الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Data Requirement for Veterinary Herbal Medicinal Products

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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

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I. Introduction

This guideline is mainly adapted from a revised version of both the EMA Guideline on quality of herbal medicinal products/traditional herbal medicinal products and the SFDA Data Requirements for Veterinary Medicinal Products.

This guideline is published to assist applicants in the preparation of Veterinary Herbal Medicinal Products (VHMP) submissions for presentation to the Saudi Food and Drug Authority (SFDA).

The data requirements for VHMP for each application will differ, based on the type of product VHMP, such as traditional medicines, vitamins, and minerals. However, the presentation and content of Part 1 (summary of the dossier) is similar for all types and will slightly differ in Parts 2, 3, and 4. For VHMP, parts 2, 3 and 4 of the dossier consist of quality, safety and residue tests, preclinical and clinical, respectively.

1. Scope

This guideline intends to cover the general quality aspects of veterinary herbal medicinal products, including traditional herbal medicinal products. Products containing chemically defined isolated constituents or a mixture thereof are not herbal medicinal products.

The guideline should also be read in conjunction with Annex 7 “Manufacture of Herbal Medicinal Products” of Good Manufacturing Practice (GMP) for Medicinal Products,

Consistent quality for products of herbal origin can only be assured if the starting materials are defined in a rigorous and detailed manner, particularly the specific botanical identification of the plant material used. It is also important to know the geographical source and the conditions under which the herbal substance is obtained to ensure material of consistent quality.

2. Veterinary Herbal Medicinal Products

Any plant or herb manufactured in a pharmaceutical dosage form and presented for the purpose of preventing or treating a disease in an animal.

However, it should be noted that preparations consisting of dried or crushed herb(s) which form a minor component of a product intended for oral administration to healthy animals, as part of the animal's diet, are not regarded as herbal veterinary medicines provided that:

- No indication for use of the product as an herbal veterinary medicine is made.
- None of the herbal substance(s) has pharmacological action on physiological function at the dose administered to the target animal, or the quantity of herb(s) is representative of that which might reasonably be expected to be ingested by an animal grazing on native pasture.

Part 1 (Summary of the dossier) for Veterinary Herbal Medicinal Products (VHMP)

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1b5	Samples
1c	**Critical Summaries**
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1c2	Safety and Residues
1c3	Efficacy

1a Administrative Information

1a1 Cover Letter

The applicant shall include a cover letter for each submission. A template provided in the SFDA Guidance for Submission.

1a2 Application Form

The completed and signed application form printed out from the Saudi Drug Registration (SDR) system should be presented in this section.

1a3 Pharmacovigilance

1a31 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.

1a32 Risk Management Plan

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

1a4 Certificates and Documents

1a41 GMP Certificate

A valid GMP Certificate should be submitted.

1a42 Certificate of Pharmaceutical Product (CPP)

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.
5. Provide official document demonstrating that the product has registered for no less than one year in the COO.
6. Provide the Summary of Product Characteristics (SPC).
7. Provide a copy of the Package Leaflet (PL).

1a43 Certificate of Analysis – Drug Substance and Finished Product

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

1a44 Certificate of Analysis – Excipients

Certificates of analysis for more than one batch of the excipients may submitted to support the application.

1a45 Certificate of Suitability for TSE

Data should be provided to confirm that the drug substance, starting materials and reagents and/ or culture media used to manufacture of the VHMP are submitted according to *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*. When available, a CEP demonstrating TSE-compliance should be submitted. A complete copy of the CEP (including any annexes) should be provided.

1a46 Patent Information

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

1a47 Letter of Access or Acknowledgment to DMF (If applicable)

A letter should be 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 authenticated refer to the DMF: Guidance for Submission.

1a5 Pricing

1a51 Price List

The applicant shall include the price of the product in countries listed in the SFDA Guidance for Submission.

1a52 Other Documents Related

1a6 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 use for supporting technical documentation, which will be included to the relevant Parts. Each question should followed by the name of section, page number and a hyperlink where the answer can be found in the concerned part.

1a7 Additional Data

Information relating to the administration of the veterinary medicinal product not covered by the previous sections may be included in this section.

1b SPC and Product Literature

1b1 Summary of Product Characteristics (SPC)

Refer to the Guidance for presenting the SPC, PL and labeling information for veterinary products.

1b2 Package Leaflet (PL)

Refer to the Guidance for presenting the SPC, PL, and labeling information for veterinary products.

1b21 Arabic Leaflet

1b22 English Leaflet

1b3 Labeling

Refer to the Guidance for presenting the SPC, PL, and labeling information for veterinary products.

1b4 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 Guidance for presenting the SPC, PL, and labeling information for veterinary products.

1b5 Samples

A number of samples should provide to perform complete testing. The required quantities of samples further described in the SFDA Guidance for Submission. The submitted samples must represent the final finished product to be marketed in Saudi Arabia.

1c Critical Summaries (CS)

1c1 Quality

1c2 Safety

1c3 Efficacy

The Quality, Safety, Efficacy Summary is a summary that follows the scope and the outline of the Body of Data. The CS should not include information, data or justification that was not already included in each part or other parts of the structure. The CS should include sufficient information from each section to provide the reviewer with an overview of each part. The CS should include a discussion of key issues that integrates information from sections in the Quality, Safety, Efficacy part and supporting information from another part. This CS normally should not exceed 40 pages of text, excluding tables and figures. For biotech, products and products manufactured using processes that are more complex, the document could be longer but normally should not exceed 80 pages of text (excluding tables and figures). The use of tables to summarize the information is encouraged, where possible.

II. Data Requirements for Veterinary Herbal Medicinal Products (VHMP)

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2b2	Description of the Manufacturing Process and Process Controls
2b3	Facility, Equipment, Controls of Critical Steps and Intermediates
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2c4	Substances of Biological Origin
2d	**Control Tests at Intermediate Process Stages**
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Part 3	**Safety and Residues Tests**
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3b	**Residue tests**

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Part 4	**Preclinical and Clinical Trials**
4a	**Preclinical Requirements**
4a1	Pharmacology
4a2	Resistance
4a3	Target Animal Tolerance
4b	**Clinical Requirements**
4b1	Clinical Trials

Part 2 Quality Documentation

All test procedures shall fulfill the criteria for analysis and control of the quality of the starting materials and the finished product. The results of the validation studies shall be provided.

The pharmaceutical data shall include information on the manufacturing process, characterization and properties, quality control procedures and requirements, stability, as well as a description of the composition, development, and presentation of the VHMP for the active substance(s) and the finished product.

2a Qualitative and Quantitative Particulars

2a1 Qualitative Particulars

Qualitative particulars of all the constituents of the VHMP shall mean the designation or description of:

- The active substance (s),
- The constituent (s) of the excipients, whatever their nature or the quantity used, including preservatives, adjuvants, stabilizers, thickeners, emulsifiers, coloring matter, flavoring, aromatic substances
- The constituents, intended to be ingested or otherwise administered to animals, of the outer covering of the veterinary medicinal products, such as capsules, gelatin capsules.

These particulars shall be supplemented by any relevant data concerning the immediate packaging and if relevant the secondary packaging and, where appropriate, its manner of closure, together with details of devices with which the Veterinary Herbal Medicinal Products will be used or administered and which will be supplied with the medicinal product.

2a2 Usual Terminology

The usual terminology to be used in describing the constituents of the VHMP:

1. in respect of constituents which appear the Pharmacopoeia

2. in respect of other constituents, the international non-proprietary name (INN) recommended by the World Health Organization (WHO), which may be accompanied by another non-proprietary name, or, failing these, the exact scientific designation; constituents not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,

2a3 Quantitative Particulars

In order to give the 'quantitative particulars' of all the active substances of the VHMP, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance.

Units of biological activity shall be used for substances, which cannot be defined chemically. Where an International Unit of biological activity has been defined by the WHO, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable pharmacopoeia Units.

Whenever possible, biological activity per units of mass or volume shall be indicated. This information shall be supplemented:

- in respect of single-dose preparations, by the mass or units of biological activity of each active substance in the unit container, taking into account the usable volume of the product, after reconstitution, where appropriate,
- in respect of VHMP to be administered by drops, by the mass or units of biological activity of each active substance contained per drop or contained in the number of drops corresponding to 1 ml or 1 g of the preparation,
- in respect of syrups, emulsions, granular preparations and other pharmaceutical forms to be administered in measured quantities, by the mass or units of biological activity of each active substance per measured quantity.

- Active substances present in the form of compounds or derivatives shall be described quantitatively by their total mass, and if necessary or relevant, by the mass of the active entity or entities of the molecule.

Active substances present in the form of compounds or derivatives shall be described quantitatively by their total mass, and if necessary or relevant, by the mass of the active entity or entities of the molecule.

All herbal substances/herbal preparations are essentially defined by their production process and their specifications

- Standardised herbal substances/herbal preparations are adjusted to a given content of constituents with known therapeutic activity within an acceptable tolerance; standardisation is achieved by adjustment of the herbal substances/herbal preparations with excipients or by blending batches of herbal substances and/or herbal preparations.
- Quantified herbal substances/herbal preparations are adjusted to a defined range of constituents (active markers); adjustment is exclusively achieved by blending batches of herbal substances and/or herbal preparations.
- Other herbal substances/herbal preparations are active substances for which neither constituents with known therapeutic activity nor active markers are known. These herbal substances/herbal preparations are not adjusted to a defined content of analytical marker.

In cases where excipients for the manufacture of active substances are used (e.g. for technological reasons or for adjustment of standardised herbal substances/preparations), the name and the quantity of these excipients have to be stated.

2a3.1 Herbal substances and herbal preparations consisting of comminuted or powdered herbal substances

For herbal substances and herbal preparations consisting of comminuted or powdered herbal.

substances the grade of comminution has to be given. Furthermore, the following has to be indicated:

- in the case of standardisation: the quantity of the herbal substance/preparation shall be given as a range corresponding to a defined quantity of constituents with known therapeutic activity.
- in the case of quantification: the quantity of the herbal substance/preparation shall be stated as a distinct content and the content of the quantified substance(s) shall be specified in a range.
- for all other cases: the quantity of the herbal substance or the quantity of the genuine herbal preparation shall be stated as a distinct content.

Examples

Active Substance Name	Quantity
Sennae Folium	415-500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B
Salicis Cortex	4 g, corresponding to 40 to 48 mg of total phenolic glycosides, expressed as salicin
Valerianae radix	900 mg

2a3.2 Herbal preparations produced by steps, which exceed comminution

In the case of a herbal preparation produced by steps which exceed comminution, the nature and concentration of the solvent and the physical state of the extract have to be given. Furthermore the following has to be indicated:

- Standardised extracts: the equivalent quantity of the herbal substance x - y (*), or the ratio (a - b): 1 (*) of the herbal substance to the genuine herbal preparation shall be stated and the quantity of the genuine herbal preparation may be given as a range corresponding to a defined quantity of these constituents (see example).
- Quantified extracts: the equivalent quantity of the herbal substance x - y (*), or the ratio (a - b): 1 (*) of the herbal substance to the genuine herbal preparation shall be stated

and the quantity of the genuine herbal preparation has to be given as a distinct content. Furthermore content of the quantified substance(s) shall be specified in a range.

- Other extracts: the equivalent quantity of the herbal substance x - y (*), or the ratio (a - b): 1 (*) of the herbal substance to the genuine herbal preparation shall be stated and the quantity of the genuine herbal preparation has to be given as a distinct content.
- *) 'a' and 'b' or 'x' and 'y' have to be justified by the applicant.

The composition of any extraction solvent or extraction solvent mixture and the physical state of the extract must be indicated. If any other substance is added during the manufacture of the herbal preparation to adjust the preparation to a defined content of constituents with known therapeutic activity, or for any other purpose, the added substance must be mentioned as an "other substance" and the genuine extract as the "active substance".

However, where different batches of the same extract are used to adjust constituents with known therapeutic activity to a defined content, or, for any other purpose, the final mixture shall be regarded as the genuine extract and listed as the "active substance" in the unit formula. Full details of production and control must however be provided in the dossier.

Examples

Active Substance Name	Quantity
Sennae Folium dry extract ethanolic 60% (V/V) ((a - b): 1) Or; Sennae Folium dry extract ethanolic 60% (V/V) (equivalent to x - y mg Sennae folium)	50-65 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B 50-65 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B

Ginkgo folium dry extract acetonic 60% (V/V) ((a – b): 1) Or; Ginkgo folium dry extract acetonic 60% (V/V) (equivalent to x - y mg Ginkgo folium)	60 mg, containing 13.2-16.2 mg of flavonoids expressed as flavone glycosides, 1.68 - 2.04 mg of ginkgolides A, B & C, 60 mg, containing 13.2-16.2 mg of flavonoids expressed as flavone glycosides, 1.68 - 2.04 mg of ginkgolides A, B & C, and 1.56 - 1.92 mg of bilobalide
Valerianae radix 125 mg dry extract ethanolic 60% (V/V) ((a - b) : 1) Or; Valerianae radix 125 mg dry extract ethanolic 60% (V/V) equivalent to x - y mg Valerianae radix	125 mg 125 mg

2a4 Development Pharmaceutics

An explanation shall be provided with regard to the choice of composition, constituents, immediate packaging, possible further packaging, outer packaging if relevant, the intended function of the excipients in the finished product and the method of manufacture of the finished product. This explanation shall be supported by scientific data on development pharmaceutics. The overage, with justification thereof, shall be stated.

The microbiological characteristics (microbiological purity and antimicrobial activity) and usage instructions shall be proven to be appropriate for the intended use of the veterinary medicinal product as specified in the marketing authorization application dossier.

2b Description of the Manufacturing Method

The manufacturing process, within the meaning of this section, is the preparation of the VHMP from herbal substance(s) and/or herbal preparation(s). In the case of traditional herbal medicinal products for Veterinary use, the manufacturing process, within the

meaning of this section, is the preparation of the herbal medicinal product from herbal substance(s) and/or herbal preparations and/or vitamins and/or minerals.

The description should include details of the process together with the controls exercised. If herbal preparations are the starting material, the manufacture of the herbal preparations and their controls should not be located under this section but under the section entitled "Control of starting materials".

Information on development pharmaceutics and process validation should also be provided

2b1 Manufacturer and Batch Formula

The name, address and responsibility of each manufacturer along with the Batch formula information should be included.

In case of using information from more than one manufacturer, the relation between both manufacturers should be indicated.

2b2 Description of the Manufacturing Process and Process Controls

Each proposed production site or facility involved in manufacturing and testing shall be indicated including at least the following:

- mention of the various stages of manufacture, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,
- in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,
- the actual manufacturing formula, with the quantitative particulars of all the substances used, the quantities of excipients, however, being given in approximate terms insofar as the pharmaceutical form makes this necessary; mention shall be made of any substances that may disappear in the course of manufacture; any overage shall be indicated and justified.
- a statement of the stages of manufacture at which sampling is carried out for in-process control tests and the limits applied, where other data in the documents supporting the application show such tests to be necessary for the quality control of the finished product.

2b3 Facility, Equipment, Controls of Critical Steps and Intermediates

All information regarding to Facility, Equipment, Controls of critical steps and intermediates should be included.

2b4 Process Validation and/or Evaluation

Detailed information regarding to Process validation and/or evaluation should be indicated including at least the following:

- experimental studies validating the manufacturing process and where appropriate a process validation scheme for production scale batches,
- for sterile products, where non-pharmacopoeial standard sterilisation conditions are used, details of the sterilisation processes and/or aseptic procedures used.

2c Control of Starting Materials

- **General Requirements**

For the purposes of this paragraph, "starting materials" shall mean all the constituents of the VHMP and, if necessary, of its container including its closure as mentioned in section 2a1.

The dossier shall include the specifications and information on the tests to be conducted for quality control of all batches of starting materials.

The routine tests carried out on each batch of starting materials must be as stated in the application for marketing authorization. If tests other than those mentioned in a pharmacopoeia are used, this shall be justified by providing proof that the starting materials meet the quality requirements of that pharmacopoeia.

Certificates of Analysis shall be presented for the starting materials in order to demonstrate compliance with the defined specification.

If the starting material is of vegetable origin, the monograph of the material should be summarized (specification with description of the test procedures). Only the substances of vegetable origin that determine the therapeutic activity of the product should be stated.

2c1 Active Substance(s)

A comprehensive specification for each herbal substance must be submitted. This also applies if the applicant is not the manufacturer of the herbal substance. If the starting material is a herbal preparation, e.g., in the case of fatty or essential oils used as active substances of VHMP, a specification for the herbal substance is required, unless fully justified. The binomial scientific name of the plant (genus, species, variety and author), chemotype (where applicable) and name of its parts, have to be stated.

If no monograph for the herbal substance is available, a comprehensive specification for the herbal substance must be supplied and should be set out in the same way where practicable, as the monographs on herbal substance in the Pharmacopoeia. Information on the site of collection, the time of harvesting and stage of growth, treatment during growth with pesticides etc, and drying and storage conditions should be included, if possible. The comprehensive specification should be established on the basis of recent scientific data. In the case of herbal substances with constituents of known therapeutic activity, assays of their content (with the test procedures) are required. The content must be included as a range, so as to ensure reproducibility of the quality of the VHMP. In the case of herbal substances where constituents of known therapeutic activity are not known, assays of marker substances (with the test procedures) are required. The choice of markers should be justified.

As a general rule, herbal substances must be tested, unless otherwise justified, for microbiological quality, for mycotoxins (aflatoxins, ochratoxin A), 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. Radioactive contamination should be tested for if there are reasons for concerns. Specifications and descriptions of the analytical procedures must be submitted, together with the limits applied. Analytical procedures not given in a Pharmacopoeia should be validated .

Reference samples of the herbal substances must be available for use in comparative tests e.g. macro- and microscopic examination, chromatography etc.

2c1.1 Detailed Requirements of the Active Substance (API)

The name, address, and responsibility of each manufacturer and each proposed production site or facility involved in manufacturing and testing of an active substance shall be indicated.

Other information to Precise identification of the active substance(s) should include the following information:

- International non-proprietary name (INN),
- International Union of Pure and Applied Chemistry Name (IUPAC),
- Chemical Abstract Service (CAS) number,
- therapeutic, pharmacological and chemical classification,
- synonyms and abbreviations,
- structural formula,
- molecular formula,
- molecular weight,
- degradation and impurity,
- qualitative and quantitative composition of impurities,
- description of physical properties,
- melting point,
- boiling point,
- vapour pressure,
- solubility in water and organic solvents expressed in g/l, with indication of temperature,
- density,
- spectra of refraction, rotation, etc,
- formulation of the product.

For a well-defined active substance, the active substance manufacturer may arrange for the following information:

1. A detailed description of the manufacturing process;
2. A description of the quality control during manufacture;

3. A description of the process validation.

In this case, the manufacturer shall however provide the applicant with all the data which may be necessary for the latter to take responsibility for the veterinary medicinal product. The manufacturer shall confirm in writing to the applicant that the shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the SFDA those documents and particulars shall also be supplied to the applicant where they concern the applicant's part of the Active Substance Master File.

Additionally, information on the method of manufacture, on quality control and on impurities as well as evidence of the molecular structure shall be provided where a Certificate of Suitability for the active substance is not available:

1. Information on the manufacturing process shall include a description of the active substance manufacturing process that represents the applicant's commitment for the manufacture of the active substance. All materials needed in order to manufacture the active substance (s) shall be listed, identifying where each material is used in the process. Information on the quality and control of those materials shall be provided. Information demonstrating that materials meet standards which are appropriate for their intended use shall be provided.
2. Information on quality control shall contain tests (including acceptance criteria) carried out at every critical step, information on the quality and control of intermediates and process validation and/or evaluation studies as appropriate. It shall also contain validation data for the analytical methods applied to the active substance, where appropriate.
3. Information on impurities shall indicate predictable impurities together with the levels and nature of observed impurities. It shall also contain information on the safety of these impurities where relevant.
4. For biotechnological veterinary medicinal products, evidence of molecular structure shall include the schematic amino acid sequence and relative molecular mass.

2c1.2 Active Substances listed in Pharmacopeia

The general and specific monographs of the Pharmacopoeia shall be applicable to all active substances appearing in it.

Constituents fulfilling the requirements of the Pharmacopoeia shall be deemed to comply sufficiently with description of the testing methods employed by the manufacturer. In this case, the description of the analytical methods and procedures shall be replaced in each relevant section by an appropriate reference to the pharmacopoeia in question.

In cases where a specification contained in a monograph of the Pharmacopoeia is insufficient to ensure the quality of the substance, SFDA may request more appropriate specifications from the applicant, including limits for specific impurities with validated test procedures.

2c1.3 Active Substances not in a Pharmacopeia

Specification and routine tests, the scientific data on nomenclature, description, manufacture, quality control during manufacture, the development chemistry (including evidence of structure, potential isomerism, physico-chemical characteristics and analytical validation,) potential and actual impurities and the batch analysis should be submitted. Constituents which are not given in any pharmacopoeia shall be described in the form of a monograph under the following headings:

a) the name of the constituent , meeting the requirements composition section, shall be supplemented by any trade or scientific synonyms;
b) the definition of the substance, set down in a form similar to that used in Pharmacopoeia, shall be accompanied by any necessary explanatory evidence, especially concerning the molecular structure. Where substances can only be described by their manufacturing method, the description shall be sufficiently detailed to characterize a substance which is constant both on its composition and in its effects;

c) methods of identification may be described in the form of complete techniques as used for production of the substance, and in the form of tests which ought to be carried out as a routine matter;

d) purity tests shall be described in relation to each individual predictable impurity, especially those which may have a harmful effect, and, if necessary, those which, having regard to the combination of substances to which the application refers, might adversely affect the stability of the medicinal product or distort analytical results;

e) tests and limits to control parameters relevant to the finished product, such as particle size and sterility shall be described and methods shall be validated where relevant;

f) with regard to complex substances of plant or animal origin, a distinction must be made between the case where multiple pharmacological effects render chemical, physical or biological control of the principal components necessary, and the case of substances containing one or more groups of principles having similar activity, in respect of which an overall method of assay may be accepted.

Those data shall demonstrate that the proposed set of test procedures is sufficient to control the quality of the active substance from the defined source.

2c1.4 Physico-Chemical Characteristics Liable to Affect Bioavailability:

The following items of information concerning active substances, whether or not listed in the pharmacopoeias, shall be provided as part of the general description of the active substances if the bioavailability of the veterinary medicinal product depends on them:

- crystalline form and solubility coefficients,
- particle size, where appropriate after pulverisation,
- state of hydration,
- oil/water coefficient of partition,
- pK/pH values.

Note: The first three indents are not applicable to substances used solely in solution.

For active substances of vegetable origin and preparations, Test for the potential contaminant (micro-organisms, pesticides, fumigants, toxic metals, radioactivity *etc.*) should be discussed.

2c2 Excipient(s)

Excipients shall comply with the requirements of the appropriate pharmacopoeia general and specific monographs. Where appropriate, additional tests to control parameters such as particle size, sterility, residual solvents shall supplement the requirements of the monograph.

In the absence of a pharmacopoeial monograph, a specification shall be proposed and justified. The requirements for specifications as set out for the active substance not in a pharmacopeia shall be followed. The proposed methods and their supporting validation data shall be presented.

For novel excipients, that is to say excipient(s) used for the first time in a veterinary medicinal product or by a new route of administration, details of manufacture, characterization, and controls, with cross references to supporting safety data, both clinical and non-clinical, shall be provided.

2c3 Container Closure

2C3.1 Active Substance

Detailed information on the container-closure system for the active substance shall be given. The level of information required shall be determined by the physical state (liquid, solid) of the active substance.

2C3.2 Finished Product

Detailed information on the container-closure system for the finished product shall be given. The level of information required shall be determined by the route of administration of the veterinary medicinal product and the physical state (liquid, solid) of the dosage form.

Packaging materials shall comply with the requirements of the appropriate pharmacopoeia monograph.

Scientific data on the choice and suitability of the packaging material shall be presented.

For novel packaging materials in contact with the product, information on their composition, manufacture and safety shall be presented.

Specifications and, if appropriate, performance data shall be presented for any dosing or administration device supplied with the veterinary medicinal product.

2c4 Substances of Biological Origin

The origin, including geographical region, and history of starting materials shall be described and documented.

The description of the starting material shall include the manufacturing strategy, purification/inactivation procedures with their validation and all in-process control procedures designed to ensure the quality, safety and batch-to-batch consistency of the finished product.

When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the passage level used for the production and beyond.

Seed materials, cell banks and pools of serum and, whenever possible, the source materials from which they are derived shall be tested for extraneous agents.

When starting materials of animal or human origin are used, the measures used to ensure freedom from potentially pathogenic agents shall be described.

If the presence of potentially pathogenic extraneous agents is inevitable, the material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.

Documentation shall be supplied to demonstrate that the seed materials, cell seeds, batches of serum and other material originating from animal species relevant for the transmission of TSE comply with the *Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*, as well as with the corresponding monograph of the European Pharmacopoeia. Certificates of Suitability issued by the European Directorate for the Quality of Medicines and HealthCare, with reference to the relevant monograph of the European Pharmacopoeia, may be used to demonstrate compliance.

2d Control Tests at Intermediate Process Stages

The dossier shall include particulars relating to the product control tests that may be carried out at an intermedia test age of the manufacturing process, with a view to ensuring the consistency of the technical characteristics and the production process.

Details of all control tests, with details of test procedures and limits applied at any intermediate

stages of the manufacturing processes, are required especially if these tests cannot be performed on the herbal medicinal product.

These tests are essential for checking the conformity of the veterinary medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient components subject to the same requirements as the active substances).

The same applies where the quality control of the finished product depends on in-process control tests, particularly if the substance is essentially defined by its manufacturing method.

Where an intermediate product may be stored prior to further processing or primary assembly, a shelf life for the intermediate product shall be defined on the basis of the data resulting from stability studies.

2e Tests on the Finished Product

Including detailed information regarding both Veterinary Herbal Preparations and Veterinary Herbal Medicinal Products.

2e1 Tests on the Veterinary Herbal Preparations

If the veterinary herbal medicinal product contains a preparation, rather than merely the herbal substance itself, the comprehensive specification for the herbal substance must be followed by a description and validation of the manufacturing process for the herbal preparation. This also applies if the applicant is not the manufacturer of the herbal preparation. The information may be supplied either as part of the marketing authorisation application or by using the European Active Substance Master File procedure. If the latter

route is chosen, the documentation should be submitted in accordance with the 'Guideline on active substance master file procedure' (EMEA/CPMP/QWP/227/02 and EMEA/CVMP/134/02 as revised).

Where the preparation is the subject of a European Pharmacopoeia monograph, the EDQM Certification procedure (for Certificates of Suitability, CEPs) can be used to demonstrate compliance with the relevant Ph. Eur. monograph.

For each herbal preparation, a comprehensive specification is required. This should be established on the basis of recent scientific data and should give particulars of the characteristics, identification tests and purity tests. Appropriate chromatographic methods should be used. If deemed necessary by analysis of the starting material, tests on microbiological quality, mycotoxins (aflatoxins, ochratoxin A), residues of pesticides and fumigation agents, toxic metals and solvents should be performed.

Radioactivity should be tested if there are reasons for concern. A quantitative determination (assay) of substances with known therapeutic activity or of markers is also required. 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 standardised (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.

2e2 Tests on the Veterinary Herbal Medicinal Products

This section should be in accordance with the 'Guideline on specifications and control tests on the finished product' (Eudralex 3AQ 11A), the 'Guideline on specifications: test procedures and

acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (EMEA/CPMP/QWP/2820/00 and EMEA/CVMP/815/00 as revised) and the analytical procedures should be validated according to the ICH/VICH guidelines 'Validation of analytical procedures: methodology' (CPMP/ICH/381/95 and CVMP/VICH/591/98).

The control tests on the finished product should allow the qualitative and quantitative determination of the active substance(s). A specification should be provided and this may include the use of markers where constituents with known therapeutic activity are unknown. In the case of herbal substances or herbal preparations with constituents of known therapeutic activity, these constituents should be specified and quantitatively determined. For traditional herbal medicinal products for vetrinary use containing vitamins and/or minerals, the vitamins and/or minerals should also be specified and quantitatively determined.

If a herbal medicinal product contains a combination of several herbal substances or preparations of several herbal substances, and if it is not possible to perform a quantitative determination of each active substance, the determination may be carried out jointly for several active substances. The need for this procedure should be justified.

The criteria given by the European Pharmacopoeia to ensure the microbiological quality should be applied unless justified. The frequency of testing for microbial contamination should be justified, according to the (V)ICH Notes for guidance on Specifications: (Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, and Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances.

2e2.1 Specifications of the Finished Product (Veterinary Herbal Preparations)

For the control of the finished product, a batch of a finished product comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and

have undergone the same series of manufacturing and/or sterilization operations or, in the case of a continuous production process, all the units manufactured in a given period of time. The test which are carried out routinely on each batch of finished product should be specified. The frequency of the tests which are not carried out routinely shall be stated. Release limits shall be indicated.

- **Specifications of the medicinal product (Veterinary Herbal Preparations)**

	Methods and Acceptance Limits	
Characteristics	of the medicinal product up to the end of shelf life	of the medicinal product at release
1. Characteristics of the pharmaceutical form	Indicate with an asterisk the specification limits which may require updating in the light of experience acquired after the first "n" production batches	
2. Identification and assay of active substance		
3. Purity tests		
4. Excipient: Identification for example of colorants, preservatives, limit values of preservatives or antioxidants etc.		

The dossier shall include particulars relating to control tests on the finished product at release. They shall be submitted in accordance with the following requirements.

If test procedures and limits other than those mentioned in the relevant monographs and general chapters of the Pharmacopoeias, this shall be justified by providing proof that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned.

For finished product specifications (Release and Shelf-life) should include the following points:

- Name of the active pharmaceutical ingredient and Finished product.
- Specification/Version number and Effective date.
- Reference(s).

- A footnote including chemical names for all known impurities.
- Signature by the concerned individual(s).

2e2.2 General Characteristics of the Finished Product (Veterinary Herbal Preparations)

Other information to Precise identification of Precise identification of the product and of its active substance(s) should include the following information:

- International non-proprietary name (INN),
- International Union of Pure and Applied Chemistry Name (IUPAC),
- Chemical Abstract Service (CAS) number,
- Therapeutic, pharmacological and chemical classification,
- Synonyms and abbreviations,
- Structural formula,
- Molecular formula,
- Molecular weight,
- Degradation and impurity,
- Qualitative and quantitative composition of impurities,
- Description of physical properties,
- Melting point,
- Boiling point,
- Vapour pressure,
- Solubility in water and organic solvents expressed in g/l, with indication of temperature,
- Density,
- Spectra of refraction, rotation, etc,
- Formulation of the product.

Certain tests of the general characteristics of a product shall always be included among the tests on the finished product. These tests shall, wherever applicable, relate to the control of average masses and maximum deviations, to mechanical, physical or microbiological tests, organoleptic characteristics, physical characteristics such as density, pH, refractive index. For each of these characteristics, standards and tolerance limits shall be specified by the applicant in each particular case.

The conditions of the tests, where appropriate, the equipment/apparatus employed and the standards shall be described in precise details whenever they are not given in the pharmacopoeia.

Furthermore, solid pharmaceutical forms having to be administered orally shall be subjected to in vitro studies on the liberation and dissolution rate of the active substance or substances, unless otherwise justified.

2e2.3 Identification and Assay of Active Substance(s)

Detailed information on Validation of Analytical Procedures of active substance(s) including Reference Standards or Materials should be included.

Identification and assay of the active substance(s) shall be carried out either in a representative sample from the production batch or in a number of dosage units analyzed individually.

Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5% at the time of manufacture.

On the basis of the stability tests, the manufacturer shall propose and justify maximum acceptable deviation limits in the active substance content of the finished product up to the end of the proposed shelf life.

It shall be supplemented by a method of quantitative evaluation, enabling the SFDA to have the conformity of the medicinal product with its specification verified after it has been placed on the market.

An *in vivo* or *in vitro* biological assay shall be obligatory when physico-chemical methods cannot provide adequate information on the quality of the product. Such an assay shall, whenever possible, include reference materials and statistical analysis allowing calculation of confidence limits. Where these tests cannot be carried out on the finished product, they may be performed at an intermediate stage, as late as possible in the manufacturing process.

Where degradation occurs during manufacture of the finished product, the maximum acceptable levels of individual and total degradation products immediately following manufacture shall be indicated.

Where the particulars given in section 2b show that a significant overage of an active substance is employed in the manufacture of the medicinal product or where the stability data show that the assay of the active substance declines on storage, the description of the control tests on the finished product shall include, where appropriate, the chemical and, if necessary, the toxico-pharmacological investigation of the changes that this substance has undergone, and possibly the characterization and/or assay of the degradation products.

2e2.4 Control of vitamins and minerals (if applicable)

Vitamin(s) and mineral(s), which could be ancillary substances in traditional herbal medicinal products for veterinary use, should fulfil the requirements of the 'Guideline on summary of requirements for active substances in the quality part of the dossier' as same as herbal medicinal products for human use.

2e2.5 Identification and Assay of Excipient Components

Detailed information on Validation of Analytical Procedures of excipient including Reference Standards or Materials should be included.

An identification test and an upper and lower limit test shall be obligatory for each individual antimicrobiological preservative and for any excipient that is liable to affect the bioavailability of the active substance, unless the bioavailability is guaranteed by other appropriate tests. An identification test and an upper limit test shall be obligatory for any antioxidant and for any excipient liable to adversely affect physiological functions, with a lower limit test also included for antioxidants at time of release.

Excipients, including those added during the manufacture of the herbal preparations, should be described.

2e2.6 Safety Tests

Apart from the toxico-pharmacological tests submitted with the application for marketing authorization, particulars of safety tests, such as sterility and bacterial endotoxins, shall be included in the analytical particulars wherever such tests must be undertaken as a matter of routine in order to verify the quality of the product.

2f Stability Tests

This section should be in accordance Stability Testing of New Veterinary Drug Substances "Active Pharmaceutical Ingredients (APIs)" and Medicinal Products "Finished Pharmaceutical Products (FPPs)" Since the herbal substance or herbal preparation in its entirety is regarded as the active substance, a mere determination of the stability of the constituents with known therapeutic activity will not suffice. The stability of other substances present in the herbal substance or in the herbal preparation, should, as far as possible, also be demonstrated, e.g., by means of appropriate fingerprint chromatograms. It should also be demonstrated that their proportional content remains comparable to the initial fingerprint.

If a VHMP contains combinations of several herbal substances or herbal preparations, and if it is not possible to determine the stability of each active substance, the stability of the medicinal product should be determined by appropriate fingerprint chromatograms, appropriate overall methods of assay and physical and sensory tests or other appropriate tests. The appropriateness of the tests shall be justified by the applicant.

In the case of a herbal medicinal product containing a herbal substance or herbal preparation with constituents of known therapeutic activity, the variation in content during the proposed shelf-life should not exceed ± 5% of the declared assay value, unless justified.

In the case of a herbal medicinal product containing a herbal substance or herbal preparation where constituents with known therapeutic activity are unknown, a variation in marker content during the proposed shelf-life of ± 10% of the initial assay value can be accepted if justified by the applicant.

In the case of traditional herbal medicinal products for veterinary use containing vitamins and/or minerals, the stability of the vitamins and/or minerals should be demonstrated.

Moreover, for more detailed Refer to the Stability Testing of New Veterinary Drug Substances "Active Pharmaceutical Ingredients (APIs)" and Medicinal Products "Finished Pharmaceutical Products (FPPs)":

2f1 Active Substance

Full Stability data including accelerated and long term stability studies shall be presented to support the defined retest period and storage conditions. The type of stability studies conducted, protocols used, the analytical procedures used and their validation together with the detailed results shall be presented. The stability commitment with a summary of the protocol shall be provided.

2f2 Finished Product

Full Stability data including accelerated and long term stability studies along with in-use stability study and stability after reconstitution, if applicable, should be submitted.

A description shall be given of the investigations by which the shelf life, the recommended storage conditions and the specifications at the end of the shelf life proposed by the applicant have been determined.

The type of stability studies conducted, protocols used, the analytical procedures used and their validation together with the detailed results shall be presented.

Where a finished product requires reconstitution or dilution prior to administration, details of the proposed shelf life and specification for the reconstituted/diluted product are required, supported by relevant stability data.

In the case of multi-dose containers, where relevant, stability data shall be presented to justify a shelf life for the product after it has been broached for the first time and an in-use specification shall be defined.

Where a finished product is liable to give rise to degradation products, the applicant shall declare and indicate the identification methods and test procedures for degradation products.

The conclusions shall contain the results of analyses, justifying the proposed shelf life and if appropriate, the in-use shelf life, under the recommended storage conditions and the specifications of the finished product at the end of the shelf life, and in-use shelf life if appropriate, of the finished product under these recommended storage conditions.

The maximum acceptable level of individual and total degradation products at the end of shelf life shall be indicated.

A study of the interaction between product and container shall be submitted wherever the risk of such interaction is regarded as possible, especially where injectable preparations are concerned.

The stability commitment with a summary of the protocol shall be provided.

2g Other Related Documents

This part is intended for a summary of any information relevant to the pharmaceutical assessment and which has not been covered by any of the previous report. Information on the analytical test procedures used in the metabolism and bioavailability studies and their validation, and a summary of the synthesis of radiolabeled active substance used in metabolic and/or pharmacokinetic studies should be provided.

Part 3 Safety and Residues Tests

Part 3 of the dossier is aimed at demonstrating the potential risks for man and the environment resulting from use of the product. In the context of human safety, it is necessary to consider possible effects on people using the product, handling treated animals and consuming food products derived from treated animals. Although a knowledge of adverse effects in the target species may be useful additional information when assessing the risk for man and the environment, Part 3 is not primarily concerned with target species safety, which should be considered in detail in Part 4 of the dossier.

Studies submitted to demonstrate safety of chemicals to man and the environment must be conducted and reported in accordance with Good Laboratory Practice (GLP).

3a Safety Tests

Safety Documentation:

Relevant data obtained from the open literature should always be included in the documentation. Copies of published data should be appended to the proprietary data. All proprietary data should be discussed in conjunction with the data from the open literature.

Residue Documentation:

Documents should be presented as dated and signed reports from named laboratories. Summaries not accompanied by the individual data will not be accepted as valid documentation.

Relevant data obtained from the open literature should always be included in the documentation. Copies of published data should be appended to the proprietary data. All proprietary data should be discussed in conjunction with the data from the open literature.

The safety documentation shall show:

a) the potential toxicity of the veterinary herbal medicinal product and any dangerous or undesirable effects which may occur under the proposed conditions of use in animals; these should be evaluated in relation to the severity of the pathological condition concerned;
b) the potential harmful effects to man of residues of the veterinary herbal medicinal product or substance in foodstuffs obtained from treated animals and what difficulties these residues may create in the industrial processing of foodstuffs;
c) the potential risks which may result from the exposure of human beings to the veterinary herbal medicinal product, for example during its administration to the animal;
d) the potential risks for the environment resulting from the use of the veterinary herbal medicinal product.

All results shall be reliable and valid generally. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results. Additionally, information shall be provided regarding the therapeutic potential of the product and about the hazards connected with its use.

In some cases, it may be necessary to test the metabolites of the parent compound where these represent the residues of concern.

An excipient used in the pharmaceutical field for the first time shall be treated like an active substance.

3a1 Precise Identification of the Product and of its Active Substance(s)

- international non-proprietary name (INN),
- International Union of Pure and Applied Chemistry Name (IUPAC),
- Chemical Abstract Service (CAS) number,
- therapeutic, pharmacological and chemical classification,
- synonyms and abbreviations,
- structural formula,
- molecular formula,
- molecular weight,
- degree of impurity,
- qualitative and quantitative composition of impurities,
- description of physical properties,
- melting point,
- boiling point,
- vapour pressure,
- solubility in water and organic solvents expressed in g/l, with indication of temperature,
- density,
- spectra of refraction, rotation, etc,
- formulation of the product.

3a2 Pharmacology

Pharmacological studies are of fundamental importance in clarifying the mechanisms by which the veterinary herbal medicinal product produces its therapeutic effects and therefore pharmacological studies conducted in experimental and target species of animal shall be included in part 4.

However, pharmacological studies may also assist in the understanding of toxicological phenomena. Moreover, where a veterinary medicinal product produces pharmacological effects in the absence of a toxic response, or at doses lower than those required to elicit

toxicity, these pharmacological effects shall be taken into account during the evaluation of the safety of the veterinary medicinal product.

Therefore, the safety documentation shall always be preceded by details of pharmacological investigations undertaken in laboratory animals and all relevant information observed during clinical studies in the target animal.

3a2.1 Pharmacodynamics

Information on the mechanism of action of the active substance(s) shall be provided, together with information on primary and secondary pharmacodynamics effects in order to assist in the understanding of any adverse effects in the animal studies.

3a2.1 Pharmacokinetics

Data on the fate of the active substance and its metabolites in the species used in the toxicological studies shall be provided, covering absorption, distribution, metabolism and excretion (ADME). The data shall be related to the dose/effect findings in the pharmacological and toxicological studies, to determine adequate exposure. Comparison with the pharmacokinetic data obtained in the studies on the target species, section 4a2, shall be included in order to determine the relevance of the results obtained in the toxicology studies for the toxicity to the target species.

3a3 Toxicology

The documentation on toxicology includes:

1. basic tests required for all new veterinary herbal medicinal products for use in food-producing animals in order to assess the safety of any residues present in food for human consumption;
2. additional tests that may be required depending on specific toxicological concerns such as those associated with the structure, class and mode of action of the active substance(s);
3. special tests which might assist in the interpretation of data obtained in the basic or additional tests.

The studies shall be conducted with the active substance(s), not with the formulated product. Where studies of the formulated product are required, this is specified in the below sections:

3a3.1 Single – Dose Toxicity

Single-dose toxicity studies may be used to predict:

- the possible effects of acute over dosage in the target species,
- the possible effects of accidental administration to humans,
- the doses which may usefully be employed in the repeat dose studies.

Single-dose toxicity studies should reveal the acute toxic effects of the substance and the time course for their onset and remission.

The studies to be carried out shall be selected with a view to providing information on user safety, e.g. if substantial exposure by inhalation or dermal contact of the user of the veterinary herbal medicinal product is anticipated, those routes of exposure shall be studied.

3a3.2 Repeat-Dose Toxicity

Repeat-dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

In the case of pharmacologically active substances or veterinary herbal medicinal products intended solely for use in non-food-producing animals, a repeat-dose toxicity study in one species of experimental animal shall normally be sufficient. This study may be replaced by a study conducted in the target animal. The frequency and route of administration, and the duration of the study shall be chosen having regard to the proposed conditions of clinical use. The investigator shall give his reasons for the extent and duration of the trials and the dosages chosen.

In the case of substances or veterinary medicinal products intended for use in food-producing animals, repeat-dose (90 day) toxicity testing shall be performed in a rodent and a non-rodent species in order to identify target organs and toxicological endpoints and identify the appropriate species and the dose levels to be used in chronic toxicity testing, if appropriate.

The investigator shall give his reasons for the choice of species, having regard to the available knowledge of the metabolism of the product in animals and man. The test

substance shall be administered orally. The investigator shall clearly state and give his reasons for the method and frequency of administration and the length of the trials.

The maximum dose should normally be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

Evaluation of the toxic effects shall be based on observation of behavior, growth, hematology and physiological tests, especially those relating to the excretory organs, and also on autopsy reports and accompanying histological data. The choice and range of each group of tests depends on the species of animal used and the state of scientific knowledge at the time.

In the case of new combinations of known substances which have been investigated in accordance with this guidance, the repeat-dose tests may, except where toxicity tests have demonstrated potentiation or novel toxic effects, be suitably modified by the investigator, who shall submit his reasons for such modifications.

3a3.3 Tolerance in the Target Species

A summary shall be provided of any signs of intolerance which have been observed during studies conducted, usually with the final formulation, in the target species in accordance with the requirements of Section 4a3. The studies concerned, the dosages at which the intolerance occurred and the species and breeds concerned shall be identified.

Details of any unexpected physiological changes shall also be provided. The full reports of these studies shall be included in part 4.

3a3.4 Reproductive Toxicity including Developmental Toxicity

3a3.4.1 Study of the Effects on Reproduction

The purpose of this study is to identify possible impairment of male or female reproductive function or harmful effects on progeny resulting from the administration of the veterinary herbal medicinal product or substance under investigation.

In the case of pharmacologically active substances or veterinary herbal medicinal product intended for use in food-producing animals, the study of the effects on reproduction shall be performed in the form of a multi-generation reproduction study, designed to detect any

effect on mammalian reproduction. These include effects on male and female fertility, mating, conception, implantation, ability to maintain pregnancy to term, parturition, lactation, survival, growth and development of the offspring from birth through to weaning, sexual maturity and the subsequent reproductive function of the offspring as adults. At least three dose levels shall be used. The maximum dose should be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

3a3.4.1 Study of Developmental Toxicity

In the case of pharmacologically active substances or veterinary herbal medicinal product intended for use in food-producing animals, tests on developmental toxicity shall be performed. These tests shall be designed to detect any adverse effects on the pregnant female and development of the embryo and foetus consequent to exposure of the female from implantation through gestation to the day before predicted birth. Such adverse effects include enhanced toxicity relative to that observed in non-pregnant females, embryo-foetal death, altered foetal growth, and structural changes to the foetus.

A developmental toxicity test in the rat is required. Depending on the results, a study in a second species may have to be performed.

In the case of pharmacologically active substances or veterinary medicinal products not intended for use in food producing animals, a study of developmental toxicity shall be performed in at least one species, which may be the target species, if the product is intended for use in female animals which may be used for breeding. However, where the use of the veterinary herbal medicinal product would result in significant exposure to users, standard developmental toxicity studies shall be performed.

3a3.5 Genotoxicity

Tests for genotoxic potential shall be performed to reveal changes which a substance may cause in the genetic material of cells. Any substance intended to be included in a v veterinary herbal medicinal product for the first time must be assessed for genotoxic properties.

3a3.6 Carcinogenicity

The decision on whether carcinogenicity testing is required shall take into account the results of genotoxicity tests, structure-activity relationships and the findings in systemic toxicity tests that may be relevant to neoplastic lesions in longer term studies.

Any known species specificity of the mechanism of toxicity shall be considered, as well as any differences in metabolism between the test species, target animal species, and human beings.

3a3.7 Exceptions

Where a veterinary herbal medicinal product is intended for topical use, systemic absorption shall be investigated in the target animal species. If it is proved that systemic absorption is negligible, the repeated dose toxicity tests, the tests for reproductive toxicity and the carcinogenicity tests may be omitted, unless:

- under the intended conditions of use laid down, oral ingestion of the veterinary medicinal product by the animal is to be expected, or
- under the intended conditions of use laid down, exposure of the user of the veterinary herbal medicinal product by other routes than the dermal route is to be expected, or
- the active substance or metabolites may enter foodstuffs obtained from the treated animal.

3a4 Other Requirements

3a4.1 Special Studies

For particular groups of substances or if the effects observed during repeated dose studies in animals include changes indicative of e.g. immunotoxicity, neurotoxicity- or, endocrine dysfunction, further testing shall be required, e.g. sensitization studies or delayed neurotoxicity tests. Depending on the nature of the product, it may be necessary to conduct additional studies to assess the underlying mechanism of the toxic effect or the irritation potential. Such studies shall usually be conducted with the final formulation.

The state of scientific knowledge shall be taken into account when designing such studies and evaluating their results.

3a4.2 Microbiological Properties of Residues

- **Potential Effects on the Microorganisms used for Industrial Food Processing**

In certain cases, it may be necessary to carry out tests to determine whether microbiologically active residues may interfere in technological processes in the industrial processing of foodstuff.

3a4.3 Observations in Humans

Information shall be provided showing whether the pharmacologically active substances of the veterinary herbal medicinal product are used as medicinal products in human therapy; if this is so, a compilation shall be made of all the effects observed (including adverse reactions) in humans and of their cause, to the extent that they may be important for the assessment of the safety of the veterinary medicinal product, where appropriate including results from published studies; where constituents of the veterinary herbal medicinal product are themselves not used or are no longer used as medicinal products in human therapy, the reasons shall be stated.

3a4.4 Development of Resistance

Data on the potential emergence of resistant bacteria of relevance for human health are necessary in the case of veterinary herbal medicinal product. The mechanism of the development of such resistance is particularly important in this regard. Where necessary, measures to limit resistance development from the intended use of the veterinary herbal medicinal product shall be proposed.

Resistance relevant for clinical use of the product shall be addressed in accordance with part 4. Where relevant, cross reference shall be made to the data set out in part 4.

3a5 User Safety (URA)

This section shall include a discussion of the effects found in the preceding sections and relate this to the type and extent of human exposure to the product with a view to formulating appropriate user warnings and other risk management measures.

3a6 Environmental Risk Assessment (ERA)

3a6.1 Environmental Risk Assessment of Veterinary Herbal Medicinal Product not containing or Consisting of Genetically Modified Organisms

An environmental risk assessment shall be performed to assess the potential harmful effects, which the use of the veterinary herbal medicinal product may cause to the environment and to identify the risk of such effects. The assessment shall also identify any precautionary measures which may be necessary to reduce such risk.

This assessment shall normally be conducted in two phases. The first phase of the assessment shall always be performed.

The details of the assessment shall be provided in accordance with accepted guidance. It shall indicate the potential exposure of the environment to the product and the level of risk associated with any such exposure taking into account in particular the following items:

- the target animal species, and the proposed pattern of use,
- the method of administration, in particular the likely extent to which the product will enter directly into environmental systems,
- the possible excretion of the product, its active substances or relevant metabolites into the environment by treated animals; persistence in such excreta,
- the disposal of unused veterinary herbal medicinal product or other waste product.

In the second phase, further specific investigation of the fate and effects of the product on particular ecosystems shall be conducted. The extent of exposure of the product to the environment, and the available information about the physical/chemical, pharmacological and/or toxicological properties of the substance(s) concerned, including metabolites in case of an identified risk, which has been obtained during the conduct of the other tests and trials required by this guidance, shall be taken into consideration.

3a6.2 Environmental Risk Assessment for Veterinary Herbal Medicinal Product Containing or Consisting of Genetically Modified Organisms

In the case of veterinary herbal medicinal product containing or consisting of genetically modified organisms the application shall also be accompanied by the documents required

by international guidance and describes the format in which the particulars relevant to the environmental risk assessment.

3a6.3 Presentation of Particulars and Documents

The dossier of safety tests shall include the following:

- An index of all studies included in the dossier, a statement confirming that all data known by the applicant at the time of submission, whether favourable or unfavourable, are included,
- A justification for the omission of any type of study,
- An explanation of the inclusion of an alternative type of study,
- a discussion of the contribution that any study that pre-dates studies performed in line with good laboratory practice (GLP).

Each study report shall include:

- A copy of the study plan (Protocol),
- A statement of compliance with good laboratory practice, where applicable,
- A description of the methods, apparatus and materials used,
- A description and justification of the test system,
- A description of the results obtained, in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author,
- A statistical analysis of the results where appropriate,
- A discussion of the results, with comment on observed and no-observed-effect levels, and on any unusual findings,
- A detailed description and a thorough discussion of the results of the study of the safety profile of the active substance, and its relevance for the evaluation of potential risks presented by residues to humans.

3b Residue Tests

3b1 Introduction

The purpose of studying the depletion of residues from the edible tissues or of eggs, milk and honey derived from treated animals is to determine under what conditions and to what extent residues may persist in foodstuffs produced from these animals. In addition, the studies shall enable the determination of a withdrawal period.

In the case of veterinary herbal medicinal product intended for use in food-producing animals, the residue documentation shall show:

1. to what extent, and how long, do residues of the Veterinary Herbal medicinal product or its metabolites persist in the edible tissues of the treated animal or in milk, eggs and/or honey obtained therefrom;
2. that in order to prevent any risk to the health of the consumer of foodstuffs from treated animals, or difficulties in the industrial processing of foodstuffs, it is possible to establish realistic withdrawal periods which can be observed under practical farming conditions;
3. that the analytical method(s) used in the residues depletion study are sufficiently validated to provide the necessary reassurance that the residues data submitted are suitable as the basis for a withdrawal period.

3b2 Identification of Product

An identification of the veterinary herbal medicinal product(s) used in the testing shall be provided, including:

- composition,
- the physical and chemical (potency and purity) test results for the relevant batch(es),
- batch identification,
- relationship to the final product,
- specific activity and radio-purity of labelled substances,
- position of labelled atoms in the molecule.

The dossier of residue tests shall include:

- an index of all studies included in the dossier,
- a statement confirming that all data known by the applicant at the time of submission, whether favourable or unfavourable, are included,
- a justification for the omission of any type of study,
- an explanation of the inclusion of an alternative type of study,
- a discussion of the contribution that any study that pre-dates GLP can make to the overall risk assessment,
- a withdrawal period proposal.

Each study report shall include:

- a copy of the study plan (Protocol),
- a statement of compliance with good laboratory practice, where applicable,
- a description of the methods, apparatus and materials used,

- a description of the results obtained, in sufficient detail to allow the results to be critically evaluated independently of
- their interpretation by the author,
- a statistical analysis of the results where appropriate,
- a discussion of the results,
- an objective discussion of the results obtained, and proposals concerning the withdrawal periods necessary to ensure that no residues which might constitute a hazard for consumers are present in foodstuffs obtained from treated animals.

3b3 Metabolism and Residue Kinetics

3b3.1 Pharmacokinetics (Absorption, Distribution, Metabolism, Excretion)

A summary of the pharmacokinetic data shall be submitted with cross reference to the pharmacokinetic studies in target species submitted in Part 4. The full study report does not need to be submitted.

The purpose of pharmacokinetic studies with respect to residues of veterinary herbal medicinal product is to evaluate the absorption, distribution, metabolism and excretion of the product in the target species.

The final product, or a formulation, which has comparable characteristics in terms of bioavailability as the final product, shall be administered to the target animal species at the maximum recommended dose.

Having regard to the method of administration, the extent of absorption of the veterinary medicinal product shall be fully described. If it is demonstrated that systemic absorption of products for topical application is negligible, further residue studies will not be required.

The distribution of the veterinary herbal medicinal product in the target animal shall be described; the possibility of plasma protein binding or passage into milk or eggs and of the accumulation of lipophilic compounds shall be considered.

The pathways for the excretion of the product shall be described. The major metabolites shall be identified and characterized.

3b3.2 Depletion of Residues

The purpose of these studies, which measure the rate at which residues deplete in the target animal after the last administration of the veterinary herbal medicinal product, is to permit the determination of withdrawal periods.

At a sufficient number of times after the test animal has received the final dose of the veterinary herbal medicinal product, the quantities of residues present shall be determined by validated analytical methods; the technical procedures and the reliability and sensitivity of the methods employed shall be specified.

3b4 Residue analytical method

The analytical method(s) used in the residues depletion study (studies) and its (their) validation shall be described in detail.

The following characteristics shall be described:

- specificity,
- accuracy,
- precision,
- limit of detection,
- limit of quantification,
- practicability and applicability under normal laboratory conditions,
- susceptibility to interference,
- stability of incurred residues.

The suitability of the analytical method proposed shall be evaluated in the light of the state of scientific and technical knowledge at the time the application is submitted.

Part 4 Preclinical and clinical trials

A written summary is essential for large, complex clinical documentation. Such documentation may be contained in numerous volumes, and a 1-2 page summary at the beginning of each volume, which details its contents and includes an index of that volume, is particularly helpful. These short summaries can then form the basis for the overall summary.

4a Pre-clinical Requirements

Pre-clinical studies are required to establish the pharmacological activity and the tolerance of the product.

4a1 Pharmacology

4a1.1 Pharmacodynamics

The pharmacodynamics effects of the active substance(s) included in the veterinary herbal medicinal product shall be characterized.

First, the mechanism of action and the pharmacological effects on which the recommended application in practice is based shall be adequately described. The results shall be expressed in quantitative terms (using, for example, dose-effect curves, time-effect curves, etc.) and, wherever possible, in comparison with a substance the activity of which is well known. Where a higher efficacy is being claimed for an active substance, the difference shall be demonstrated and shown to be statistically significant.

Secondly, an overall pharmacological assessment of the active substance shall be provided, with special reference to the possibility of secondary pharmacological effects. In general, the effects on the main body functions shall be investigated.

Any effect of the other characteristics of the products (such as the route of administration or formulation) on the pharmacological activity of the active substance shall be investigated.

The investigations shall be intensified where the recommended dose approaches a dose likely to produce adverse reactions.

The experimental techniques, unless they are standard procedures, shall be described in such detail as to allow them to be reproduced, and the investigator shall establish their validity. The experimental results shall be set out clearly and, for certain types of tests, their statistical significance quoted.

Unless good reasons are given to the contrary, any quantitative modification of responses resulting from repeated administration of the substance shall also be investigated.

Fixed combinations may be prompted either on pharmacological grounds or by clinical indications. In the first case, the pharmacodynamics and/or pharmacokinetic studies shall demonstrate those interactions, which might make the combination itself of value in clinical use. In the second case, where scientific justification for the medicinal combination is sought through clinical experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals and, at least, the importance of any adverse reactions shall be checked. If a combination includes a new active substance, the latter shall have been previously studied in depth.

4a2 Resistance

Where relevant, data on the potential emergence of resistant organisms of clinical relevance are necessary for veterinary herbal medicinal product. The mechanism of the development of such resistance is particularly important in this regard.

Measures to limit resistance development from the intended use of the veterinary medicinal product shall be proposed by the applicant.

Where relevant, cross reference shall be made to data set out in part 3.

4a2.1 Pharmacokinetics

Basic pharmacokinetic data concerning a new active substance are required in the context of assessment of the clinical safety and efficacy of the veterinary herbal medicinal product.

The objectives of pharmacokinetic studies in the target animal species can be divided into three main areas:

1. descriptive pharmacokinetics leading to the determination of basic parameters;
2. use of these parameters to investigate the relationships between dosage regimen, plasma and tissue concentration over time and pharmacological, therapeutic or toxic effects;
3. where appropriate, to compare the kinetics between different target species and to explore possible species differences having an impact on target animal safety and efficacy of the veterinary herbal medicinal product.

In the target animal species, pharmacokinetic studies are, as a rule, necessary as a complement to the pharmacodynamics studies to support the establishment of effective dosage regimens (route and site of administration, dose, dosing interval, number of administrations, etc.). Additional pharmacokinetic studies may be required to establish dosage regimens according to certain population variables.

Where pharmacokinetic studies have been submitted under Part 3 cross reference to such studies may be made.

In the case of new combinations of known substances which have been investigated in accordance with this guidance, pharmacokinetic studies of the fixed combination are not required if it can be justified that the administration of the active substances as a fixed combination does not change their pharmacokinetic properties.

Appropriate bioavailability studies shall be undertaken to establish bioequivalence:

- when comparing a reformulated veterinary medicinal product with the existing one,
- where necessary for the comparison of a new method or route of administration with an established one.

4a3 Target Animal Tolerance

The local and systemic tolerance of the veterinary herbal medicinal product shall be investigated in the target animal species. The purpose of these studies is to characterize signs of intolerance and to establish an adequate margin of safety using the recommended route(s) of administration. This may be achieved by increasing the therapeutic dose and/or the duration of treatment. The report on the trials shall contain details of all expected pharmacological effects and all adverse reactions.

4b Clinical Requirements

4b1 Clinical Trials

The purpose of clinical trials is to demonstrate or substantiate the effect of the veterinary herbal medicinal product after administration at the proposed dosage regimen via the proposed route of administration and to specify its indications and contra-indications according to species, age, breed and sex, its directions for use as well as any adverse reactions which it may have.

Experimental data shall be confirmed by data obtained under normal field conditions.

Unless justified, clinical trials shall be carried out with control animals (controlled clinical trials). The efficacy results obtained should be compared with those from the target animal species that have received a veterinary herbal medicinal product authorized in the SFDA for the same indications for use in the same target animal species, or a placebo or no treatment. All the results obtained, whether positive or negative, shall be reported.
Established statistical principles shall be used in protocol design, analysis and evaluation of clinical trials, unless justified.

4b1.1 Conduct of Clinical Trials

All veterinary clinical trials shall be conducted in accordance with a detailed trial protocol.

Clinical field trials shall be conducted in accordance with established principles of good clinical practice, unless otherwise justified.

Before the commencement of any field trial, the informed consent of the owner of the animals to be used in the trial shall be obtained and documented. In particular, the animal owner shall be informed in writing of the consequences of participation in the trial for the subsequent disposal of treated animals or for the taking of foodstuffs from treated animals. A copy of this notification, countersigned and dated by the animal owner, shall be included in the trial documentation.

4b1.2 Particulars and Documents

The dossier on efficacy shall include all pre-clinical and clinical documentation and/or results of trials, whether favorable or unfavorable to the veterinary herbal medicinal product, in order to enable an objective overall assessment of the risk/benefit balance of the product.

4b1.2.1 Results of Pre-clinical Trials

Wherever possible, particulars shall be given of the results of:

a) Tests demonstrating pharmacological actions;
b) Tests demonstrating the pharmacodynamics mechanisms underlying the therapeutic effect;
c) Tests demonstrating the main pharmacokinetic profile;
d) Tests demonstrating target animal safety;
e) Tests investigating resistance.
f) Should unexpected results occur during the course of the tests, these should be detailed.

Additionally, the following particulars shall be provided in all pre-clinical studies:

a) A summary;
a) A detailed experimental protocol giving a description of the methods, apparatus and materials used, details such as species, age, weight, sex, number, breed or strain of animals, identification of animals, dose, route and schedule of administration;
b) a statistical analysis of the results, where relevant;
c) An objective discussion of the results obtained, leading to conclusions on the efficacy and safety of the veterinary medicinal product.

Total or partial omission of any of these data shall be justified.

4b1.2.2 Results of Clinical Trials

All the particulars shall be supplied by each of the investigators on individual record sheets in the case of individual treatment and collective record sheets in the case of collective treatment.

The particulars supplied shall take the following form:

a) Name, address, function and qualifications of investigator in charge;
b) Place and date of treatment; name and address of owner of the animals;

c) Details of the clinical trial protocol giving a description of the methods used, including methods of randomisation and blinding, details such as the route of administration, schedule of administration, the dose, identification of trial animals, species, breeds or strains, age, weight, sex, physiological status;

d) Method of animal management and feeding, stating the composition of the feed and the nature and quantity of any feed additives;

e) Case history (as full as possible), including occurrence and course of any intercurrent diseases;

f) Diagnosis and means used to make it;

g) Clinical signs, if possible according to conventional criteria;

h) Precise identification of the formulation of the veterinary herbal medicinal product used in the clinical trial and the physical and chemical test results for the relevant batch(es);

i) Dosage of the veterinary herbal medicinal product, method, route and frequency of administration and precautions, if any, taken during administration (duration of injection, etc.);

j) Duration of treatment and period of subsequent observation;

k) All details concerning other veterinary medicinal products which have been administered during the period of examination, either prior to or concurrently with the test product and, in the latter case, details of any interactions observed;

l) All results of the clinical trials, fully describing the results based on the efficacy criteria and end points specified in the clinical trial protocol and including the results of the statistical analyses, if appropriate;

m) All particulars of any unintended event, whether harmful or not, and of any measures taken in consequence; the cause-and-effect relationship shall be investigated if possible;

n) Effect on animals' performance if appropriate;

o) Effects on the quality of foodstuffs obtained from treated animals, particularly in the case of veterinary medicinal products intended for use as performance enhancers;

p) A conclusion on the safety and efficacy in each individual case or, summarized in terms of frequencies or other appropriate variables where specific mass treatment is concerned.

Omission of one or more items (a) to (p) shall be justified.

In respect of each clinical trial, the clinical observations shall be summarized in a synopsis of the trials and the results thereof, indicating in particular:

a) The number of control and test animals treated either individually or collectively, with a breakdown according to species, breed or strain, age and sex;
b) The number of animals withdrawn prematurely from the trials and the reasons for such withdrawal;
c) In the case of control animals, whether they have:
- received no treatment, or
- received a placebo, or
- received the same active substance under investigation in a different formulation or by a different route;
d) The frequency of observed adverse reactions;
e) Observations as to the effect on animal performance, if appropriate;
f) Details concerning test animals which may be at increased risk owing to their age, their mode of rearing or feeding, or the purpose for which they are intended, or animals the physiological or pathological condition of which requires special consideration;
g) A statistical evaluation of the results.

Finally, the investigator shall draw general conclusions on the efficacy and safety of the veterinary herbal medicinal product under the proposed conditions of use, and in particular any information relating to indications and contraindications, dosage and average duration of treatment and where, appropriate, any interactions observed with other veterinary herbal medicinal product or feed additives as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage, when observed.

In the case of fixed combination products, the investigator shall also draw conclusions concerning the safety and the efficacy of the product when compared with the separate administration of the active substances involved.

3. Glossary

The definitions given below apply to the terms used in this guideline and provided to facilitate interpretation of the guidelines.

Accelerated testing:

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or medicinal product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long-term stability studies, should be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Acceptance criteria:

Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures

Active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Batch

A defined quantity of starting material, packaging material or finished pharmaceutical product (FPP) processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its

intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Bracketing:

The design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing may be applied to different container sizes or different fills in the same container closure system.

Climatic zones:

The four zones in the world that are distinguished by their characteristic based on the prevailing annual climatic conditions.

Five climatic zones can be distinguished for the purpose of worldwide stability testing.

Climatic Zone	**Definition**
I	Temperate climate
II	Subtropical and Mediterranean climate
III *	Hot/dry climate
IV a *	Hot/humid climate
IV b	Hot/very humid climate

* GCC States are categorized in climatic zones III & IV a.

Commitment batches:

Production batches of a drug substance or medicinal product for which the stability studies are initiated or completed postapproval through a commitment

made in the registration application.

Constituents with known therapeutic activity:

Are chemically defined substances or groups of substances which are generally accepted to contribute substantially to the therapeutic activity of a herbal substance, a herbal preparation or a herbal medicinal product.

Container closure system:

The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the medicinal product. A packaging system is equivalent to a container closure system.

Drug extract ratio (DER):

Means the ratio between the quantity of herbal substance used in the manufacture of a herbal preparation and the quantity of the herbal preparation obtained. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the herbal preparation obtained.

Dosage form:

A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Excipient:

A substance or compound, other than the API and packaging materials, that is intended or designated to be used in the manufacture of a FPP. In other words; Anything other than the drug substance in the dosage form.

Expiration date:

The date given on the individual container (usually on the label) of a product up to and including which the API and FPP are expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture. If stored under defined conditions and after

which it should not be used.

Extraction solvents:

Are solvents which are used for the extraction process.

Finished pharmaceutical product (FPP)

A product that has undergone all stages of production, including packaging in its final container and labeling. An FPP may contain one or more APIs.

Formal stability studies:

Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a medicinal product.

Genuine (Native) herbal preparation:

Refers to the preparation without excipients, even if for technological reasons the genuine herbal preparation is not available. However, for soft and liquid herbal preparations the genuine herbal preparation may contain variable amounts of (extraction) solvent.

Herbal medicinal products:

any medicinal product, exclusively containing as active substances one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

Herbal preparations:

Are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

Herbal substances:

All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh. Certain exudates that have

not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

Herbal teas:

Consist exclusively of one or more herbal substance(s) intended for oral aqueous preparations by means of decoction, infusion or maceration. The preparation is prepared immediately before use. Herbal teas are usually supplied in bulk form or in sachets.

Impermeable containers:

Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions and aluminium/aluminium blisters for solid dosage forms.

Long-term testing:

Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an API or FPP, during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the re-test period or the shelf-life, to confirm the projected re-test period and shelf-life, and to recommend storage conditions.

Markers:

are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the Herbal Medicinal Product if the marker has been quantitatively determined in the herbal substance or herbal preparations. There are two categories of markers:

- ***Active Markers:*** are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.

- ***Analytical Markers:*** are constituents or groups of constituents that serve for analytical purposes.

Mass balance:

The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error.

Matrixing:

The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same medicinal product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Mean kinetic temperature:

A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or veterinary herbal medicinal product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and considers the Arrhenius equation. When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes *(J. Pharm. Sci.*, 60:927-929, 1971) may be used.

New Veterinary Drug Substance (also referred to as "drug substance or Active pharmaceutical ingredient (API)" in this guidance):

The designated therapeutic moity that has not been previously registered in a region or member state for use in a veterinary medicinal product (also referred to as

a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved substance.

New veterinary herbal medicinal product (also referred to as "medicinal product or Finished pharmaceutical product (FPP)" in this guidance):

A veterinary herbal medicinal product type, for example, tablet, capsule, solution, cream, etc., containing a new or existing drug substance which has not previously been registered in a region or member state, and which contains a drug ingredient generally, but not necessarily, in association with excipients.

Ongoing stability study

The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected re-test period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP.

Pilot scale batch:

A batch of a drug substance (API) or medicinal product (FPP) manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger; unless otherwise adequately justified.

Primary batch:

A batch of a drug substance (API) or medicinal product (FPP) used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively. A primary batch of a drug substance (API) should be at least a pilot scale batch. For a medicinal product (FPP), two of the three batches should be at least pilot scale batch, and the third batch may be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production batch:

A batch of a drug substance (API) or medicinal product (FPP) manufactured at production scale by using production equipment in a production facility as specified in the application.

Provisional shelf-life

A provisional expiry date which is based on acceptable accelerated and available long-term data for the FPP to be marketed in the proposed container closure system.

Quantification:

means adjusting the herbal preparation to a defined range of constituents exclusively achieved by blending different batches of herbal substances and/or herbal preparations (e.g. quantified extracts).

Ratio of herbal substance to genuine herbal preparation (DER genuine):

Is the ratio of the quantity of the herbal substance to the quantity of the resulting genuine herbal preparation. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the genuine herbal preparation obtained.

Release specification

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of an API or FPP at the time of its release.

Re-test date:

The date after which samples of the drug substance (API) should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given medicinal product.

Re-test period:

The period of time during which the drug substance (API) is expected to remain

within its specification and, therefore, may be used in the manufacture of a given medicinal product (FPP), provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance (API) destined for use in the manufacture of a medicinal product (FPP) should be re-tested for compliance with the specification and then used immediately. A batch of drug substance (API) may be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a re-test period. The same may be true for certain antibiotics.

Semi-permeable containers:

Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial pressure gradient. Examples of semipermeable containers include plastic bags and semirigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Significant change

In general, "significant change" for an FPP is defined as:

- A 5% or more change in assay from its initial content of API(s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures. (*Note*: other values may be applied, if justified, to certain products, such as multivitamins and herbal preparations.)
- Any degradation product exceeding its acceptance criterion.
- Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. color, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g.

softening of suppositories, melting of creams or partial loss of adhesion for transdermal products) may be expected under accelerated conditions.

Also, as appropriate for the dosage form:

- Failure to meet the acceptance criterion for pH; or
- Failure to meet the acceptance criteria for dissolution for 12 dosage units.

Shelf life (also referred to as expiration dating period):

The time period during which a medicinal product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Solvent:

An inorganic or an organic liquid used for the preparation of solutions or suspensions in the manufacture of a herbal preparation or the manufacture of a herbal medicinal product.

Specification:

A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a herbal preparation / herbal substance or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal preparation / herbal substance and / or herbal medicinal product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant.

Specification - Release:

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a medicinal product at the time of its release.

Specification - Shelf life:

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its re-test period, or that a medicinal product should meet throughout its shelf life.

Stability indicating methods

Validated analytical procedures that can detect the changes with time in the chemical, physical or microbiological properties of the API or FPP, and that are specific so that the content of the API, degradation products, and other components of interest can be accurately measured without interference.

Stability studies (stability testing)

Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period (or shelf-life) of an API or the shelf-life of an FPP.

Standardisation:

means adjusting the herbal substance / herbal preparation to a defined content of a constituent or a group of constituents with known therapeutic activity respectively either by adding excipients or by blending batches of the herbal substance and/or herbal preparation (e.g. standardised extracts).

Storage condition tolerances:

The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guidance. The actual temperature and humidity (when controlled) should be monitored during stability storage. Short term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in

the study report and their effect assessed.

Stress testing (drug substance):

Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (medicinal product (FPP)):

Studies undertaken to assess the effect of severe conditions on the medicinal product. Such studies include photostability testing (see SFDA GL5) and specific testing of certain products (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting data:

Data, other than those from formal stability studies, that support the analytical procedures, the proposed re-test period or shelf life, and the label storage statements. Such data include:

1. stability data on early synthetic route batches of drug substance, small-scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing;
2. information regarding test results on containers;
3. other scientific rationales.

Traditional herbal medicinal products:

Medicinal Products for human/veterinary use that fulfil the conditions laid down in article 16a (1) of Directive 2001/83/EC, as amended.

Appendix 1: Examples of testing parameters

Section I for active pharmaceutical ingredients

In general, appearance, assay and degradation products should be evaluated for all active pharmaceutical ingredients (APIs). Other API parameters that may be susceptible to change should also be studied where applicable.

Section II for finished pharmaceutical products

The following list of parameters for each dosage form is presented as a guide to the types of tests to be included in a stability study. In general, appearance, assay and degradation products should be evaluated for all dosage forms, as well as the preservative and antioxidant content if applicable.

The microbial quality of multiple-dose sterile and non-sterile dosage forms should be controlled. Challenge tests should be carried out at least at the beginning and at the end of the shelf-life. Such tests would normally be performed as part of the development programme, for example, within primary stability studies. They need not be repeated for subsequent stability studies unless a change has been made which has a potential impact on microbiological status.

It is not expected that every test listed be performed at each time point. This applies in particular to sterility testing, which may be conducted for most sterile products at the beginning and at the end of the stability test period. Tests for pyrogens and bacterial endotoxins may be limited to the time of release. Sterile dosage forms containing dry materials (powder filled or lyophilized

References

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- Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to testing.