الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Data Requirements for Herbal & Health Products Submission

Content of the Dossier

Version 3.0

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Saudi Food & Drug Authority

Drug Sector

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

Version	Author	Date	Comments
1.1	Executive Directorate of Products Evaluation	16 April 2013	Final
1.2	Executive Directorate of Products Evaluation	12 February 2014	Update
Draft	Executive Directorate of Products Evaluation	-	Two drafts published for public review: Data Requirements for Health Supplements Submission, Date: 3 January 2019 Data Requirements for Herbal & Health Products Submission, Date: 5 March 2019
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2.2	Executive Directorate of Products Evaluation	06 June 2022	Update
3.0	Executive Directorate of Products Quality Evaluation	14 February 2024	Update (Next page shows the updated details)

What is New in version No. 3.0?

The following table shows the update to the previous version:

Section	Description of Change
1.7.9 Patent Information	**Add:** A declaration letter stating the patent status of the product.
1.7.11	**Add:** Marketing Authorization Holder
1.7.12	**Change:** Commercial Agency contract "Agent"
1.9. Responses to questions	**Add:** Instructions to the response document.
3.2.S.3.2 Impurities	**Add:** Note for Guidance on Specifications for Class 1 and Class 2 residual solvents in active substances
3.2.P.3.2 Batch Formula	**Modify and Add:** Providing a batch formula for all proposed individual batch sizes with an official letter.
3.2.P.4.1 Specifications	**Modify and Add:** Excipients Specifications.
3.2.P.5.1 Specifications	**Modify and Add:** Finished product specifications.
3.2.P.5.4 Batch Analyses	**Modify and Add:** A description of batches and results of batch analyses**.**
3.2.P.8 Stability	**Add:** Stability Summary and Conclusion.

Table of Contents

1. INTRODUCTION

1.1. Objectives

This guideline provides recommendations on the documentation requirements for the registration of herbal & health products.

1.2. Background

The SFDA has classified products that fall under this guidance into two categories:

- Health Products.
- Herbal Products.

SFDA will employ a risk-based approach taking into consideration elements of the product's quality, safety and efficacy.

1.3. Scope

This guideline clarifies the requirements for registration of products that are classified as herbal products or health products.

For more information, please refer to the SFDA's Products Classification Guidance.

1.4. Related guidelines

- Guidance for Presenting PIL and Labeling Information of Herbal and Health Products
- General Rules for Products containing Vitamins and Minerals
- SFDA's Products Classification Guidance
- Guidance for submission

2. DOCUMENTATION

Table 1: The CTD Structure for both health and herbal product 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[2]
1.3.2	Labeling	R
1.3.3	Patient information leaflet (PIL)	
1.3.3.1	Arabic leaflet	IA[3]
1.3.3.2	English leaflet	IA
1.3.4	Artwork (Mock-ups)	R
1.3.5	Samples	R
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	IA
1.7.9	Patent Information	IA
1.7.10	Letter of access or acknowledgment to DMF	IA
1.7.11	Marketing Authorization Holder	R
1.7.12	Commercial Agency contract "Agent"	R
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 or not needed at all depending on the product status and the course of the evaluation process) [3] IA: if applicable

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	R
3.2.S.2.3	Control of Materials	O
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	IA
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	IA
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	IA
3.2.S.6	Container/Closure Systems	O
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)	O
3.2.P.2.1.2	Excipients	O
3.2.P.2.2	Drug Product	
3.2.P.2.2.1	Formulation Development	IA
3.2.P.2.2.2	Overages	R
3.2.P.2.2.3	Physiochemical and Biological Properties	IA
3.2.P.2.3	Manufacturing Process Development	O
3.2.P.2.4	Container Closure System	O

3.2.P.2.5	Microbiological Attributes	O
3.2.P.2.6	Compatibility	O
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	O
3.2.P.4.3	Validation of Analytical Procedures	O
3.2.P.4.4	Justification of Specifications	IA
3.2.P.4.5	Excipients of Human or Animal Origin	IA
3.2.P.4.6	Novel Excipients	IA
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	IA
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	IA
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	IA

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	IA

2.1. Part 1 Administrative Information

Module 1 Regional Administrative Information

1.0 Cover letter

The applicant shall include a cover letter for each submission. The content of the cover letter should follow the cover letter template in Guidance for Submission guideline.

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 should be presented in this section.

1.3. Product Information

This section contains the Labeling, Patient Information Leaflet (PIL) in Arabic and English, Artwork and the Samples. (For more information, please refer to the *Guidance for Presenting PIL and Labeling Information of Herbal & Health Products*). The leaflet in Arabic and English should be provided if available.

1.7. Certificates and Documents

1.7.1. GMP Certificate

A valid GMP Certificate (or equivalent) 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.

Note: the certificate must be issued from a regulatory agency and authenticated by the Saudi embassy.

1.7.3. Certificate of analysis – Drug Substance / Finished Product

- Certificates of analysis for at least one batch of the drug substance should be submitted from the supplier (drug substance manufacturer).
- Certificates of analysis for at least 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 – 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 pharmacopeial parameters

1.7.5. Alcohol-free declaration

This section should contain a declaration letter in a Finished Product Manufacturer letterhead and stamped by Marketing Authorization holder in KSA stating that the product is free from alcohol.

1.7.6. Pork- free declaration

This section should contain a declaration letter in a Finished Product Manufacturer letterhead and stamped by Marketing Authorization holder in KSA 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 declaration or valid TSE Certificate of Suitability issued by the European Directorate for the Quality of Medicines (EDQM), which confirms 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, if any.

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

The DMF owner should specify which of the following options is chosen to present the drug substance information:

- Certificate of suitability (CEP); or
- Drug master file (DMF); or
- Complete information on the "3.2.S drug substance" sections.

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

1.7.11. Marketing Authorization Holder

This section should contain an Authorization Letter in a Finished Product Manufacturer letterhead appointing the Marketing Authorization Holder which is a company that owns the right to market the product in the Kingdom and is fully responsible for its quality, effectiveness, Safety and post-marketing surveillance after it is marketed as well as related procedures from the sale, withdrawal or discard.

1.7.12. Commercial Agency Contract "Agent"

A valid commercial agency registration certificate.

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.

2.2. Part 2 Technical Information

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 Drug Substance (Active Ingredients)

A maximum of two active ingredient sources are acceptable at the initial submission. 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. 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 retest 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 through3 .2.S.7.1

3. Information on the "3.2.S Drug Substance" Sections.

Information on the 3.2.S Drug Substance sections, including relevant 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(s) and complete postal address(es) of the manufacturing, packaging and testing site(s) of the active ingredient(s) should be provided, In the case of multiple sites, the role of each site should be clarified.

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

This applies to both health and herbal products. Additionally, 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.
- A list of all residual solvents and their limits of control, if any, were used during the manufacturing process.

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) can be listed identifying where each material is used in the process. Information on the quality and control of these materials can be provided in addition to information demonstrating that materials meet standards appropriate for their intended use.

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

It should be known that some solvents (e.g. acetone, toluene, ethanol, methanol, isopropanol, xylene, hexane, petroleum ether, chloroform and dichloromethane (methylene chloride)) may be contaminated with Class 1 solvents (e.g. benzene, carbon tetrachloride). Therefore, when these solvents are used in the manufacturing process of the final substance, and in particular in the purification steps, potential residues of their contaminant in an intermediate or in the final substance should be addressed *(refer to CPMP/QWP/450/03 Rev. 1, Annex I, B: Class 1 Solvents Present as an Impurity).*

According to the European "*Note for Guidance on Specifications for Class 1 and Class 2 residual solvents in active substances, annex to the CPMP/ICH/283/95 Impurities: Guideline for Residual Solvents,* three options may be used that support the absence of routine testing of the contaminant in the final substance. When one of the three options is met and demonstrated in the application, a routine test for Class I solvent in a suitable intermediate or in the final active substance is not required.

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 is 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.

− 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 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 (non-pharmacopeia)

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

Certificates of analyses should be submitted for at least two batches of each active ingredient.

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, 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 provide

3.2.S.6 Container/Closure Systems

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

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 can 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 are to be discussed. For combination products, the compatibility of drug substances with each other are to 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 is expected be discussed relative to their respective functions.

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

Any overages added to the formulation should be justified. If overages are added to compensate for losses of the active ingredient(s) during the manufacturing process, the stage(s) of manufacture where the loss of active ingredient(s) occurs should be identified. Overages for the sole purpose of extending the shelf-life of the finished product are generally not acceptable.

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.

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 is to 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 (s*uch 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 nonsterile 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*) can 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 (s) and complete postal address (es) of the manufacturing, packaging and testing site (s) of the finished product should be provided.

3.2.P.3.2 Batch Formula

A batch formula for all proposed individual batch sizes 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).

In addition, an official letter indicating the expected production size range and confirming that this range will not be changed before getting the SFDA approval.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

A flow diagram and a narrative description of the process should be presented and should include steps at which process controls are conducted.

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 can be provided.

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).

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 US 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 can 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 can be provided.

3.2.P.4.4 Justification of Specifications

Justification for the proposed excipient specifications should be provided in case of inhouse specifications.

3.2.P.4.5 Excipients of Human or Animal Origin

Excipients that are of human or animal origin (including country of origin) are to be listed. 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

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.

Generally, stability indicating parameters in specifications should have tighter release limits than shelf life.

The specification(s) sheet should include, but not be limited to, the following:

- The tests;
- Acceptance criteria;
- The standard declared by the applicant *(e.g. compendial or 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, pharmaceutical tests *(e.g. disintegration)*, 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 Q6A)*.

3.2.P.5.2 Analytical Procedures

The analytical procedures used for testing the product should be provided. Copies of 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 strength, batch number, batch size, batch type, date and site of production and API manufacturer.

The information on finished product batch analyses is recommended to be presented as follows:

Batch number	Batch size	Batch type	Site(s) of:		Date(s) of:		API manufacturer
			Manufacturing	Analysis	Manufacturing	Analysis	

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 system should be provided, including the identity of materials of construction of each primary and secondary packaging component.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusions

Every manufacturer should define the period of time during which, after being packaged for sale, the product will maintain its purity and physical characteristics and its medicinal ingredients will maintain their quantity per dosage unit and their potency. Therefore, the sponsor of the products is responsible for the shelf life. The sponsor must ensure that stability data exists to support the shelf life. The shelf life must be based on scientific data. SFDA may check the data through the internal regulatory mechanisms. The maximum shelf life permitted is five years and applies to the product in its final container. The maximum shelf life permitted is five years and applies to the product in its final container. Long-term stability study performed at storage condition (25 ^{o}C ± 2 ^{o}C / 60% RH ± 5% RH) can be accepted, however for products containing chemically synthesized material(s) (e.g.: antiseptic or antilice..etc), the study should be conducted at (30 ^{o}C ± 2 ^{o}C / 65% RH ± 5% RH).

A summary of stability study information is recommended to be presented as follows:

	Accelerated stability studies	Long term stability studies
Storage conditions (□C, % RH)		
FPP batch number		
Batch type		
Batch size		
Drug substance manufacturer(s)		
Completed testing intervals		
Proposed testing intervals		
Container closure system		
Manufacturing site		
Manufacturing date		
Stability starting date		
Conclusions with respect to storage conditions and proposed shelf-life		
Conclusions with respect to in-use storage conditions and shelf-life, if applicable		

In-use stability studies should be conducted in accordance with the GCC Guidelines for Stability Testing on at least two batches taking into consideration the following requirements:

- Stability protocol to be submitted including: number of batch(s), size of batch(s), tested parameters, manufacturing date and the starting date of the in-use stability study.
- The study design simulates the use of the product in practice.
- **ONE** of the batches should be chosen towards the **END** of its shelf-life (if available).
  If such results are not available:
  - **ONE** of the batches should be tested at the **FINAL POINT** of the submitted stability studies with
  - A **commitment** to conduct in-use stability study at the **END** of shelf-life and to report immediately any out of specifications to the SFDA.

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.

The information on the in-use stability study is recommended to be presented as follows:

Number of batches		
Batch numbers		
Batch type		
Batch size		
Manufacturing date		
Starting date of the study		
Tested parameters		
Is the study protocol submitted?	❍ Yes	❍ No

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 for at least 12 months should be available at submission and 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 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 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.

5.4 Literature References

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

The Recommended Types of Evidence to Support the safety and efficacy of a Herbal and Health Product Submission (Module 5)

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 as well as the type of the product.

1. Herbal Product:

Products containing herbs are divided into two categories depending on the nature and the intended usage of the herbal product:

1.1. Traditional herbal 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 meet at least one or more of the following criteria:

- A period of at least 30 years of traditional use. The dose and the method of preparation must be the same as those traditionally used.
- A corresponding product registered in any of the Stringent Regulatory Authorities (US FDA, EMA, MHRA, SwissMedic, Health Canada and TGA). The corresponding product should have the same active ingredients, indication, strength, pharmaceutical dosage form, dosing frequency and the same route of administration.
- A corresponding product registered by the SFDA. The corresponding product should have the same active ingredients, indication, strength, pharmaceutical dosage form, dosing frequency and the same route of administration.

Sources of evidence of traditional usage include:

- Regulatory documents related to traditional use, e.g. assessment report, community herbal monograph etc.
- Official expert committee reports or monographs from learned societies, e.g. WHO, Commission E, ESCOP etc
- Bibliographic evidence, e.g. pharmacopoeia
- Published information referring to specific product formulations, e.g. Old editions: Martindale: List of Preparations; Potter's New Cyclopaedia etc.
- List of traditionally used herbs currently in use in Stringent Regulatory Authorities.

Note: The supporting evidence must show that product has been used in practice for at least 30 years. Reference to a source published 30 years ago is not sufficient, as this simply demonstrates that the product was in use 30 years ago. There must also be a connection between the duration of use and the claimed use.

1.2. Non-Traditional herbal products (Stand-alone application):

Non-traditional herbal products must be supported by scientific evidence. Sources of acceptable evidence include:

- 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; systematic reviews, such as meta-analyses of randomized controlled trial, randomized controlled trials and non-experimental observational studies, such as epidemiological, cohort studies.
- Regulatory documents e.g. assessment report, community herbal monograph etc.

2. Health Product:

Depending on the nature and status of the health product, sources of acceptable evidence include:

- 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; systematic reviews, such as meta-analyses of randomized controlled trial, randomized controlled trials and non-experimental observational studies, such as epidemiological, cohort studies.
- Regulatory documents e.g. assessment report, community herbal monograph etc.

3. APPENDIX

Appendix 1

This appendix is a part of the "*Data Requirement for Herbal and Health Products Submission*" and addresses health products that have previously been required to be listed at the Saudi Food and Drug Authority and are now required to be **registered as Health product** in order to be marketed in Saudi Arabia.

This group of products includes the following:

1. Alcohol hand sanitizers composed of these ingredients:
   - Ethanol 60-80%.
   - Isopropanol 70 %.
2. Throat lozenges which consist only of volatile oils, ascorbic acid (or its salts) and at least menthol with no unacceptable claim and at a concentration of 5 mg or higher. The concentration of the individual ingredients (menthol, eucalyptus oil and Ascorbic acid) must not exceed the maximum value as follows:
   - Menthol 5-20 mg
   - Eucalyptus oil 0.5-15 mg
   - Ascorbic acid 100 mg
3. Topical products containing organic acids (Alpha-hydroxy acids (AHAs)) where the total concentration of organic acids is higher than 10%.
4. Skin Care Products containing urea in a concentration greater than the recommended by the GSO standards for cosmetic products.
5. Aromatic and medicinal herbal oils that contain one or more of the oils that are extracted from medicinal plants, that have non nutritional claims and are used internally.
6. Products containing medicinal herbs that are not in their natural form and have gone through any manufacturing processes such as grinding, extraction, packaging or any other manufacturing process.

7. Insect repellents in direct contact with human skin.
8. Topical patches, creams, ointments and gels containing counter irritant ingredient as an externally applied substance that causes irritation or mild inflammation of the skin for the temporary relieve of pain in muscles or joints by reducing inflammation in deeper adjacent structures (these products should comply with the Canadian Counterirritant monograph).

The following requirements are considered minimum at the time of submission and are subject to change. The Saudi Food and Drug Authority reserves the right to request additional documents on a case-by-case basis:

Section	Requirements	
Module 1	**Regional Administrative Information**	
1.0	Cover letter	R
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
1.7	Certificates and Documents	
1.7.1	GMP Certificate	O
1.7.2	CPP or Free-sales	R
1.7.3	Certificate of analysis – Drug Substance / Finished Product	IA
1.7.4	Certificate of analysis – Excipients	O
1.7.5	Alcohol-free declaration	IA

1.7.6	Pork- free declaration	R
1.7.7	Certificate of suitability for TSE	IA
1.7.8	The diluents and coloring agents in the product formula	IA
1.7.9	Patent Information	IA
1.7.10	Letter of access or acknowledgment to DMF	IA
1.7.11	Marketing Authorization Holder	R
1.7.12	Commercial Agency contract "Agent"	R
1.8	Pricing	
1.8.1	Price list	IA
1.8.2	Other documents related	IA
1.9	Responses to questions	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	O
3.2.S.1.2	Structure	O
3.2.S.1.3	General Properties	O
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	O
3.2.S.2.3	Control of Materials	O
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	O
3.2.S.3.2	Impurities	O
3.2.S.4	Control of Drug Substance	
3.2.S.4.1	Specifications	O
3.2.S.4.2	Analytical Procedures	O

3.2.S.4.3	Validation of Analytical Procedures	O
3.2.S.4.4	Batch Analyses	O
3.2.S.4.5	Justification of Specification	O
3.2.S.5	Reference Standards or Materials	O
3.2.S.6	Container/Closure Systems	O
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)	O
3.2.P.2.1.2	Excipients	O
3.2.P.2.2	Drug Product	
3.2.P.2.2.1	Formulation Development	O
3.2.P.2.2.2	Overages	O
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	O
3.2.P.2.5	Microbiological Attributes	O
3.2.P.2.6	Compatibility	O
3.2.P.3	Manufacture	
3.2.P.3.1	Manufacturer(s)	R
3.2.P.3.2	Batch Formula	O
3.2.P.3.3	Description of Manufacturing Process and Process Controls	O
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	O
3.2.P.4.3	Validation of Analytical Procedures	O

3.2.P.4.4	Justification of Specifications	O
3.2.P.4.5	Excipients of Human or Animal Origin	O
3.2.P.4.6	Novel Excipients	O
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	O
3.2.P.5.4	Batch Analyses	R
3.2.P.5.5	Characterization of Impurities	O
3.2.P.5.6	Justification of Specifications	O
3.2.P.6	Reference Standards or Materials	R
3.2.P.7	Container/Closure System	R
3.2.P.8	Stability[3]	
3.2.P.8.1	Stability Summary and Conclusions	IA
3.2.P.8.2	Post-Approval Stability Protocol and Stability Commitments	O
3.2.P.8.3	Stability Data	IA
3.3	Literature References	IA

[3] Is required for products that claim a shelf life of more than two years