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VETERINARY MEDICINES DIRECTORATE



**GUIDELINES
ON
SUBMISSION OF
DOCUMENTATION FOR
MARKETING AUTHORIZATION FOR VETERINARY MEDICINES**

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Authorization of these guidelines

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Introduction

As a rule, before a veterinary medicinal product can be sold or used in Kenya, Veterinary Medicine Directorate (VMD) of Kenya must authorize it. This applies to all types of veterinary medicinal products, namely pharmaceutical products as well as vaccines, alternative medicines and biological products. A marketing authorization (also called ‘registration or licensing’) is the approval by VMD that the product can be sold and used, specifying the details of the medicine (name of active ingredient(s), animals for which it can be used, indications for use, dose and duration of treatment), the conditions of use (storage conditions, shelf life, withdrawal period, instructions for safe use or instructions for safe disposal of waste) and any precautions or warnings for safe use, including possible contraindications. These details and instructions for use of a veterinary medicinal product are part of the labelling and package leaflet of the product, as it is brought on the market.

The Control of veterinary medicines by the Veterinary Medicines Directorate is provided for in legal notice no. 209 of 2015 ‘the veterinary surgeons and veterinary paraprofessionals act (the veterinary medicines directorate) regulations, 2015’ with the establishment of the VMD. VMD has been established as the National Regulatory Authority (NRA) for veterinary products (VP). The daily operations of veterinary medicine regulation, together with monitoring and surveillance activities have been delegated to the VMD.

The guidelines outlined in this document are primarily drawn up in accordance to the legal requirements of the VMD. This guideline applies only to veterinary pharmaceuticals. In the case of **veterinary biological, veterinary pesticides, feed supplements, alternative veterinary medicines** and **veterinary devices**, separate guidelines are available and can be obtained from VMD offices/website (vmd.go.ke).

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Applicants are reminded that it is still their responsibility to ensure that their veterinary medicines duly comply with the requirements of VMD and OIE.

This guideline provides recommendations for applicants preparing application for a registration of VP for submission to VMD. The document describes how to organize applications based on the ICH & VICH guidelines. Guidelines on Submission of Documentation for Prequalification of Multi-source Finished Pharmaceutical Products and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for VICH guidelines on the common technical document (dossier).

The purpose of this document is to provide guidance on the information and documentation to be submitted. This is to ensure uniformity in the way dossiers application documents are prepared and consistency in the way the information and documentation is presented.

It is expected that all applicants comply and do not attempt to modify the general organization of the application document that could lead to its rejection. Detailed information, which may include studies required, data obtained, expert comments, references and other technical contents may be added as an appendix to the document that is expected to be presented in the approved format. Data information and analysis that is submitted must be based on current scientific knowledge, specifications, standards, processes and procedures and must be appropriately referenced. These guidelines will form the basis for dossier evaluation.

One original hard copy of thread and tape bound dossier should be submitted and one electronic copy.

The guidelines are arranged as per the dossier format as follows:

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Part 1: Administrative Information

Part 2: Chemical, Pharmaceutical, Non-clinical and Clinical Overviews and Summaries

Part 3: Chemical and Pharmaceutical Documentation

Part 4: Non-clinical study reports for new chemical entities only

Part 5: Clinical Study Reports

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ABBREVIATIONS

AI- Active Ingredient

ATC -The Anatomical Therapeutic Chemical (ATC) Classification System

CTD- Common Technical Document

GMP – Good Manufacturing Practice

cGMP – current Good Manufacturing Practice

ICH- International Conference on Harmonization

INN- International Non-Proprietary Name

NCE- New Chemical Entities

VMD- Veterinary Medicines Directorate

VICH-Veterinary International Conference on Harmonization

IL– Information Leaflet (inserts)

POM– Prescription Only Medicines

SPC-Summary Product Characteristics

OIE – World Organization for animal Health

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Definition

Active ingredient(s) (AI)

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

Authorized local technical representative/Agent

Every applicant who is not resident in Kenya shall appoint a person in Kenya and authorized by VMD to deal in Veterinary products to be an AGENT (authorized Local Technical Representative (ALTR). The appointment shall be notified to the Authority by submitting a letter of appointment supported by original copy of power of attorney. Dully notarized in country of origin, and registered with registrar of Companies in Kenya.

Authorized person

The person recognized by the VMD as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the laws and regulations in force in Kenya.

or

A person responsible for the release of batches of finished product for sale or distribution. An authorized person must sign the batch documentation of a batch of a finished product and the batch test results from the quality control department for batch release.

Applicant:

A person who owns a formula or trademark of a product, who may be a manufacturer or a person to whose order and specifications the product is manufactured and who shall be the registration holder and have the primary responsibility of the product on the Kenyan market

Batch records

All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bioavailability

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The rate and relative amount of the administered drug which reaches the systemic circulation intact, or the rate and extent to which the AI is absorbed from a medicinal product and becomes available for distribution to the site(s) of action.

Bio-equivalence:

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailability (rate and extent of availability’), after administration in the same molar dose, are similar to such a degree that their effects can he expected to be essentially the same

Comparator product:

A pharmaceutical product with which, the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established.

Critical process:

A process that may cause variation in the quality of the pharmaceutical product.

Cross-contamination:

Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Drug Master File:

A drug master file (DMF) is a file that provides a full set of’ data on an AI and an excipient or a component of a product such as a container.

Finished veterinary medicines (Finished Veterinary Medicine)

A finished veterinary medicine is a dosage form that has undergone all stages of manufacture, including packaging in its final container closure system and labeling.

Existing AI:

An AI that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority.

Generic product:

A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Innovator product:

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Generally the pharmaceutical product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality.

In-process control:

Checks performed during production in order to monitor and if necessary to adjust the process to ensure that, the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Interchangeability:

An interchangeable pharmaceutical product is one that is therapeutically equivalent to an innovator (reference) product. Have the same qualitative and quantitative composition in each of their active substances. Are in the same pharmaceutical form and have the same route of administration

Intermediate product

Partly processed product that must undergo further manufacturing steps before it becomes a finished product.

Manufacture

Any stage in the manufacturing of a veterinary medicine until the finished product is ready for sale in its final form as specified in the marketing authorization, and includes re-packaging, repacking or labeling of a veterinary medicine in an authorized facility but does not include the breaking open of the package of a veterinary medicine by retailers.

or

All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labeling and re-labelling, to completion of the finished product

Marketing authorization (product license, registration certificate)

A legal document issued by the competent Medicine Regulatory Authority that establishes the detailed composition and formulation of the product and the pharmacopoeia or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling and shelf-life

Master formula

A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

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Batch Manufacturing Record

A document or set of documents that serve as a basis for the batch documentation

Veterinary medicines

Any material or medicine intended for veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form that is subject to control by veterinary pharmaceutical legislation in the exporting state and/or the importing state.

Specification

A list of detailed requirements with which the medicines or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation

Standard Operating Procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting material:

Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

System:

A regulated pattern of interacting activities and techniques that are united to form an organized whole.

Validation protocol (or plan):

A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process or a part thereof for routine use.

Validation report:

A document in which the records, results and evaluation of a completed validation program are assembled. It may also contain proposals for the improvement of processes and/or equipment.

Validation:

The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Variation:

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Means a change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

GENERAL PRINCIPLE LANGUAGE

All applications and supporting documents shall be in English. In cases where there is the need to translate any document from its original language into the English language, the accuracy of the translations is the responsibility of the applicant. Recognized institutions must notarize the translations

DATA PRESENTATION

For all printed submissions, all information, data, tables, diagrams, attachments must be legible, of minimum font size 12 Times New Roman and shall be presented on A4 and 80g/m²paper. All pages shall be numbered appropriately with the format 'page x of y' to facilitate easy reference. Each section of the dossier must have a table of content and must be accurately referenced. Acronyms and abbreviation should be defined the first time they are used in each part.

REFERENCES AND TEXTS

International standards for citing references in any parts of the dossier must be followed. The latest edition of any reference source where applicable, specifying the year of publication must be used. Where necessary, especially for analytical methods, specifications and procedures, copies of the relevant portions of the reference source(s) must be included. All in-house processes quoted in the documentation must have been validated and appropriate references cited.

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GENERAL POLICIES ON APPLICATIONS

A separate application is required for each product. For purposes of clarification, one application shall be submitted for products containing the same active ingredients and the same strength made by the same manufacturer, to the same specifications and dosage form, but differing only in packing or pack sizes. On the other hand, separate applications shall be submitted for products that contain the same active ingredient(s) but of different salts, different strength, dosage form and proprietary or brand name.

Classes of Applications

Applications shall be classified into three (3)

- New Applications
- Renewal of applications
- Retentions applications
- Variation of Applications

New Applications

Applications for the registration of a veterinary medicinal product submitted to VMD for the very first time shall be considered a new application. In addition to the dossier submitted, the applicant shall provide

1. One dully-filled thread and tape bound hard copy of application form and one electronic copy.
2. Artwork for the inserts, secondary closures and primary Label of the commercial pack of the product.
2. Certificate of Pharmaceutical Product issued in accordance with the format approved by the WHO and issued by the competent Medicine Regulatory Authority of the country of origin / manufacture (where applicable)

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3. A site master file of the plant in which the product was manufactured.
4. For New Chemical Entities (NCEs) and innovator products, the pharmacovigilance plan shall be submitted.
5. Six samples of the smallest commercial pack(s) from one batch with batch certificates of analysis of the medicine to be registered for every new application for registration.
6. Other documentation requirements as stated in the Guidelines for Registration of Medicines
7. Non-refundable application fee for registration of medicines in Kenya and GMP inspection fees for facilities not yet inspected by VMD as per the schedules.
8. Cover letter to registrar of veterinary medicines: Every submission must be accompanied by a cover letter. The cover letter should include sufficient information such as the trade name and chemical name of the drug product, submission purpose, and the number of enclosures to facilitate the initial administrative processing of submissions. If the name of the veterinary medicinal product proposed for marketing in Kenya is different from that used during the product development stages and in the data submitted, clarification should be given in the cover letter to explain the difference.

Note

A separate application is required for each veterinary medicine. For purposes of clarification, one application could be submitted for products containing the same active ingredients and the same strength made by the same manufacturer at the same manufacturing site, to the same specifications and dosage form, but differing only in packing or pack sizes. On the other hand, separate

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applications shall be submitted for products that contain the same active ingredient(s) but of different salts, different strength, dosage form and proprietary or brand name.

Applications for Renewal of Registration

Applications for renewal of registration shall be made at least 3 months before the expiry of existing registration by submitting the following:

- i. Dully filled application form for renewal of registration
- ii. Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months before the submission of the application.
- iii. Periodic Safety Update Reports (PSUR)
- iv. Proof of interchangeability for generics as explained in Part 5.
- v. Any other requirements that VMD may determine.
- vi. A site master file of the plant in which the product was manufactured.

Application for variation of a registered product

Applications for variation to a registered product shall be made according to requirements stipulated below:

- i. Dully filled application form for variation of registration.
- ii. Artwork and Label of the product reflecting the variation.
- iii. A site Master File of the manufacturer (if the variation is or includes a change in the name, site and/or address of the manufacturer).
- iv. Documents to support or justify the variation.

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SUBMISSION OF APPLICATION

Applications for the registration of products for market authorization being sought shall be made to the Registrar of Veterinary Medicines in accordance with the approved format.

APPLICATION FEES

Application fees shall be paid for each application submitted. This shall be through a direct deposit to the VMD bank account.

RECEIPT AND EVALUATION OF DOSSIERS

A technical personnel should present the dossier to VMD Registrar. Applications, submitted to VMD shall be accompanied by the appropriate application fees deposit slips.

PAYMENT OF FEES

Appropriate fees shall accompany every application at the time of application. Any application, which will not be accompanied by appropriate fees, shall not be accepted. **Mode of Payment:** make Payments by a crossed cheque, direct deposit into VMD bank account or use of Mpesa pay bill number in favor of **Veterinary Medicines Directorate.**

Shillings account: **01071203347300**
 USD account: **02071203347300**
 Paybill: **471524 Account: 01071203347300**

Application for registration of Veterinary Medicines Directorate:

Imported in to Kenya: USD 1000
 Fully manufactured in Kenya: USD 500
 Application for retention of registration of a product: USD 300

Disclaimer

The Directorate acknowledges that the data is commercial, privileged and confidential.

Evaluation process

VMD will assign application numbers serially to applications received and evaluate them on a first in first out (FIFO) basis unless the product meets the fast track criteria as set out in this guideline.

An application may be fast tracked if the product is

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- Locally manufactured in Kenya. Note that contract manufacturing outside Kenya by a Kenyan company will not qualify the product to be locally manufactured.
- A **Priority Medicine**. Essential **medicines**, as **defined** by the World Health Organization (WHO), are the **medicines** that "satisfy **the priority** health care needs of the population". The population should have access at all times in sufficient amounts to these medications. The product is indicated for diseases that at the time of application have no registered alternative medicine or evidence has been submitted to show that the product has significant advantages in terms of safety and efficacy over existing products indicated for treatment or prevention of life threatening diseases.

Pre-registration analysis of the veterinary medicine

The samples will be analysed for all medicines and a certificate of analysis from a VMD recognized Quality Control Laboratory in Kenya and within the region shall be submitted with the application (See section 1.13). Laboratory analysis of the samples will be done against the claimed in-house or pharmacopoeia specifications using the analytical method provided by the applicant.

The following quality control laboratories are recognized

TIMELINES

Complete applications for Fast-tracked registration (Locally manufactured and Priority Medicines only), Post Approval Variation and Retention of registration will be processed within 3 months of receiving the applications.

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Evaluation of new applications

Complete new applications will be processed within 9 months of receipt of the application including GMP audits. The applicant will be required to provide any requested additional data within 3 months. In case additional time is required, a formal request must be submitted.

WITHDRAWAL OF AN APPLICATION

When the applicant fails to submit written responses to queries within 6 months from the date of their issuance, it will be deemed that the applicant has withdrawn the application. If the applicant provides unsatisfactory responses to same queries three times, the product will be disqualified and the application will be withdrawn. The applicant will be required to apply afresh.

VALIDITY OF REGISTRATION

The registration of a pharmaceutical product at VMD shall be valid for five (5) years unless otherwise suspended or revoked or withdrawn by applicant / VMD.

APPEALS

Any person aggrieved by a decision in relation to rejection of any application for marketing authorization of a veterinary pharmaceutical product by VMD council may within three (3) months from the date of notice of the decision, make representations in writing to VMD and submit additional data to support the appeal

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PART 1: ADMINISTRATIVE INFORMATION

The whole document shall be submitted in a firmly thread and tape bound dossier and one electronic copy. Any cross references made to other sections of the dossier must be clearly indicated.

SECTION 1: PARTICULARS OF THE VETERINARY MEDICINES

1.1 Name and address of Applicant

- (a) The manufacturer shall make an application for registration of a Veterinary product.

In case of a manufacturer outside a duly authorized local technical representative shall represent Kenya such.

- (b) An applicant for a manufacturer outside Kenya must file evidence of Power_of Attorney from the manufacturer-, which authorizes him to act for his principal on all matters relating to the latter's specialties. The original Power of Attorney should be certified and submitted to VMD.

Or

- (c) Contract Manufacturing Agreement where applicable. This should be certified and submitted to VMD.

NOTE:

The applicant will be held responsible for ensuring that the competent authority in the country is informed of any serious hazard associated with a veterinary product. In addition to, any criminal abuse of the certificate in particular to the importation of falsely labeled, unauthentic, counterfeited or sub-standard medicinal products.

- (d) The manufacturer, in the case of imported veterinary medicine must show evidence that he or she is licensed to manufacture medicines for sale in the country of origin (Manufacturer's Certificate). Such evidence must be by the competent Veterinary Authority in the country of manufacture and shall be authenticated by the Kenyan Mission in that country. In countries where

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no Kenyan Embassy or High Commission exists, any other Embassy or High Commission of any Commonwealth.

2. (a) The applicant must submit to registrar of veterinary medicines, a written application, stating name of the manufacturer, generic name (brand name, where applicable) strength, indications and obtain the prescribed application form which must be properly filled with all information required. The application form shall be obtained from the VMD office or VMD websites.

1:2 Trade name of veterinary medicine (proprietary veterinary medicine name)

Trade /Proprietary name mean the trade or brands name which has been given by the applicant to a particular product and which generally identify it. Where a trademark is registered in a particular country or region, evidence must be provided.

1:3 International Non-proprietary Name INN or generic name of the active ingredient.

The /INN/generics name of a product is the internationally recognized non-proprietary name of the active ingredient.

1:4 Strength of the active ingredient (AI) per unit dosage of veterinary medicine

Strength of the product shall be given per unit dosage form or per specified quantity.

1:5 pharmaceutical dosage form and route of administration of the veterinary medicine

Dosage form of the veterinary medicine is the pharmaceutical form in which the product is presented, e. g solution, suspension, emulsion, ointment, boluses etc.

For injections, the type of presentation and the type of content (e.g. powder for reconstitution, solution, suspension, oily solution etc.) shall also be stated. Route of administration should be stated.

1:6 Packaging/Pack size of the veterinary medicine

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Packaging/Pack size of the veterinary medicine shall mean the quantity of units per the package in which the medicine is to be registered and marketed in Kenya. State the primary package to be used

1:7 Visual Description of the veterinary medicine

Visual Descriptions of the product means a full visual description of the Medicine unit such as colour, size, shape and other relevant features,

1.8 Proposed Shelf life (In months)

Proposed Shelf life of a product(s) means the specified length of time for which pharmaceutical products are deemed to remain fit for use under prescribed conditions.

1.9 Pharmacotherapeutic Group and Anatomical Therapeutic Chemical ATC codes

The pharmacotherapeutic group is the therapeutic group in which the product has been put, and which is supported by specific indication(s) and relevant information provided in part 3 and 5 of the dossier. The Anatomical Therapeutic Chemical (ATC) Classification System is used for the classification of Medicines. The classification system divides Medicines into different groups according to the organ or system on which they act and / or their therapeutic and chemical characteristics.

1.10 Legal Category

This will be based on the proposed dispensing category or classification. Although countries differ in placing specific products into different classification, products will generally be classified as follows: according to part IV of the VMD regulation section 33(2) as described in a, b, c, and d of this section

1.10.1 Proposed dispensing category/classification: Product is subject to medical prescription or not subject to medical prescription.

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Category IB relating to other prescription only medicine, comprising products intended for administration following a diagnosis or clinical assessment by a veterinary surgeon or dispensed by a veterinary surgeon or a person with equivalent qualification;

Category II relating to prescription only medicine veterinary surgeon, pharmacist, and veterinary technologist who has served for at least five years in a veterinary pharmacy which contains—

1.10.2. For veterinary medicine subject to veterinary prescription: Controlled veterinary medicine (POM-V category IA) or Prescription Only Medicine, (IB-POM-V)

Controlled (POM-V category IA)

These are products containing narcotic or psychotropic substances and other substances very dangerous at small quantities; are to be supplied strictly on medical prescription, and must be dispensed by veterinary surgeons only or supervised use by veterinary surgeons. Should dispensed from veterinary pharmacy outlets only and records kept in accordance with guidelines issued by the International Narcotics Control Board (INCB).

These shall be supplied on medical prescription and shall be dispensed from veterinary pharmacy premises only.

1.10.3 The category of veterinary medicine general sales list which may be traded by veterinary surgeons and all categories of veterinary paraprofessionals. These medicines may or may not be on a medical prescription but may be dispensed from a veterinary pharmacy or non-veterinary pharmacy outlets.

1.11 Country of Origin or country of release

Country of Origin shall refer to the country in which the product was manufactured or the country in which the final release is made where the veterinary medicine is manufactured at multiple sites.

1.12 Product Marketing Authorization in country of origin and others

Applicants shall provide the regulatory information on the medicine to be registered in the country of origin and other countries. List the countries in which the product has been granted a marketing authorization or has been withdrawn from any market or where an application for marketing in any country has been rejected, suspended, deferred or withdrawn.

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Where necessary the certificate of pharmaceutical product from the registering Authority shall be submitted in the dossier and appropriately referenced.

1.13 Pre-registration Analysis of the veterinary medicine:

Any pre-registration analysis submitted shall be based on the validated analytical methods submitted in the dossier. Only VMD and / or accredited Quality Control laboratories shall be used.

1.14 Name and Complete Address(es) of the Manufacturer(s) of the finished veterinary medicine

The name, physical address, telephone number, fax, website and e-mail address of the manufacturer shall be provided. Where different activities of manufacture of a given veterinary medicine are carried out at different manufacturing sites, the above particulars shall be provided for each site and the activity carried out at the particular site shall be stated.

1.15 Good Manufacturing Practice (GMP) Status of the Manufacturer(s) of the veterinary medicine.

Provide valid GMP certificate for manufacturing site by country of origin and VMD

1.16 Name and complete address of the market authorization holder of the manufacturer

The name, physical address, telephone number, fax, website and e-mail address of the authorized local technical representative shall be provided.

1.17 Summary Product Characteristics (SPC)

Proposed Summary of Product Characteristics (SPC) aimed at animal health practitioners and approved by competent authority of the Country of Origin at the time of licensing. Post approval changes to the SPC cannot be made without the consent of VMD as appropriate.

1 NAME OF THE MEDICINAL PRODUCT

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(Invented) name of the medicinal product, strength, pharmaceutical form

In those sections of the SPC in which full information on the name of the medicinal product is specifically required, both the strength and the pharmaceutical form should follow the name. However, when otherwise referring to the medicinal product throughout the text, the strength and the pharmaceutical form do not have to be mentioned in the name. The International Non-proprietary Name (INN) or the usual common name of the active substance should be used when referring to properties of the active substance(s) rather than those of the product.

The use of pronouns (e.g. “it”) is encouraged whenever possible.

Strength

The strength should be the relevant quantity for identification and use of the product and should be consistent with the quantity stated in the quantitative composition and in the posology. Different strengths of the same medicinal product should be stated in the same way, e.g. 250 mg, 500 mg, 750 mg. The use of decimal points should be avoided where these can be easily removed (e.g. 250 microgram, not 0.25 mg). However, where a range of medicinal products of the same pharmaceutical form includes strengths of more than one unit (e.g. 250 microgram, 1 mg and 6 mg), it may be more appropriate in certain cases to state the strengths in the same unit for the purpose of comparability (e.g. 0.25 mg, 1 mg and 6 mg). For safety reasons, micrograms and millions (e.g. for units) should always be spelled out in full rather than be abbreviated.

Pharmaceutical form

The Pharmacopoeia full standard term using plural form if appropriate (e.g. bolus) should describe the pharmaceutical form. If an appropriate standard term does not exist, a new term may be constructed from a combination of standard terms. No reference should be made to the route of administration or to the container unless these elements are part of the standard term or where there are identical products, which may be distinguished only by reference to the container.

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For the expression of the name and strength of (traditional) herbal medicinal products, the declaration should be in accordance with the *Note for Guidance on Quality of Herbal Medicinal Products*.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Full details of the qualitative and quantitative composition in terms of the active substance(s) and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product should be provided and if appropriate in section 4.3 or 4.4. A standard statement should be included at the end of the section, i.e. ‘for full list of excipients, see section 6.1’.

If a diluent is part of the medicinal product, information should be included in the relevant sections (usually sections 3, 6.1, 6.5 and 6.6).

Qualitative declaration

It has recommended INN, accompanied by its salt or hydrate form if relevant or the n Pharmacopoeia name if that name represents an established international name, should declare the active substance. If no INN exists, the Pharmacopoeia name should be used or if the substance is not in the pharmacopoeia, the usual common name should be used. In the absence of a common name, the exact scientific designation should be given. A statement should describe substances not having an exact scientific designation on how and from what they were prepared. References to the pharmacopoeia quality should not be included.

Where the medicinal product is a (traditional) herbal medicinal product, the qualitative declaration should be in accordance with the *Note for Guidance on Quality of Herbal Medicinal Products*.

When the medicinal product is a radiopharmaceutical kit, the qualitative declaration should clearly indicate that the radioisotope is not part of the kit.

Quantitative declaration

The quantity of the active substance must be expressed per dosage unit (for metered dose inhalation products, per delivered dose and/or per metered dose), per unit volume, or per unit of weight and must be related to the declaration of strength in section 1.

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Salts and hydrates

Where the active substance is present in the form of a salt or hydrate, the quantitative composition should be expressed in terms of the mass (or biological activity in International (or other) units where appropriate) of the active entity (base, acid or anhydrous material), e.g. ‘60 mg piperazine (as citrate)’ or piperazine citrate equivalent to 60 mg Piperazine’.

Where a salt is formed *in situ* during manufacture of the finished product, the quantity of the active entity should be stated, with a reference to the *in situ* formation of the salt.

In the case of established active substances in medicinal products where the strength has traditionally been expressed in the form of a salt or hydrate, the quantitative composition may be declared in terms of the salt or hydrate, e.g. ‘60 mg oxytetracycline hydrochloride’. This may also apply when the salt is formed *in situ*.

Powders for reconstitution prior to parenteral administration

When the product is a powder to be reconstituted prior to administration, the total quantity of active substance in the container should be stated not including overages or overfills, as well as the quantity per ml when reconstituted, unless there are several means of reconstituting, or different quantities used, which result in different final concentrations.

Multidose solid or semi-solid products

Quantity of active substance should be stated, where possible, per unit dose, otherwise per gram, per 100 g or percentage, as appropriate.

Herbal medicinal products

The quantitative declaration should be in accordance with the *Note for Guidance on Quality of Herbal Medicinal Products*.

3 PHARMACEUTICAL FORM

The pharmaceutical form should be described by the Pharmacopoeia full standard term (see section 1). The term used in this section should be the same as the term used in section 1. However, where Pharmacopoeia short standard term is used on small immediate packaging material, the short term should be added in brackets in this section.

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It is recommended that a visual description of the appearance of the product (colour, markings, etc.) is given, in a separate paragraph to the standard term, including information on pH and osmolality as required e.g.

'Bolus

White, circular flat bevelled-edge bolus marked '100' on one side'

In case of bolus designed with a score line, information should be given whether or not reproducible dividing of the bolus has been shown. e.g., 'the score line is only to facilitate breaking for ease of swallowing or administrative and not to divide into equal doses', 'the bolus can be divided into equal halves'. In case of products to be reconstituted before use, the appearance before reconstitution should be stated in this section. Appearance of the product after reconstitution should be stated in section 4.2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the target population especially when restrictions to the animal populations apply.

Where results from subsequent studies provide further definition or information on a licensed indication, such information, provided it does not itself constitute a new indication, may be considered for inclusion in section 5.1.

Mandatory conditions of product usage not covered more appropriately in other parts of the SPC may also be included when relevant, e.g. concomitant dietary measures, lifestyle changes, or other therapy.

When the product is indicated in a specific age group such as calves, lambs and foals, the indication should state the age limit.

4.2 Posology and method of administration

In case of restricted medical prescription, this section should be started by specifying the conditions.

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The dosage has to be clearly specified for each method/route of administration and for each indication.

Where appropriate, a reference to official recommendations should be made (e.g. for primary vaccination and antibiotics as well as for booster dose).

Specify dose recommendations per dose interval in an appropriate way (e.g. mg, mg/kg, mg/m²) for each age category where appropriate (specify age ranges)

Short relevant instruction for correct administration/use should also be given here.

Where appropriate, the following points should be addressed:

- the maximum recommended single, daily and/or total dose,
- the normal duration of use and any restrictions on duration and/ or advice on discontinuation,
- advice on action to be taken if one or more dose(s) is (are) missed
- the intake of the product in relation to food intake,
- advice regarding repeat use, with any information on intervals to be observed between courses of treatment, as appropriate, and
- Interactions requiring specific dose adjustments with cross-reference to other appropriate sections of the SPC (e.g. 4.4, 4.5, 4.8, 5.1, 5.2).

(e) Other concomitant diseases.

Advice relevant for dosage adjustment e.g. from monitoring of clinical symptoms and signs, and/or laboratory investigations, including medicinal product concentrations should be mentioned when appropriate.

4.3 Contraindications

Situations where the medicinal product must not be given for safety reasons, i.e. contraindications, are the subject of this section. Such circumstances could include particular clinical diagnosis, concomitant

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Diseases, or predispositions (e.g. metabolic or immunological factors, prior adverse reactions to the medicine or class of medicines). The situations must be unambiguously, comprehensively and clearly outlined.

Only if pregnancy is strictly contraindicated, should it be mentioned here.

Hypersensitivity to any of the excipients or residues from the manufacturing process should be included, as well as any contraindication arising from the presence of certain excipients.

For herbal medicinal products, hypersensitivity extended to other plants of the same family or to other parts of the same plant should be labelled as a contraindication, where applicable.

4.4 Special warnings and precautions for use

The order of warnings and precautions should be determined by the importance of the safety information provided.

The exact content of this section will be different for each product and the therapeutic conditions it is intended to treat. Clinically relevant interactions where in general the use of the combination should be avoided should be mentioned here. Any warnings necessary for excipients or residues from the manufacturing process.

Descriptions of warnings and precautions regarding pregnancy and lactation.

4.5 Interaction with other medicinal products and other forms of interaction

This section should provide information on the potential for clinically relevant interactions based on the pharmacodynamic properties and *in vivo* pharmacokinetic studies of the medicinal product, with a particular emphasis on the interactions, which result in a recommendation regarding the use of this medicinal product This includes *in vivo* interaction results which are important for extrapolating an effect on a marker ('probe') substance to other medicinal products having the same pharmacokinetic property as the marker.'

Interactions affecting the use of this medicinal product should be given first, followed by those interactions resulting in clinically relevant changes on the use of others.

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Interactions referred to in other sections of the SPC should be described here and cross-referenced from other sections.

4.6 Pregnancy and lactation

General recommendation

‘Contra-indication in pregnancy’ should be supported by data (teratogenicity or fetotoxicity) or by strong nonclinical data. When a contra-indication in pregnancy or lactation is made, this should be included in section 4.3.

Efforts should be made by the Marketing Authorisation Holder to provide the reasons for recommendations for use in pregnant or lactating animals or Heifers

4.7 Adverse effects

This section should provide comprehensive information based on all adverse reactions (ADRs) from clinical trials, post-marketing studies

4.9 Overdose

Describe acute symptoms and signs and potential sequelae of different dose levels of the medicinal product based on accidental mistakes.

- PHARMACOLOGICAL PROPERTIES

Sections 5.1 – 5.3 should normally mention information, which is relevant to the prescriber *and to other health-care professionals*, taking into account the approved therapeutic indication(s) and the potential adverse drug reactions. Statements should be brief and precise.

5.1 Pharmacodynamic properties

Describe:

- Pharmacotherapeutic group (ATC code). If an ATC code is not yet available, this should be mentioned as ‘not yet assigned’.
- Mechanism of action (if known)
- Pharmacodynamic effects.
- Clinical efficacy and safety

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5.2 Pharmacokinetic properties

Pharmacokinetic properties of the active substance(s) relevant for the advised dose, strength and the pharmaceutical formulation marketed should be given in this section. If these are not available, results obtained with other administration routes, other pharmaceutical forms or doses can be given as alternative. Basic primary pharmacokinetic parameters, for instance bioavailability, clearance and half-life, should be given as mean values with a measure of variability.

Pharmacokinetics items, which could be included in this section when relevant, are given below.

5.3 Preclinical safety data

Information should be given on any findings in the preclinical testing which could be of relevance for the prescriber, in recognising the safety profile of the medicinal product used for the authorised indication(s), and which is not already included in other relevant sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

A list should be given of the excipients, expressed qualitatively only. All excipients, which are present in the product, should be included, even those present in small amounts, such as printing inks. Further details on the excipients to be declared may be found in the section on definitions and examples.

6.2 Incompatibilities

Information on physical and chemical incompatibilities of the medicinal product with other products with which it is likely to be mixed or co-administered should be stated.

- *'In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.'*
- *'This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.'*

6.3 Shelf life

The shelf life should be given for the medicinal product as packaged for sale and after dilution or reconstitution or after first opening if appropriate.

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A clear statement of the shelf life should be given, in an appropriate unit of time.

No reference should be made to the container unless there are different shelf lives for different containers.

Storage conditions should not be included, except for the storage conditions after opening (see the corresponding guideline). Statements such as ‘Do not use after the expiry date’ should not be included.

6.4 Special precautions for storage

Storage warnings should use one or more of the standard statements from the *Note for Guidance on declaration of storage conditions in the product information of medicinal products*.

For storage of sterile products that have been opened, diluted or reconstituted, a cross-reference should be made to section 6.3.

Note that if a specific storage warning is required, the warning should be consistent between the SPC, label and PL.

6.5 Nature and contents of container

Reference should be made to the immediate container using the Pharmacopoeia standard term; the material of construction of the immediate container should be stated (‘Type I glass vials’, ‘PVC/Aluminum blisters’, ‘HDPE bottles’); and any other component of the product should be listed,

All pack sizes should be listed. Pack sizes mentioned should include the number of units, number of doses (for e.g. multi-dose vaccines, inhalers, etc.), total weight or volume of the immediate container, as appropriate, and the number of containers present in any outer carton. If appropriate, a standard statement, ‘Not all pack sizes may be marketed’, should be included, in order to alert VMD to the fact that not all listed pack sizes may be available for prescribing or dispensing.

Multiple unit packs for distribution purposes only do not constitute new pack sizes for marketing of the product and should therefore not be included in this section.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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Instructions for disposal should be included here, if appropriate for the product.

7 MARKETING AUTHORISATION HOLDER

Name and permanent address or registered place of business of the Marketing Authorisation Holder.

Telephone, fax numbers or e-mail addresses may be included (no websites or emails linking to websites).

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1.18 Batch number(s) of the Veterinary Medicines used in the production

1.18 Batch number(s) of the veterinary medicine used in										(Add as many rows as necessary)
Clinical/bioequivalence studies										
Stability studies										
Validation/production scale batches										
Comments [e.g., batch size, explanation of NA (not applicable) answers]										
Composition of clinical, primary stability and validation/ veterinary medicines batches (kg)										
Ingredients	Administration Unit		Bioequivalence <batch number>		Primary stability <batch number>		Production <batch number>			
	Mg	%*	Kg	%*	Kg	%*	kg	%*		
Powder / Bolus contents / injections / suspensions, etc. (Please delete / change which does not apply)										
AI 1										
AI 2										
AI 3										
<i>Please add / delete as many rows as necessary</i>										
Excipient 1										
Excipient 2										
Excipient 3										
<i>Please add / delete as many rows as necessary</i>										
Subtotal 1										
Purified water/other solvent(s)										
Film coat / capsule shell / printing ink (Please delete / change which does not apply)										
Proprietary film-coating mixture**										
<i>Please add / delete as many rows as necessary</i>										
Subtotal 2										
Grand total										
Purified water/other solvent(s)										
Equivalence of the composition or justified differences			The compositions of the bioequivalence, stability and validation batches are the same and differences are justified. (Please delete / change which does not apply)							
* Each ingredient is expressed as a percentage of the grand total.										
** All components (.....) of the proprietary mixture are described in the compendia										

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Part 2: CHEMICAL, PHARMACEUTICAL, NON-CLINICAL AND CLINICAL OVERVIEWS AND SUMMARIES

2.1 Overall table of contents

This section of the dossier follows ICH: M4Q guidelines for registration of Pharmaceutical products and provides a harmonized structure and format for presenting CMC (Chemistry, Manufacturing and Controls) information. The table of contents for this section should include information on AI, veterinary medicine and Pharmaceutical Development. Any information provided here must be appropriately cross-referenced to the dossier by clearly indicating to volume, page number in other Parts.

2.2 INTRODUCTION

The introduction should include proprietary name, non-proprietary name or common name of the AI, company name, dosage form(s), strength(s), route(s) of administration, and proposed indication(s).

2.3 OVERALL QUALITY SUMMARY (OQS)

The Overall Quality Summary is a summary that follows the scope and the outline of Part 2. The OQS should not include detailed information, data or justification that will be included in Part 2 or in other parts of the document. The OQS would be used by the Quality Evaluator and should include sufficient information from each section to provide the Evaluator with an overview of Part 2. All critical parameters of the product should be described in this section and where parts of the guidelines were not followed, these must be explained. Wherever references are made to any sections of the Quality Part of the dossier the appropriate page number and section must be indicated. This OQS normally should not exceed 40 pages of text, excluding tables and figures.

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For biotech products and products manufactured using more complex processes, the document could be longer but normally should not exceed 80 pages of text (excluding tables and figures).

2.3.1 OVERVIEW OF THE ACTIVE INGREDIENT(S) [AI(S)]

2.3.1.1. General Information

2.3.1.1.1 Nomenclature

Information on the nomenclature of the AI should be provided. For example:

Recommended International Nonproprietary Name (INN);

Compendial (official) name if relevant;

Chemical name(s);

Company or laboratory code;

Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN),

Japanese Accepted Name (JAN); British Approved Name (BAN), and

Chemical Abstracts Service (CAS) registry number.

2.3.1.1.2 Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided

NCE:

The structural, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

Generic:

Compendia requirement or equivalent information from the manufacturer.

2.3.1.1.3 General properties

A list should be provided of physicochemical and other relevant properties of the AI.

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This information can be used in developing the specifications, in formulating finished veterinary products and in the testing for release and stability purposes. The physical and chemical properties of the AI should be discussed including the physical description, solubility in common solvents (e.g. water, alcohols, dichloromethane, and acetone), quantitative aqueous pH solubility profile (e.g. pH 1.2 to 6.8, dose/solubility volume), polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc.

This list is not intended to be exhaustive but provides an indication as to the type of information that could be included.

Some of the more relevant properties to be considered for AIs are discussed below in greater detail.

Physical description

The description should include appearance, colour and physical state. Solid forms should be identified as being crystalline or amorphous.

Solubility/quantitative aqueous pH solubility profile

The solubility in a number of common solvents should be provided (e.g. water, alcohols, dichloromethane, and acetone).

Reference VICH Guidelines: NCE: SZSGL39Q:GL39D

2.3.1.2 Manufacture of the AI(s)

2.3.1.2.1 Name and address of AI(s) Manufacturer

Name and full addresses including the city and country of the manufacturer of active ingredient.

2.3.1.2.2 Description of manufacturing process and process controls

A brief description of the manufacturing process (including, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of

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appropriate quality; this could be presented as a flow diagram. The following information should be provided to adequately describe the manufacturing process and process controls:

NCE:

A schematic flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights and yields, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

A progressive procedural narrative of the manufacturing process that provides quantities of raw materials, solvent, catalysts and reagent reflecting the representative batch scale, and includes process controls, equipment and operating conditions, such as temperature, pressure, pH, time etc.

Alternative process should be explained and described with the same level of details as the primary process. Reprocessing steps should be identified and justified.

Reference VICH Guidelines: GL11

2.3.1.2.3 Control of materials used in manufacture of AI

Materials used in the manufacture of the AI (e.g. raw materials, solvents, reagents, catalysts) should be listed, identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided.

2.3.1.2.4 Controls of critical steps and intermediates

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

Intermediates: Specifications and analytical procedure, if any, for intermediates isolated during the process.

Validation of an analytical method is the process that establishes, by laboratory studies, that the test parameters of the method meet the requirements for the intended analytical applications. The *GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR MARKETING AUTHORIZATION FOR VETERINARY MEDICINES*

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test parameters that should be generally considered in the validation include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range and ruggedness. However, the test parameters to be established for a particular method depend on the nature and the intended purpose of the analytical procedure being evaluated.

Reference VICH Guidelines: GL39Q

The critical steps should be identified. These can be among others: steps where significant impurities are removed or introduced, steps introducing an essential molecular structural element such as a chiral centre or resulting in a major chemical transformation, steps having an impact on solid-state properties and homogeneity of the AI that may be relevant for use in solid dosage forms. Specifications for isolated intermediates should be provided and should include tests and acceptance criteria for identity, purity and assay, where applicable.

2.3.1.2.5 Process validation and/or evaluation

Process validation and/or evaluation studies for aseptic processing and sterilization should be included. It is expected that the manufacturing processes for all AIs are properly controlled. If the AI is prepared as sterile, a complete description should be provided for aseptic processing and/or sterilization methods. The controls used to maintain the sterility of the AI during storage and transportation should also be provided. Alternate processes should be justified and described.

2.3.1.3 Characterization of the AI(S)

Characterization of a biotechnological or biological product (which includes the determination of physicochemical properties, biological activity, immunochemical properties, purity and impurities) by appropriate techniques is important to allow relevant specifications to be established. Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency and data from stability studies, and relevant development data.

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Reference guidelines VICH: GL 39, GL40

Physical characteristics

- State
- Colour
- Melting point/range for solids
- Boiling point/range (atmospheric pressure) for liquids
- Specific gravity
- Particle size (sieve tests, median, range)
- Viscosity (liquids only)
- Odour.

Chemical characteristics

- Isomeric content (enantiomeric, rotational, diastereomeric and/or geometric)
- Solubility (in water and organic solvents)
- Hydrolytic properties
- Photolytic properties
- Polymorphism
- PKa and (aqueous) pH values
- Hygroscopicity
- N-octanol/water partition coefficient
- Chelating and/or encrypting properties

For both Chemical and Biotech entities, OQS should summarize the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarize the basis for setting the acceptance criteria for individual and total impurities. The OQS should also

summarize the impurity levels in batches of the AI used in the non-clinical studies, in the clinical
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trials, and in typical batches manufactured by the proposed commercial process. The OQS should state how the proposed impurity limits are qualified.

2.3.1.4 Control of the AI(S)

A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included. Specification and justification of specification (s). Summary of analytical procedure and validation.

Specification

Detailed specification, tests and acceptance criteria for the medicinal substance should be provided. Validation of an analytical method is the process that establishes, by laboratory studies, that the test parameters of the method meet the requirements for the intended analytical applications. The test parameters that should be generally considered in the validation include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range and ruggedness. However, the test parameters to be established for a particular method depend on the nature and the intended purpose of the analytical procedure being evaluated.

Reference VICH Guidelines: GL2A

2.3.1.5 Reference Standards or Materials of the AI(S)

For materials applications for new molecular entities, it is unlikely that an international or national standard will be available. At the time of submission, the manufacturer should have established an appropriately characterized in-house primary reference material, prepared from lot(s) representative of production and clinical materials. In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material. Where an international or national standard is available and appropriate, reference materials should be calibrated against it. Quality information of Reference standard or material used for testing of medicinal substance should be provided.

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Reference VICH Guidelines: GL 40.

2.3.1.6 Container Closure System of the AI(S)

Container closure system refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the veterinary product. A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compensatory methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

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

2.3.1.7 Stability of the AI(S)

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, the types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results from three batches for real time and accelerated, for example, from forced degradation studies and stress

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conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Reference VICH Guidelines: GL3R

2.3.2 APPENDICES

2.3.2.1 Facilities and Equipment

Provide a site master file and a diagram illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product.

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included.

A summary description of product-contact equipment, and its use (dedicated or multi-use) should be provided. Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for the compounding and product manufacturing are performed.

2.3.2.2 Adventitious Agents Safety Evaluation

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section. For excipients of animal, or microbial origin, provide information regarding adventitious agents (e.g., sources specifications; description of the testing performed). The following excipients should be addressed in this section: gelatin, phosphates, *GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR MARKETING AUTHORIZATION FOR VETERINARY MEDICINES*

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stearic acid, magnesium stearate and other stearates. If from plant origin a declaration to this effect will suffice. For these excipients from animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the finished veterinary medicine are without risk of transmitting agents of animal spongiform encephalopathies.

2.3.2.3 Novel Excipients

For excipient(s) used for the first time in a finished veterinary product or by a new route of administration, full details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical and/or clinical), should be provided according to the AI and/or Finished veterinary product format. For any material of animal origin used in the manufacture of the medicine, information should be provided in accordance with the most stringent requirements set out in monographs (e.g. USP, Ph. Eur, and B.P.)

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2.4 SUMMARY OF NON-CLINICAL DOCUMENTATION AND CLINICAL DOCUMENTATION

2.4.1 FOR NEW CHEMICAL ENTITIES

The Nonclinical Overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overview should not exceed about 30 pages. This section is not applicable for generic medicines.

2.4.1.1. NON-CLINICAL OVERVIEW

General Aspects

The Non-clinical Overview should present an integrated and critical assessment of the pharmacological, pharmacokinetic, and toxicological evaluation of the pharmaceutical. Where relevant guidelines on the conduct of studies exist, these should be taken into consideration, and any deviation from these guidelines should be discussed and justified. The nonclinical testing strategy should be discussed and justified. There should be comment on the GLP status of the studies submitted. Any association between nonclinical findings and the quality characteristics of the animal pharmaceutical, the results of clinical trials, or effects seen with related products should be indicated, as appropriate.

Except for biotechnology-derived products, an assessment of the impurities and degradatory products present in the AI and product should be included along with what is known of their potential pharmacological and toxicological effects. This assessment should form part of the justification for proposed impurity limits in the AI and product and be appropriately cross-referenced to the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the nonclinical studies and the product to be marketed should be discussed. For biotechnology-derived products, *GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR MARKETING AUTHORIZATION FOR VETERINARY MEDICINES*

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comparability of material used in nonclinical studies, clinical studies, and proposed for marketing should be assessed. If a veterinary product includes a novel excipient, an assessment of the information regarding its safety should be provided. Relevant scientific literature and the properties of related products should be taken into account. If detailed references to published scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guideline. In addition, the availability of information on the quality of batches of AI used in these referenced studies should be discussed. The nonclinical overview should contain appropriate reference citations to the tabulated summaries.

Content and Structural Format

The Nonclinical Overview should be presented in the following sequence:

- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics
- Toxicology
- Integrated overview and conclusions
- List of literature references

Studies conducted to establish the pharmacodynamics effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise. The assessment of the pharmacokinetic, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (e.g. impact of the disease states, changes in

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physiology, anti-product antibodies, and cross-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Inter-species comparisons of metabolism and systemic exposure comparisons in animals and animals (AUC, Cmax, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in animals highlighted. The onset, severity, and duration of the toxic effects, their dose-dependency and degree of reversibility (or irreversibility), and species- or gender-related differences should be evaluated and important features discussed, particularly with regard to:

-Pharmacodynamics -toxic signs

-causes of death

-pathological findings

Genotoxic activity - the chemical structure of the compound, its mode of action, and its -relationship to known genotoxic compounds

-carcinogenic potential in the context of the chemical structure of the compound, its -relationship to known carcinogens, its genotoxic potential, and the exposure data. The carcinogenic risk to animals - if epidemiological data are available, they should be taken into account. Fertility, embryo-fetal development, pre-and post-natal toxicity studies in juvenile animals the consequences of use before and during pregnancy, during lactation, and during young animal development -local tolerance

-other toxicity studies/ studies to clarify special problems

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a certain

effect / phenomenon are brought together. Extrapolation of

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the data from animals to animals should be considered in relation to:

- animal species used
- numbers of animals used
- routes of administration employed
- dosages used
- duration of treatment or of the study
- systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in animals at the maximum recommended animal dose. Tables or figures summarizing this information are recommended.
- the effect of the AI observed in nonclinical studies in relation to that expected or observed in animals.

If alternatives to whole-animal experiments are employed, their scientific validity should be discussed. The Integrated Overview and Conclusions should clearly define the characteristics of the animal pharmaceutical as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the nonclinical findings for the safe animal use of the pharmaceutical should be discussed (as applicable to labeling).

2.4.1.2 NONCLINICAL WRITTEN AND TABULATED SUMMARIES

Nonclinical Written Summaries

Introduction

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This guideline is intended to assist authors in the preparation of nonclinical pharmacology, pharmacokinetics, and toxicology written summaries in an acceptable format. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired. The sequence and content of the nonclinical written summary sections are described below. It should be emphasized that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results. Whenever appropriate, age- and sex-related effects should be discussed. Relevant findings with stereoisomers and/or metabolites should be included, as appropriate. Consistent use of units throughout the Summaries will facilitate their review. A table for converting units might also be useful. In the Discussion and Conclusion sections, information should be integrated across studies and across species, and exposure in the test animals should be related to exposure in animals given the maximum intended doses.

Order of Presentation of Information within Sections

When available, in vitro studies should precede in vivo studies. Where multiple studies of the same type need to be summarized within the Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first). Species should be ordered as follows: • Mouse • Rat • Hamster • other rodent • Rabbit • Dog • • other non-rodent mammal • Non-mammals. Routes of administration should be ordered as follows: • the intended route for animal use • Oral • Intravenous • Intramuscular • Intraperitoneal • Subcutaneous • Inhalation • Topical • Others;

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Although the Nonclinical Written Summaries are envisaged to be composed mainly of text, some information contained within them might be more effectively and/or concisely communicated through the use of appropriate tables or figures. To allow authors flexibility in defining the optimal structure for the Written Summaries, tables and figures should preferably be included within the text. Alternatively, they could be grouped together at the end of each of the nonclinical written summaries. Throughout the text, reference citations to the tabulated summaries should be included. Length of nonclinical written summaries: Although there is no formal limit to the length of the nonclinical written summaries, it is recommended that the total length of the three nonclinical written summaries in general should not exceed 100-150 pages. Sequence of written summaries and tabulated summaries The following order is recommended:

- Introduction
- Written Summary of Pharmacology
- Tabulated Summary of Pharmacology
- Written Summary of Pharmacokinetics
- Tabulated Summary of Pharmacokinetics
- Written Summary of Toxicology
- Tabulated Summary of Toxicology

Content of Nonclinical Written and Tabulated Summaries

Introduction

The aim of this section should be to introduce the reviewer to the pharmaceutical and to its proposed clinical use. The following key elements should be covered:

- Brief information concerning the pharmaceutical's structure (preferably, a structure diagram should be provided) and pharmacologic properties.

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-Information concerning the pharmaceutical's proposed clinical indication, dose, and duration of use.

Pharmacology Written Summary

Within the Pharmacology Written Summary, the data should be presented in the following sequence:

- Brief Summary
- Primary Pharmacodynamics
- Secondary Pharmacodynamics
- Safety Pharmacology
- Pharmacodynamics Medicine Interactions
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

Brief Summary

The principal findings from the pharmacology studies should be briefly summarized in approximately 2 to 3 pages. This section should begin with a brief description of the content of the pharmacologic data package, pointing out any notable aspects such as the inclusion/exclusion of particular data (e.g., lack of an animal model).

Primary Pharmacodynamics

Studies on primary pharmacodynamics should be summarized and evaluated. Where possible, it would be helpful to relate the pharmacology of the Medicine to available data (in terms of selectivity, safety, potency, etc.) on other Medicines in the class.

Secondary Pharmacodynamics

Studies on secondary pharmacodynamics should be summarized by organ system, where appropriate, and evaluated in this section.

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Reference: VICH Guideline 43&44, **Safety Pharmacology Studies target animals Animal Pharmaceuticals**,

Safety Pharmacology

Safety pharmacology studies should be summarised and evaluated in this section. In some cases, secondary Pharmacodynamic studies can contribute to the safety evaluation when they predict or assess potential adverse effect(s) in animals. In such cases, these secondary Pharmacodynamic studies should be considered along with safety pharmacology studies.

Pharmacodynamics Drug Interactions

If they have been performed, Pharmacodynamic drug interaction studies should be briefly summarised in this section.

Discussion and Conclusions

This section provides an opportunity to discuss the pharmacologic evaluation and to consider the significance of any issues that arise. Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

Pharmacokinetics Written Summary

The sequence of the Pharmacokinetics Written Summary should be as follows:

- Brief Summary
- Methods of analysis
- Absorption
- Distribution
- Metabolism

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- Excretion
- Pharmacokinetic Drug Interactions
- Other Pharmacokinetic Studies
- -Discussion and Conclusions
- Tables and Figures (either here or included in text)

Brief Summary

The principal findings from the pharmacokinetics studies should be briefly summarized in approximately 2 to 3 pages. This section should begin with a description of the scope of the pharmacokinetic evaluation, emphasizing, for example, whether the species and subspecies examined were those used in the pharmacology and toxicology evaluations, and whether the formulations used were similar or identical.

Methods of Analysis

This section should contain a brief summary of the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure. If possible, validation data for the analytical method and stability of biological samples should be discussed in this section. The potential impact of different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.

Absorption

The following data should be summarized in this section:

Absorption (extent and rate of absorption, in vivo and in situ studies)

Kinetic parameters, bioequivalence and/or bioavailability (serum/plasma/blood PK studies).

Distribution

The following data should be summarized in this section:

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Tissue distribution studies

Protein binding and distribution in blood cells

Placental transfer studies

Metabolism (interspecies comparison)

The following data should be summarized in this section:

Chemical structures and quantities of metabolites in biological samples

Possible metabolic pathways

Pre-systemic metabolism (GI/hepatic first-pass effects)

In vitro metabolism including P450 studies

Enzyme induction and inhibition

Excretion

The following data should be summarised in this section:

Routes and extent of excretion

Excretion in milk

Pharmacokinetic Drug Interactions

If they have been performed, nonclinical pharmacokinetic Drug-interaction studies (in vitro and/or in vivo) should be briefly summarised in this section.

Other Pharmacokinetic Studies

If studies have been performed in nonclinical models of disease (e.g., renal impaired animals), they should be summarised in this section.

Discussion and Conclusions

This section provides an opportunity to discuss the pharmacokinetic evaluation and to consider the significance of any issues that arise.

Tables and Figures

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Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, there is the option of including tables and figures at the end of the summary.

Toxicology Written Summary

The sequence of the Toxicology Written Summary should

be as follows:

- Brief Summary
- Single-Dose Toxicity
- Repeat-Dose Toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Studies in Juvenile Animals
- Local Tolerance
- Other Toxicity Studies
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

2.4.1.3 Clinical overview

This section should be a summary of data relevant to safety in the intended animal population, integrating the results of individual clinical study reports as well as other relevant reports, e.g., the integrated analyses of safety that are routinely submitted in some regions.

The display of safety-related data can be considered at three levels (ICH E3):

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- i. The extent of exposure (dose, duration, number of animals, type of animals) should be examined to determine the degree to which safety can be assessed from the database.
- ii. The more common adverse events and changes in laboratory tests should be identified and classified, and their occurrence should be summarized.
- iii. Serious adverse events (defined in ICH E2A) and other significant adverse events (defined in ICH E3) should be identified and their occurrence should be summarized. These events should be examined for frequency over time, particularly for Medicines that may be for long time

The safety profile of the Medicine, described on the basis of analysis of all clinical safety data, should be outlined in a detailed, clear, and objective manner, with use of tables and figures.

2.4.1.4 Clinical Summary

The Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the dossier. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross study analyses for which full reports have been included in PART4; and post- marketing data for products that have been marketed in other regions.

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals: Efficacy for guidance on the content of this section.

2.4.2 GENERIC MEDICINE APPLICATIONS ONLY

2.4.2.1 CLINICAL OVERVIEW AND SUMMARY

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

The Clinical Overview will necessarily refer to application data provided in the comprehensive

Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it
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should primarily present the conclusions and implications of those data. Specifically, the Clinical Summary should provide a detailed factual summarization of the clinical information in the dossier, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information (e.g., pertinent animal data or product quality issues that may have clinical implications).

The Clinical Overview is primarily intended for use by regulatory agencies in the review of the clinical section of a marketing application. It should also be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application. The Clinical Overview should present the strengths and limitations of the development program and study results, analyse the benefits and risks of the medicinal product in its intended use and describe how the study results support critical parts of the prescribing information.

In order to achieve these objectives, the Clinical Overview should:

- Describe and explain the overall approach to the clinical development of a medicinal product, including critical study design decisions.
- Assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance.
- Provide a brief overview of the clinical findings, including important limitations (e.g., lack of comparisons with an especially relevant active comparator, or absence of information on some patient populations, on pertinent endpoints, or on use in combination therapy).

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- Provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will optimize benefits and manage risks.
- Address particular efficacy or safety issues encountered in development, and how they have been evaluated and resolved.
- Explore unresolved issues, explain why they should not be considered as barriers to approval, and describe plans to resolve them.
- Explain the basis for important or unusual aspects of the prescribing information.

The Clinical Overview should generally be a relatively short document (about 30 pages). The length, however, will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged for brevity and to facilitate understanding. It is not intended that material presented fully elsewhere be repeated in the Clinical Overview; cross-referencing to more detailed presentations provided in the Clinical Summary or in PART 5 is encouraged.

2.4.2.1.1 Veterinary Medicines Development Rationale

The Pharmaceutical Development section should contain information summarizing the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container/closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the submission. The discussion of the rationale for the development of the medicinal product should:

- Identify the pharmacological class of the medicinal product.

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- Describe the particular clinical/pathophysiological condition that the medicinal product is intended to treat, prevent, or diagnose (the targeted indication).
- Briefly summarize the scientific background that supported the investigation of the medicinal product for the indication(s) that was (were) studied.

2.4.2.1.2 Overview of Biopharmaceutics studies

The purpose of this section is to present a critical analysis of any important issues related to bioavailability that might affect efficacy and/or safety of the to-be-marketed formulation(s) (e.g., dosage form/strength proportionality, differences between the to-be-marketed formulation and the formulation(s) used in clinical trials, and influence of feed on exposure).

2.4.2.1.3 Summary of Biopharmaceutics Studies and Associated Analytical Methods

Background and Overview

This section should provide the reviewer with an overall view of the formulation development process, the *in vitro* and *in vivo* dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE), and *in vitro* dissolution profile database. Reference should be made to any guidelines or literature used in planning and conducting the studies. This section should also provide the reviewer with an overview of the analytical methods used, with emphasis on the performance characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality control (e.g., accuracy and precision). This section should not include detailed information about individual studies

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Summary of Results of Individual Studies

A tabular listing of all biopharmaceutics studies should generally be provided, together with narrative descriptions of relevant features and outcomes of each of the individual studies that provided important *in vitro* or *in vivo* data and information relevant to BA and BE. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. These narratives may be abstracted from the ICH E3 synopsis. References or electronic links to the full report of each study should be included in the narratives.

Comparison and Analyses of Results across Studies

This section should provide a factual summary of all *in vitro* dissolution, BA, and comparative BA studies carried out with the AI or veterinary product, with particular attention to differences in results across studies. This overview should typically summarize the findings in text and tables and should consider the following:

Evidence of the effects of formulation and manufacturing changes on *in vitro* dissolution and BA and conclusions regarding BE. When manufacturing or formulation changes are made for products containing complex AIs (e.g., a protein), pharmacokinetic (PK) studies comparing the product before and after the changes may be performed to ensure that the PK characteristics have not changed as a result of product changes. Although such studies are sometimes referred to as BE studies, they generally do not focus on assessing release of AI from veterinary product. Nonetheless, such studies should be reported in this section. Note also that PK studies alone may not be sufficient to assure similarity between such veterinary products. In many situations,

pharmacodynamics studies or clinical trials may be necessary. Additionally, depending on the *GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR MARKETING AUTHORIZATION FOR VETERINARY MEDICINES*

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circumstances, antigenicity data may also be needed. Results of these other types of studies, when they are needed, should be reported in the appropriate places in the dossier.

Evidence of the extent of feed effects on BA and conclusions regarding BE with respect to feed type or timing of the feed (where appropriate).

Evidence of correlations between *in vitro* dissolution and BA, including the effects of pH on dissolution, and conclusions regarding dissolution specifications.

Comparative bioavailability, including BE conclusions, for different dosage form strengths.

Comparative BA of the clinical study formulations (for clinical studies providing substantial evidence of efficacy) and the formulations to be marketed. The source and magnitude of observed inter- and intrasubject variability for each formulation in a comparative BA study.

2.4.2.1.4 Overview and summary of *In vitro* dissolution tests complementary to bioequivalence studies

Provide a brief overview and summary of the results of *in vitro* dissolution tests at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for veterinary product release (QC media), obtained with the batches of test and reference products that were used in the bioequivalence study should be reported. Particular dosage forms like ODT (oral dispersible tablets) may require investigations using different experimental conditions. The results should be reported as profiles of percent of labelled amount dissolved versus time displaying mean values and summary statistics.

2.4.2.1.5 Overview and summary *In vitro* dissolution tests in support of biowaiver.

Provide an overview and summary to justify for waiving of bioequivalence testing. Refer to the BE exemption criteria in Section 5.2.2.1.2

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Part 3: CHEMICAL AND PHARMACEUTICAL DOCUMENTATION

3.0 Purpose

This part is intended to provide guidance on the format of a registration application for AIs and their corresponding veterinary products as defined in the scope of the ICH guidelines Q6 A (“NCE”) . This format may also be appropriate for certain other categories of products though it has been modified to suit generic Medicine applications.

3.1 Table of contents of part 3

Provide a table of contents for ease of reference

3.2 Body of data

The “Body of data” in this guideline merely indicates where the information should be located. Neither the type nor extent of specific supporting data has been addressed in this guideline.

3.2.1. PARTICULARS OF ACTIVE INGREDIENT(s) (AI (s))

The information on the AI can be submitted according to the following order of preference:

- Provide the latest, valid Certificate of suitability with all appendices. The information, which may not be covered by the Certificate, should be provided under points 3.2.1.1.
- Provide a Drug master files(s) (DMF (s)) submitted by the AI manufacturer, provided that the DMF contains all the information listed under section 3.2.1.1
- By completing section 3.2. 1.4 in this case, the AI manufacturer should provide a signed declaration that the synthesis and subsequent purification is conducted in accordance with what is presented in the dossier. For a veterinary product containing more than one AI, the information requested for “part labeled particulars of active ingredient(s) {AI(s)}” should be provided in its entirety for each AI.

3.2.1.1 General information

Information on the nomenclature of the AI should be provided, for example:

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- Recommended International Nonproprietary Name (INN)
- Compendial name if relevant
- Chemical name(s)
- Company or laboratory code

3.2.1.2 Manufacturer of AI(s)

State the name and street address of each facility where manufacture (synthesis, production) of AI occurs, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided. Provide phone number(s) and E-mail addresses. Include any alternative manufacturers.

Provide a valid manufacturing Authorization for the production of AIs. If available, attach a certificate of GMP compliance

Description of manufacturing process and process controls (name, manufacturer)

The description of the AI manufacturing process represents the applicant's commitment for the manufacture of the AI. Information should be provided to adequately describe the manufacturing process and process control. For example, a flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and AI reflecting stereochemistry, and identified operating conditions and solvents. Reprocessing steps should be identified and justified and any data to support this justification should be either referenced.

Specifications of raw materials and intermediates used in the synthesis

Provide specifications for starting materials, reagents, solvents, catalysts, and intermediate (if isolated during the process) in the synthesis. Provide information demonstrating that materials meet standards appropriate for their intended use (including the clearance or control of adventitious agents) as appropriate.

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3.2.1.3 Characterization of the AI(S)

Elucidation for structure and other characteristics of the AI(s)

Confirmation of structure based on eg. Synthetic route and spectral analyses should be provided.

Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should be included.

Impurities

Information on impurities should be provided.

Identification of potential and actual impurities arising from the synthesis, manufacture and/or degradation. List of impurities (e.g. starting materials, by-products, intermediates, chiral impurities degradation products) including chemical name, structure and origin.

Basis for setting the acceptance criteria for impurities:

Maximum daily dose (i.e. the amount of AI administered per day) ICH reporting/identification/qualification. Thresholds for AI-related impurities, and concentration limits (ppm) for process limited impurities (eg residual solvents): Data on observed impurities for relevant finished veterinary medicine batches (eg clinical comparative) Include strength, if reporting impurity levels found in the finished veterinary medicine (e.g. for comparative studies).

Control of AI

Specification of the AI-The specification for the AI should be provided

Characterize and analyze synthesis impurities, including residual solvents, which may be present in AI. Particular attention should be given to justify cases where testing for possible impurities are omitted eg due to the fact that the impurity has not been detected in any batches or will not potentially be present due to a particular method of production.

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Provide analytical validation information, including experimental data for the analytical procedures used for testing the AI and impurities. Analytical procedures should be in sufficient details to be replicated by another laboratory.

Provide information on the preparation and studies to establish the identity, purity and assay value of in-house primary (absolute) and secondary (working) standards. Submit certificate of analysis (COA) of in-house primary standards for use in assays, including;

- Assay by two different validated methods.
- Identification and control of impurities
- Storage instructions, and
- Duration of use of the standards.

Provide verified certificates of analysis for at least two batches produced at each site of manufacture by each synthetic method, including results for impurities.

Provide a copy of the monograph together with any test methods referenced in the monograph but not appearing in it. Note that the current monograph should always control the quality of the AI.

The quality of the AI should meet not only the requirements of specific monographs but also those described in the general monographs of a pharmacopoeia on AIs, excipients and other substances for pharmaceutical use.

Tests and limits should, as a minimum, comply with the relevant pharmacopoeial requirements. Whenever, an AI has been prepared by a method liable to leave impurities not controlled in the pharmacopoeial monograph, these impurities (based on 3 to 10 batch analysis results) including residual organic solvent, as well as their maximum tolerance limits should be declared and controlled by a suitable test procedure.

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Provide details of certificates of analysis for at least two batches produced at each site of manufacture by each synthetic method, including results for impurities.

- Analytical procedures for testing the AI

The analytical procedures used for testing the AI should be provided.

- Validation of analytical procedures

Analytical validation information, including experimental data for the analytical procedures used for testing the AI should be provided.

3.2.1.5 Reference standards or materials of the AI(S)

Information on the reference standards or reference materials used for testing of the AI(S) should be provided. Information on primary and secondary reference standard(s) used in the testing of the AI to generate analytical results included in the submission.. However, compendial reference standard should be employed as a primary reference standard, if available, in order to be able to claim a compendial standard. For all reference standards, the following information should be provided:

- Source
- Lot number
- Date of manufacture
- Copies of the certificate of analysis

3.2.1.6 Container closure system of the AI(S)

Container closure system refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the veterinary product.

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

For non-functional secondary packaging components (e.g. those that do not provide additional protection) only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

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

3.2.1.7 Stability of the AI(s)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life as appropriate.

Post-approval stability protocol and stability commitment

The post –approval stability protocol and stability commitment should be provided.

Stability data of the AI(S)

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical narrative. Information on the analytical procedures used to generate the data validation of the procedures should be included.

For AIs not described in an official pharmacopoeial monograph, there are two options:

- When available, it is acceptable to provide the relevant data published in the “peer review” literature to support the proposed degradation pathways.

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- When no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed. Results from these studies will form an integral part of the information provided to VMD.

Regulatory stability testing

Summarize the stability testing program and report the results of stability testing of not less than three (minimum one production scale and two pilot scale) batches of the AI. The data for each attribute should be discussed; trends, analyzed and a re-test date should be proposed. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the dossier, a cross-reference will suffice. If different methodology was used, provide validation of tests of impurities including degradants and for other tests as necessary.

Provide the post-approval stability protocol and stability –testing commitment, when applicable.

A strong statement should be proposed for the labeling (if applicable) which should be based on the stability evaluation of the AI

Study	Storage Conditions	Time Period Covered by Data at the time of Submission
Long term	25 °C ± 2 °C / 60% RH ± 5% RH Or 30 °C ± 2 °C / 65% RH ± 5% RH	24 months
Accelerated	40 °C ± 2 °C / 75% RH ± 5% RH	6 months

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3.2.2 PARTICULARS OF FINISHED VETERINARY MEDICINE (FINISHED VETERINARY MEDICINE)

3.2 .2.1 Description and composition of the finished veterinary medicine

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

a) Description of the dosage form

The description of the finished veterinary medicine should include the physical description, strength, release mechanism (e.g. immediate, modified (delayed or extended)), as well as any other distinguishable characteristics.

b) composition, i.e. list of all components of the dosage form, and their amount on a per unit basis (including overages, if any), the function of the ingredients, and a reference to their quality standards [e.g. compendial monographs (BP, USP, Ph. Eur etc) or manufacturer’s specifications (IH)].

c) All ingredients used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the finished veterinary medicine is formulated using an active part, then the composition for the active ingredient should be clearly indicated (e.g. “1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride”). All overages should be clearly indicated (e.g. “contains 2% overage of the AI to compensate for manufacturing losses”).

The ingredients should be declared by their proper or common names, quality standards (e.g. BP, Ph. Eur, Ph.Int, USP, in-house) and, if applicable, their grades (e.g. “Microcrystalline Cellulose NF (PH 102)”) and special technical characteristics (e.g. lyophilized, micronized, solubilized, emulsified).

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The function of each component (e.g. diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative) should be stated. If an excipient performs multiple functions, the predominant function should be indicated.

d) Description of accompanying reconstitution diluent(s)

For Finished veterinary medicines supplied with reconstitution diluent(s), information on the diluent(s) should be provided in a separate section within the information leaflet.

3.2.2.2 Pharmaceutical development of veterinary medicine (s)

A brief summary describing the development of veterinary product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (ie composition) described should be discussed.

The Pharmaceutical development section should contain information on the developmental studies conducted to establish that the dosage form, the formulation, manufacturing process, container-closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the product dossier (For generic formulation the innovator formulation data provided be used). The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and finished veterinary medicine quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the product dossier.

Pharmaceutical development information should include, at a minimum:

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- a) the definition of the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering for example the route of administration, dosage form, bioavailability, strength and stability;
- b) Identification of the potential critical quality attributes (CQAs) of the finished veterinary medicine so as to adequately control the product characteristics that could have an impact on quality;
- c) discussion of the potential CQAs of the AI(s), excipients and container-closure system(s) including the selection of the type, grade and amount to deliver veterinary product of the desired quality.
- d) Discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

These features should be discussed as part of the product development using the principles of risk management over the entire life-cycle of the product.

References:

- a) ICH Q8 guidelines: Pharmaceutical Development
- b) ICH Q9 guidelines: Quality Risk Management

3.2.2.3 Manufacture of the veterinary medicine(s)

a. Sites of manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

State the name and street address of each facility where any aspect of manufacture of the finished veterinary medicine occurs, including production, sterilization, packaging and quality control.

Indicate the activity performed at each site. Provide phone number(s) fax numbers, website and
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e-mail address, include any alternative manufacturing sites. For each site where the major production step(s) is/are carried out, attach an original certificate of a pharmaceutical product (CPP) issued by the competent authority in terms of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce.

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

A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g. tumble blender, in-line homogenizer) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in section 3.2.2.4. In certain cases, environmental conditions (e.g. low humidity for an effervescent product) should be stated.

The maximum holding time for bulk-finished veterinary medicine prior to final packaging should be stated. The holding time should be supported by the submission of stability data, if longer than 30 days. For an aseptic finished veterinary medicine, the holding time of the filtered product prior to filling should be supported by the submission of stability data/validation, if longer than 24 hours.

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

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Provide a copy of a batch manufacturing record for a commercial /trial batch.

For sterile products, details of sterilization process and/or aseptic procedures used must be described.

The stages of manufacture at which sampling is carried out for in-process control tests; should be indicated in this section. The in-process test should be described in full and frequency that they carried out, though reference to methods in other parts of the dossier or an acknowledged pharmacopoeia will suffice.

Documented evaluation of at least three production scale batches should be submitted to provide assurance that the manufacturing process will reliably meet predetermined specifications. A batch formula should be provided that includes a list of components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis including overages, and a reference to their quality standards.

Process Validation

Manufacturing process should be controlled to assure that the finished product consistently meets all quality attributes including specifications. The applicant should provide a suitable written protocol that specifies the manufacturing formula, processing procedures, environmental conditions, critical controls, testing, and expected outcomes. The protocol should discuss the following elements of the manufacturing conditions, including operating parameters, processing limits, and component (raw material) inputs and should be done on minimum three batches.

- a) The data to be collected and when and how it will be evaluated.
- b) Tests to be performed (in process, release, characterization) and acceptance criteria for each significant processing step.

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- c) The sampling plan, including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches.

The analytic test results from the batches should include the test parameters, specification, result, remarks and conclusion should be provided in tabular form. The conclusion should be based on a documented justification for the approval of the process, and release of batches for market in consideration

3.2.2.4 Control of excipients for the veterinary medicine(S)

The specifications for excipients should be provided. The specifications from the finished veterinary medicine manufacturer should be provided for all excipients, including those that may not be added to every batch (e.g. acid and alkali), those that do not appear in the final finished veterinary medicine (e.g. solvents) and any others used in the manufacturing process (e.g. nitrogen, silicon for stoppers).

If the standard claimed for an excipient is an officially recognized compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognized compendial monograph.

If the standard claimed for an excipient is a non-compendial standard (e.g. in house standard) or includes tests that are supplementary to those appearing in the officially recognized compendial monograph, a copy of the specification for the excipient should be provided. For excipients of natural origin, microbial limit testing should be included in the specifications.

For oils of plant origin (e.g. soy bean, peanut) the absence of aflatoxins or biocides should be demonstrated.

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The colours permitted in official monograph. For proprietary mixtures, the supplier's product sheet with the qualitative formulation should be submitted, in addition to the finished veterinary medicine manufacturer's specifications for the product including identification testing.

For flavours the qualitative composition should be submitted, as well as a declaration that the excipients comply with food grade quality.

Information that is considered confidential may be submitted directly to VMD by the applicant with reference to the specific related product.

If additional purification is undertaken on commercially available excipients details of the process of purification and modified specifications should be submitted.

3.2.2.5 Control of the Veterinary medicine(s)

Critical steps: Test and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps of the manufacturing process, to ensure that the process is controlled.

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

The specification(s) for the veterinary product should be provided. A list of general characteristics, specific standards, tests and limits for results for the finished veterinary medicine must be provided. Justification for the proposed specification should be provided.

All analytical test procedures, including biological and microbiological methods where relevant, must be described in sufficient detail to enable the procedures to be repeated if necessary

If the product is tested on the basis of a monograph in a pharmacopoeia, it is sufficient to provide a copy of the monograph together with any test methods referenced in the monograph but not

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appearing in it. Provide details of any specifications and test methods additional to those in the pharmacopoeia.

3.2.2.6 Reference standards or materials of the veterinary medicine(S)

Information on the reference standards or reference materials used for testing of the finished veterinary medicine should be provided, if not previously provided in “2.3.1.5 Reference standards or materials”.

See section 2.3.1.5 for information that should be provided in reference standards or materials. Information should be provided on reference materials of finished veterinary medicine degradation products, where not included in 2.3.1.5.

3.2.2.7 Container closure system for the veterinary medicine(S)

Container closure system refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the veterinary product. A description of the container-closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided. A description of the container closure system should be provided, including the identity of materials of construction of each primary packaging component and its specification. The *GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR MARKETING AUTHORIZATION FOR VETERINARY MEDICINES*

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suitability of the container closure system used for the storage, transportation (shipping) and use of the finished veterinary medicine should be discussed. This discussion should consider, eg choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including adsorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the finished veterinary medicine). The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Reference Guidelines VICH: GL 3R

Container Closure Integrity Tests

The container closure integrity tests should be provided as the per pharmacopeia standard (USP, BP). A report must be provided to confirm that the closure container maintain a sterile barrier for sterile finished products. Also provide leak tests and microbial contamination tests. In case of plastic container closure systems should be pharmaceutical grade

The following information should be provided in this section

Labeling of the primary packaging

The following minimum information shall be required on the label of the immediate packaging.

- a) Brand name where appropriate
- b) International non-proprietary name/generic name
- c) Pharmacopeias status of the finished medicine and the AI where applicable
- d) Pharmaceutical dosage form, quantity of active ingredient per dosage unit

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- e) Total contents of container
- f) Date of manufacture
- g) Date of expiry
- h) Batch number
- i) Specific storage conditions
- j) Name and full location address of manufacturer
- k) Withdrawal periods

All finished veterinary medicines must have the instructions FOR ANIMAL USE ONLY. Any veterinary product whose name, package or label bears close resemblance to an already registered product or is likely to be mistaken for such a registered product, shall not be considered for registration. Disputes regarding trademark infringements not identified by VMD at the time of registration or amendment shall be the responsibility of the applicants. If however, valid concerns are identified, the new applicant shall be advised to make appropriate amendments.

Due to lack of space, the date of manufacture, address of the manufacturer and storage conditions may be omitted on the primary container if it is a blister or strip pack, or a vial or an ampoule less than 10ml. The name of the manufacturer may be substituted with a trade –mark or other symbol.

Blisters and strips should include, as a minimum, the following information:

- a) Name, strength and pharmaceutical form of the finished veterinary medicine
- b) Name of the manufacturer or log
- c) The manufacturing and expiry date in an encoded form
- d) Batch number

However, these details shall appear in full on the secondary packaging
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Labels shall not contain material written or graphical that targets to directly promote use of the products by infants and children. Pictograms intended to clarify certain information (e.g. age /species for which product is intended; dosage etc) may be included on the product package. All particulars on the label shall be easily legible, clearly comprehensible and indelible.

Labeling of secondary packaging

Labeling of secondary packaging or, where there is no secondary packaging, on the immediate packaging should include at least the following:

- a) The name of the finished veterinary medicine(Brand Name/trade name)where applicable
- b) Route of administration
- c) A list of AI(s) (using INNs if applicable) shows the amount of each ingredient
- d) Present in a dosage unit, and a statement of the net contents of the container, e.g. number of dosage units, weight or volume.
- e) List of excipients known to be of safety concern for some animals where applicable
- f) Indications(s) and recommended dosage
- g) The batch number assigned by the manufacturer
- h) The manufacturing and expiry dates in an encoded form
- i) Specific storage conditions or handling precautions that may be necessary
- j) Directions for use
- k) Precautions or warning that may be necessary
- l) The name , address and physical address of the manufacturer
- m) The name and address of the company responsible for placing the product on the market if different from the manufacturer.
- n) VMD registration /marketing authorization number (to be included after approval) may

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- o) Legal category
- p) Withdrawal periods (eg. Eggs, Milk and meat) where applicable.
- q) Keep out of reach of children

The labeled storage conditions should be achievable in practice in distribution network. For containers of less than or equal to 10ml capacity that are marketed in an outer pack such as a carton, and the outer pack still bears the required information, the immediate container need only contain items (i), (ii), (iii), (vi), (ix) and (x)- or all logos that unambiguously identifies the company and the name of the dosage form or the route of administration.

Leaflet/insert requirements

- a) Brand/Trade Name(where applicable).
- b) Name of Active ingredients INN,/International Non-Proprietary name/ Generic name should come immediately below the Brand name & in bold.
- c) Quantity of Active ingredient/ Strength per dosage units,mg,ml,gm.
- d) Dosage form.eg Injection, Bolus,Powder, Suspension etc.
- e) .Pharmacology-description of Mechanism/Mode of Action & Pharmacological effects.
- f) Pharmacokinetics- Absorption, Distribution,Metabolism and Excretion
- g) Indications;That includes,diseases and conditions,treated,prevented or alleviated and animal species targetedDosage regimens;That includes dosage ranges per weight of animals spp.or per volume of water or weight of feed depending with the drug.
- h) Route/mode of administration;eg.Oral,IM,SC or I.V Inj. IV Infusion. Etc.
- i) Precautions,warnings,Contraindications, drugs interactions,adverse reactions etc in pregnancy,lactation, etc where applicable.
- j) Withdrawal period for milk,meat and eggs as applicable.

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- k) Storage Conditions; as may be applicable depending with the drug e.g Store at 15-25c in a cool, dry place.
- l) Protect from light. Keep out of reach of Children.
- m) For Veterinary Use Only/ Animal Treatment Only.
- n) Distribution Category eg POM, GS (as per National Legislation).
- o) Registration No. of the product(as Applicable with the Regulator)
- p) Pack sizes; Include all pack sizes applicable to the product.
- q) Name with Physical & Postal address of the Manufacturer & Country of Origin.

3.2.2.8 Stability testing of the veterinary medicine

3.2.2.8.1 General

The design of the formal stability studies for the medicinal product should be based on knowledge of the behavior and properties of the AI and from stability studies on the AI and on experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

3.2.2.8.2 Photostability Testing

Photostability testing should be conducted on at least one primary batch of the medicinal product if appropriate. The standard conditions for photostability testing are described in VICH GL5.

3.2.2.8.3. Selection of Batches

Data from stability studies should be provided on at least three primary batches of the medicinal product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary

batches should simulate that to be applied to production batches and should provide product of the *GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR MARKETING AUTHORIZATION FOR VETERINARY MEDICINES*

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same quality and meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches, and the third one can be smaller if justified. Where possible, batches of the medicinal product should be manufactured by using different batches of the AI.

Stability studies should be performed on each individual strength and container size of the medicinal product unless bracketing or matrixing is applied.

Other supporting data can be provided.

3.2.2.8.4. Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label).

In some cases, a smaller container closure system simulating the actual container closure system for marketing may be acceptable. In these instances, a justification for using a smaller container closure system should be provided. Any available studies carried out on the medicinal product outside its immediate container, in other packaging materials can form a useful part of the stress testing of the dosage form, or can be considered as supporting information, respectively.

3.2.2.8.5. Specification

Specification, which is a list of tests, references to analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf life specifications, is addressed in VICH GL39 and GL40. In addition, specification for degradation products in a medicinal product is addressed in GL11.

Stability studies should include testing of those attributes of the medicinal product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy.

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The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf life acceptance criteria for antimicrobial preservative content should be supported by data demonstrating preservative effectiveness of a development batch of the proposed formulation artificially prepared to contain the lowest permitted levels of the antimicrobial preservative(s) according to the shelf-life specification. A single primary stability batch of the medicinal product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

3.2.2.8.6. Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the medicinal product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

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At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

Reduced designs, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified.

3.2.2.8.7. Storage Conditions

In general, a medicinal product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the medicinal product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long-term data will not be

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available before submission, at 12 months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

The long term testing should cover a minimum of 6 months' duration on at least three primary batches at the time of submission and should be continued for a period sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

3.2.2.8.7. General case

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or	6 months

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	30°C ± 2°C/65% RH ± 5% RH	
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

Long term, accelerated, and, where appropriate, intermediate storage conditions for medicinal products are detailed in the sections below. The general case should apply if the medicinal product is not specifically covered by a subsequent section. Alternative storage conditions can be used.

Note: That the recommended storage for injectable in zone-IV stored in the temperatures range 20-25°C with temperature excursions permitted between 15-30°C, the maximum recommended shelf life for VMD is 36 months

* It is up to the applicant to decide whether long-term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and “significant change” occurs at any time during 6 months’ testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months’ data from a 12-month study at the intermediate storage condition.

In general, “significant change” for a medicinal product is defined as:

1. A 5% change in assay from its initial value, or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
2. Any degradation product’s exceeding its acceptance criterion;
3. Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness); however, some changes in

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physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions; and, as appropriate for the dosage form:

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

3.2.2.8.7.2. Medicinal products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for medicinal products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition

Medicinal products packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based medicinal products stored in semi-permeable containers can withstand low relative humidity environments.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long-term *	25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH	6 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/not more than	6 months

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(NMT) 25% RH

* It is up to the applicant to decide whether long-term stability studies are performed at $25 \pm 2^\circ\text{C}/40\% \text{RH} \pm 5\% \text{RH}$ or $30^\circ\text{C} \pm 2^\circ\text{C}/35\% \text{RH} \pm 5\% \text{RH}$.

** If $30^\circ\text{C} \pm 2^\circ\text{C}/35\% \text{RH} \pm 5\% \text{RH}$ is the long-term condition, there is no intermediate condition.

For long-term studies conducted at $25^\circ\text{C} \pm 2^\circ\text{C}/40\% \text{RH} \pm 5\% \text{RH}$, additional testing at the intermediate storage condition should be performed as described under the general case to evaluate the temperature effect at 30°C if significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the medicinal product will not have significant water loss throughout the proposed shelf life if stored at 25°C and the reference relative humidity of 40% RH.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of 3 months' storage at $40^\circ\text{C}/\text{NMT } 25\% \text{RH}$. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of 3 months' storage at $40^\circ\text{C}/\text{NMT } 25\% \text{RH}$ may be acceptable, if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worstcase scenario (e.g., the most diluted of a series of concentrations) for the proposed medicinal product.

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Example of an approach for determining water loss:

For a product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

For example, at a given temperature, e.g., 40°C, the calculated water loss rate during storage at NMT 25% RH is the water loss rate measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Alternative relative humidity	Reference relative humidity	Ratio of water loss rates at a given temperature
60% RH	25% RH	1.9
60% RH	40% RH	1.5
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

3.2.2.8.7.4. Medicinal products intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5°C ± 3°C	6 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

If the medicinal product is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

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Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long-term storage condition.

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If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g., during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the medicinal product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

3.2.2.8.7.5. Medicinal products intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	-20°C ± 5°C	6 months

For medicinal products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for medicinal products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition.

3.2.2.8.7.6. Medicinal products intended for storage below -20°C

Medicinal products intended for storage below -20°C should be treated on a case-by-case basis.

3.2.2.8.8 Stability Commitment

When available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval to firmly establish the shelf life.

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Where the submission includes long-term stability data from three production batches covering the proposed shelf life, a post approval commitment is considered unnecessary.

Otherwise, one of the following commitments should be made:

1. If the submission includes data from incomplete stability studies on at least three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months.
2. If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.
3. If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

Where intermediate testing is called for by a significant change at the accelerated storage condition for the primary batches, testing on the commitment batches can be conducted at either the intermediate or the accelerated storage condition. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should also be conducted.

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Stability summary and conclusion

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example conclusions with respect to storage and shelf-life and if applicable, in –use storage conditions and shelf-life. The design of the stability studies for the finished product should be based on knowledge of the behavior and properties of the AI and the finished veterinary medicine(s).

Note

The shelf-life (stability) of the finished sterile products after first opening, reconstitution and dilutions must be provided.

Post – approval stability protocol and stability commitment

The post-approval stability protocol and stability commitment should be provided. When available long-term stability data on primary batches do not cover the proposed re-test period granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the re-test period. Where the submission includes long-term stability data on three production batches covering the proposed re-test period, a post approval commitment is considered unnecessary.

Shelf life acceptance criteria should be derived from consideration of all available stability information. The proposed storage conditions should be achievable in practice.

The summary should include conclusions with respect to in-use storage conditions and shelf life, when applicable.

Storage conditions

In general, a finished veterinary medicine should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential of solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use. Stability testing

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of the finished product after constitution or dilution, if applicable, should be conducted to provide information for the labeling of the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product.

Batch analyses of the finished veterinary medicine

Results for not less than three batch analyses (including the date of manufacture, place of manufacture, batch size and use of batch tested) must be presented. The batch analysis must include the results obtained for all specifications at release.

Reference VICH: GL3R GL10R, GL 39

3.2.3 APPENDICES

3.2.3.1 Facilities and Equipment

A diagram should be provided illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product.

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included.

A summary description of product-contact equipment, and its use (dedicated or multi-use) should be provided. Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed.

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3.2.3.2 Adventitious Agents Safety Evaluation

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

For excipients of animal, animal or microbial origin, provide information regarding adventitious agents (e.g., sources specifications; description of the testing performed; viral safety data).

The following excipients should be addressed in this section: gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If from plant origin a declaration to this effect will suffice.

For these excipients from animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the finished veterinary medicine are *without* risk of transmitting agents of animal spongiform encephalopathies.

3.2.3.3 Novel Excipients

For excipient(s) used for the first time in a finished veterinary product or by a new route of administration, full details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical and/or clinical), should be provided according to the AI and/or Finished veterinary product format

PART 4: NON-CLINICAL STUDY REPORTS FOR NEW CHEMICAL ENTITIES

ONLY

This section of the Guideline is not required for generic products

4.1 Table of Contents of Part 4

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A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the technical document.

4.2 NONCLINICAL STUDY REPORTS FOR NEW CHEMICAL ENTITIES

This guideline presents the organization of the nonclinical reports in the applications that will be submitted. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The appropriate location for individual-animal data is in the study report or as an appendix to the study report. REFERENCE VICH: GL9 (GCP)

4.2.1 Study Reports

The study reports should be presented in the following order:

a. Pharmacology

Primary Pharmacodynamics

Secondary Pharmacodynamic

Safety Pharmacology

Pharmacodynamic Medicine Interactions

b. Pharmacokinetics

Analytical Methods and Validation Reports (if separate reports are available)

Absorption

Distribution

Metabolism

Excretion

Pharmacokinetic Medicine Interactions (nonclinical)

Other Pharmacokinetic Studies

c. Toxicology

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

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Repeat-Dose Toxicity (in order by species. by route, by duration; including supportive toxic kinetics evaluations)

Overdose(should be provided incase of accidental use)

d. Genotoxicity

In vitro

In vivo (including supportive toxicokinetics evaluations)

Carcinogenicity (including supportive toxicokinetics evaluations)

Long—term studies (in order by species: including range—finding studies that cannot appropriately be included under repeat—dose toxicity or pharmacokinetics)

Short- or medium—term studies (including range—finding studies that cannot appropriately be included under repeat—dose toxicity or pharmacokinetics).

e. Other studies

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

Fertility and early embryonic development

Embryo-fetal development

Prenatal and postnatal development, including maternal function

Studies in which the offspring (young animals) are dosed and/or further evaluated.

Local Tolerance

Other Toxicity Studies (if available)

Immunotoxicity

Mechanistic studies (if not included elsewhere)

Dependence

Metabolites

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Impurities

Other

4.3 Literature References

PART 5: CLINICAL STUDY REPORTS

This section of the guideline is applicable only for medicines where a Bioequivalence (BE) study is a requirement and where the medicine is not yet registered in Kenya. For finished veterinary medicines in which the molecule(s) is new to the Kenyan market, the applicant should submit full safety and efficacy data as outlined in this guideline. For multisource generic products having a molecule(s) already registered in Kenya and requiring BE study, only section 5.2.1 of Part 5 needs to be supported with actual experimental evidence and where applicable reference to literature can be considered for other section. For generic products requiring clinical equivalence study, in cases where comparative clinical evidence of a pharmacokinetics (PK) BE study cannot be conducted, section 5.2.1.1 of Part 5 may be required, to be determined on a case-by-case basis.

5.1 NEW CHEMICAL ENTITIES ONLY

Substantial evidence from clinical studies should be submitted in support of efficacy for the proposed indications. Each study should include information on the investigators, site of study, description of facilities, number of animals, criteria for inclusion and exclusion of animals, groups or replicates, sex of animals, age of animals, type of animals, diagnosis, diagnostic procedures and tests, drug formulation, dosage, criteria ,effectiveness, morbidity and mortality rates, lesion descriptions and scores, duration of study, results, description of adverse effects, statistical procedures used and conclusions and interpretations.

The individual case reports are to be collated by relevant claim and by the investigator. All case reports and other raw data from a study should be included towards the end of a study

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report. All data generated from individual experiments should be properly summarized and statistically analyzed using appropriate statistical procedures. A pooled statistical analysis of the data generated from studies designed specifically for pooling should be included. A probability level of five percent ($P < 0.05$) should be used in deciding to accept or to reject the null hypothesis. Detailed information on the statistical methodology used, including computer programs, should be provided or referenced.

5.1.1 Table of Contents of Part 5

5.1.2 Tabular Listing of All Clinical Studies

A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table of contents part 5.1.1 of this Guideline. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in Section 5.3 below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

5.1.3 Clinical Study Reports

Reports of Biopharmaceutic Studies

BA studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or in vitro dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in Section 5.3.1, and referenced in Sections 5.3.1.1 and/or 5.3.1.2.

Bioavailability (BA) study reports

BA studies in this section should include:

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- a) Studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously or as an oral liquid dosage form;
- b) Dosage form proportionality studies; and,
- c) Feed-effect studies. Reference to literature suffices for generic products.

5.1.4 Literature and references

5.2. INTERCHANGEABILITY OF GENERIC MEDICINES (GENERIC MEDICINE APPLICATIONS ONLY)

Introduction

This guideline describes the principles of procedures of bioequivalence studies of generic products. The objective of the study is to assure therapeutic equivalence of generic products to innovator products. In the bioequivalence study, bioavailability should be compared for innovator and generic products. If this is not feasible, pharmacological effects supporting therapeutic efficacy or therapeutic effectiveness in major indications should be compared (These comparative tests are hereafter called Pharmacodynamic studies and clinical studies, respectively). For oral products, dissolution tests should be performed, since they provide important information concerning bioequivalence.

Interchangeable medicines are those that

1. Have the same qualitative and quantitative composition in each of their active substances
2. Are in the same pharmaceutical form
3. Have the same route of administration
4. Have not more than two active substances

5.2.1. Reports of Biopharmaceutic Study (ies)

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BA studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or in vitro dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a Medicine but also includes BA information, the study report should be submitted and referenced in Sections.

5.2.1.1. Bioavailability (BA) Study Reports

BA studies in this section should include

Studies comparing the release and systemic availability of an AI from a solid oral dosage form. Form to the systemic availability of the AI given intravenously or as an oral liquid dosage form. Dosage form proportionality studies, and Feed-effect studies. Similar studies of equivalent molecules can be used.

Comparative BA and Bioequivalence (BE) Study Reports

Studies in this section compare the rate and extent of release of the AI from similar veterinary products (e.g., Boluses). Comparative BA or BE studies may include comparisons between the Medicine, product used in clinical studies supporting effectiveness and the to-be-marketed veterinary product.

The veterinary product used in clinical studies supporting effectiveness and the to-be-marketed veterinary product. Similar veterinary products from different manufacturers.

5.2.1.2 In vitro dissolution tests

General aspects of in vitro dissolution experiments are briefly outlined in Dissolution testing and Similarity of Dissolution as per relevant pharmacopeias.

5.2.2.1.1 In vitro dissolution tests complementary to bioequivalence studies

The results of in vitro dissolution tests at three different buffers and the media intended for veterinary product release (QC media), obtained with the batches of test and reference products that were used in the bioequivalence study should be reported. Particular dosage

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forms like solid dosage forms may require investigations using different experimental conditions. The results should be reported as profiles of percent of labelled amount dissolved versus time displaying mean values and summary statistics. Unless otherwise justified the specifications for in vitro dissolution to be used for quality control of the product should be derived from the dissolution profile of the test product batch that was found to be bioequivalent to the reference product.

In the event that the results of comparative in vitro dissolution of the bio-batches do not reflect bioequivalence as documented in vivo the latter prevails. However possible reasons for the discrepancy should be addressed and justified.

5.2.2.1.2 In vitro dissolution tests in support of bio-waiver

Appropriate in vitro dissolution should confirm the adequacy of waiving additional in vivo bioequivalence testing. Accordingly, dissolution should be investigated at different pH values as outlined in the previous section (normally pH 1.2, 4.5 and 6.8) unless otherwise justified. Similarity of in vitro dissolution as the pharmacopeia references should be demonstrated at all conditions within the applied product series.

At pH values where sink conditions may not be achievable for all strengths in vitro dissolution may differ between different strengths however, the comparison with the respective strength of the reference medicinal product should then confirm that this finding is AI rather than formulation related. In addition, the applicant could show similar profiles at the same dose (e.g. as a possibility two tablets of 5 mg Medicine versus one tablet of 10 mg could be compared).

Choice of Reference Product

This note is intended to provide applicants with some additional guidance and clarification on existing guidance documents with respect to selecting an appropriate reference product

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for a bioequivalence study conducted with a generic product for submission to the VMD. The following should be considered when selecting a reference product: The applicant should select and purchase the innovator pharmaceutical products approved in ICH or and VICH and other well-regulated markets. The applicant should choose from the WHO comparator product list or FDA Reference Product List. In case of any clarification the applicant can request VMD for guidance on the choice of reference

Analysis of Results

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

If data of a quantitative attribute that have changed significantly during the stability tests, present them in a graph and determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis show that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate.

Conclusion shall be drawn from the stability studies report to justify the shelf life.

5.2. 2. 1. 2 REQUEST FOR BIOWAIVER

Omission of BE studies must be justified. Generally BE studies are not necessary if a product fulfils one or more of the following conditions:

The following dosage forms are exempted from bioequivalence study requirements:

- a. The product is a solution intended solely for intravenous, subcutaneous and intramuscular administration.
- b. The product is to be parenterally or orally administered as a solution.
- c. The product is an oral dosage form which is not intended to be absorbed (e.g. Radio-opaque Contrast Media etc).

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- d. The product is an oral solution or other similarly soluble form:
- e. The product is a solution intended for ophthalmic or optic administration.
- f. The product is an inhalant volatile anesthetic solution, Inhalation and nasal Preparations
- g. The product is a reformulated product by the original manufacturer that is identical to the original product except for coloring agents, flavoring agents or preservatives, which are recognized as having no influence upon bioavailability
- h. Gases
- i. Solutions for oral use which contain the active substance(s) in the same concentration as the innovator Product and do not contain an excipient that affects gastro intestinal transit or absorption of the active substance.
- j. Powders for reconstitution as a solution and the solution meet the criteria indicated in i above.
- k. Topical preparations.

5.3 SAFETY AND RESIDUES DOCUMENTATION (FOR VETERINARY MEDICINES IN FOOD ANIMALS)

5.3.1. REQUIREMENTS FOR ANIMAL SAFETY

5.3.1.1 Laboratory Animal Studies

Laboratory animal studies will normally be required for new chemical entities proposed for use as veterinary drugs. The information available in the published scientific literature may be accepted in instead of studies outlined in this section. For the purpose of these guidelines, these studies are required to determine potential toxic effects for the target animal species.

The basic toxicity data obtained in laboratory animals complement the data required to support the safety of a new drug in the target animal species. Depending on the intended route(s) of administration of the drug for the target animal species, the toxicity studies may

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be conducted by oral and/or parenteral routes of administration of drugs. The laboratory animal toxicity studies in general may be classified as acute, sub chronic or chronic.

5.3.1.2 Target Animal Safety Studies

The objectives of these studies are to document: signs and effects associated with the toxicity of the new drug for the test species and its organs, tissues and functions; minimum toxic dose; maximum no-toxic-effect dose; and margin of safety. The data required for the safety in the intended target animal species may vary according to the nature of the basic toxicological data, the intended use of the proposed drug and the intended use of the target animal. The basic toxicology data are generally obtained from studies in laboratory animals. The data to establish safety of the proposed drug to the intended target animal species are obtained from the studies conducted in the target animal species. For the design and conduct of these studies a reference may be made to the Target Animal Safety Guidelines VICH GL 43-ST7.

5.3.2 REQUIREMENTS FOR HUMAN SAFETY

This Part of the pertains to the drugs used in food-producing animals. However, basic toxicity data obtained in laboratory animals are used to complement the data required to support the safety of the drug residues in food-producing animals. Under certain circumstances, the microbiological safety assessment may be required for veterinary antimicrobial products intended for use in non-food-producing animals.

Before a new drug intended to be used in food-producing animals can be sold, manufacturers are required by law to submit scientific evidence demonstrating that the drug has been carefully assessed for the safety of drug residues in meat and other food products intended for human consumption. Microbiological safety assessment is also considered as a key aspect of the requirements for human safety of veterinary antimicrobials.

5.3.2.1 Laboratory Animal Toxicity Studies

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Toxicity studies are used to determine toxic effects of veterinary drugs and/or their metabolites in laboratory animal species, usually rodents and non-rodents (e.g., dogs), so that adequate extrapolations can be made to estimate the potential risks of the residues of veterinary drugs for consumers ingesting foods of animal origin. All laboratory animal toxicity studies, except for tests of mutagenicity, submitted in support of human safety for use in food-producing animals are conducted using the oral route of administration. Data generated under the toxicity studies are used to establish a no observable effect level (NOEL) in the most sensitive species/sub species. The established NOEL is then used to calculate an Acceptable Daily Intake (ADI) for the specific drug and/or its metabolites by using an appropriate safety factor. Specific requirements for toxicity studies may vary from one drug to another depending on the class of veterinary drug and the extent of its proposed use.

5.3.2.2 Microbiological Safety Studies (for antimicrobial products)

In this section of the Human Safety Requirements, information is provided regarding the data requirements expected for demonstrating the microbiological safety of a drug product. This section pertains to antimicrobial drug products as well as products containing probiotics, for example, direct-fed microbial products.

Veterinary Antimicrobial Products(Antimicrobial resistance)

This section pertains to antimicrobial drug products (including antibacterial, antiparasitics and antivirals). However, information in this guidance is often targeted to antibacterial products. Applicants submitting applications for other antimicrobial products may wish to consult with the Directorate for the specific requirements for their submission.

The impact of the use of antimicrobial products in food-producing animals on the development and the potential for enrichment and dissemination of antimicrobial resistant

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human bacterial pathogens is considered one of the principal aspects of the human safety review.

The objective of this guidance is for the sponsor to provide information necessary for assessing the potential impact of the use of veterinary antimicrobial products on the development of antimicrobial resistance in bacteria of animal origin, which may affect antimicrobial therapy in veterinary and human medicine.

Reference VICH Guideline: GL 22, GL 23R, GL 28, GL 33, GL36 R, GL37 and GL54

REFERENCES

1. Approach to Establish a Microbiological ADI. VICH Guideline 36
2. Chronic Toxicity. VICH Guideline 28
3. Genetic Toxicity Studies. VICH Guideline 23
4. Genetic Toxicity Studies. VICH Guideline 23
5. Impurities in New Drug Substances, VICH GL 10
6. Impurities in New Drug Substances, VICH GL 10
7. Impurities in New Veterinary Medicinal Products, VICH GL 11
8. Impurities in New Veterinary Medicinal Products, VICH GL 11
9. Impurities: Residual Solvents in New Veterinary Medicinal Products, VICH GL 18
10. Impurities: Residual Solvents in New Veterinary Medicinal Products, VICH GL 18
11. Pre-approval Information for Registration of New Veterinary Medicinal Products for Food Producing Animals with respect to Antimicrobial Resistance. VICH Guideline 27
12. Producing Animals with respect to Antimicrobial Resistance. VICH Guideline 27
13. Reproductive Studies. VICH Guideline 22
14. Stability Testing of New Drug Substances and Products, VICH GL 3

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15. Stability Testing: Photostability Testing of New Drug Substances and Products, VICH GL 5
16. Stability Testing: Requirements for New Dosage Forms, VICH GL 4
17. Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI. VICH Guideline 36
18. Validation of Analytical Procedures: Definition and Terminology, VICH GL 1
19. Validation of Analytical Procedures: Methodology, VICH GL 2
20. WHO Technical Report Series, No. 902, 2002 Annex 9: Guidelines on packaging for pharmaceutical products