal function
d) Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.

4.5.6 Local Tolerance

Refer the Committee for Medicinal Products for Human Use (CHMP) guideline on Non-clinical local tolerance testing of medicinal products for recommendations on the evaluation of local tolerance to be performed prior to human exposure to the product. The purpose of these studies is to ascertain whether medicinal products are tolerated at sites in the body, which may come into contact with products as the result of its administration in clinical use.

4.5.7 Other Toxicity Studies (if available)

When appropriate Antigenicity, Immunotoxicity, Mechanistic studies (if not included elsewhere), Dependence, Metabolites, Impurities, Other toxicity studies, Photosafety evaluation should be submitted.

4.6 Literature References

A list of cited references should be provided. References that have not been provided should be available upon request.

MODULE 5: CLINICAL STUDY REPORTS

This module provides guidance on the organization of clinical study reports, other clinical data, and references within a Common Technical Document (CTD) for registration of a herbal product for human use. These elements should facilitate the preparation and review of a marketing application.

This section is not intended to indicate what studies are required for successful registration. It only indicates an appropriate organization for the clinical study reports that are in the application.

5.1 Table of Contents of Module 5

The table of content should list all documents included in Module 5.

5.2 Tabular Listing of All Clinical Studies

If applicable, if data is available or have been requested it should be presented in a tabular format to facilitate the understanding and evaluation of the results.

5.3 Clinical Study Reports

Efficacy of the product as well as information on the safety of use should be addressed in this section. Refer ICH Guidance on the Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy (M4E) for guidance on the content of this section.

Refer ICH guidelines for the structure and content of clinical study reports (E3).

a) Reports of Biopharmaceutical Studies
b) Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials where applicable,
    (i) Plasma Protein Binding Study Reports
    (ii) Reports of Hepatic Metabolism and Drug Interaction Studies
    (iii) Reports of Studies Using Other Human Biomaterials
c) Reports of Human Pharmacokinetic (PK) Studies where applicable,
    (i) Healthy Subject PK and Initial Tolerability Study Reports
    (ii) Patient PK and Initial Tolerability Study Reports
    (iii) Intrinsic Factor PK Study Reports
    (iv) Extrinsic Factor PK Study Reports
    (v) Population PK Study Reports
d) Reports of Human Pharmacodynamic (PD) Studies
    (i) Healthy Subject PD and PK/PD Study Reports
    (ii) Patient PD and PK/PD Study Reports
e) Reports of Efficacy and Safety Studies
    (i) Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
    (ii) Study Reports of Uncontrolled Clinical Studies
    (iii) Reports of Analyses of Data from More Than One Study
    (iv) Other Clinical Study Reports
f) Reports of Post-Marketing Experience if available
g) Case Report Forms and Individual Patient Listings. *Refer* ICH Guidelines on clinical trial studies

5.4 Literature References

A list of cited references should be provided. References that have not been provided should be available upon request.

Bibliography

1. Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products. Rev. 2. Committee on Herbal Medicinal Products (2007). EMA/HMPC/71049/2007
2. Guidance for industry. Botanical drug products. Rev. 1 (draft document). Rockville, Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration, 2016
3. ICH M3: Guidance on Nonclinical Safety Studies for the conduct of Human clinical trials and Marketing Authorization for Pharmaceuticals. ICH M3. CPMP/ICH/286/95, 2008
4. Guidance on equivalence of herbal extracts in Complementary Medicines. Version 1.0 Therapeutic Goods Administration, 2011.
5. Australian regulatory guidelines for complementary medicines. ARGCM Version 5.3 Therapeutic Goods Administration, 2015
6. Toxicological principles for the safety of food ingredients (Redbook 2000). US-FDA
7. Guidelines for assessing quality of herbal medicines with reference to contaminants and residues. WHO, 2007.
8. WHO Handbook of Non-Clinical Safety Testing

ANNEXURES

Annex I: CTD Format

Section	Requirements	
Module 1	**Administrative Information and Product Information**	
1.1	Cover letter	R
1.2	Comprehensive table of content	R
1.3	Application Form	R
1.4	Product Information	
1.4.1	Summary of Product Characteristics (SPC)	O
1.4.2	Labeling	R
1.4.3	Patent information leaflet (PIL)	IA
1.4.4	Artwork (Mock-ups)	R
1.4.5	Samples	R
1.5	Information on the experts	
1.5.1	Quality	O
1.5.2	Non-clinical	O
1.5.3	Clinical	O
1.6	Environmental Risk Assessment	IA
1.7	Pharmacovigilance	
1.7.1	Pharmacovigilance System	R
1.7.2	Risk Management Plan	O
1.8	Certificates and Documents	
1.8.1	GMP Certificate	R
1.8.2	CPP or Free-sales	R
1.8.3	Certificate of analysis – Drug Substance / Finished Product	R
1.8.4	Certificate of analysis – Excipients	R
1.8.5	BSE Certificate	R
1.8.6	CEP	R
1.8.7	Certificate of suitability for TSE	R
1.8.8	The diluents and coloring agents in the product formula	R
1.8.9	Patent Information	O
1.7.10	Letter of access or acknowledgment to DMF	IA
1.7.11	GCP or GLP Certificate	IA
1.7.12	List of Countries in which similar product is registered	R
Module 2	**Overview and Summaries**	
2.1	Table of Contents of Module 2-5	R
2.2	Introduction	R
2.3	Quality Overall Summary (QOS)	
2.3.S	Drug Substance/Active Ingredient	R
2.3.P	Drug Product/Finished Product	R
2.4	Nonclinical Overview	IA
2.5	Clinical overview	IA
2.6	Non-clinical Summaries	
2.6.1	Introduction	IA
2.6.2	Pharmacology Written Summary	IA

		2.6.3	Pharmacology Tabulated Summary	IA
		2.6.4	Pharmacokinetics Written Summary	IA
		2.6.5	Pharmacokinetics Tabulated Summary	IA
		2.6.6	Toxicology Written Summary	IA
		2.6.7	Toxicology Tabulated Summary	IA
	2.7	Clinical Summaries		
		2.7.1	Summary of Biopharmaceutic and Associated Analytical Methods	IA
		2.7.2	Summary of Clinical Pharmacology Studies	IA
		2.7.3	Summary of Clinical Efficacy	IA
		2.7.4	Summary of Clinical Safety	IA
		2.7.5	References	R
		2.7.6	Synopses of Individual Studies	R
Module 3		**Quality**		
	3.1	Table of Contents of Module 3		R
	3.2	Body of data		
		3.2.S	Drug Substance/Active Ingredient	
			3.2.S.1 General Information	
			3.2.S.1.1 Nomenclature	R
			3.2.S.1.2 Structure	R
			3.2.S.1.3 General Properties	R
			3.2.S.2 Manufacture	
			3.2.S.2.1 Manufacturer(s)	R
			3.2.S.2.2 Description of Manufacturing Process and Process Controls	IA
			3.2.S.2.3 Control of Materials	IA
			3.2.S.2.4 Control of Critical Steps and Intermediates	O
			3.2.S.2.5 Process Validation and/or Evaluation	O
			3.2.S.2.6 Manufacturing Process Development	O
			3.2.S.3 Characterization	
			3.2.S.3.1 Elucidation of Structure and Other Characteristics	R
			3.2.S.3.2 Impurities	R
			3.2.S.4 Control of Drug Substance	
			3.2.S.4.1 Specifications	R
			3.2.S.4.2 Analytical Procedures	R
			3.2.S.4.3 Validation of Analytical Procedures	R
			3.2.S.4.4 Batch Analyses	R
			3.2.S.4.5 Justification of Specification	R
			3.2.S.5 Reference Standards or Materials	R
			3.2.S.6 Container/Closure Systems	R
			3.2.S.7 Stability	
			3.2.S.7.1 Stability Summary and Conclusions	O
			3.2.S.7.2 Post-approval Stability Protocol and Commitment	O
			3.2.S.7.3 Stability Data	O
		3.2.P	Drug Product	

	3.2.P.1	Description and Composition of the Finished Product	R
	3.2.P.2	Pharmaceutical Development	
		3.2.P.2.1 Components of the Finished Product	
		3.2.P.2.1.1 Drug substance/Active Ingredient(s)	R
		3.2.P.2.1.2 Excipients	R
		3.2.P.2.2 Finished Product	
		3.2.P.2.2.1 Formulation Development	O
		3.2.P.2.2.2 Overages	R
		3.2.P.2.2.3 Physiochemical and Biological Properties	O
		3.2.P.2.3 Manufacturing Process Development	O
		3.2.P.2.4 Container Closure System	R
		3.2.P.2.5 Microbiological Attributes	R
		3.2.P.2.6 Compatibility	IA
	3.2.P.3	Manufacture	
		3.2.P.3.1 Manufacturer(s)	R
		3.2.P.3.2 Batch Formula	R
		3.2.P.3.3 Description of Manufacturing Process and Process Controls	R
		3.2.P.3.4 Controls of Critical Steps and Intermediates	O
		3.2.P.3.5 Process Validation and/or Evaluation	O
	3.2.P.4	Control of Excipients	
		3.2.P.4.1 Specifications	R
		3.2.P.4.2 Analytical Procedures	R
		3.2.P.4.3 Validation of Analytical Procedures	R
		3.2.P.4.4 Justification of Specifications	R
		3.2.P.4.5 Excipients of Human or Animal Origin	R
		3.2.P.4.6 Novel Excipients	R
	3.2.P.5	Control of Finished Product	
		3.2.P.5.1 Specifications	R
		3.2.P.5.2 Analytical Procedures	R
		3.2.P.5.3 Validation of Analytical Procedures	R
		3.2.P.5.4 Batch Analyses	R
		3.2.P.5.5 Characterization of Impurities	R
		3.2.P.5.6 Justification of Specifications	R
	3.2.P.6	Reference Standards or Materials	R
	3.2.P.7	Container/Closure System	R
	3.2.P.8	Stability	
		3.2.P.8.1 Stability Summary and Conclusions	R
		3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitments	R
		3.2.P.8.3 Stability Data	R
3.3	Literature References		
Module 4	**Non-Clinical Study Reports**		
4.1	Table of Contents of Module 4		R
4.2	Study Reports		IA
4.3	Literature References		R

Module 5	Clinical Study Reports	
5.1	Table of Contents of Module 5	R
5.2	Tabular Listing of All Clinical Studies	IA
5.3	Clinical Study Reports	IA
5.4	Literature References	R

Important Note:
R: Required
O: Optional (optional means that it might not be needed at this stage)
IA: If Applicable

It should be noted that Module 2 reflect the information provided in modules 3, 4 and 5.

Annex II: Application form

Application Number	TMDA use only
Date of submission of the dossier	TMDA use only
1.0 ADMINISTRATIVE AND PRODUCT INFORMATION	
1.1	Type of the medicinal product application New Renewal* * If variation has been made, information supporting the changes should be submitted (See TMDA variation guidelines for registered medicinal products)
1.2	Botanical name of the plant from which herbal substance is obtained
1.3	Active herbal Substance and solvent used for extraction e.g cinchona root bark 80% aqueous ethanol
1.4	Strength of Active Herbal Substance per unit dosage form
1.5	Name and address (physical and postal) of Applicant
(Company) Name: Address: Country: Telephone: Telefax: E-mail:	
1.6	Name and address (physical and postal) of Applicant
(Company) Name: Physical Address: Postal address Region Country: Telephone: Telefax: E-mail:	
1.7	Dosage form and route of administration
1.7.1	Dosage form:
1.7.2	Route(s) of administration
1.8	Packing/pack size:
1.9	Visual description (Add as many rows as necessary)
1.10	Proposed shelf life (in months):
1.10.1	Proposed shelf life (after reconstitution or dilution):
1.10.2	Proposed shelf life (after first opening container):
1.10.3	Proposed storage conditions:

1.10.4	Proposed storage conditions after first opening:
1.11	Other sister medicinal products registered or applied for registration
1.11.1	Do you hold Marketing Authorization(s) of other medicinal product(s) containing the same herbal substance(s) in the TMDA? If yes state; ▪ Product name(s), strength(s), pharmaceutical dosage form(s): ▪ Partner States where product is authorized: ▪ Marketing authorization number(s): ▪ Indication(s):
1.11.2	Have you applied for marketing authorization medicinal product(s) containing the same active substance(s) in the TMDA? If yes state; ▪ Product name(s), strength(s), pharmaceutical dosage form(s): ▪ Indication(s):
1.12	Pharmacotherapeutic group and ATC Code
1.12.1	Pharmacotherapeutic group:
1.12.2	ATC Code:
1.12.3	If no ATC code has been assigned, please indicate NA
1.13	Distribution category: Controlled Drug ☐ POM ☐ Pharmacy Only ☐ OTC ☐ General sale ☐ (Applicants are invited to indicate which categories they are requesting, however, the NMRAs reserve the right to change and/or apply only those categories provided for in their national legislation)
1.14	Country of origin:
1.15	Product Marketing Authorization in the country of origin (Attach Certificate of Pharmaceutical Product or free sale certificate from National Medicines Regulatory Authority). If not registered, state reasons

☐Authorized Country: Date of authorization (dd-mm-yyyy): Authorization number: ☐ Refused Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	☐ Withdrawn (by applicant after authorization) Country: Date of withdrawal (dd-mm-yyyy): Reason for withdrawal: ☐ Suspended/revoked (by competent authority) Country: date of suspension/revocation (dd-mm-yyyy): Reason for suspension/revocation:

1.16	Name(s) and complete physical address(es) of the manufacturer(s)
1.16.1	Name(s) and physical address (es) of the manufacturing site of the finished herbal product (FPP), including the final product release if different from the manufacturer. Alternative sites should be also declared here. state the role of each site (Add as many rows as necessary)

Name:
Company name:
Address:
Country:
Telephone:
Telefax:

E-Mail:	
1.16.2	**Name(s) and physical address(es) of the manufacturer(s) of the active pharmaceutical ingredient(s) (API)** (Add as many rows as necessary) All manufacturing sites involved in the manufacturing process of the herbal substance should be listed.
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.17	Name and address (physical and postal) of the local
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.18	State the reference/monograph standard such as WHO monograph of selected medicinal plants, British Pharmacopeia, United States Pharmacopeia, Ph. Eur, Japanese Pharmacopeia, In-house monograph e.t.c. used for herbal substance
1.19	Qualitative and Quantitative composition of the active substance(s) and excipient(s) A note should be given as to which quantity the composition refers (e.g. 1 capsule).

Name of active ingredient(s)*	Quantity / dosage unit	Unit of measure	Reference/ monograph
1.			
2.			
3.			
e.t.c			
Name Excipient(s)			
1.			
2.			
3			
e.t.c			

1.20	Name and address (physical and postal) of the Contract Research Organisation(s) where the clinical studies of the product were conducted.
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
2.0 DECLARATION BY AN APPLICANT	
I, the undersigned certify that all the information in this form and accompanying	

documentation is correct, complete and true to the best of my knowledge.

I further confirm that the information referred to in my application dossier is available for verification during GMP inspection.

I also agree that I shall carry out pharmacovigilance to monitor the safety of the product in the market and provide safety update reports to the TMDA.

I further agree that I am obliged to follow the requirements of the TMDA Legislations and Regulations which are applicable to medicinal products.

I also consent to the processing of information provided by the TMDA.

It is hereby confirmed that fees will be paid/have been paid according to the TMDA Fees and Charges Regulations*

Name: ……..…….
Position in the company:.……
Signature: ……..……
Date:……..
Official stamp:……..

* Note: If fees have been paid, attach proof of payment

Annex III: Expert Declaration Form

The following is an example of a suitable declaration form:

Quality /Non-clinical / Clinical (delete those not appropriate)

I, the undersigned, declare that I have:

i. The suitable technical or professional qualifications to act in this capacity (for more information, refer to the enclosed *curriculum* vitae).

ii. Fully examined the data provided by the applicant and have provided references to the literature to support statements made that are not supported by the applicant's original data. This report presents an objective assessment of the nature and extent of the data.

iii. Provided a report based on my independent assessment of the data provided.

iv. Based my recommendations, regarding suitability for registration, on the data provided herewith. I have considered the attached data and have recommended as to suitability for registration of the intended dose forms and presentations according to the proposed product information document.

I further declare that this expert report represents my own view.

Further, I declare the following to be the full extent of the professional relationship between myself and the applicant:

.....
.....
.....
.....

All rights reserved:
This is a controlled document. It must not be copied without authorization from the Manager Quality Management or Director General. Only originals or authorized copies shall be used as working documents.