

Data Requirements for Herbal & Health Products Submission

Content of the Dossier

Version 1.2

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Drug Sector
Saudi Food & Drug Authority
Kingdom of Saudi Arabia

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Note: For most recent update please refer to annex 2.

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Introduction

The information presented in this guidance is based on recommendations of the:

- EMA, as described in the “*Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products (2008)*”;
- WHO, as described in the “*Guideline on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part (2010)*”;
- EU, as described in the “*Notice to Applicants, Volume 2B: Presentation and content of the dossier (2006)*”; and
- EMA, as described in the “*Guideline on quality of herbal medicinal products/traditional herbal medicinal products (2006)*”;
- Health Canada, as described in the “*Evidence for Safety and Efficacy of Finished Natural Health Products (2006)*”.

All the required data should be in accordance with the CTD structure (*i.e. applicants should not modify the overall organization of the CTD as outlined in this guideline*).

The **requirements** in this guidance (table1) are applicable to **both** herbal and health product submission*. However, some **descriptions** are only specific for herbal products. Based on that, certain sections may not be relevant to Non-herbal products (Health products) such as vitamins, minerals, amino acids etc.. Examples on those sections include (Nomenclature 3.2.S.1.1, Structure 3.2.S.1.2, Description of Manufacturing Process and Process Controls 3.2.S.2.2, Manufacturing Process Development 3.2.S.2.6, Elucidation of Structure and other Characteristics 3.2.S.3.1, Impurities 3.2.S.3.2). Therefore, this guidance should be read in conjunction with the other relevant and applicable guidance documents such as Data Requirements for Human Drugs Submission. A copy of this document can be found on SFDA website.

*: This requirements is not applicable to products contain chemically synthesized material(s) (e.g.: antiseptic or antilice..etc) requirements for human drugs submission is more likely to be considered.

Table 1: The CTD Structure for Herbal and Health Submission

Section	Requirements	
Module 1	Regional Administrative Information	
1.0	Cover letter	R ¹
1.1	Comprehensive table of content	R
1.2	Application Form	R
1.3	Product Information	
1.3.1	Summary of Product Characteristics (SPC)	O
1.3.2	Labeling	R
1.3.3	Patient information leaflet (PIL)	
1.3.3.1	Arabic leaflet	IA
1.3.3.2	English leaflet	IA
1.3.4	Artwork (Mock-ups)	R
1.3.5	Samples	R
1.4	Information on the experts	
1.4.1	Quality	O ²
1.4.2	Non-clinical	O
1.4.3	Clinical	O
1.5	Environmental Risk Assessment	
1.5.1	Non-Genetically Modified Organism (Non-GMO)	IA
1.5.2	GMO	IA
1.6	Pharmacovigilance	
1.6.1	Pharmacovigilance System	R
1.6.2	Risk Management Plan	O
1.7	Certificates and Documents	
1.7.1	GMP Certificate	R
1.7.2	CPP or Free-sales	R
1.7.3	Certificate of analysis – Drug Substance / Finished Product	R
1.7.4	Certificate of analysis – Excipients	R
1.7.5	Alcohol-free declaration	R
1.7.6	Pork- free declaration	R
1.7.7	Certificate of suitability for TSE	R
1.7.8	The diluents and coloring agents in the product formula	R
1.7.9	Patent Information	O
1.7.10	Letter of access or acknowledgment to DMF	IA
1.8	Pricing	
1.8.1	Price list	IA
1.8.2	Other documents related	IA
1.9	Responses to questions	R

¹ R: Required

² O: Optional (optional means that it might not be needed at this stage)

Module 2³	Common Technical Document 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	R
2.3.P	Drug Product	R
2.3.A	Appendices	R
2.3.R	Regional Information	IA
2.4	Nonclinical Overview	IA ⁴
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	
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	
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 Module 2 Should reflect the information provided in modules 3, 4 and 5.

⁴ IA: If Applicable.

*: applicable for herbal medicinal product.

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 Drug Product	R
3.2.P.2	Pharmaceutical Development	
3.2.P.2.1	Components of the Drug Product	
3.2.P.2.1.1	Drug substance(s)	R
3.2.P.2.1.2	Excipients	R
3.2.P.2.2	Drug 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 Drug 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	IA
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	R
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

Module 1 Regional Administrative Information

1. Cover letter

The applicant shall include a cover letter for each submission. A template is provided in the *SFDA Guidance for Submission* (<http://www.sfda.gov.sa/En/Drug/Topics/Regulations+-+Guidelines.htm>).

1.1. Comprehensive table of content

The table of content for the entire submission should list all documents included in all Modules.

1.2. Application Form

The completed and signed application form printed out from the Saudi Drug Registration (SDR) system (<https://sdr.sfda.gov.sa/frmLogin.aspx>) should be presented in this section.

1.3. Product Information

This section contains the Summary of Product Characteristics (SPC), Labeling, Patient Information Leaflet (PIL) in Arabic and English, Artwork and the Samples.

1.3.1. Summary of Product Characteristics (SPC)

The SPC should include the name of the product, strength, pharmaceutical form, quantity of active ingredients, posology, method of administration, indications, contraindications, excipients, shelf-life and any special warnings and precautions for use ... etc.

Refer to the GCC Guidance for Presenting the SPC, PIL and Labeling Information (<http://www.sfda.gov.sa/En/Drug/Topics/Regulations+-+Guidelines.htm>).

1.3.2. Labeling

The labeling forms part of the authorization of the product and must therefore be approved by the SFDA. The text of the labeling must be in compliance with the SPC.

Refer to the GCC Guidance for Presenting the SPC, PIL and Labeling Information (<http://www.sfda.gov.sa/En/Drug/Topics/Regulations+-+Guidelines.htm>).

1.3.3. Patient Information Leaflet (PIL)

1.3.3.1. Arabic leaflet

1.3.3.2. English leaflet

The Patient Information Leaflet (PIL) forms part of the authorization of the product and must therefore be approved by the SFDA. The text of the PIL must be in compliance with the SPC. The application for a marketing authorization must include a draft for the PIL.

Refer to the GCC Guidance for Presenting the SPC, PIL and Labeling Information (<http://www.sfda.gov.sa/En/Drug/Topics/Regulations+-+Guidelines.htm>).

1.3.4. Artwork (Mock-ups)

A *mock-up* is a flat artwork design in full color, presented so that, following cutting and folding, where necessary, it provides a full size replica of both the outer and immediate packaging so that the two dimensional presentation of the label text is clear.

The application for a marketing authorization must include one or more mock-ups of the outer packaging and of the immediate packaging of the product.

Refer to the GCC Guidance for Presenting the SPC, PIL and Labeling Information (<http://www.sfda.gov.sa/En/Drug/Topics/Regulations+-+Guidelines.htm>).

1.3.5. Samples

A number of samples should be provided in order to perform complete testing. The required quantities of samples is further described in *the SFDA Guidance for Submission (<http://www.sfda.gov.sa/En/Drug/Topics/Regulations+-+Guidelines.htm>)*. The submitted samples must represent the final finished product to be marketed in Saudi Arabia.

1.4. Information on the experts

1.4.1. Quality

1.4.2. Non-Clinical

1.4.3. Clinical

It is important to emphasize that well prepared expert reports greatly facilitate the task of the SFDA in evaluating the 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 field concerned. The experts should preferably not have been personally involved in the conduct of the tests included in the dossier.

Each expert report should consist of:

- An abbreviated product profile;
- A critical evaluation of the dossier;
- The opinion of the expert as to whether sufficient guarantees have been provided as to the suitability of the product for its proposed use;
- A summary of all the important data;
- The signature of the expert and the place and date of the report's issue;
- 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.

1.5. Environmental Risk Assessment

1.5.1. Non-Genetically Modified Organism (Non-GMO)

1.5.2. GMO

The applicant shall 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.

1.6. Pharmacovigilance

1.6.1. 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. The detailed description of the pharmacovigilance system that the applicant should include it in this section is described in the *Saudi pharmacovigilance guideline of registered medicines* (http://www.sfda.gov.sa/NR/rdonlyres/6C3D8558-8406-45F6-88BF-121B9F1B2373/0/SaudiPharmacovigilanceGuidelineofRegisteredMedicines_2011.pdf).

1.6.2. Risk Management Plan

A detailed description of the risk management system which the applicant will introduce should be provided, where appropriate. The detailed description of a risk management system should be submitted in the form of SFDA Risk Management Plan (SFDA-RMP), as outlined in the *Saudi pharmacovigilance guideline of registered medicines* (http://www.sfda.gov.sa/NR/rdonlyres/6C3D8558-8406-45F6-88BF-121B9F1B2373/0/SaudiPharmacovigilanceGuidelineofRegisteredMedicines_2011.pdf).

1.7. Certificates and Documents

1.7.1. GMP Certificate

A valid GMP Certificate should be submitted.

1.7.2. CPP or Free-sales

The CPP should 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 (COO) should be submitted. Marketing authorization (or free sales certificate) should include the following:

1. Product trade name in the COO.
2. Number and date of marketing authorization in the COO.
3. Name of active and inactive substances with their concentrations.
4. A statement that certifies the product is marketed in the COO. If not, please specify the

reasons and provide a marketing authorization showing that the product is marketed in one of the countries approved by SFDA (reference member state in EU, USA, Canada, Switzerland, Australia, and Japan).

5. Provide official document demonstrating that the product has been registered for no less than one year in the COO.
6. Provide the Summary of Product Characteristics (SPC).
7. Provide a copy of the patient information leaflet (PIL).

1.7.3. Certificate of analysis – Drug Substance/Finished Product

- Certificates of analysis for more than one batch of the drug substance should be submitted from the supplier (drug substance manufacturer).
- Certificates of analysis for more than one batch of the drug substance should be submitted from the supplier finished product manufacturer.
- Certificates of analysis for more than one batch of the finished product should be submitted.

1.7.4. Certificate of analysis – Excipients

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

1.7.5. Alcohol-free declaration

This section should contain a declaration letter in an official company letterhead stating that the product is free from alcohol.

1.7.6. Pork-free declaration

This section should contain a declaration letter in an official company letterhead stating that the product is free from any materials of pork/porcine source.

1.7.7. Certificate of suitability for TSE

This section should contain a valid TSE Certificate of Suitability issued by the European Directorate for the Quality of Medicines (EDQM), which conforms the compliance of a substance with the relevant monograph of the European Pharmacopoeia.

1.7.8. The diluents and coloring agents in the product formula

This section should contain a declaration letter in an official company letterhead stating the diluents and coloring agents used in the product formula.

1.7.9. Patent Information

This section should contain a declaration letter in an official company letterhead stating the patent status of the product.

1.7.10. Letter of access or acknowledgment to DMF

A letter written by the DMF Owner or authorized Agent permitting SFDA to reference information in the DMF on behalf of the Applicant.

For more information about the certificates that must be authenticated *refer to the SFDA Guidance for Submission* (<http://www.sfda.gov.sa/En/Drug/Topics/Regulations+-+Guidelines.htm>).

1.8. Pricing

The applicant shall include the price of the product in countries listed in the *SFDA Guidance for Submission* (<http://www.sfda.gov.sa/En/Drug/Topics/Regulations+-+Guidelines.htm>).

1.9. Responses to questions

The response document should follow the same presentation as the initial dossier. The applicant should include in this section a document which lists the questions with the corresponding narrative text response for each question. This section will not be used for supporting technical documentation which will be included to the relevant Modules. Each question should be followed by the name of section, page number and a hyperlink where the answer can be found in the concerned Module.

2.1 Table of Contents of Module 2-5

The table of content should 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;
- 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*);
- Description of accompanying reconstitution diluent(s); and
- 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 justification that was not already 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 integrates 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.

⁵ Module 2 Should reflect the information provided in modules 3, 4 and 5.

The QOS normally should not exceed 40 pages of text, excluding tables and figures. The use of tables to summarize the information is encouraged, *where possible*.

2.4 Nonclinical Overview

A bibliographic review of the safety data and (upon additional request by the SFDA) 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 of module 2.4.

For more information regarding the recommended types of evidence to support a herbal and health product application, please refer to *Annex 1*.

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. For more information regarding the recommended types of evidence to support a herbal and health product application, please refer to *Annex 1*.

2.6 Non-Clinical Summaries

The Clinical Overview is intended to provide a critical analysis of the clinical data in the CTD. A 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 Summaries

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.

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.

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 Drug Substance

The drug substance information can be submitted in one of the following options:

1. Certificate of suitability (CEP); or
2. Drug master file (DMF); or
3. Complete information on the “3.2.S drug substance” sections.

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

1. 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:

a) 3.2.S.1.3 General properties

Discussions on any additional applicable physicochemical and other relevant drug substance properties that are not controlled by the CEP and Ph. Eur. monograph, *e.g. solubilities and polymorphs*.

b) 3.2.S.3.1 Elucidation of structure and other characteristics

Studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable.

c) 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 polymorphs and/or particle size distribution.

d) *3.2.S.4.2 / 3.2.S.4.3 Analytical procedures and validation*

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

e) *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.

f) *3.2.S.5 Reference standards or materials*

Information on the finished product manufacturer's reference standards.

g) *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.

h) *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.

2. Drug Master File (DMF)

Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the drug substance 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 3.2.S. In addition, the applicant/finished product manufacturer can complete the following sections:

a) *3.2.S.1 General information 3.2.S.1.1 through 3.2.S.1.3.*

b) *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

- c) 3.2.S.3.1 Elucidation of structure and other characteristics
- d) 3.2.S.3.2 Impurities
- e) 3.2.S.4 Control of Drug Substance 3.2.S.4.1 through 3.2.S.4.5
- f) 3.2.S.5 Reference standards or materials
- g) 3.2.S.6 Container closure system
- h) 3.2.S.7 Stability 3.2.S.7.1 through 3.2.S.7.1

3. Complete Information on the “3.2.S Drug Substance” Sections.

Information on the 3.2.S Drug Substance 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 this guideline.

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 **herbal substance(s)**, the following information should be provided:

- Binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable).
- Other names (synonyms mentioned in Pharmacopoeias).

- Parts of the plants.
- Laboratory code.

For the **herbal preparation**, the following information should be provided:

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

3.2.S.1.2 **Structure**

The following information where applicable, should be provided:

- Physical form.
- 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*).
- Other constituent(s).

3.2.S.1.3 **General Properties**

A list should be provided of physicochemical and other relevant properties of the drug substance. This includes the physical description, solubilities in common solvents, polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, 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 drug substance should be provided. In addition, a valid manufacturing authorization for the production of drug substance(s) and a certificate of GMP compliance should be provided.

3.2.S.2.2 **Description of Manufacturing Process and Process Controls**

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

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

For the **herbal preparation**, Information should be provided to adequately describe the manufacturing process of the herbal preparation as follows, including data on the herbal substance as described above.

- Description of processing (including flow diagram).
- Solvents, reagents.
- Purification stages.
- Standardisation.
- Batch size.

3.2.S.2.3 **Control of Materials**

Materials used in the manufacture of the drug substance (*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 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 Control of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps of the manufacturing process to ensure that the process is controlled.

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

3.2.S.2.5 Process Validation and/or Evaluation

Process validation and/or evaluation studies for aseptic processing and sterilization

3.2.S.2.6 Manufacturing Process Development

A brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable, taking into consideration the proposed route of administration and usage. Results comparing the phytochemical composition of the herbal substance(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 be discussed, where appropriate.

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and Other Characteristics

For herbal substances

Information on the botanical, macroscopical, microscopical, phytochemical characterization, and biological activity if necessary, should be provided.

For herbal preparations

Information on the phytochemical and physicochemical characterization, and biological activity if necessary, should be provided.

3.2.S.3.2 Impurities

For herbal substances

As a general rule, herbal substances must be tested, unless otherwise justified, for microbiological quality and for residues of pesticides and fumigation agents, toxic metals, likely contaminants and adulterants, etc. The use of ethylene oxide is prohibited for the decontamination of herbal substances.

For herbal preparations

In addition to the above, the concentration limits for process-related impurities (e.g., residual solvents) as per the applicable ICH guidance document should be discussed.

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specifications

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 drug substance specifications, dated and signed by the concerned individual(s) should be provided, including specifications for each drug substance manufacturer as well as those of the finished product manufacturer.

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

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

For standardised 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 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.

3.2.S.4.2 Analytical Procedures

All analytical procedures used for testing of drug substance(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 compendial 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 drug substance 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, date and 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.

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*” or “*conforms*”.

3.2.S.4.5 Justification of Specification

Justification for the proposed specification(s) should be provided. This should include a discussion on the inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria. If the compendial methods have been modified or replaced, a discussion should 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

Information on the reference standards or reference materials used for testing of the drug substance (*including their source(s)*) should be provided.

3.2.S.6 Container/Closure Systems

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 drug substance(s), including sorption to container and leaching, and/or safety of materials of construction.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

The GCC 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 drug substance(s) and finished product(s).

The types of studies conducted, protocols used, and the results of the studies can be summarized. The summary includes 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 can be provided.

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

The post-approval stability protocol and stability commitment can 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:

- 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.
- 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.
- 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.
- 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:

- Number of batch(es) and different batch sizes, if applicable;
- Relevant physical, chemical, microbiological and biological test methods;
- Acceptance criteria;
- Reference to test methods;
- Description of the container closure system(s);
- Testing frequency;
- 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
- Other applicable parameters specific to the drug substance.

The stability of the drug substance can 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 drug substance (*unless none is produced during that year*). In certain situations, additional batches can 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 can be presented in a tabular format and data for all testing parameters per each batch should be presented in one summary table. 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 can be included.

3.2.P Drug Product

3.2.P.1 Description and Composition of the Drug Product

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

- Description of the dosage form;
- 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*);

- Description of accompanying reconstitution diluent(s); and
- 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 Drug Product

3.2.P.2.1.1 Drug substance(s)

The compatibility of the drug substance(s) with excipients listed in 3.2.P.2.1.2 should be discussed. Additionally, key physicochemical characteristics (*e.g., water content, solubility, particle size distribution*) of the drug substance(s) that can influence the performance of the product should be discussed. For combination products, the compatibility of drug substances with each other should be discussed.

3.2.P.2.1.2 Excipients

The choice of excipients, their concentration, their characteristics that can influence the performance of the 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 3.2.P.2.5.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

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

3.2.P.2.2.2 Overages

In general, use of an overage of a drug substance 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 drug 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 drug substance listed in the batch formula (3.2.P.3.2).

3.2.P.2.2.3 Physiochemical and Biological Properties

Parameters relevant to the performance of the product, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity.

3.2.P.2.3 Manufacturing Process Development

The selection and optimization of the manufacturing process and, in particular its critical aspects, should be explained. The scientific rationale for the choice of the manufacturing, filling, and packaging processes that can influence drug product quality and performance can be discussed. The equipment can be identified by type and working capacity.

Differences between the manufacturing process(es) used to produce pilot scale batches and the process used for commercial batches that can influence the performance of the product should be discussed.

3.2.P.2.4 Container Closure System

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the 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*), and performance (*such as reproducibility of the dose delivery from the device when presented as part of the product*). In case of using new packaging materials, the discussion should include the safety of those materials, in addition to the above mentioned requirements.

For a device accompanying a multidose container, the discussion should provide the results that demonstrate the reproducibility of the device (e.g. consistent delivery of the intended volume), generally at the lowest intended dose.

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

The compatibility of the product with reconstitution diluent(s) or dosage devices (*e.g., precipitation of substance(s) in solution, stability*) should be addressed 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 the product should be provided, where appropriate. A valid manufacturing authorization and marketing authorization should be submitted. A GMP certificate should be submitted for each site where the major production step(s) are carried out, when applicable.

3.2.P.3.2 Batch Formula

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process (*including those that may not be added to every batch [e.g. acid and alkali], those that may be removed during processing [e.g. solvents] and any others [e.g. nitrogen, silicon for stoppers]*), and their amounts on a per batch basis, including overages. 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 described with a greater level of detail.

Equipment should, at least, be identified by type (*e.g., tumble blender*) and working capacity, where relevant. Steps in the process should have the appropriate process parameters identified, *such as time, temperature, or pH*. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 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:

– ***Granulations:***

Moisture (limits expressed as a range), blend uniformity (*e.g. low dose tablets*), bulk and tapped densities, particle size distribution, ...etc.

– ***Solid oral products:***

Average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating, ...etc.

– ***Semi-solids:***

Viscosity, homogeneity, pH, ...etc.

– ***Transdermal dosage forms:***

Assay of drug substance-adhesive mixture, weight per area of coated patch without backing, ...etc.

– ***Metered dose inhalers:***

Fill weight/volume, leak testing, valve delivery, ...etc.

– ***Dry powder inhalers:***

Assay of drug substance-excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters, ...etc.

– ***Liquids:***

Specific gravity, pH, clarity of solutions, ...etc.

3.2.P.3.5 Process Validation and/or Evaluation

Description, documentation, and results of the validation and/or evaluation studies can be provided for critical steps or critical assays used in the manufacturing process (*e.g., validation of the sterilization process or aseptic processing or filling*).

The following information can be provided:

- 1) A copy of the *process validation protocol*, specific to this finished product, that identifies the critical equipment and process parameters that can affect the quality of the finished product and defines testing parameters, sampling plans, analytical procedures and acceptance criteria;
- 2) A *commitment* that three consecutive, production-scale batches of this finished product will be subjected to *prospective validation* in accordance with the above protocol; and

3) If the process validation studies have already been conducted (*e.g. for sterile products*), a copy of the *process validation report* should be provided in the dossier in lieu of (1) and (2) above.

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 compendial analytical procedures.

3.2.P.4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data, for the non-compendial analytical procedures used for testing the excipients should be provided.

3.2.P.4.4 Justification of Specifications

Justification for the proposed excipient specifications should be provided, where appropriate.

This should include a discussion on the tests that are supplementary to those appearing in the compendial monograph.

3.2.P.4.5 Excipients of Human or Animal Origin

List of excipients that are of human or animal origin (including country of origin). Summary of the information (*e.g., sources, specifications, description of the testing performed, viral safety data*) regarding adventitious agents for excipients of human or animal origin should be provided.

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 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 Drug Product

3.2.P.5.1 Specifications

The specification(s) for the 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:

- The tests;
- Acceptance criteria;
- The standard declared by the applicant (*e.g.* compendial or a in-house standard);
- The specification reference number and version (*e.g. revision number and/or date*);
- 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 product should be provided. Copies of the non-compendial 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 compendial 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 drug 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 compendial methods can be necessary. The compendial methods, as published, are typically validated based on drug substance or a finished product originating from a specific manufacturer. Different sources of the same drug substance 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 compendial method(s) should be demonstrated suitable for the control of the proposed finished product.

For compendial assay methods, verification should include a demonstration of specificity, accuracy and repeatability (method precision). If a compendial 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 compendial standard is claimed and an in-house method is used in lieu of the compendial method (*e.g. for assay or related substance*), equivalency of the in-house and compendial 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 and results of batch analyses should be provided. The information provided should include such as strength, batch number, batch size, batch type, date and site of production.

Analytical results tested by the company responsible for the batch release of the finished product should be provided for not less than two batches of at least pilot scale batches. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

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 Specifications

Justification for the proposed drug 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 compendial standard(s), ... etc. If the compendial 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 product should include the following, if not previously provided in "3.2.S.5 Reference Standards or Materials":

1. The source of reference standards or reference materials (e.g., House, USP, BP, Ph. Eur.).
2. Certificate of analysis for reference standards or reference materials.
3. Characterization and evaluation of non-official (e.g., non-compendial) 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/Closure 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-compendial 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 3.2.P.2.4. Information to establish the suitability (*e.g. qualification*) of the container closure system should be discussed in Section 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 GCC guidelines for “*Stability Testing of 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 drug substance 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.

*: Long stability study performed at storage condition ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $60\% \text{RH} \pm 5\% \text{RH}$) can be accepted.

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitments

The 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:

- 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.
- 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.
- 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:

- Number of batch(es) and different batch sizes, if applicable;
- Relevant physical, chemical, microbiological and biological test methods;

- Acceptance criteria;
- Reference to test methods;
- Description of the container closure system(s);
- Testing frequency; and
- 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 every 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.P.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.

3.3 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 Study Reports

4.1 Table of Contents of Module 4

The table of content should list all documents included in Module 4.

4.2 Study Reports

A bibliographic review of the safety data and (upon additional request by the SFDA) data necessary for assessing the safety of the product should be provided. The review must be up-to-date, comprehensive and objective. For more information regarding evidence to support herbal and health product applications, please refer to *Annex 1*.

4.3 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

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. For more information regarding evidence to support herbal and health product applications, please refer to *Annex 1*.

5.4 Literature References

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

Annex 1: The Recommended Types of Evidence to Support a Herbal and Health Product Application

Introduction

Applicants must submit evidence from all relevant sources to support the safety and efficacy of the product. The required evidence will vary depending on the type of claim and it must be derived from non-clinical and/or clinical studies. However, non-clinical and clinical studies may not be required for traditional herbal medicine and health product applications.

Products are divided into two categories:

1. Traditional products; and
2. Non-traditional products.

1. Traditional products

- Traditional medicine (TM) refers to the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures.
- For products to be considered traditional, they should have at least 50 consecutive years of traditional use. This time span was chosen to represent two generations, allowing possible reproductive side effects to be identified.
- The dose and the method of preparation must be the same as those traditionally used.
- Products are divided into two sub-categories according to the evidence provided:
 - a) Pharmacopoeial evidence for traditional products; and
 - b) Non-pharmacopoeial evidence for traditional products.

a) Pharmacopoeial Evidence for Traditional products:

Products meeting this criteria only require one pharmacopoeial reference. The applicant must show that the following items in the dossier are identical to the pharmacopoeial reference:

- Medicinal ingredients;
- Quantity of crude material equivalent;

- Recommended dose;
- Recommended route of administration;
- Recommended duration of use;
- Dosage form;
- Directions of use;
- Risk information; and
- Method of preparation (traditional).

Applicants must ensure that copies of the relevant pages from a recognized pharmacopoeia are included as supporting evidence and accompanied by an English translation when the language of publication is not English.

b) Non-pharmacopoeial Evidence for Traditional products:

Applicants who make a traditional evidence but do not meet the requirements of the pharmacopoeia must provide at least two independent references⁶. The references must be reliable and from a reputable source.

2. Non-Traditional products:

Non-traditional products must be supported by scientific evidence (non-clinical and clinical studies).

Types of evidence

1. Clinical Studies

Evidence from clinical studies can provide valuable information about the efficacy and safety of the herbal product.

There are several types of clinical studies, including the following:

- Systematic reviews, such as meta-analyses of randomized controlled trials;

⁶ i.e. references that do not cite the same source, or each other, as the main source of information regarding the traditional use.

- Randomized controlled trials; and
- Non-experimental observational studies, such as epidemiological, cohort studies, or case-control studies.

2. Pharmacopoeias and Textbooks

Applicants may consult pharmacopoeias and relevant textbooks, since they may provide information that are not available from other sources (e.g. recommended duration of use).

3. Peer-Reviewed Published Articles

Applicants are encouraged to provide evidence from peer-reviewed sources.

4. Non-Clinical Studies

Data from non-clinical studies can also provide valuable information on pharmacokinetics, pharmacodynamics, toxicity information, reproductive effects and the potential genotoxicity or carcinogenicity of a particular ingredient.

5. Previous Marketing Experience

When available, information based on previous marketing experience of a finished product may be provided to supplement the evidence supporting the safety of the product.

Annex 2:

What's New in The Data Requirements for Herbal & Health Products Submission (version 1.2)?

The following table shows statements which added, deleted or replaced to the past version 1.1 April 16, 2013:

Section	Added statement
<i>Introduction</i>	*: This requirements is not applicable to products contain chemically synthesized material(s) (e.g.: antiseptic or antilice..etc) requirements for human drugs submission is more likely to be considered.
Section	Type of change
<i>Table 1: The CTD Structure for Herbal & Health Submission</i>	Update the requirements of the following sections of module 3 (quality): 3.2.S.2.2, 3.2.S.2.3, 3.2.S.7.1, 3.2.S.7.2, 3.2.S.7.3, 3.2.P.2.2.1, 3.2.P.2.2.3 and 3.2.P.2.3.
<i>3. Complete Information on the “3.2.S Drug Substance” Sections.</i>	Delete “and process validation” from the paragraph.
Section	Added statement
<i>3.2.P.8.1 Stability Summary and Conclusions</i>	*: Long stability study performed at storage condition (25o C ± 2o C/ 60% RH ± 5% RH) can be accepted