



Data Requirements for Veterinary Medicinal Products

Pharmaceutical and Immunological

Version 1.0



Data Requirements for Veterinary Medicinal Products

Pharmaceutical and Immunological

Version 1.0

Central Registration

Please visit the GHC website

for the latest updates

For Inquiries

drug.registration@ghc.sa

[vet.registration@ghc.sa](mailto:veter.registration@ghc.sa)



Contents

I. Introduction	6
II. Part 1 (Summary of the dossier) for pharmaceutical and immunological veterinary medicinal products	9
Part 1 Summary of the dossier	10
III. Data Requirements for Veterinary Pharmaceutical Products	15
Part 2 Quality Documentation	17
Part 3 Safety and Residues Tests	32
Part 4 Preclinical and clinical trials	46
IV. Data Requirements for Veterinary Immunological Products	54
Part 2 Quality Documentations	57
Part 3 Safety Documentation	67
Part 4 Efficacy documentation	73
V. References	76

I. Introduction

This guidance published to assist applicant in the preparation of Veterinary medicinal products submissions for presentation to Gulf Health Council (GHC).

The data requirements for veterinary medicinal product for each application will differ, based on the type of product pharmaceutical or immunological. However, presentation and content of part 1 (summary of the dossier) is similar for both types and will differ in Parts 2, 3 and 4:

- For pharmaceutical product; Parts 2, 3 and 4 of the dossier consist of quality, safety and residues tests and preclinical and clinical respectively.
- For immunological product; Parts 2, 3 and 4 of the dossier consist of quality, safety and efficacy respectively.

About preparing the dossier for generic and similar biological veterinary medicinal products, it is acknowledged that certain parts or sections would generally not be applicable, as explained in the following sections:

- **For veterinary generic products**

The dossier shall contain the data referred to in Parts 1 and 2 with an environmental risk assessment and data demonstrating that the product has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product and data showing bioequivalence with the reference medicinal product.

The detailed and critical summaries on safety and efficacy shall particularly focus on the following elements:

- the grounds for claiming essential similarity,
- a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed together with an evaluation of these impurities,

- an evaluation of the bioequivalence studies or justification as to why studies were not performed concerning to established guidance,
- if applicable, additional data in order to demonstrate the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorised active substance shall be provided by the applicant; those data shall include evidence that there is no change in the pharmacokinetic or pharmacodynamics properties of the therapeutic moiety and/or in toxicity, which could influence the safety/efficacy profile.

For products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided:

- evidence to demonstrate equivalent or differing depletion of residues from the administration site, which may be substantiated by appropriate residue depletion studies,
- evidence to demonstrate target animal tolerance at the administration site, which may be substantiated by appropriate target animal tolerance studies.

- **Similar biological veterinary medicinal products**

Where a biological veterinary medicinal product which is similar to a reference biological veterinary medicinal product does not meet the conditions in the definition of the generic medicinal product, information to be supplied shall not be limited to Parts 1 and 2, supplemented with bioequivalence and bioavailability data. In such cases, additional data shall be provided, in particular on the safety and efficacy of the product:

- The type and amount of additional data (i.e. toxicological and other safety studies and appropriate clinical studies) shall be determined on a case-by-case basis in accordance with relevant scientific guidelines.



- Due to the diversity of biological veterinary medicinal products, GHC shall determine the necessary studies foreseen in Parts 3 and 4, taking into account the specific characteristic of each individual biological veterinary medicinal product.

If the reference biological veterinary medicinal product has more than one indication, the efficacy and safety of the biological veterinary medicinal product claimed to be similar shall be justified or, if necessary, demonstrated separately for each of the claimed indications.

II. Part 1 (Summary of the dossier) for pharmaceutical and immunological veterinary medicinal products

Section	Requirements
1a	Administrative information
1a1	Cover letter
1a2	Application form
1a3	Pharmacovigilance
1a31	Pharmacovigilance system
1a32	Risk management plan
1a4	Certificates & documents
1a41	GMP certificate
1a42	CPP
1a43	Certificate of analysis – Drug substances & Finished product
1a44	Certificate of analysis - Excipients
1a45	Certificate of suitability
1a46	Patent Information
1a47	Letter of access or acknowledgment to DMF
1a5	Pricing
1a51	Price list
1a52	Other documents related
1a6	Responses to questions
1a7	Additional data
1b	SPC and Product Literature
1b1	Summary of Product Characteristics (SPC)
1b2	Package leaflet (PL)
1b21	Arabic leaflet
1b22	English leaflet
1b3	Labeling
1b4	Artwork (Mock-ups)
1b5	Samples
1c	Critical Summaries
1c1	Quality
1c2	Safety & residues
1c3	Efficacy

Part 1 Summary of the dossier

1a Administrative information

1a1 Cover letter

The applicant shall include a cover letter for each submission. A template is provided in the GHC website in (Forms) section.

1a2 Application form

The completed application form printed out from the Taawon system (<https://taawon-ghc.com/esop/ksa-ghc-host/public/web/login.html?ncp=1593319562575.1635302-1>) 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 and legalized 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 be legalized and 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 & finished product

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

1a44 Certificate of analysis – excipients

Certificates of analysis for more than one batch of the excipients may be 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 veterinary medicinal products are submitted according to *Note for guidance on minimising 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 was written by the DMF Owner or authorized Agent permitting GHC to reference information in the DMF on behalf of the Applicant.

1a5 Pricing

1a51 Price list

The applicant shall include the price of the product in countries listed in the GHC Guidance for Submission. A template is provided in the GHC website in (Forms) section.

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

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 GHC 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.



III. Data Requirements for Veterinary Pharmaceutical Products



Section	Requirements
Part 2	Quality Documentation
2a	Qualitative and Quantitative Particulars
2a1	Qualitative Particulars
2a2	Usual Terminology
2a3	Quantitative Particulars
2a4	Development pharmaceuticals
2b	Description of the Manufacturing Method
2c	Control of Starting Materials
2c1	Active substance(s)
2c2	Excipient(s)
2c3	Container / Closure system
2c4	Substances of biological Origin
2d	Control Tests at intermediate process stages
2e	Tests on the finished Product
2e1	General characteristics of the finished product
2e2	Identification and assay of active substance(s)
2e3	Identification and assay of excipient components
2e4	Safety tests
2f	Stability Tests
2f1	Active substances(s)
2f2	Finished product
2g	Other Information
Part 3	Safety and residues tests
3a	Safety tests
3a1	Precise Identification of the Product and active
3a2	Pharmacology
3a3	Toxicology
3a4	Other requirements
3a5	URA (User safety)
3a6	ERA (Environmental risk assessment)
3b	Residue tests
3b1	Identification of product
3b2	Metabolism and residue kinetics
3b3	Residue analytical method
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

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

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.

2a Qualitative and quantitative particulars

2a1 Qualitative particulars

Qualitative particulars of all the constituents of the veterinary medicinal product 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 medicinal product 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 veterinary medicinal product:

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 veterinary medicinal products, 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 veterinary medicinal products 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.

2a4 Development pharmaceuticals

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

it shall include at least:

- 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,
 - 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 veterinary medicinal product 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)

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.

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 **GHC** 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.

- **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, **GHC** may request more appropriate specifications from the applicant, including limits for specific impurities with validated test procedures.

- **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.

- **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 pharmacopoeia 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

• Active substance

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.

- **Finished product**

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 intermediate test stage of the manufacturing process, with a view to ensuring the consistency of the technical characteristics and the production process.

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

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**

Characteristics	Methods and Acceptance Limits	
	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.

2e1 General characteristics of the finished 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 Identification and assay of active substance(s)

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 $\pm 5\%$ 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 **GHC** 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.

2e3 Identification and assay of excipient components

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.

2e4 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

Refer to the VICH stability testing guidelines:

<http://www.vichsec.org/guidelines/pharmaceuticals/pharma-quality/pharma-stability.html>

2f1 Active substance

Stability data 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

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 breached 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 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 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 medicinal product, for example during its administration to the animal;
- d) the potential risks for the environment resulting from the use of the veterinary 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 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.

- **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.

- **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 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:

- **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 medicinal product is anticipated, those routes of exposure shall be studied.

- **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 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.

- **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.

- **Reproductive toxicity including developmental toxicity**

- **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 medicinal products or substance under investigation.

In the case of pharmacologically active substances or veterinary medicinal products 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.

o Study of developmental toxicity

In the case of pharmacologically active substances or veterinary medicinal products 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 medicinal product would result in significant exposure to users, standard developmental toxicity studies shall be performed.

- **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 veterinary medicinal product for the first time must be assessed for genotoxic properties.

- **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.

- **Exceptions**

Where a veterinary 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 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

- **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.

- **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.

- **Observations in humans**

Information shall be provided showing whether the pharmacologically active substances of the veterinary 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 medicinal products are themselves not used or are no longer used as medicinal products in human therapy, the reasons shall be stated.

- **Development of resistance**

Data on the potential emergence of resistant bacteria of relevance for human health are necessary in the case of veterinary medicinal products. 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 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.

3.a.5 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)

- **Environmental risk assessment of veterinary medicinal products 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 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 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.

- **Environmental risk assessment for veterinary medicinal products containing or consisting of genetically modified organisms**

In the case of veterinary medicinal products 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.

- **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

• 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 medicinal products intended for use in food-producing animals, the residue documentation shall show:

1. to what extent, and how long, do residues of the veterinary 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.

3b1 Identification of product

An identification of the veterinary 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.

3b2 Metabolism and residue kinetics

- **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 medicinal products 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 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 from the target animal shall be described.

The major metabolites shall be identified and characterized.

- **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 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 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.

3b3 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

- **Pharmacodynamics**

The pharmacodynamics effects of the active substance(s) included in the veterinary 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 medicinal products. 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.

- **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 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 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 the 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 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 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 medicinal product authorized in the **GHC** 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.

- **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.

- **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 medicinal products, in order to enable an objective overall assessment of the risk/benefit balance of the product.

- **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.

- **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 medicinal product used in the clinical trial and the physical and chemical test results for the relevant batch(es);
- i) Dosage of the veterinary 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 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



medicinal products 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.



IV. Data Requirements for Veterinary Immunological Products



Section	Requirements
Part 2	Quality Documentation
2a	Quantitative and Qualitative Particulars
2a1	Qualitative Particulars
2a2	Usual terminology
2a3	Quantitative particulars
2a4	Product development
2b	Description of the Manufacturing Method
2c	Production and Control of Starting Materials
2c1	Starting Materials listed in Pharmacopeias
2c2	Starting Materials not listed in Pharmacopeias
2d	Control tests during the manufacture process
2e	Control tests on the finished product
2e1	General Characteristics
2e2	Identification of active substance(s)
2e3	Batch titre or potency
2e4	Identification and assay of adjuvants
2e5	Identification and assay of excipients components
2e6	Safety tests
2e7	Sterility and purity test
2e8	Residual humidity
2e9	Inactivation
2f	Batch to Batch Consistency
2g	Stability tests
2h	Other information
Part 3	Safety Documentation
3a	General Requirements
3b	Laboratory Tests
3b1	Safety of one dose
3b2	Safety of an overdose
3b3	Safety of the repeated administration of one dose
3b4	Examination of reproductive performance
3b5	Examination of immunological functions
3b6	Special requirements for live vaccines



3b7	User safety (URA)
3b8	Study of residues
3b9	Interactions
3c	Field Studies
3d	ERA (Environmental Risk Assessment)
3e	Assessment of products containing or consisting of GMOs
Part 4	Efficacy Documentation
4a	General Requirements
4b	Laboratory Trials
4c	Field Trials

Part 2 Quality Documentations

All test procedures shall fulfil the necessary criteria for analysis and control of the quality of the starting materials and the finished product and shall be validated procedures. The results of the validation studies shall be provided. Any special apparatus and equipment which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the manufacturing method.

In the case of test procedures included in the Pharmacopoeias, this description may be replaced by a detailed reference to the pharmacopoeia in question.

Where available, chemical and biological reference material of the Pharmacopoeia shall be used. If other reference preparations and standards are used, they shall be identified and described in detail.

2a Qualitative and quantitative particulars

2a1 Qualitative particulars

Qualitative particulars of all the constituents of the immunological veterinary medicinal product shall mean the designation or description of:

- the active substance(s),
- the constituents of the adjuvants,
- the constituent (s) of the excipients, whatever their nature or the quantity used, including preservatives, stabilisers, emulsifiers, colouring matter, flavouring, aromatic substances, markers, etc.),
- the constituents of the pharmaceutical form administered to animals.

These particulars shall be supplemented by any relevant data concerning the container and, where appropriate, its manner of closure, together with details of devices with which the immunological veterinary medicinal product will be used or administered and which will be delivered with the medicinal product. If the device is not delivered together with

the immunological veterinary medicinal product, relevant information about the device shall be provided, where necessary for the assessment of the product.

2a2 Usual terminology

The usual terminology, to be used in describing the constituents of immunological veterinary medicinal products:

- In respect of substances which appear in the pharmacopoeia, the main title of the monograph in question, which will be obligatory for all such substances, with reference to the pharmacopoeia concerned.
- In respect of other substances, the international non-proprietary name recommended by the World Health Organization, which may be accompanied by another non-proprietary name or, failing these, the exact scientific designation; substances 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 the active substances of an immunological veterinary medicinal product, it is necessary to specify whenever possible the number of organisms, the specific protein content, the mass, the number of International Units (IU) or units of biological activity, either per dosage-unit or volume, and with regard to the adjuvant and to the constituents of the excipients, the mass or the volume of each of them. with due allowance for the details provided in section 2b.

Where an International Unit of biological activity has been defined, this shall be used.

The units of biological activity for which no published data exist shall be expressed in such a way as to provide unambiguous information on the activity of the ingredients, e.g. by stating the immunological effect on which the method of determining the dose is based.

2a4 Product development:

An explanation shall be provided with regard to the composition, and components, supported by scientific data on product development. The overage, with justification thereof, shall be stated.

2b Description of the manufacture method

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

For this purpose the description it shall include:

- the various stages of manufacture (including production of the antigen and purification procedures) so that an assessment can be made of the reproducibility of the manufacturing procedure and of the risks of adverse effects on the finished products, such as microbiological contamination; the validation of key stages in the production process shall be demonstrated and the validation of the production process as a whole shall be demonstrated with provision of results of three consecutive batches produced using the method described,
- in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity and consistency of each batch of the finished product,
- listing of all the substances at the appropriate steps where they are used, including those which cannot be recovered in the course of manufacturing,
- the details of the blending, with the quantitative particulars of all the substances used,
- a statement of the stages of manufacture at which sampling is carried out for control tests during production.

2c Production and control of the starting materials

For the purposes of this paragraph “starting materials” means all components used in the production of the immunological veterinary medicinal product. Culture media consisting of several components used for production of the active substance shall be regarded as one starting material. Nevertheless, the qualitative and quantitative composition of the

any culture media shall be presented in so far as **GHC** consider that this information is relevant to the quality of the finished product and any risks that might be posed. If materials of animal origin are used for preparation of these culture media, the animal species and the tissue used have to be included.

The dossier shall include the specifications, information on the tests to be conducted for the quality control of all batches of starting materials and results for a batch for all components used and shall be submitted.

2c1 Starting materials listed in pharmacopoeias

The monographs of the pharmacopoeia shall be applicable to all substances appearing in it.

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 the pharmacopoeia are used, proof must be supplied that the starting materials meet the quality requirements of that pharmacopoeia.

In cases where a specification contained in a monograph of the pharmacopoeia might be insufficient to ensure the quality of the substance, **GHC** may request more appropriate specifications from the applicant for marketing authorization.

When starting materials of animal origin are used, they shall comply with the relevant monographs including general monographs and general chapters of the pharmacopoeia. The tests and controls conducted shall be appropriate to the starting material.

The applicant shall supply documentation to demonstrate that the starting materials and the manufacturing of the veterinary medical product is in comply with the requirements of the *Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*, as well as with the requirements of the corresponding monograph of the Pharmacopoeia.

Certificates of Suitability issued by the European Directorate for the Quality of Medicines and Health Care, with reference to the relevant monograph of the Pharmacopoeia, may be used to demonstrate compliance.

2c2 Starting materials not listed in pharmacopoeias

- **Starting materials of biological origin**

The description shall be given in the form of a monograph. Whenever possible, vaccine production shall be based on a seed lot system and on established cell seeds. For the production of immunological veterinary medicinal products consisting of serums, the origin, general health and immunological status of the producing animals shall be indicated and defined pools of source materials shall be used.

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

For genetically engineered starting materials this information shall include details such as the description of the starting cells or strains, the construction of the expression vector (name, origin, function of the replicon, promoter enhancer and other regulator elements), control of the sequence of DNA or RNA effectively inserted, oligonucleotidic sequences of plasmid vector in cells, plasmid used for co-transfection, added or deleted genes, biological properties of the final construct and the genes expressed, copy number and genetic stability.

Seed materials, including cell seeds and raw serum for anti-serum production shall be tested for identity and extraneous agents.

Information shall be provided on all substances of biological origin used at any stage in the manufacturing procedure. The information shall include:

- details of the source of the materials,
- details of any processing, purification and inactivation applied, with data on the validation of these process and controls during production,
- details of any tests for contamination carried out on each batch of the substance.

If the presence of extraneous agents is detected or suspected, the corresponding material shall be discarded or used in very exceptional circumstances only when further processing of the product ensures their elimination and/or inactivation; elimination and/or inactivation of such extraneous agents shall be demonstrated.

When cell seeds are used, the cell characteristics shall be shown to have remained unchanged up to the highest passage level used for the production.

For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given.

Documentation shall be supplied to demonstrate that the seed materials, cell seeds, batches of serum, Culture media 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 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, can be used to demonstrate compliance.

- **Starting materials of non - biological origin**

The description shall be given in the form of a monograph under the following headings:

1. The name(s) of the starting material meeting the requirements of 2.a.2 shall be supplemented by (any trade-name or scientific synonyms),
2. Description of starting material (set down in a form similar to that used in a descriptive item in the Pharmacopoeia),
3. the function of the starting material,
4. methods of identification,
5. any special precautions which may be necessary during storage of the starting material and, if necessary, its storage life shall be given.

2d Control tests during the manufacturing process

The dossier shall include particulars relating to the control tests, which are carried out on intermediate products with a view to verifying the consistency of the manufacturing process and the final product. For inactivated or detoxified vaccines, inactivation or detoxification shall be tested during each production run as soon as possible after the end of the inactivation or detoxification process and after neutralisation if this occurs, but before the next step of production.

2e Control tests on the finished product

For all tests, the description of the techniques for analyzing the finished product shall be set out in sufficiently precise detail for quality assessment.

The dossier shall include particulars relating to control tests on the finished product. Where appropriate monographs exist, if test procedures and limits other than those mentioned in the monographs of the Pharmacopoeia, proof must be supplied that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned. The application for marketing authorization shall list those tests which are carried out on representative samples of each batch of finished product. The frequency of the tests which are not carried out on each batch shall be stated. Release limits shall be indicated.

Where available, chemical and biological reference material of the Pharmacopoeia shall be used. If other reference preparations and standards are used, they shall be identified and described in detail.

2e1 General characteristics

The tests of general characteristics shall, wherever applicable, relate to the control of average masses and maximum deviations, to mechanical, physical or chemical tests, physical characteristics such as density, pH, viscosity, etc. For each of these characteristics, specifications, with appropriate confidence limits, shall be established by the applicant in each particular case.

2e2 Identification the active substance(s)

Where necessary, a specific test for identification shall also be carried out.

2e3 Batch titre or potency

A quantification of the active substance shall be carried out on each batch to show that each batch will contain the appropriate potency or titre to ensure its safety and efficacy.

2e4 Identification and assay of adjuvants

Insofar as testing procedures are available, the quantity and nature of the adjuvant and its components shall be verified on the finished product.

2e5 Identification and assay of excipient components

Insofar as is necessary, the excipient(s) shall be subject at least to identification tests.

An upper and lower limit test shall be obligatory in respect of preserving agents; an upper limit test for any other excipient components liable to give rise to an adverse reaction shall be obligatory.

2e6 Safety tests

Apart from the results of tests submitted in accordance with Part 3 particulars of safety tests shall be submitted. These tests shall preferably be over dosage studies carried out in at least one of the most sensitive target species and by at least the recommended route of administration posing the greatest risk.

2e7 Sterility and purity test

Appropriate tests to demonstrate the absence of contamination by adventitious agents or other substances shall be carried out according to the nature of the immunological veterinary medicinal product, the method and the conditions of manufacture.

2e8 Residual humidity

Each batch of lyophilised product shall be tested for residual humidity.

2e9 Inactivation

For inactivated vaccines, a test to verify inactivation shall be carried out on the product in the final container unless it has been conducted at a late stage in-process.

2f Batch-to-batch consistency

In order to ensure that quality of the product is consistent from batch to batch and to demonstrate conformity with specifications a full protocol of three consecutive batches giving the results for all tests performed during production and on the finished product shall be provided.

2g Stability

Description shall be given of the tests undertaken to support the shelf life proposed by the applicant. These tests shall always be real-time studies; they shall be carried out on a sufficient number of batches produced according to the described production process and on products stored in the final container(s); these tests include biological and physicochemical stability tests.

The conclusions shall contain the results of analyses, justifying the proposed shelf life under all proposed storage conditions.

In the case of products administered in feed, information shall also be given as necessary on the shelf life of the product, at the different stages of mixing, when mixed in accordance with the recommended instructions.

Where a finished product requires reconstitution prior to administration or is administered in drinking water, details of the proposed shelf life are required for the product reconstituted as recommended. Data in support of the proposed shelf life for the reconstituted product shall be submitted.

Stability data obtained from combined products may be used as preliminary data for derivative products containing one or more of the same components.

The proposed in-use shelf life shall be justified. The efficacy of any preservative system shall be demonstrated.

Information on the efficacy of preservatives in other similar immunological veterinary medicinal products from the same manufacturer may be sufficient.

Refer to the VICH stability testing guidelines:

<http://www.vichsec.org/guidelines/biologicals/bio-quality/stability.html>



2h Other information

Information relating to the quality of the immunological veterinary medicinal product not covered by the previous sections may be included in the dossier.



Part 3 Safety Documentation

3a General requirements

The safety tests shall show the potential risks from the immunological veterinary medicinal product, which may occur under the proposed conditions of use in animals: these shall be evaluated in relation to the potential benefits of the product.

Where immunological veterinary medicinal products consist of live organisms, especially those, which could be shed by vaccinated animals, the potential risk to unvaccinated animals of the same or of any other potentially exposed species shall be evaluated.

The safety studies shall be carried out in the target species. The dose to be used shall be the quantity of the product to be recommended for use and the batch used for safety testing shall be taken from a batch or batches produced according to the manufacturing process described in Part 2 of the application.

In the case of an immunological veterinary medicinal product containing a live organism, the dose to be used in the laboratory tests described in sections 3b1 and 3b2 shall be the quantity of the product containing the maximum titre. If necessary the concentration of the antigen may be adjusted to achieve the required dose. For inactivated vaccines the dose to be used shall be that quantity recommended for use containing the maximum antigen content unless justified.

The safety documentation shall be used for assessment of the potential risks which may result from the exposure of human beings to the veterinary medicinal product, for example during its administration to the animal.

3b Laboratory tests

3b1 Safety of one dose

The immunological veterinary medicinal product shall be administered at the recommended dose and by each recommended route of administration to animals of each species and category in which it is intended for use, including animals of the minimum age of administration. The animals shall be observed and examined for signs of systemic and local reactions. Where appropriate, these studies shall include detailed post-mortem macroscopic and microscopic examinations of the injection site. Other objective criteria shall be recorded, such as rectal temperature and performance measurements.

The animals shall be observed and examined until reactions may no longer be expected, but in all cases, the observation and examination period shall be at least 14 days after

administration.

This study may be part of the repeated dose study required under section 3b3 or omitted if the results of the overdose study required section 3b2 have revealed no signs of systemic or local reactions.

3b2 Safety of an overdose

Only live immunological veterinary medicinal products require overdose testing. An overdose of the immunological veterinary medicinal product shall be administered by each recommended route(s) of administration to animals of the most sensitive categories of the target species, unless the selection of the most sensitive of several similar routes is justified. In the case of immunological veterinary medicinal products administered by injection, the doses and route(s) of administration shall be chosen to take account of the maximum volume, which can be administered at any one single injection site. The animals shall be observed and examined for at least 14 days after administration for signs of systemic and local reactions. Other criteria shall be recorded, such as rectal temperature and performance measurements.

Where appropriate, these studies shall include detailed post-mortem macroscopic and microscopic examinations of the injection site if this has not been done under section 3b1.

3b3 Safety of the repeated administration of one dose

In the case of immunological veterinary medicinal products to be administered more than once, as part of the basic vaccination scheme, a study of the repeated administration of one dose shall be required to reveal any adverse effects induced by such administration. These tests shall be carried out on the most sensitive categories of the target species (such as certain breeds, age groups), using each recommended route of administration.

The animals shall be observed and examined for at least 14 days after the last administration for signs of systemic and local reactions. Other objective criteria shall be recorded, such as rectal temperature and performance measurements.

3b4 Examination of reproductive performance

Examination of reproductive performance shall be considered when data suggest that the

starting material from which the product is derived may be a potential risk factor. Reproductive performance of males and non-pregnant and pregnant females shall be investigated with the recommended dose and by the most sensitive route of administration. In addition, harmful effects on the progeny, as well as teratogenic and abortifacient effects, shall be investigated.

These studies may form part of the safety studies described in sections 3b1, 3b2 and 3b3 or of the field studies provided for in section 3c.

3b5 Examination of immunological functions

Where the immunological veterinary medicinal product might adversely affect the immune response of the vaccinated animal or of its progeny, suitable tests on the immunological functions shall be carried out.

3b6 Special requirements for live vaccines

- **Spread of the vaccine strain**

Spread of the vaccine strain from vaccinated to unvaccinated target animals shall be investigated, using the recommended route of administration most likely to result in the spread. Moreover, it may be necessary to investigate the spread to non-target animal species which could be highly susceptible to a live vaccine strain.

- **Dissemination in the vaccinated animal**

Faeces, urine, milk, eggs, oral, nasal and other secretions shall be tested for the presence of the organism as appropriate. Moreover, studies may be required of the dissemination of the vaccine strain in the body, with particular attention being paid to the predilection sites for replication of the organism. In the case of live vaccines for zoonoses to be used for food producing animals, these studies must take particularly into account the persistence of the organism at the injection site.

- **Reversion to virulence of attenuated vaccines**

Reversion to virulence shall be investigated with the master seed. If the master seed is not available in sufficient quantity the lowest passage seed used for the production shall be examined. Use of another passage option shall be justified. The initial vaccination shall be carried out using the route of administration most likely to lead to reversion to

virulence. Serial passages shall be made in target animals through five groups of animals, unless there is justification to make more passages or the organism disappears from the test animals sooner. Where the organism fails to replicate adequately, as many passages as possible shall be carried out in the target species.

- **Biological properties of the vaccine strain**

Other tests may be necessary to determine as precisely as possible the intrinsic biological properties of the vaccine strain(e.g. neurotropism).

- **Recombination or genomic reassortment of strains**

The probability of recombination or genomic reassortment with field or other strains shall be discussed.

3b7 User safety (URA)

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

3b8 Study of residues

For immunological veterinary medicinal products, it will normally not be necessary to undertake a study of residues.

However, where adjuvants and/or preservatives are used in the manufacture of immunological veterinary medicinal products, consideration shall be given to the possibility of any residue remaining in the foodstuffs. If necessary, the effects of such residues shall be investigated.

A proposal for a withdrawal period shall be made and its adequacy shall be discussed in relation to any residue studies which have been undertaken.

3b9 Interactions

If there is a compatibility statement with other veterinary immunological products in the summary of product characteristics the safety of the association shall be investigated. Any other known interactions with veterinary medicinal products shall be described.

3c Field Studies

Unless justified, results from laboratory studies shall be supplemented with data from field studies, using batches according to the manufacturing process described in the marketing authorization application. Both safety and efficacy may be investigated in the same field studies.

3d ERA (Environmental Risk Assessment)

The purpose of the environmental risk assessment is to assess the potential harmful effects, which the use of the product may cause to the environment and to identify any precautionary measures, which may be necessary to reduce such risks.

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

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 the environmental system,
- the possible excretion of the product, its active substances into the environment by treated animals, persistence in such excreta,
- the disposal of unused or waste product.

In the case of live vaccine strains which may be zoonotic, the risk to humans shall be assessed.

Where the conclusions of the first phase indicate potential exposure of the environment to the product, the applicant shall proceed to the second phase and evaluate the potential risk(s) that the veterinary medicinal product might pose to the environment. Where necessary, further investigations on the impact of the product (soil, water, air, aquatic systems, non-target organisms) shall be carried out.

3e Assessment of products containing or consisting of GMO (Genetically Modified Organisms)

In this section the applicant should describes the format in which the particulars relevant to the environmental risk assessment.

In the case of veterinary medicinal products 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.

Part 4 Efficacy documentation

• General principles

The purpose of the trials described in this Part is to demonstrate or to confirm the efficacy of the immunological veterinary medicinal product. All claims made by the applicant with regard to the properties, effects and use of the product, shall be fully supported by results of specific trials contained in the application for marketing authorization.

• Performance of trials

All efficacy trials shall be conducted in accordance with a fully considered detailed protocol, which shall be recorded in writing prior to commencement of the trial. The welfare of the trial animals shall be subject to veterinary supervision and shall be taken fully into consideration during the elaboration of any trial protocol and throughout the conduct of the trial.

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

4a General requirements

The choice of antigens or vaccine strains shall be justified on the basis of epizootological data.

Efficacy trials carried out in the laboratory shall be controlled trials, including untreated control animals unless this is not justified for animal welfare reasons and efficacy can be otherwise demonstrated.

In general, these laboratory trials shall be supported by trials carried out in field

conditions, including untreated control animals.

All trials shall be described in sufficiently precise details so as to be reproducible in controlled trials, carried out at the request of the **GHC**. The investigator shall demonstrate the validity of all the techniques involved. All results obtained, whether favorable or unfavorable, shall be reported.

The efficacy of an immunological veterinary medicinal product shall be demonstrated for each category of target animal species recommended for vaccination, by each recommended route of administration and using the proposed schedule of administration. The influence of passively acquired and maternally derived antibodies on the efficacy of a vaccine shall be adequately evaluated, if appropriate. Unless justified, the onset and duration of immunity shall be established and supported by data from trials.

The efficacy of each of the components of multivalent and combined immunological veterinary medicinal products shall be demonstrated. If the product is recommended for administration in combination with or at the same time as another veterinary medicinal product, they shall be shown to be compatible.

Whenever a product forms part of a vaccination scheme recommended by the applicant, the priming or booster effect or the contribution of the veterinary immunological product to the efficacy of the scheme as a whole shall be demonstrated.

The dose to be used shall be the quantity of the product to be recommended for use and the batch used for efficacy testing shall be taken from a batch or batches produced according to the manufacturing process described in part 2 of the application.

If there is a compatibility statement with other immunological products in the summary of product characteristics, the efficacy of the association shall be investigated. Any other known interactions with any other veterinary medicinal products shall be described. Concurrent or simultaneous use may be allowed if supported by appropriate studies.

For diagnostic immunological veterinary medicinal products administered to animals, the applicant shall indicate how reactions to the product are to be interpreted.

For vaccines intended to allow a distinction between vaccinated and infected animals

(marker vaccines), where the efficacy claim is reliant on in vitro diagnostic tests, sufficient data on the diagnostic tests shall be provided to allow adequate assessment of the claims related to the marker properties.

4b Laboratory trials

In principle, demonstration of efficacy shall be undertaken under well-controlled laboratory conditions by challenge after administration of the immunological veterinary medicinal product to the target animal under the recommended conditions of use. Insofar as possible, the conditions under which the challenge is carried out shall mimic the natural conditions for infection. Details of the challenge strain and its relevance shall be provided.

For live vaccines, batches containing the minimum titre or potency shall be used unless justified. For other products, batches containing the minimum active content shall be used unless otherwise justified.

If possible, the immune mechanism (cell-mediated/humoral, local/general classes of immunoglobulin) which is initiated after the administration of the immunological veterinary medicinal product to target animals by the recommended route of administration shall be specified and documented.

4c Field trials

Unless justified, results from laboratory trials shall be supplemented with data from field trials, using batches representative of the manufacturing process described in the marketing authorization application. Both safety and efficacy may be investigated in the same field study.

Where laboratory trials cannot be supportive of efficacy, the performance of field trials alone may be acceptable.



V. References

- Notice to applicants of veterinary medicinal products (Presentation and content of the dossier), Directorate – General for Health and Food safety, European Commission, 2015.
- Regulations (law) of veterinary products in Gulf Cooperation Council (GCC).
- VICH stability guidelines.