Medicines Control Authority of Zimbabwe

GUIDELINE ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION OF VETERINARY MEDICINES IN ZIMBABWE

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EFFECTIVE DATE: 1ST JANUARY 2016

Applications already submitted are being evaluated using this guideline.

Please direct any comments or queries to:

Director General
106 Baines Avenue
P O Box 10559
Harare

Fax: +263 4 736980
E-mail: mcaz@mcaz.co.zw

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1.1 PROCESS AND ADOPTION OF THE GUIDELINE

Drafting of guideline	August – October 2014
Discussion and review within the Evaluations and Registration Division	September 2014
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Collation and review of comments	August 2015
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Approval of the final draft by the DG	December 2015
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1.2 INTRODUCTION

These guidelines have been adopted mainly from the guidelines for Registration of Veterinary medicines in the SADC, VICH guidelines region and the Health Canada Preparation of Veterinary Abbreviated New Drug Submission – Guidance for Industry Generic Drugs. Applicants interested in having their FPPs evaluated for registration in Zimbabwe should submit a product dossier reflecting the data and information requested below. The current version of any guideline or pharmacopoeia referred to in this guideline shall be applicable in all instances. Any deviations must be highlighted, justified and require approval by the MCAZ.

The present guidelines have been prepared taking into consideration the need for worldwide harmonization, which will assist the medicine manufacturers in the preparation of a well-structured dossier to be submitted for the registration of veterinary medicines in order to facilitate their screening and subsequent review.

Veterinary medicine use and residues are some of the most important issues with regard to health, food safety and trade. Misuse of medicines in animal production, prohibited medicines residue levels on food of animal origin, agricultural commodities and feedstuffs can endanger human life and lead to constraints in trade within the region and internationally. To exercise the necessary management and control over veterinary medicines it is necessary to have the relevant legislation in place to enable management and control all aspects related to the registration, availability, use, labelling, marketing, manufacture, import, export, transport and disposal of these products. Therefore structures must also be put in place to ensure compliance to legislation and to monitor the use of veterinary medicines.

1.3 SCOPE

This document is intended to provide guidance on the format of the information required for active pharmaceutical ingredients (APIs) and their corresponding FPPs. The text under the section titles is intended to be explanatory and illustrative only. The content of these sections

may include relevant information as described in existing guidelines of the SADC, the OIE and VICH guidelines.

In assembling the product dossier, applicants should also take into account other MCAZ or MCAZ – adopted guidelines relating to the safety, efficacy and quality of FPPs. The veterinary medicines guidelines are necessary to ensure appropriate health care to animals, in Member States of the SADC Region and to authorise only the use of veterinary medicines of proven safety, efficacy and quality.

One important method of ensuring the safety, efficacy and quality of these products is thorough evaluation and registration of veterinary medicines, which are to be imported or locally manufactured in Zimbabwe before they are offered for sale.

1.4 OBJECTIVES OF THE VETERINARY MEDICINES REGISTRATION GUIDELINES

The Veterinary Medicines Registration Guidelines provide a general scientific framework including basic methodology, technical requirements, ethical principles as well as regulatory aspects for registration of veterinary medicines in Zimbabwe with the following objectives:

- Provide appropriate health care to animals
- Provide the Zimbabwean and regional market with medicines that have proven safety, efficacy and quality
- Provide transparency in trade of agricultural products including animal and animal products within and outside the region
- Raise public awareness in the use of veterinary medicines
- Protect public health against zoonotic diseases
- Protect the environment
- Provide the regulatory basis for management and control of veterinary medicines
- Provide a relevant approach for the observance and compliance with Maximum Residues Limits.

1.5 TERMS AND DEFINITIONS

For the purposes of these guidelines, the following have the meanings hereby assigned to them.

1. **ACTIVE PHARMACEUTICAL INGREDIENT (API)** - A substance or mixture of substances with a therapeutic, diagnostic or prophylactic activity used in a pharmaceutical product. 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 the function of the body
2. **ADVERTISING** - means the promotion for the sale and use of veterinary medicines by printed and electronic media, signs, displays, gift, demonstration or word of mouth
3. **BIOAVAILABILITY** - The rate and extent to which the active ingredient is absorbed from a medicine product and becomes available at the site(s) of action.

4. **BIOEQUIVALENCE** - A high degree of similarity in the bioavailabilities of two pharmaceutical products (of the same galenic form) from the same molar dose, that are unlikely to produce clinically relevant differences in therapeutic effects, or adverse effects or both.
5. **BIOEQUIVALENT** - Two products are considered to be bioequivalent when their active ingredient(s) is (are) equal in their rate and extent of absorption, and availability at the site(s) of action.
6. **GENERIC MEDICINE PRODUCT** - means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a license from the innovator company and marketed after expiry of patent or other exclusivity rights.
7. **CONTAINER** - is that which holds the medicine and is or may be in direct contact with the medicine.
8. **DISPOSAL** means any operation to recycle, neutralize, destruct or isolate pesticide waste, used containers and contaminated materials.
9. **DISTRIBUTION** means the process by which veterinary medicines are supplied through trade channels to local or international markets.
10. **DOSAGE FORM** - Formulation of an active ingredient(s) so that it can be administered to an animal in specified quantity/strength e.g. tablets, capsules, injection solution, syrups, ointments, suppositories, etc.
11. **ENVIRONMENT** means surroundings, including water, air, soil and their interrelationship as well as all relationship between them and any living organism.
12. **MANUFACTURER** means a corporation or other entity in the public or private sector or any individual engaged in the business or function (whether directly or through an agent or entity controlled by or under contract with it) of manufacturing a veterinary medicinal active ingredient or preparing its formulation or product.
13. **INNOVATOR MEDICINE** - Generally, the innovator pharmaceutical product is that which was authorized for marketing (normally as a patented medicine) on the basis of documentation of efficacy, safety and quality (according to contemporary requirements). In the case of medicines, which have been available for many years, it may not be possible to identify an innovator pharmaceutical product
14. **LABELLING** - All labels and other written, printed, or graphic matter upon an immediate container of a veterinary medicine, any package or wrapper in which it is enclosed, except any outer shipping container.
15. **MEDICATED PREMIX (FEED ADDITIVE)** - A medicine specifically formulated for blending into animal feed.
16. **MARKETING** means the overall process of FPP promotion, including advertising, FPP public relations and information services as well as the distribution and sales on local and international markets.
17. **MAXIMUM RESIDUE LIMIT (MRL)** means the maximum concentration of a residue that is legally permitted or recognized as acceptable in or on a food or agricultural commodity or animal feedstuff.
18. **NEW VETERINARY MEDICINE**- One which has not been previously registered or marketed for veterinary purposes, including any new salts and esters of an API, new fixed combinations of substances previously marketed or any veterinary medicine previously marketed if its indication, mode of administration, or formulation are changed.

19. **PROPRIETARY PRODUCT** - A medicinal product sold or supplied under a special name (a brand or trade name) rather than the generic name of the ingredient alone.
20. **REFERENCE STANDARD** - Authentic specimens that have been verified for suitability for use as comparison standards in compendia tests and assays.
21. **PHARMACEUTICAL PRODUCT**- Any preparation for veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.
22. **PHARMACEUTICAL EQUIVALENCE**- It refers to medicine products, which contain the same active ingredient in the same strength (concentration) and dosage form, and is intended for the same route of administration. In general, it has the same labelling and meets compendia and other standards of strength, quality, purity, and identity but does not necessarily contain the same non-medicinal ingredients
23. **PHARMACO-DYNAMICS** - The study of biochemical and physiological effects of medicines, their mechanisms of action, their structure activity relationships and their interaction with other medicines.
24. **PHARMACOKINETICS** - The study of the time course of medicines: absorption, distribution, metabolism and excretion.
25. **PHARMACO-VIGILANCE** - Means adverse medicine reaction reporting and post-market surveillance to monitor the safety and efficacy of veterinary medicines
26. **PIVOTAL TRIALS** - Studies providing the basic evidence to determine the efficacy, properties and conditions of use of the medicine conducted by qualified investigators at the recommended doses with the proposed formulation and for indications which are being claimed.
27. **REGISTRATION** means the process whereby the responsible national government or regional authority approves the sale and use of a veterinary medicine following the evaluation of comprehensive scientific data demonstrating that the product is effective and safe for the intended purposes and does not pose an unacceptable risk to human or animal health or the environment.
28. **RESIDUE** means any specific substance in or on food, agricultural commodities or animal feed resulting from the use of veterinary medicines. The term includes any derivatives of a medicine such as conversion products, metabolites, reaction products and impurities considered to be of toxicological concern. The term “veterinary medicine residue” includes residues from unknown as well as known uses of the medicine.
29. **TOXICITY** means a physiological or biological property, which determines the capacity of a chemical to do harm or produce injury to a living organism by other than mechanical means.
30. **SUBMISSION** - A submission is documentation consisting of data related to a medicine product submitted by a named party and provided in response to a regulatory requirement.
31. **MEDICINE** - Any substance or combination of substances that is manufactured, sold, offered for sale, or represented for use for medicinal purpose means any of the following:
    • Alleviating, treating, curing, or preventing a disease or pathological condition, or symptoms of a disease
    • Diagnosing a disease or ascertaining the existence, degree or extent of a physiological pathological condition
    • Contraception

• Inducing anaesthesia
• Maintaining mitigation, prevention, or diagnosis of disease, abnormal physical state, or the symptoms therefore in animal, or
• The restoration, correction, or modification of organic functions in man or animal.
• Vitamins, minerals, and other nutrients in injectable and bolus dosage forms for use in animals are also considered to be medicines.

32. **WITHDRAWAL PERIOD** -The minimum time that must elapse between the cessation of treatment of a food -producing animal and either the slaughter of the animal for human consumption or the resumption of the supply for human consumption of products, such as eggs, milk derived from the animal

1.6 ABBREVIATIONS

API	Active Pharmaceutical Ingredient
BAN	British Approved Name
BP	British Pharmacopoeia
CAS	Chemical Abstracts Service registry number
CEP	European certificate of suitability
CVM	Centre for Veterinary Medicine of US FDA
CoA	Certificate of Analysis
DMF	Drug Master File
DP	Drug Product
DS	Drug Substance
DSC	Differentia Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines and HealthCare
EMEA	European Medicines Agency
EP	European Pharmacopeia (see Ph.Eur.)
EU	European Union
F	Bioavailability
f_2	Similarity factor
FAO	Food and Agricultural Organisation for United Nations
FDA	United States Food and Drug Administration
FDC	Fixed Dose Combination
FPP	Finished Pharmaceutical Product
FTIR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GCP	Good Clinical Practice
GL	Guideline
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
i.m.	Intramuscular
ICH	International Conference on Harmonisation
INN	International Non-proprietary Name
Int.Ph.	International Pharmacopoeia
IR	Infrared

i.v.	intravenous
LOD	Limit of Detection
LOQ	Limit of Quantitation
JP	Japanese Pharmacopoeia
LOD	Loss on drying
MCAZ	Medicines Control Authority of Zimbabwe
MRA	Medicine Regulatory Authority
MIC	Minimum Inhibitory Concentration
MMTS	Maximum Mean Total Score
MRL	Maximum Residue Limit
MS	Mass Spectra
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
OIE	*Office International des Epizooties* (World Organisation for Animal Health)
SADC	Southern African Development Community
SI 150	Statutory Instrument 150 of 1991
SmPC	Summary of Product Characteristics
SMACS	WHO pharmaceutical starting materials certification scheme
TLC	Thin Layer Chromatography
TSE	Transmissible Spongiform Encephalopathy
PD	Product dossier
PDE	Permissible Daily Exposure
Ph. Eur	European Pharmacopoeia
QA	Quality Assurance
RH	Relative Humidity
USAN	United States Adopted Name
USP	United States Pharmacopoeia
USD	United States Dollars
VICH	International Cooperation on Harmonisation of Technical Requirements for the Registration of Veterinary Products
WHO	World Health Organisation
WHO TRS	WHO Technical Report Series
XRD	X-ray Diffraction

1.7 CONTEXT FOR THE DESIGN OF NATIONAL VETERINARY MEDICINES

1.7.1 LEGISLATION IN THE SADC REGION

The recommended international code of practices for control of the use of veterinary medicines (FAO, CAC/RCP 38, 1993) and the Legislation for Veterinary Medicines Control (FAO, 2004) as well as the VICH Guidelines set out the guidelines on the prescription, distribution administration and control of medicines used for treating animals, preserving animal health or improving animal production. These codes of practices together with the OIE recommendations (OIE 2010) provide guidance to countries to achieve sound veterinary medicines management. In particular it addresses the responsibilities of national governments, the veterinary services, manufacturers, resellers and users of veterinary medicines.

The development and improvement of international and regional collaboration in the establishment and enforcement of legislation to harmonise the regulatory framework between Members so as to assist countries in need to effectively institute and maintain such mechanisms is cardinal to ensure the safe circulation and distribution of registered veterinary medicines.

Presently SADC Member States' legislations and regulations dealing with the registration of veterinary medicines are not in accordance with international requirements. In particular they do not take into account the transparency in the registration of veterinary medicines including licensing, labelling, efficacy, import/export procedures, good manufacturing processes, accreditation of foreign manufacturers, distribution, quality control, use, storage, disposal, training, and update of the legislation.

The implementation of these guidelines will promote the responsible and prudent use of veterinary medicines, in particular of antibiotics used in veterinary medicine, which are responsible for antimicrobial resistance in humans. Indeed the current registration and distribution practices of veterinary medicines in some SADC Member States result in the proliferation of poor quality and counterfeit products in the Region.

More details on the most important responsibilities of governments and manufacturers can be found in the International code of practices for control of the use of veterinary medicines (FAO, CAC/RCP 38, 1993), the OIE Terrestrial Animal Health Code (Section 6) the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products guidelines. The codes set out guidelines on the prescription, application, distribution and control of medicines used for treating animals, preserving animal health or improving animal production. A summary is given below.

1.7.2 VETERINARY MEDICINES MANAGEMENT

- Regulate the availability, distribution and use of veterinary medicines and allocate adequate resources for this mandate.
- Countries exporting veterinary medicines should provide technical assistance to other countries and ensure that good trading practices are ensured, especially to those countries with limited or no technical and regulatory schemes.

Testing of veterinary medicines

Analytical laboratories should be available on a national basis to verify the quality of veterinary medicines offered for sale or export and to conduct residue and monitoring studies. These laboratories should adhere to sound scientific procedures and guidelines for good laboratory practice and preferably be accredited by a designated authority according to ISO 17025 and participate to laboratory proficiency testing schemes related to veterinary medicines of concern.

Reducing health and environmental risks

- Where necessary conduct periodic reviews of veterinary medicines available in the countries.
- Implement a program to monitor veterinary medicines residues in food and the environment.

- In cooperation with industry, ensure the proper location of medicines manufacturing plants, designing plants and storage facilities
- Adequately control wastes, effluents and the establishment of quality assurance procedures for compliance with the relevant standards of purity, performance, stability and safety according to Good Manufacturing Practices (GMP) and ISO 14000 standards.

Availability and use

- All veterinary medicines made available to the general public must be packaged and labelled in a manner consistent with the appropriate national regulations.
- All veterinary medicines must be classified at the time of registration in the following categories
  - Prescription Preparation (PPVet)
  - Veterinary Medicines General Dealer (VMGD)
  - Household Remedy (HR Vet)
- Prohibition of the importation, sale and purchase of veterinary medicines of unknown quality, counterfeit, expired medicines, medicines withdrawn from sales from other countries
- Prohibition of the importation, sale and purchase of hazardous products may be desirable, if other control measures, such as restriction to certified users or similar measures are insufficient to ensure that the product can be handled with acceptable risk to the user.

Distribution and trade

The necessary regulatory measures should be available to prevent the repacking or decanting or misuse of any veterinary medicines into food or beverage containers.

Information exchange

Facilitate the exchange of regulatory decisions (banning or severely restricting veterinary medicines, potential risks to human and animals, toxicological, environmental and safety data, availability of resources and expertise etc.) through national institutions, international, regional and sub-regional organizations and public sector groups

1.8 REGISTRATION PROCEDURES

The registration should cover all categories of veterinary medicines. The authorization process is an exhaustive investigation involving all aspects of the new product. It is based on trial results and data submitted by the applicant company.

The objectives of registration are to ensure:

- The veterinary medicine is safe for the animal itself, the consumer of food derived from treated animals, those handling the medicine, and the environment,
- The product is of consistently high quality, does not deteriorate and has the stability to last at least until the expiry date.
- The veterinary medicine efficacy conforms to the claims made on its information leaflet and label.
- The veterinary medicine itself and the excreta of treated animals do not have potential adverse impact on the environment

1.8.1 REVIEW OF DOSSIERS

Brief outline of the evaluation process

1. *Receiving a new application*

The Secretariat receives application files, samples and fees. The applicants may physically deliver or courier the new applications, samples and fees at MCAZ offices located at 106 Baines Avenue, Harare, Zimbabwe. New applications are entered into the Authority's systems upon payment and/or confirmation of payment of the application fees. Therefore the date of receipt of an application is the date when payment or confirmation has been received.

2. *Screening new applications*

A pre-evaluation screening checklist (Annexure II) is used to check completeness of the application files by the secretariat. Only complete application files will be accepted for the next step.

3. *Clearance of new applications by the Veterinary Committee:*

The Veterinary Committee that comprises of experts from various scientific disciplines considers all applications for registration of medicines at MCAZ. This Committee meets once every other month.
New applications received are tabled at the next Veterinary Committee meeting for consideration. At this stage, the Committee decides whether the application should be rejected, evaluated and/or analyzed.

The Committee may reject an application for the following reasons:

- If the FPP contains an undesirable excipient (see Annex IV – list of medicines considered undesirable for use in pharmaceuticals)
- The manufacturer has pending unresolved GMP issues
- If the FPP is not registered in the country of origin
- If its registration is viewed as being not in the interests of the Zimbabwean public

The Authority advises the applicant, in writing, of receipt of a new application within 1 calendar month of receipt of the application file, samples and application fees.

The Committee also considers requests for priority evaluation of applications. For such request to be considered, applicants must write a motivation letter stating reasons why registration of their product should be prioritized. As a policy priority evaluation will generally be afforded for products for use in the public sector and for which a public tender has been awarded. Motivation for registration of novel dosage forms, novel medicine delivery and new chemical entities will also be considered.

The Committee also decides whether the product samples should be analyzed in the laboratory. When the Committee is satisfied that it is in the public interest to consider the application it will authorize the next stage of the evaluation process.

4. *Evaluation of applications*

Regulatory Officers who are trained in evaluation of product dossiers evaluate the applications on a first come first served basis, unless priority evaluation has been authorized

by the Veterinary Committee. Two or more regulatory officers are normally responsible evaluating a Product Dossier. This guideline is used to guide the evaluation process.

Normally, the first review is completed within 6 months of receipt. Applicants are often asked to provide additional data. This should be provided within 30 days of receiving such a request. If more time be needed, a formal request must be submitted and approved by MCAZ before the deadline.

5. *Laboratory analyses of product sample*

The samples are analyzed in the MCAZ laboratory Division against the claimed in-house or pharmacopoeial specifications using the analytical method provided by the applicant. The laboratory generates a laboratory analysis report.

6. *GMP inspection of the facility*

If the Authority has received the first application from a new manufacturer, the applicant will be advised of the need for GMP inspection of the manufacturing facility. An inspection fee is payable. The MCAZ inspectors will inspect the manufacturing facility and prepare an inspection report of the manufacturing facility. The Authority will consider previous satisfactory inspection results, provided the inspection was conducted within 24 months preceding receipt of the application, and GMP certification from a Stringent Regulatory Authority.

7. *Consideration of application for approval for registration*

The evaluation report, laboratory analysis report and the GMP inspection report are tabled before the Veterinary Committee.

A sample of the product is also circulated in the meeting to enable members to examine the FPP. The evaluators will give oral presentations and recommendations for the Committee's consideration. If the Committee is satisfied, it may **approve registration** of the product or grant **conditional approval pending resolution of the minor outstanding issues** depending on the individual case. If there are unresolved safety, quality or efficacy issues the Committee often **defers approval pending resolution of the outstanding issues**. The applicant is normally given a period of 60 days to resolve the outstanding issues. Failure to do so within the specified period of time may result in the Committee **refusing to register** the product.

In summary: Applications for which the applicant has failed to submit the requested additional data will be refused registration. Applications which have been open for **one calendar year** (12 months) from date of receipt due to the applicant's failure to address registration requirements specified in this guideline, the MC8 form, Medicines and Allied Substances Control (General) Regulations, Statutory Instrument 150 of 1991 ("the Regulations") and the Medicines and Allied Substances Control Act (Chapter 15:03) ("the Act") will be refused registration.

2.1 MODULE 1: ADMINISTRATIVE INFORMATION

2.1.1 COVER LETTER

The covering letter submitted with the application for registration should include a clear statement by the responsible person submitting the dossier, indicating the contact details (telephone number, e-mail, and fax) of the person to whom all correspondences should be addressed.

2.1.2 TABLE OF CONTENTS

A Table of Contents for the filed product dossier should be provided with corresponding page numbers.

2.1.3 A COMPLETED AND SIGNED MC8 FORM (SEE ANNEXURE 1)

A completed, signed and dated MC8 form should be submitted for each FPP. A copy of the form can be obtained from the MCAZ website: www.mcaz.co.zw. For clarity, the following considerations apply in determining whether the FPP requires one or separate applications

a) Tablets/Capsules/Suppositories/Lozenges:
   i) Different pack-sizes of the same strength and formulation will require one application
   ii) Different strengths and/or formulations will require separate applications.
b) Syrups/Elixirs/Liquids/Solutions (non parenterals)/Creams/ointments
   i) Different container sizes of the same strength and formulation will require one application
   ii) Same container size of different strengths and/or formulations will require separate applications.
c) Ampoules, Vials and Large Volume Parenterals
   i) Ampoules containing identical solutions of the same strength but of different volumes will require one application
   ii) Ampoules containing solutions of different strengths will require separate applications;
   iii) Ampoules and/or single dose vials containing dry powder, crystals etc., of different mass will require separate applications;
   iv) Dry powders or crystals etc. of the same respective mass, packaged in ampoules and single dose vials will require separate applications;
   v) Ampoules, single dose vials, as well as disposable syringes and cartridges containing identical solutions of the same strength and same volume of liquid will require one application;
   vi) Dental cartridges containing fluids of different volumes will require one application;
   vii) Ampoules containing "water for injection", but of different volumes will require one application;
   viii) Special ampoules of dry powder and "water for injections" contained in the same unit, but intended for mixing at the time of injection, will require one application;
   ix) Ampoules containing identical solutions of different volumes used only as a diluent in the reconstitution of a preparation for parenteral use will require separate applications;
   x) Multi-dose vials of the same strength and formulation in different volumes will require separate applications;
   xi) Multi-dose vials and a single dose ampoule of the same formulation will require

separate applications;

xii) Multi-dose vials containing dry powder of different masses and the same formulation, and having the same concentration when reconstituted will require one application;

xiii) A container of diluent to be used with any preparation in (iii), (iv) or (xii) will require one application provided that the diluent is also fully described in the dossier together with the product;

xiv) An ampoule of diluent to be used with any biological preparation will require one application;

xv) Infusion solutions of the same or different volumes and of the same formulation, which are packed in containers of exactly the same type of material, will require one application;

xvi) Infusion solutions of the same or different volumes and of the same formulation, which are packed in containers made of different types of materials, will require separate applications;

xvii) A preparation, packed in plastic containers and intended also to be marketed in glass containers containing the same volume and the same formulation, will require one application provided the following data are submitted: -
- Characteristics of the rubber stopper;
- Specifications for the glass;
- A comprehensive manufacturing process with particular reference to the washing and sterilization cycles and apparatus used;
- Data on particulate matter (contamination);
- Stability data with reference to the effect of the pH of the solution.

xviii) Products with the same strength and formulation but with different colours and/or flavours will require separate applications;

xix) Applications containing the same active ingredient(s), and where additional indications are sought, where such new indications render the product in a different category of distribution (scheduling status), or different pharmacological classification or have any other restrictions imposed other than the original application, will require separate registration.

d) Different applicants/proprietary names for the same formula;

i) Same formula applied under different proprietary names will require separate applications.

ii) Same formula from different applicants will require separate applications.

2.1.4 DECLARATION BY THE APPLICANT

A declaration should be made by the applicant or a responsible person nominated by the applicant and who must have the requisite skills and necessary qualifications. It is stressed that only a person who can attest to the accuracy of the contents in the application should sign on behalf of the applicant. False / misleading declarations will lead to prosecution.

Failure to make the declaration will lead to the rejection of the application.

2.1.5 SCREENING CHECKLIST

A screening checklist in Annex II should be completed by the applicant. The Authority will assess the application for completeness upon submission before it is accepted for evaluation by MCAZ. Incomplete applications will be rejected and the applicant requested to submit a

complete application. The Authority may charge a re-submission fee for products that fail screening.

2.1.6 PROOF OF PAYMENT OF APPROPRIATE FEES

A copy of the invoice or proof of payment of registration fees should be attached to the application for registration. Applicants should consult the current fee schedule for the correct and appropriate fee. Note that registration fees can be split into three main tiers, depending on the site of manufacture of the FPP. Fees for products wholly manufactured outside Zimbabwe attract a different fee from products wholly or partly (e.g. re-labelled and re-packaged) manufactured in Zimbabwe. All fees are payable according to the gazetted fee schedule Unless the full application fee is received, the application will not be accepted.

Applicants can remit payment of fees in cash, bank draft, telegraphic transfers and direct deposit into the Authority account. Please note that direct transfers usually attract a commission charged by the banks leading to a shortfall in fees. Provision should, therefore, be made to cover such shortfalls.
Applicants are further advised to specify very clearly in their instructions to the bank that such direct deposits are for application for registration of a medicine to avoid unnecessary delays.

Note that the application fee covers the cost of evaluating the initial submission and a single laboratory analysis of the product sample. Samples that require repeat analysis after failure of the first analysis, or as a result of modification or revalidation of the analytical method, attract an additional re-analysis fee. Any amendments to the original submission will attract amendment fees according to the gazetted fee schedule. The application fee excludes the GMP inspection fees, for which a separate charge is applicable.

Fees once received are not refundable, including those for rejected applications or voluntary withdrawals by the applicant.

2.1.7 MANUFACTURING AND MARKETING AUTHORIZATION(S) / INTERNATIONAL REGISTRATION STATUS

List the countries in which:
• the FPP (or set of FPPs) has been granted a marketing authorisation;
• the FPP (or one or more of the set of FPPs) has been withdrawn from the market; and
• an application for the marketing of the FPP (or one or more of the set of FPPs) has been rejected, deferred or withdrawn

The details of registration in the country of origin are required. Reasons for non-registration should be stated if the medicine is not registered in the country of origin.
Registration status in the country of manufacture should be indicated including any withdrawal, cancellations, suspension / revocations. The reasons for these should also be indicated.

2.1.8 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC) AND PACKAGE INSERT

Copies of all package inserts and any information intended for distribution with the product to the patient should be submitted. These should be written in English, be legible and comprehensible.

The Authority will determine the appropriate category for distribution of a medicine as set out in the sixth schedule of the Medicines and Allied Substances Control Regulations (Statutory Instrument 150 of 1991).

The categories are:
a) Narcotic Medicines or Dangerous Drug (abbreviated as "N") – products containing ingredients stated as such in the legislation and which may be subject to control by the International Narcotics Board.
b) Prescription Preparations (P.P Vet) – medicines belonging to this category are available on prescription only
c) Household Remedies (H.R Vet) - Medicines in this category are available in pharmacies, dispensaries and all licensed trade supermarkets.
d) Veterinary Medicines (General Dealer) (V.M.G.D.) – veterinary medicines in this category are available in all licensed shops.

Name of product
Trade name of product should be provided. The proposed proprietary name of the product should not infringe on the INN stem. It should not imply superiority over other products. It should not be the same or similar to the name of another medicine so as to cause confusion.

Name of Active Substance(s)/API
[use International Non-proprietary Name (INN), if any], dosage form and strength of the product The English INN of all the active ingredients, Dosage form and the strength in the formulation should be given.

Target Species
Applicant should indicate target species for which the medicine is intended.

Visual description of the FPP
E.g., round / oval / capsule (indicate dimensions), flat face / (shallow, or standard, or deep) convex / modified ball, flat edge / bevel edge, white, scored, film-coated tablets engraved (debossed) / embossed with XX on one side and Y to the left and 7 to the right of the score on the other side; Bi-layer tablets.

Description of pack sizes and pack type
Visual description of the pack sizes and pack types.

Primary packing materials
Primary packaging components are those that are in direct contact with the API or FPP. The specifications for the primary packaging components should be provided and should include a specific test for identification (e.g. IR). Copies of the labels applied on the secondary packaging of the API should be provided and should include the conditions of storage. In

addition, the name and address of the manufacturer of the API should be stated on the container, regardless of whether relabeling is conducted at any stage during the API distribution process.

The material of construction of the immediate container should be stated ('Type I glass vials', 'PVC/Aluminium blisters', 'HDPE bottles'); and any other component of the product should be listed, e.g., needles, swabs, measuring spoons, inhaler devices, desiccants, and so on. The container of any solvent provided with the medicinal product should also be described.

Secondary packing
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 API, including sorption to container and leaching, and/or safety of materials of construction.

The WHO *Guidelines on packaging for pharmaceutical products* (WHO Technical Report Series, No. 902, Annex 9, 2002) and the officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for APIs.

Sample
Provide a sample of the FPP(s) to enable visual inspection of the FPP(s). The quantity of samples submitted to the Authority for laboratory analysis should be, in general, twice the amount that is normally required for carrying out the full finished product analytical tests by the applicant`s own quality control laboratory.
This amount will enable the Authority to conduct the full finished product analytical tests and any repeat testing, if required. Applicants are referred to the MCAZ guide on number of samples required for laboratory analysis, which is appended to this guideline (Annex II)

Details of applicant
The name and addresses (physical and postal) for applicant, including email, fax, telephone numbers.

Details of Manufacturer(s) of the FPP
The name and addresses (physical and postal) for all the manufactures involved in the manufacture of the product are to be indicated. The steps of manufacturing process performed should also be indicated for each site. The details of any contract company used at development of the formulation, bioavailability or bioequivalence trials should be indicated.

Source (manufacturers) of Active Pharmaceutical Ingredient(s) (API)
The name and addresses (physical and postal) of manufacturer(s) of the API should be indicated.

Route of administration
The route of administration e.g. oral, IM injection, rectal, should be indicated

Container, closure and administration devices
The type(s) of the container/closure and administration devices should be stated.

Shelf life
The proposed shelf life of each dosage form in each of the different package type(s) and sizes should be stated.
• the shelf life after first opening of container should be indicated.
• the shelf life after reconstitution should be indicated

Storage conditions
The conditions under which the finished packaged product should be stored, e.g. store in a cool dark place below 25°C, should be stated.

Proposed indications
The uses for which the medicine is being registered should be indicated

Withdrawal periods
The applicants should state the withdrawal periods supported by experimental data. The withdrawal periods should be comparable with that of the reference product (for milk refer as the Withholding Time) this is the length of time that must elapse after treating an animal with a drug before the animal or its products can be marketed. Withdrawal Period/Withholding Time varies for different drugs, reflecting the amount of time needed for an animal to metabolize that drug and for the drug's concentration level in the animal tissue or product to decrease to a safe, acceptable level.

2.1.9 LABELLING

All labels of the test product should be the same as the reference product labelled claims and instructions. Fewer or reduced claims (partial labels) compared to the reference product may be acceptable as long as the partial claim does not raise any potential safety, efficacy, and human safety concerns for the MCAZ. The applicant is requested to submit the most recent English versions of all the reference product labels (inner and outer labels and package inserts) along with the proposed English draft labels [hard copy and electronic format (if available)].

The label of the primary container for each pharmaceutical and vaccine products shall meet the WHO Good Manufacturing Practices: Main Principles for
Pharmaceutical Products, (WHO Technical Report Series, No. 908, 2003)

The W210 GMP standard and include:

- The international non-proprietary name (INN) or generic name prominently displayed and above the brand name, where a brand name has been given. Brand names should not be bolder or larger than the generic name;
- Dosage form, e.g. tablet, ampoule, etc.;
- The active ingredient "per unit, dose, tablet or capsule, etc."
- The applicable pharmacopoeia standard;
- The manufacturer's logo and code number and any specific colour coding if required;
- Content per pack;

- Instructions for use;
- Special storage requirements;
- Batch number;
- Date of manufacture and date of expiry (in clear English language, not code);
- Name and address of manufacture;
- Category for distribution; and
- Any additional cautionary statement.

The outer case or carton should also display the above information.

- All cases should prominently indicate the following:
- Manufacturer's line and code numbers;
- The generic name of the product;
- The dosage form (tablet, ampoule, syrup);
- Date of manufacture and expiry (in clear English language not code);
- Batch number;
- Quantity per case;
- Special instructions for storage;
- Name and address of manufacture; and
- Any additional cautionary statements.

MODULE 2

MODULE 2.1: QUALITY OVERALL SUMMARY – PRODUCT DOSSIERS (QOS-PD)

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD. The QOS should include sufficient information from each section to provide the Quality assessor with an overview of Module 3. The QOS should also emphasise critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed.

The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g., qualification of impurities via toxicological studies), including cross-referencing to volume and page numbers in other Modules.

The MCAZ Quality Overall Summary – Product Dossiers (QOS-PD) template should be completed for multisource pharmaceutical products containing APIs of synthetic or semisynthetic origin and their corresponding FPPs. All sections and fields in the QOS-PD template that would be applicable should be completed.

It is understood that certain sections and fields may not apply and should be indicated as such by reporting “not applicable” in the appropriate area with an accompanying explanatory note.

The use of tables to summarise the information is encouraged, where possible. The tables included in the template may need to be expanded or duplicated (e.g. for multiple strengths), as necessary. These tables are included as illustrative examples of how to summarise information. Other approaches to summarise the information can be used if they fulfil the same purpose.

MODULE 2.2: QUALITY INFORMATION SUMMARY (QIS)

The QIS template should be completed to provide a condensed summary of the key quality information for the PD and constitutes part of the submission package. The QIS provides an accurate record of technical data in the PD. The QIS is a condensed version of the QOS-PD and represents the final agreed upon key API and FPP information from the PD assessment (inter alia identification of the manufacturer[s]/site addresses API/FPP specifications, stability conclusions and relevant commitments).

The QIS template is structured according to the numbering and section headings of the ICH M4Q (CTD-Q) guideline to permit the rapid assembly of the QIS by copying requisite information from the corresponding portions of the QOS-PD filed with the PD. It is acknowledged that the numbering of the sections in the QIS may not be entirely sequential. Those sections not considered necessary to be included in the QIS have been removed (e.g.

The QIS will serve as an official reference document in the course of GMP inspections, variation assessments and re-registration assessments as performed by MCAZ.

3.1 MODULE 3: QUALITY

Table of contents of Module 3

A Table of Contents for the filed product dossier should be provided.

Medicine substance (or active pharmaceutical ingredient (API)) Active pharmaceutical ingredient

Particulars under this section are required for products containing the following:-
i. New medicine substances or combination of new medicine substances.
ii. New medicine substances in combination with well-established ingredients.
iii. Products containing little known ingredients or non-pharmacopoeia substances poorly documented in literature.
iv. Products containing pharmacopoeia substances when there is reason to doubt the validity of specifications i.e. when obtained from a new source using different method of manufacture/synthesis.

The API information can be submitted to MCAZ in one of the following two options:
Option 1: Certificate of Suitability of the European Pharmacopoeia (CEP), including all its annexes;

Option2: Full details in the PD.
The applicant should clearly indicate at the beginning of the API section (in the PD and in the MCAZ QOS) how the information on the API for each API manufacturer is being submitted. The API information submitted by the applicant/FPP manufacturer should include the following for each of the options used.

• ***Option 1: Certificates of Suitability of the European Pharmacopoeia (CEP)***
A complete copy of the CEP (including any annexes) should be provided in *Module 1.* The declaration of access for the CEP should be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the MCAZ. In addition, a written commitment should be included that the applicant will inform MCAZ in the event that the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP will require additional consideration of the API data requirements to support the PD. The written commitment should accompany the copy of the CEP in *Module 1*.

Along with the CEP, the applicant should supply the following information in the dossier, with data summarised in the MCAZ QOS.

- *3.2.S.1 General information* - discussions on any additional, applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubility and polymorphs as per guidance in this section.
- *3.2.S.3.1 Elucidation of structure and other characteristics* - studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section.
- *3.2.S.4.1 Specification* - the specifications of the FPP manufacturer, including all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.

- *3.2. S.4.2 / 3.2.S.4.3 Analytical procedures and validation* – for any tests in addition to those in the CEP and Ph.Eur. monograph.
- *3.2. S.4.4 Batch analysis* - results from three batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
- *3.2. S.6 Container closure system* - specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a retest period.
- *3.2. S.7 Stability* - exception: where the CEP specifies a retest period that is the same as or of longer duration than the retest period proposed by the applicant.

In the case of sterile APIs, it should be noted that sterilization of the API is generally regarded by the MCAZ as part of finished product manufacture. Therefore data on the sterilization process of the API, including validation data, should be included in the application for registration.

• ***Option 2: Full details in the PD***

Information on the *3.2.S. Active pharmaceutical ingredient* sections, including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the application file as outlined in the subsequent sections of this guideline.

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

The applicant should provide information on the nomenclature of the drug substance, including, if available

- Recommended International Non-proprietary Name (INN);
- Compendial name, if relevant;
- Chemical name or names;
- Company or laboratory code;
- Other non-proprietary names, such as the United States Adopted Name (USAN) and the British Approved Name (BAN); and
- Chemical Abstracts Service (CAS) registry number.

3.2.S.1.2 Chemical Structure

The applicant should provide the structural formula, including relative and absolute stereochemistry including geometric isomerism or a mixture of isomers, the molecular formula, and the relative molecular mass. For drug substances existing as salts or hydrates, the applicant should submit data to demonstrate compliance to the policy on Interpretation of "Identical Medicinal Ingredient."

3.2.S.1.3 Physicochemical Properties

The applicant should provide data on the physicochemical and other relevant properties of the drug substance, such as physical description, solubility in common solvents (e.g., water, alcohols, chloroform, acetone,), quantitative aqueous pH solubility profile (e.g., pH 1 to 8, dose/solubility volume), polymorphism, particle size distribution, pH and pKa values, ultraviolet (UV) absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, and partition coefficient. The following paragraphs discuss in greater detail some of the more important properties to be considered for all drug substances.

3.2.S.1.4 Physical Description

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

3.2.S.1.5 Solubility/Quantitative Aqueous pH Solubility Profile

Applicants should consider generating data that is specific to the target species. The physiological pH range may differ from species to species. Data should be relevant to demonstrating an understanding of the *in-vivo* performance of the drug product as it relates only to the quality attributes. The submission should provide solubility for a number of common solvents (e.g., water, alcohols, chloroform, acetone). The solubility over the physiological pH range (pH 1 to 8) in several buffered media should also be provided expressing the results in mg/mL. If this information is not readily available from the literature or from the open part of the DMF, it should be generated in-house. With respect to the target species, the submissions should provide the dose/solubility volume if the drug product is in solid oral dosage form. The dose/solubility volume is calculated based on the lowest aqueous media solubility of the drug in mg/mL, determined over the physiological pH range at a temperature of 37±1°C for the highest dosage strength of the product.

3.2.S.1.6 Polymorphs

Generally, polymorphism is not a concern for drug substances that are considered to be highly soluble under aqueous conditions or that are present in solution in the drug product. Information on the potential for polymorphism can often be obtained from the literature. If the polymorphic form has the potential to affect product performance in the targeted species, the submission should include data from a test in the drug substance specifications that were established from the characterization of the lot of drug substance used in the manufacturing of the drug product intended for the bioequivalence studies.

3.2.S.1.7 Particle Size Distribution

Generally, particle size distribution is not a concern if the drug product is a solution or if the drug substance is dissolved during the drug product manufacturing process such as wet granulation or is considered to be highly soluble in water. Furthermore, if the manufacturing process of the drug product includes a compaction step that alters the dimensions of the particle size, then analysis for the drug substance is not required provided a justification is presented in developmental pharmaceutics. Particle size distribution of poorly soluble drugs may affect *in vitro* and *in vivo* performance of the drug product. Although particle size distribution may be important for other reasons related to drug product manufacture and performance such as content uniformity, the most important regulatory concern relates to its possible impact on dissolution and bioavailability. For poorly soluble drugs, the submission should appropriately characterize the particle size distribution of batches used in comparative clinical or bioavailability studies and include a test in the drug substance specification that ensures that commercial batches match the batch or batches used in the comparative studies. If a particle size distribution test is included in the drug substance specification, it is recommended that limits be set for d_{10}, d_{50}, and d_{90}. The following formulae are provided for illustrative purposes as possible acceptance criteria for particle size limits:

- d10: NMT 10% of total volume less than X µm
- d50: XX µm - XXX µm
- d90: NLT 90% of total volume less than XXXX µm

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturers

The submission should provide the name, address, and responsibility of each manufacturer, including contract manufacturers or testing sites, involved in the manufacturing, packaging, labelling, and testing of the drug substance. The addresses provided should be for the site where the activity takes place, rather than for the administrative offices. The list of manufacturers/companies should specify the *actual addresses* of production or manufacturing site(s) involved (including block(s) and units(s)), rather than the administrative offices. Telephone number(s), fax number(s) and e-mail address (es) should be provided.

A valid manufacturing authorisation (license) should be provided for the production of APIs. A certificate of GMP compliance in the format of a WHO-type GMP certificate from the competent authority of the country of manufacture should be provided in the PD in Module 1.

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

The submission should provide a flow diagram or diagrams of the synthetic process or processes. The diagrams should include the chemical structures of starting materials, intermediates, and drug substance reflecting stereochemistry and also include reagents, solvents, and operating conditions. The submission should provide a narrative description of the manufacturing process. The narrative should include quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, and all process controls, equipment, and operating conditions (e.g., temperature, pressure, pH, time). If a cross referenced DMF includes a detailed description of the manufacturing process, the applicant need only to include a brief summary of the manufacturing process including a flow diagram representing the route of synthesis in the submission. The manufacturing process should start from commercially available or well characterized starting materials.

For sterile drug substances, the submission should include a complete description of the method of sterilization and the controls used to maintain sterility during storage and shipping. For drug substances produced by fermentation, the submission should contain additional information, including source and type of micro-organisms used, precursors, composition of media, details on how the reaction conditions are controlled (e.g., times, temperatures, rates of aeration), and name and composition of preservatives. For drug substances of plant origin, the submission should include a description of the botanical species and the part of plant used, the geographical origin, and the time of year of harvest, when relevant. The submissions should record the nature of chemical fertilizers, pesticides, fungicides, and so on, if these have been employed during cultivation. It may be necessary to include in the drug substance specification limits for residues resulting from such treatments. The submission may also have to confirm the absence of toxic metals and radioactivity.

3.2.S.2.3 Control of Materials

The submissions should list materials such as starting materials, solvents, reagents, and catalysts used in the manufacture of the drug substance, including the synthesis, fermentation, extraction, isolation, and purification steps, and identify where each material is used in the process. The submission should provide copies of the specifications for each of these materials and the specifications should meet the standards appropriate for their intended use.

The submission should evaluate drug substances of animal origin as to the likelihood of the presence of Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE) agents. Additionally, for any material of animal origin used in the manufacture of the drug substance, the submission should provide information in accordance with the most stringent requirements set out in compendial monographs e.g., United States Pharmacopoeia [USP], European Pharmacopoeia [PhEur], The British Pharmacopoeia [BP], International Pharmacopoeia [Int.Ph] and Japanese Pharmacopoeia [JP].

3.2.S.2.4 Controls of Critical Steps and Isolated Intermediates

The submission should provide information on the tests, including acceptance criteria and justification, performed at critical steps of the manufacturing process to ensure that the process is properly controlled. The submission should also include specifications for isolated intermediates, including tests and acceptance criteria for identity, purity, and potency, where applicable.

3.2.S.2.5 Process Validation and Evaluation

The submission should include process validation or evaluation studies or both for drug substances produced using aseptic processing or sterilization.

3.S.3 Characterisation

3.S.3.1 Structure Elucidation and Confirmation

For generic drugs, it is generally sufficient for the submission to provide copies of the infrared (IR) and UV spectra of the drug substance from the proposed supplier's run in coordination with a suitable reference standard. A suitable primary reference standard could be obtained from the compendia (e.g., USP, Ph.Eur, BP, JP and Int.Ph.). In the case where a compendial monograph does not exist, a batch of the drug substance should be fully characterized (e.g., IR, UV, nuclear magnetic resonance [NMR], mass spectra [MS], etc.). When a drug substance is chiral, the submission should specify whether specific stereoisomers or a mixture of stereoisomers have been used in the bioequivalence studies, and the submission should include information as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing**.**

3.2.S.3.2 Impurities

The submission should include a discussion of potential impurities arising from the method of manufacture. The discussion should place particular emphasis on possible impurities arising from a method of manufacture that differs from that used to produce the compendial material. Applicants should consider drug-related impurities, such as starting materials, intermediates, by-products, and degradation products, and process-related impurities, such as solvents, catalysts, and reagents.

The submission should include a table that for each potential impurity lists the name, chemical structure, and origin (e.g., synthetic intermediate, by-product, residual solvent from crystallization step). The submission should provide actual impurities found in batches tested and include quantitative results, or indicate that the impurities are below the limit of quantitation (LOQ) or not detected. The impurity profile of the drug substance batches should be compared with the impurity profile of the Reference Product (RP). If the generic drug

substance contains impurities not present in the RP or in compendium, or contains impurities at higher levels found in the RP, it may be necessary to qualify the limits for these impurities.

Unidentified impurities that are specified by relative retention time (RRT) at a limit greater than 0.2% require qualification, as do identified impurities at a limit greater than 0.5%. VICH limits of no more than (NMT) 0.2% for unspecified impurities apply, rather than the general limits for unspecified impurities that appear in the compendial monograph, unless the compendial limits are more stringent. It is possible that there are specified impurities in the compendial monograph that are not likely to be present in the generic product due to a different method of synthesis. Appropriate justification should be provided for their exclusion from the submission.

Some latitude may be appropriate for drug substances of semi-synthetic origin such as those obtained from chemical modification of a precursor molecule of plant or animal origin, or derived from a fermentation process. A limit of NMT 0.5% for unspecified impurities would generally be considered appropriate. If there is a need to qualify a limit for a specified impurity, there are two possible approaches. The first approach is to use the RP for comparative purposes, while the second approach is to use the VICH guideline, “Impurities in New Drug Substances” (VICH GL 10), Attachment II, “Decision Tree for Safety Studies.” The RP approach is possible only if the impurity appears in the RP at levels that exceed the VICH qualification threshold. It is recommended that a minimum of three batches of the RP be selected for analysis using the same validated analytical procedure used to test the generic product. It is also recommended that the batches selected for analysis be close to but not past the expiry date for the RP. It is not acceptable to expose these batches to accelerated or stressed storage conditions before testing. The proposed limit for the impurity in the generic product is considered qualified if supported by the levels of the same impurity found in the batches of the RP. Impurities that are also significant metabolites present in animal or human studies are generally considered qualified.

Impurities classified as residual solvents must conform to the levels specified in the VICH guideline, “Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances and Excipients” (VICH GL 18).

Note: Solvents such as benzene and chloroform will not be tolerated. In the absence of limits under VICH GL 18, limits recommended in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline, “Impurities: Guideline for Residual Solvents” (ICH Q3C), would be considered acceptable without further justification. The submission should justify solvent levels exceeding the VICH GL 18 or ICH Q3C limits, on a case-by-case basis, and provide supporting data. Supporting data could be based upon concepts of qualification outlined in the VICH and ICH impurity guidelines.

3.2.S.4 Control of the Drug Substance

3.2.S.4.1 API Specifications

The submission should contain a copy of the drug substance specification from the manufacturer responsible for release testing. The person in charge of quality control at the responsible company should sign and include the date for the specification in accordance with the Good Manufacturing Practice (GMP) guidelines. The submission should provide the specification reference number, version, and date for version control purposes.
Although the drug substance specification will normally include tests for appearance, identity, potency, and purity, additional tests (e.g., for particle size distribution, crystal form determination [polymorphism], chirality, bacterial endotoxins, etc.) will be required depending on the characteristics of the drug substance and its end use (e.g., oral, parenteral).
Reference documents VICH guidelines: *VICH GL4 and VICH GL 39.*

3.2.S.4.2 Analytical Procedures

The submission should contain copies of the analytical procedures used for testing the drug substance. It is not necessary to provide copies of compendial analytical procedures unless the procedures are modified. High performance liquid chromatography (HPLC) is normally considered the method of choice for determining drug-related impurities, and some other chromatographic methods such as gas chromatography (GC) or thin layer chromatography (TLC) may also be used, if appropriate. For impurity methods, it is recommended that the applicant prepare reference standards for each of the identified impurities, particularly those known to be toxic, and the concentration of the impurities quantified against their own reference standards. It is considered acceptable, however, to use the drug substance as an external standard or to use area normalization to estimate the levels of impurities, provided the response factors of those impurities are sufficiently close to that of the drug substance (e.g., 80% or more). In cases where the response factor is not close, a correction factor should be applied. Chromatographic analytical procedures should include system suitability testing (SST) and depending on the method should include tests such as accuracy, specificity, precision, tailing factor, and sensitivity. For greater understanding of the details, definitions, and design of system suitability testing, applicants should refer to the USP, General Chapter <621> Chromatography, which is found in the annual publication of the USP monographs.

3.2.S.4.3 Validation of Analytical Procedures

The submission should contain copies of validation reports for the analytical procedures proposed for release and shelf-life testing of the drug substance. The reports should include the interpretations of the test results. Depending on the method, the parameters to be examined might include accuracy, precision, specificity, linearity, detection limit, quantitation limit, and ruggedness. Further guidance regarding the validation of analytical procedures is available in VICH guidelines, "**Validation of Analytical Procedures: Definition and Terminology**" *(VICH GL 1)* and "**Validation of Analytical Procedures: Methodology**" *(VICH GL 2).* If a compendial method is used for the determination of impurities in a drug substance and the drug substance is manufactured by a method that differs from the method used to obtain the compendial material (i.e., different specified impurities), validation of the method with respect to impurities not present in compendial material is required. If a house method is developed for potency or impurity determination to replace a compendial method, validation data are required, as well as comparative data obtained using the two methods.

3.2.S.4.4 Batch Analysis

The submission should contain descriptions, including batch number, batch size, date and site of manufacture, type of study (bioequivalence and stability), and analytical results, for at least two batches from each site of manufacture. The data should be generated by the company responsible for release testing and should include certificates of analysis. The submission should provide quantitative results for all quantitative tests (e.g., potency, impurities, and loss on drying). A statement such as "within limits" or "complies" is not considered acceptable for a quantitative test.

3.2.S.4.5 Justification of Specification

The justification of the specification should include the rationale for the inclusion or the exclusion of tests, discussion of the development of methods and acceptance criteria, and the rationale for differences from compendial tests, methods, or acceptance criteria. Certain specific tests on the drug substance may be justified by the manufacturing process of the drug product that was realized during developmental pharmaceutics such as particle size determination or other unique physicochemical property. The justification for certain tests, analytical procedures, or acceptance criteria may have been discussed in other sections of the submission and cross-references to those sections are sufficient for the justification of the specification.

3.2.S.5 Reference standards

The submission should provide the sources of reference standards or materials used to test the drug substance. Primary reference standards obtained from official sources such as the compendia do not need further characterization. The submission should fully characterize and structurally elucidate any other primary standard (e.g., IR, UV, NMR, MS, etc.). The submissions can use a secondary or in-house reference standard by providing a copy of its certificate of analysis and validating it against a suitable primary reference standard. The submission should provide copies of the IR and UV spectra of the secondary and primary reference standards run concomitantly. The submission should provide a brief description of the manufacturing process of the secondary reference standard, if it differs from thecommercial process for the drug substance.

3.2.S.6 Container Closure System

The submission should provide a description of the container closure system or systems, including the identity of materials used for the primary packaging components with a brief description of the secondary packaging, if warranted. The choice of packaging materials should be based on protecting the drug substance from light and moisture, as well as the compatibility of the materials with the drug substance. Specifications for packaging materials should be relevant and include an identification test for the packaging materials that are in contact with the drug substance.

3.2.S.7 Stability

The applicant should conduct stability studies, including stress, accelerated, and long-term stability studies, on the drug substance to establish appropriate packaging and storage conditions, and the re-test period. The applicant should include the protocols used for the studies and the results obtained.

3.2.S.7.1 Forced Degradation (Stress) Studies

The results of stress testing provide information on the intrinsic stability of the drug substance, potential degradation pathways, likely degradation products, and the stability indicating power of the analytical procedures. Stress testing is normally carried out on one batch of the drug substance and generally includes the effect of heat, humidity, light, oxidation, and acid/base hydrolysis. The submissions should present the results in tabular form, including treatment conditions and quantitative results, which are normally assay and degradation products.

Note: If information on stress testing is available in the public domain (Literature), it may not be necessary to repeat the testing.

3.2.S.7.2.1 Accelerated and Long-term Studies

The submission should provide results of stability studies on a minimum of three batches of the drug substance stored at accelerated and long-term conditions. At the time of submission of the application for registration to MCAZ, studies for a minimum of six months at each condition are required. The accelerated and long-term studies should be conducted at 40°C ± 2°C / 75% ± 5% relative humidity (RH) and 30°C ±2°C / 65% ± 5% RH respectively. Information on the stability lots/batches should include date of manufacture, batch number and size, packaging, storage conditions, test intervals completed and to be completed, tests performed with acceptance criteria, and description and validation of analytical procedures, if different from those described in Subsection 3.2.S.4.2. The submission should present the results in tabular form, including quantitative results for all quantitative tests. The submission should provide a discussion of the results and the conclusions reached.

3.2.S.7.2.2 Drug substances intended for storage in a refrigerator

Study	Storage Conditions	Minimum time period covered by data at submission
Long Term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

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 re-test period should be based on the real-time data available at the long-term storage condition.

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 shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance for a period shorter than 3 months but with more frequent testing than usual. It is considered

unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

3.2.S.7.2.3 Drug substances intended for storage in a freezer

Study	Storage Conditions	Minimum time period covered by data at submission
Long Term	5°C ± 3°C	12 months

For drug substances intended for storage in a freezer, the re-test period should be based on the real-time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug substances 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, e.g., during shipping or handling.

3.2.S.7.2.4 Drug substances intended for storage below -20°C

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

3.2.S.7.3 Proposed Storage Conditions and Re-test Period

The submission should provide proposed storage conditions and re-test period for the drug substance, based on the results of the stability studies. For drug substances that are shown to be unstable, it is more appropriate to establish a shelf-life (expiry period) rather than a re-test period. In certain cases, information available in the public domain may be sufficient to establish an appropriate re-test period, for example when a substantial body of evidence exists that establishes that the drug substance is inherently stable.

Reference documents: *VICH GL3, GL4, GL5 and GL45. For all pre-medicated premixes and Biotechnological products refer to VICH GL8 and VICH GL17 respectively*.

3.2.P.1 FINISHED PHARMACEUTICAL PRODUCT

3.2.P.1 Description of the Drug Product

The submission should provide a detailed description of the drug product to be marketed in Zimbabwe, including the form in which it is to be sold, the strengths, appearance, type of container and closure system, proposed storage conditions, and expiration period. When applicable, the submission should also provide a description of the accompanying reconstitution diluent or diluents and their container and closure systems, and dosing devices

3.2.P.2 Pharmaceutical Development

The pharmaceutical development section of the submission should contain information on 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 studies to be described in this section are distinguished from routine control tests conducted according to specifications. Additionally, the sponsor should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance, and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached as a narrative to this section. Additional supportive data can be cross-referenced to the relevant sections as needed. Reference documents: EMEA/CVMP/315/98.

3.2.P.2.1 Formulation and Process Development

The submission should provide a brief summary describing the development of the drug product, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e., composition) described in Subsection 3.2.P.1 should be discussed. Results from comparative *in vitro* studies (e.g., dissolution) or comparative *in vivo* studies (e.g., bioequivalence) should also be discussed, when appropriate.

3.2.P.2.2 Physicochemical Characteristics of the Drug Substance

The discussion of the physicochemical characteristics of the drug substance should include the possible influence of the drug substance solubility, particle size distribution, crystal form, or any other characteristic on the performance of the drug product.

3.2.P.2.3 Compatibility

This section of the submission should include a discussion of the compatibility of the drug substance with each of the excipients of the optimized formulation that was used to support the bioequivalence studies. These studies can be avoided if the sponsor of the generic drug product uses the approach of qualitative and quantitative analysis in developing their formulation that translates to reproducing the formulation of the RP. If the applicant generates a formulation that does not comply with the approach of qualitative and quantitative analysis, then the applicant should submit complete compatibility studies. These studies should examine the interaction of the active pharmaceutical ingredient (API) with each individual excipient. For fixed dose combination medicinal products, the applicant should examine the interactions of API/API in combination with each excipient. Colour tests

through visual examination are considered to be insufficient and testing should consist of chromatographic methods.

3.2.P.2.4 Physicochemical Characteristics of the Drug Product Relevant to Performance

The submission should address physicochemical characteristics relevant to the performance of the drug product, such as pH, ionic strength, dissolution, dispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and immunological activity.

3.2.P.2.5 Microbiological Attributes

Where applicable, the submission should discuss the microbiological attributes of the dosage form, including the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the submission should address the integrity of the container closure system to prevent microbial contamination.

3.2.P.2.6 Container Closure System

The submission should discuss the suitability of the container closure system used for the storage, transportation, and use of the drug product. The discussion should consider choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug product (including sorption 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 drug product).

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturers

The submission should provide the name, address, and responsibility of all sites, including those contracted, involved in the manufacture, packaging, labelling, testing, importing, storage, and distribution of the drug product. The address provided should be for the site where the activity takes place rather than the administrative offices. The list of manufacturers/companies should specify the *actual addresses* of production or manufacturing site(s) involved (including block[s] and unit[s]), rather than the administrative offices.

A valid manufacturing authorisation for pharmaceutical production, as well as a marketing authorisation, should be submitted to demonstrate that the product is registered or licensed in accordance with national requirements in the country of origin or country of manufacture. For each site where the major production step(s) are carried out, when applicable, attach a WHOtype certificate of GMP issued by the competent authority in terms of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

3.2.P.3.2 Formulae

3.2.P.3.2.1 Unit Formula

Submission should provide the quantitative formula presented in tabular form, including for each component the amount on a per unit basis (e.g., mg/tablet, mg/mL) and percentage basis, the standard (e.g., USP, Ph.Eur., In-house, etc.), and the function (e.g., filler, binder, disintegrant, lubricant, etc.), as well as the total weight or volume. The components should be listed by their proper, common, or compendial names, and their grades should be indicated, if applicable. The submission should provide the quantitative composition, including the standard for each component, for proprietary items such as capsule shells, colouring blends, and flavours. The quantitative composition can be provided in a DMF, but the qualitative composition should be included in the submission. Alternatives or ranges for excipients are generally not accepted, but ranges may be accepted if supported by appropriate process validation data and, in extreme cases, comparative bioavailability studies.

Overages: All overages should be clearly indicated (e.g., "Contains 2% overage of the drug substance to compensate for manufacturing losses that are justified by process validation studies."). Any overage used to extend the shelf life of the drug product is considered to be unacceptable practice and will not be approved.

3.2.P.3.2.2 Batch Formula

The submission should provide the batch formula in tabular form for each proposed batch size, indicating the amount of each component on a per batch basis and the corresponding quality standard. The batch formula should include all components used in the manufacturing process regardless of whether the component appears in the final drug product (e.g., solvents, nitrogen, etc.). If the amount of active ingredient added to the batch formula does not correspond to the label claim (e.g., active ingredient added as a salt while label claim is as the base), the appropriate conversion factors should be indicated as a footnote to the table.
The following table provides an example of how to summarize unit and batch formulae as it relates to product development.

Table 1: Example Summary of Unit and Batch Formulae

Core tablets (components in Production technological order)	Unit		Clinical		Stability		Production	
	mg	%	mg	%	mg	%	mg	%
Active pharmaceutical ingredient	400.00	82.73	280.00	82.81	280.00	82.81	40.00	82.81
Maize starch	5.00	1.03	3.72	1.10	3.72	1.10	0.53	1.10
Micro Crystalline Cellulose (PH 302)	4.92	1.02	3.44	1.02	3.44	1.02	0.49	1.02
Povidone (PVPK-30)	20.00	4.14	14.00	4.14	14.00	4.14	0.20	4.14
Stearic acid	2.00	0.41	1.40	0.41	1.40	0.41	1.05	2.17
Maize starch	10.49	2.17	7.34	2.17	7.34	1.90	0.92	1.89
Micro Crystalline Cellulose (PH 302)	9.15	1.89	6.41	1.90	6.41	1.02	0.49	1.02
Sodium starch glycollate	4.92	1.02	3.44	1.02	3.44	1.04	0.50	1.04
Colloidal anhydrous silica	5.00	1.03	3.50	1.04	3.50	0.81	0.39	0.81

Purified Talc	3.92	0.81	2.74	0.81	2.74	0.95	0.46	0.95
Magnesium Stearate	4.60	0.95	3.22	0.95	3.22	0.95	0.46	0.95
Subtotal 1:	470.00	97.21	329.21	97.36	329.21	97.36	47.03	97.36
Film coating (components of two layers in technological order)								
Hypromellose (5 cps)	5.56	1.15	0.58	0.17	0.58	0.17	0.08	0.17
Ethyl Cellulose	0.13	0.03	0.14	0.04	0.14	0.04	0.02	0.04
Macrogol 6000	0.14	0.03	0.15	0.04	0.15	0.04	0.02	0.04
Purified Talc	0.19	0.04	0.20	0.06	5.26	0.06	0.03	0.06
Hypromellose (5 cps)	5.00	1.03	5.26	1.56	0.40	1.56	0.75	1.55
Purified Talc	0.38	0.08	0.40	0.12	0.40	0.12	0.06	0.12
Titanium dioxide	0.38	0.08	0.40	0.12	0.40	0.12	0.06	0.12
Macrogol 6000	1.72	0.36	1.80	0.53	1.80	0.53	0.26	0.53
Subtotal 2:	13.50	2.79	8.93	2.64	8.93	2.64	1.27	2.64
Grand total:	483.50	100.00	338.14	100.00	338.14	100.00	48.30	100.00

3.2.P.3.3 Manufacturing processes

The submission should provide a flow diagram showing each step of the process, where materials enter the process, and where samples are taken for in-process testing. The submission should also provide a narrative summary of the manufacturing process, including packaging and labelling describing the sequence of steps. The summary should include the amount of ingredient added at each step, the equipment type and capacity, process parameters such as mixing times and speeds, processing temperatures, and any precautions necessary to ensure product quality, such as control of humidity, temperature, light, and maximum hold times, where necessary. The in-process testing should be indicated and it is recommended that the testing be presented in tabular form, including the process step, test conducted, and acceptance criteria. All stages involved in the manufacture of the dosage form should be described. An example is provided below for manufacturer of a. tablet.

Stages:

1. Dispensing of ingredients
2. Mixing of ingredients
3. Moist granulation
4. Fluid bed drying at 60ºC
5. Rotatory punching etc.

3.2.P.3.4 Process Validation

Process validation should be conducted on all drug products, but the filing requirements differ depending on whether the drug product is sterile or nonsterile. It is normally expected that process validation for solid oral drug products be completed prior to the distribution of a finished product and after the issuance of a Registration Certificate that is intended to authorize the product for sale (prospective validation). Where this is not possible, as in the case of a new drug product recently marketed in other jurisdictions, it may be necessary to validate processes during routine production (concurrent validation). For long established processes and marketing in other jurisdiction that have been in use for some time without any significant changes, the process may also be validated according to an approved protocol (retrospective validation).

3.2.P.3.4.1 Sterile Products

For a sterile product, the submission should provide a copy of the process validation report, including **protocol** and **results**. The report should identify the critical steps, equipment, and process parameters that can affect the quality of the drug product, and define testing parameters, sampling plans, analytical procedures, and acceptance criteria. The drug product sterilization process should be validated. Since terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the drug product, if any other method of sterilization is selected, the submission should provide scientific justification for the selection. In addition to validating the drug product sterilization process, the submission should also provide reports on the validation of the processes for washing, treatment, sterilizing, and depyrogenating containers, closures, and equipment.

3.2.P.3.4.2 Non-sterile Products

For a non-sterile product, the submission should provide a copy of the process validation protocol, specific to the drug product. The protocol should identify the critical steps, equipment, and process parameters that can affect the quality of the drug product; define testing parameters, sampling plans, analytical procedures and acceptance criteria; and confirm that three consecutive production scale batches will be subjected to validation.
If process validation studies have already been completed, the submission should include a copy of the process validation report.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

The submission should provide specifications for all excipients, including those that do not appear in the drug product (e.g., solvents, nitrogen, silicon for stoppers, etc.), and these specifications should be relevant to ensure that the performance of the quality characteristics of the drug product are maintained. If the excipient complies with compendial monograph, it is acceptable for the submission to state that the excipient will be tested according to that standard. There is no need to reproduce the tests and acceptance criteria found in the standard. If the excipient is non-compendial or is compendial with additional tests or tighter limits, the submission should provide a copy of the specification. For oils of plant origin (e.g. soy bean oil, peanut oil) the absence of aflatoxins or biocides should be demonstrated.
The colours permitted for use are limited to those listed in the “Japanese pharmaceutical excipients”, the EU “List of permitted food colours”, and the FDA “Inactive ingredient guide”.

Annexure III contains ingredients which MCAZ has gazetted as undesirable in pharmaceutical preparations. Any applications containing such ingredients will be rejected.

3.2.P.4.2 Analytical Procedures and Validation

The submission should provide copies of analytical procedures and validation reports, where appropriate, for tests supplementary to those appearing in a compendial monograph, as well as for all tests in specifications form non-compendial excipients.

3.2.P.4.3 Justification of Specifications

The submission should provide justification for tests and acceptance criteria supplementary to those appearing in a compendial monograph, as well as for all tests in specifications for non-compendial excipients.

3.2.P.4.4 Excipients of Animal Origin

For excipients of animal origin, the submission should provide information concerning adventitious agents, including sources, specifications, and descriptions of the testing performed, and viral safety data. Or excipients obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE) or Transmissible Spongiform Encephalopathy (TSE) agents, the submission should provide a letter of attestation with supporting documentation.

3.2.P.4.5 Novel Excipients

For excipients used for the first time in a drug product or by a new route of administration, the submission should provide full details of the manufacture and characterization of the novel excipient, as well as information required in the previous four subsections. The submission should also include cross references to any supporting clinical safety data.

3.2.P.5 Control of FPP

3.2.P.5 .1 Finished product specifications

The submission should provide proposed regulatory specifications for release and shelf life testing. The specifications are a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. The specifications establish the criteria to which a drug product should conform to be considered acceptable for its intended use.

A copy of the drug product specifications from the FPP manufacturer should be provided, dated, and signed by authorized personnel (i.e., the person in charge of the quality control department). The submission should provide the specification reference number, version, and date for version control purposes. Consult *VICH GL39.*

Tests for product appearance, identity and assay of the medicinal ingredients, and determination of degradation products are standard for all dosage forms. The other tests to be included in the specification will depend on the dosage form and route of administration. Proposed limits for degradation products that exceed the VICH qualification threshold of 1.0% can be qualified by comparison with the RP as discussed in the VICH guideline, “Impurities in New Veterinary Medicinal Products” (*VICH GL 11*).

3.2.P.5 .2 Analytical Procedures

The submission should contain copies of analytical procedures proposed for testing the drug product. It is not necessary to provide copies of compendial analytical procedures unless the procedures are modified. Chromatographic analytical procedures should include system suitability testing (SST). For HPLC and GC procedures, the SST should include as a minimum, resolution and precision (minimum five replicates), but may also include tests such as number of theoretical plates and tailing factor. For TLC procedures, SST might include confirmation of sensitivity and component separation. For greater understanding of the

details, definitions, and design of SST, applicants should refer to the USP, General Chapter <621> Chromatography, which is found in the annual publication of the USP monographs.

3.2.P.5 .3 Validation of Analytical Procedures

The submission should provide copies of the validation reports for the analytical procedures proposed for testing the drug product. The reports should include the protocol used, the results obtained for each validation characteristic, interpretation and discussion of the results, and conclusions reached. The choice of characteristics to be validated should be consistent with the type of analytical procedure and intended purpose. Procedures drawn from compendial monographs normally require at least partial validation since the composition of the product used for validation of compendial procedures is likely to be different from the composition (sample matrix) of the generic product. If a house procedure is developed to replace a compendial procedure for assay or determination of degradation products, the house procedure should be fully validated and its equivalency to the compendial procedure demonstrated.

Further guidance regarding the validation of analytical procedures is available in VICH guidance documents [*VICH GL1, VICH GL2* and *VICH GL 49(analysis of tissue samples obtained in residue depletion studies*)].

3.2.P.5 .4 Batch Analysis

The submission should provide results of batch analyses, including certificates of analysis, for the batches used in batch anyses, as well as a minimum of two batches of each strength. The batch size should be at least 10% of full production scale. Bracketing and matrixing of proportional strengths can be applied. The batch number, size, and strength, as well as the date and site of manufacture should be included for each batch reported. The submission should supply quantitative results for quantitative tests. Content uniformity and dissolution results should include the mean, range, and relative standard deviation (RSD).

3.2.P.5 .5 Justification of Specification

The justification of the specification should include the rationale for the inclusion or the exclusion of tests, discussion of the development of methods and acceptance criteria, and the rationale for differences from compendial tests, methods, or acceptance criteria.

3.2.P.6 Reference Standards

The submission should provide the sources of reference standards or materials used to test the drug substance. Primary reference standards obtained from official sources such as the compendia do not need further characterization. The submission should fully characterize and structurally elucidate any other primary standard (e.g., IR, UV, NMR, MS, etc.).
The submissions can use a secondary or in-house reference standard by providing a copy of its certificate of analysis and validating it against a suitable primary reference standard. The submission should provide copies of the IR and UV spectra of the secondary and primary reference standards run concomitantly. The submission should provide a brief description of the manufacturing process of the secondary reference standard, if it differs from the commercial process for the drug substance.

3.2.P.7 Packaging/ Container closure system

3.2.P.7 .1 Description and Specifications

The submission should provide a description, including packaging materials and specifications, for each primary packaging component that comes into direct contact with the drug product and for functional secondary packaging components that act to protect the product or have a function in drug delivery. The tests to be included in the specification will depend on the packaging material, but would normally include a specific identity test such as IR, and tests related to performance such as thickness.

3.2.P.8 Stability

3.2.P.8.1 Accelerated and Long-term Studies (General Case)

The submission should include a stability protocol indicating storage conditions studied and providing information on accelerated and long-term conditions, time points at which samples are taken for analysis, and the tests to be conducted. Results should be provided for a minimum of three batches of each strength in each proposed container/closure system. Bracketing and matrixing can be applied if scientifically justified. For example, if the drug product has a common formulation (compressed to different tablet weights) for a number of strengths, then a minimum of one lot of each strength should be studied for stability. At the time of filing the product application, data covering a minimum of six months at the long-term and accelerated conditions should be included. Normally, 30°C ± 2°C / 65% ± 5% RH would be the long-term condition and 40°C ± 2°C / 75% ± 5% RH would be the accelerated condition (Zone IVB conditions). Frequency of testing for the long-term condition would normally be every three months.

Stability results should be presented in tabular form and include batch number, date of manufacture, batch size, container/closure, storage conditions, test intervals completed and proposed, and tests performed with acceptance criteria. If there is more than one packaging format, such a blisters and bottles, then each format should be studied. Analytical procedures that differ from those described in Subsection 3.2.P.5 .2 should be included along with appropriate validation data. All studies should report appearance, assay, and degradation products, while the other tests to be conducted will depend on the dosage form and route of administration. The submission should supply quantitative results for quantitative tests. Some tests, such as sterility, particulate matter, and bacterial endotoxins, need not be performed at every test interval. For drug products that require reconstitution or dilution, the submission should supply stability results to support the proposed storage periods of the reconstituted or diluted product. Drug products containing preservatives to prevent oxidation or microbial activity should be studied at time zero and at the end of the proposed shelf life to ensure protection of the drug product and the submission should include the results of these studies. Where the antimicrobial preservative lower assay limit is less than 90%, preservative effectiveness studies at the proposed lower limit for preservative content should be conducted.

3.2.P.8.1.1 Medicinal substances intended for storage in a refrigerator

Study	Storage Conditions	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. 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. 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.P.8.1.2 Medicinal substances intended for storage in a freezer

Study	Storage Conditions	Minimum time period covered by data at submission
Long Term	5°C ± 3°C	12 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.P.8.1.3 Medicinal substances intended for storage below -20°C

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

3.2.P.8 .2 Proposed Storage Conditions and Shelf-life

The submission should provide the proposed storage conditions and shelf-life of the drug product in each commercial container/closure system based on the results of the stability studies. The storage conditions will normally include a temperature storage instructions such as 'do not store above 30°C' and may include storage precautions such as "protect from light" or "protect from humidity," depending on the results of the stability studies.

3.2.P.8.3 Stability Commitment

When the available long-term stability data does not cover the proposed shelf-life, the submission should make a commitment to complete the studies to the proposed shelf-life. If these studies were not conducted on production scale batches, the submission should make a commitment to place two production scale batches of each strength on stability, along with the stability protocol. Bracketing and matrixing can be applied in the same manner as stated earlier, if scientifically justified. The submission should make a commitment to establish a continuing stability program of on-going studies for the product, along with a stability protocol.

3.2.8. Additional Information

Because premixes are not intended to be administered directly to animals, but are formulated for blending into feeds, there are certain special requirements for mixing and stability studies.

3.2.8. Stability of Medicated Feeds

The submission should provide the results from the study of at least two batches of medicated feed for three months at 30°C ± 2°C / 65% ± 5% RH and at 40°C ± 2°C / 75% ± 5% RH. Assay is the only test typically required. Testing should be carried out initially and then at one-month intervals. If the premix is to be incorporated at various concentrations into feed, stability studies, known as in-use studies, should be carried out at both the lowest and highest levels recommended. The applicant should perform assays on feed before and after pelletizing to determine the effects of pelletizing and include this data in the submission. These assays should be repeated at monthly intervals up to three months. If it is expected that pellet-binding agents will be used, then the three-month study should include at least one feed pelletized with and without the binding agents at the recommended use level.

3.2.8. Mixing Studies

Drugs in medicated feeds, although present in only small amounts, must be evenly distributed throughout the feed. To demonstrate homogeneity, samples should be taken for assay from various points in the blender following the usual mixing cycle. The submission should provide data from the assays. Note should also be taken of any demixing tendencies or electrostatic separation so that suitable precautionary statements can be included in the Directions for Use.

3.2.8. Premixes Proposed for Concurrent Use

For premixes that are recommended for concurrent use, the submission should demonstrate that the analytical method used for the assay of each drug retains its accuracy and precision in the presence of the other drugs. If the other drugs interfere in the analysis, a new analytical method will be required.

3.2.8. Feed Assay Validation

If a drug is to be administered as a medicated feed, the submissions should provide an acceptable method of analysis for the drug, when mixed in typical complete feeds at the recommended level. The submission should include the following information:

- A clear and concise description of the methodology;
- Method performance standards (i.e., recoveries, analytical ranges, limits of quantification and detection, and coefficients of variation for repeatability);
- Critical control points;
- Experimental designs and statistical plans;
- Raw data, chromatograms, tracings, calculated results, statistical results, and quality control for methods;
- Interference studies and documentation;
- Familiarization procedures for new analysts;
- Other related documentation such as ruggedness studies, confirmatory and trace level procedures, collaborative studies, and references; and
- Stability data for two or more lots of typical complete feeds, medicated at the recommended level and stored for three months at room temperature and at 37°C as mash or pellets.

3.2.8. *Samples*

The submission should provide samples for analysis, as described below:

- The active ingredient reference standard, in a sufficient quantity to validate the method, with a purity percentage indicated on the label;
- The technical product (10 g), with a purity percentage indicated

The drug in finished pharmaceutical form (500 g);

- Medicated feed in finished form, that is, mash, pellets, or both. Supply five one-kilogram samples of feed, each obtained from a different nutrient formulation. The level of active ingredient is to be verified through analysis, and the method of analysis is to be indicated.
- Unmedicated feed blank (1 kg). Supply unmedicated samples of feed from each of the five feeds requested for medicated feed (above). The feeds are to be analyzed to verify the absence of the active ingredient or of interference.

Reference VICH Documents: Stability Testing of New Drug Substances and Products (*VICH GL 3)* and Photostability Testing of New Drug Substances and Products (*VICH GL5*), Requirements for New Dosage Forms (*VICH GL4*) and Stability Testing for Medicated Premixes (*VICH GL8*).

3.2. R REGIONAL INFORMATION

3.2. R.1 Production documentation

3.2. R.1.1 Master Production Documents

The submission should provide copies of the drug product master production documents for each proposed strength, commercial batch size, and manufacturing site. The details in the master production documents should include, but not be limited to, the following items:

- Dispensing, processing, and packaging sections, with relevant material and operational details;
- Relevant calculations (e.g., if the amount of drug substance is adjusted based on the potency results or on the anhydrous basis);
- Identification of all equipment by type and working capacity;
- Process parameters (e.g., mixing time, mixing speed, milling screen size, processing temperature range, tablet machine speed, etc.);
- List of in-process tests (e.g., appearance, pH, potency, blend uniformity, viscosity, particle size distribution, loss on drying, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity, etc.);
- Sampling plan with regard to the steps where sampling should be done (e.g., drying, lubrication, and compression); the number of samples that should be tested (e.g., blend drawn using a sampling thief from *x* number of different parts of the blender), and the frequency of testing (e.g., weight variation every *x* minutes during compression or capsule filling);
- Precautions necessary to ensure product quality (e.g., temperature and humidity control, maximum holding times, etc.);
- Theoretical and actual yield; and
- Compliance with the GMP requirements

3.2. R.1.2 Executed Production Documents

A minimum of two batches of each strength should be manufactured. Bracketing and matrixing of proportional strengths can be applied, if scientifically justified. The batches should be manufactured using a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral drug products, a pilot scale is generally considered, at a minimum, to be one-tenth that of a full production scale, whether tablets or capsules. Copies of the executed production documents should be provided for the batches used in the pivotal comparative clinical or bioavailability studies. Operators should ensure that any notations they make on the executed production documents are clearly legible

4.1 MODULE 4: NON-CLINICAL PHARMACO- TOXICOLOGICAL DATA

Information on this part is required for new pharmaceutical active ingredients. The objective of toxicological/safety studies is to define the pharmacological actions (pharmacodynamics and pharmacokinetics) and toxicological effects of the active ingredient in test animals and target species, users, consumers and the environments. This normally involves initial studies in laboratory animals and later on pre-clinical studies in the target species, which should take into consideration the following:

1.1 Selection of the relevant animal species
1.2 Age of the animals
1.3 Physiological state of the animals
1.4 The manner of delivery, including dose, route of administration and treatment regimen and the effect on the animals
1.5 Stability of the test medicine under the condition of use
1.6 Safety of personnel.

4.2 DATA PRESENTATION

The pre-clinical documentation should be presented in the following sequence:

1. Pharmacology
2. Toxicology
3. Discussions and conclusions
4. Expert report

4.3 PHARMACODYNAMICS

Provide a full description of tests performed to establish the pharmacological actions that are relevant to the proposed indication(s) of the API and mechanisms of action. Where possible it will be helpful to relate the pharmacodynamics of the medicine to available data (in terms of selectivity, safety, potency etc.) on other medicines in the same class.

4.4 OTHER ACTIONS (DESIRED/UNDESIRED)

Give evaluation summary of action(s) other than those of therapeutic use. The results of two or three dosage levels studied should be submitted, with the lowest level representing the ED_{50} for the API's primary action on the animal species being investigated. For effects, which may be expected to have significant adverse reactions, attempts should be made to estimate the threshold levels.

4.5 PHARMACODYNAMIC INTERACTIONS

The applicant shall submit data either to establish that such interactions do not occur or that they are clearly recognised and defined. Discuss the pharmacodynamic interactions and mechanisms of interactions of the API with other compounds (medicine or other substances), which are relevant to proposed therapeutic use. Where there is evidence of antagonism or additive/synergistic effects, these should be well elucidated. In case of fixed dose combination or combination packs appropriate data to justify the benefit of combination against single API should be given.

4.6 PHARMACOKINETICS

Pharmacokinetics studies should be made with single dose by various routes. Repeated dose studies should also be performed when relevant, to establish the pharmacokinetics of chronic

medicine administration. Metabolic studies should be conducted on species used in toxicological and reproduction studies using the proposed clinical routes of administration. Where radioactive labelled materials are used in studies, position of label stability and specificity of material should be stated.
Where the product contains a combination of medicines, the effect of use of two or more medicines on the pharmacokinetics of one or the other medicines should be established. Provide studies done to establish the pattern and time course of absorption, distribution, biotransformation, pharmacokinetic interactions and excretion of the API and/or its metabolites as described below.

4.7 ABSORPTION

Provide summary of mechanism of absorption, factors affecting absorption, rate and extent of absorption, plasma levels of the API and metabolites (peak levels, half-life, etc.). This information should be discussed for different routes. Correlation between plasma levels and pharmacological effects should be discussed.

4.8 DISTRIBUTION OF API AND METABOLITES

Provide a summary and time course of distribution of the API and metabolites in body fluids, tissues, and organs. Accumulation, retention of the medicine/metabolites in tissues, organs, penetration of blood-brain and placental barriers, plasma binding all these parameters should be reported in quantitative form.

4.9 BIOTRANSFORMATION

Give the pattern and time-course of biotransformation of the medicine, i.e. sites of metabolism and their importance, metabolic pathway(s), nature and quantities of metabolites, rate of metabolism, pre-systemic metabolites enzyme inhibition or induction, activity of metabolites, if any.

4.10 PHARMACOKINETIC INTERACTIONS

Discuss the pharmacokinetic interactions and mechanisms of interactions of the API with other compounds (medicine or other substances), which are relevant to proposed therapeutic use. Where there is evidence of antagonism or additive/synergistic effects, these should be well elucidated.

4.11 EXCRETION

Summarise the routes and extent of excretion of the medicine and its metabolites. State also its excretion in milk in case of lactating animals. Discuss the rate of elimination and factors influencing elimination.

4.12 TOXICOLOGICAL STUDIES

The scope of toxicological evaluation should be described in relation to the proposed clinical use. Information obtained from experimental and biological studies of all aspects of toxicology (general toxicity, acute toxicity studies, sub-acute toxicity and long term toxicity studies including teratology, reproduction effects, carcinogenicity, genotoxicity, immunogenicity, Microbial affects (e.g. development of resistance), local tolerance (potential for adverse effects at site of administration, etc) is required to establish the safe use of the medicine and must be submitted for all new medicine applications.

The investigation should, if possible, include experiments conducted with the medicine in the vehicle intended for therapeutic application or its final pharmaceutical formulation (product).

4.13 GENERAL TOXICITY STUDIES

In general toxicity studies, at least three or more routes of administration should be used including one for therapeutic use and at least one other which ensures systemic absorption, i.e. intravenous, intramuscular or subcutaneous.
Different dose levels spaced logarithmically should be used. The maximum tolerated dose should be indicated. All animals dying during the experiment should be autopsied and cause of death determined where possible. Full post-mortem should be carried out on all animals and histopathological studies undertaken on control and dosed groups. Results should be tabulated. Full data for all parameters measured, with mean, range for groups, should be included. If it is expected that the product will be used in children, studies should be conducted on both adult and young (weaning) animals.

4.14 ACUTE, SUB-ACUTE AND LONG TERM TOXICITY STUDIES

Principles governing general toxicity studies shall be applicable to acute, sub-acute and long term toxicity studies and local torelability studies.

4.15 SAFETY TO USERS

Residue study data should be provided to justify withdrawal periods for milk, meat, eggs for each species for which the product is indicated. Studies on potential harmful effects to exposure by various routes, e.g. inhalation, topical contact, oral ingestion, performed on laboratory animals, shall be presented. The implications to humans using the product should be described and, where appropriate, precautions during preparation and use of the product should be proposed.

4.16 RISK ASSESSMENT OF VETERINARY MEDICINES RESIDUES IN FOOD OF ANIMAL ORIGIN

Safety assessment of veterinary medicines residues in food of animal original should be performed for all new medicines. Relevant pharmacological, toxicological, microbiological end points should be used to establish acceptable daily intake. Maximum residue limits in food producing animals should be provided. Withdrawal period should be indicated on the labels. All the analytical methods used should be provided. Pre and post antimicrobial resistance surveillance should be performed on indicator pathogens e.g. *E.coli, Salmonella* spp. Quinolones - usage should be restricted to avoid resistance in zoonotic pathogens.

4.17 TOXICITY TO THE ENVIRONMENT

Assessment of the environmental safety should be given for all veterinary medicinal products. Requirements for safety are important to avoid persistent damage to the environment.
Products requiring environmental assessment include:
(a) Antibiotics in poultry, pig and fish feeds
(b) Antihelmintics in large animals e.g. invermectins
(c) Expired medicines from veterinary hospitals/clinics, pharmacies and manufacturing plants
(d) Effluents from manufacturing plants
(e) Hazardous or potentially hazardous non pharmaceutical imaterials (used devices e.g. needles, syringes and gloves)

(f) External parasticides
An assessment of the potential of exposure of the medicine and its active metabolites to the environment shall be made taking into account:
(i) The target species and likelihood of and method of excretion of the product and its active metabolites into the environment.
(ii) Pattern of use and therefore quantity medicine to be used (herd/flock medication or individual medication)
(iii) The method of administration and whether it may lead to direct entry of the product into the environment, e.g. sprays
(iv) The method of disposal of the unused, used products and containers
Studies on potential harmful effect of the product to the environment shall be provided. The environment shall include soil, water and air such studies shall include:
(i) fate and behaviour in the soil
(ii) effects on soil organisms
(iii) fate and behaviour in water
(iv) effect on aquatic organisms
(v) effects of other non-target organisms
Proposed measures to minimise the above potential risks during use of the product shall be described.

4.17 GENERIC AND WELL ESTABLISHED DOSAGE FORM

In case of generic or interchangeable multi-source medicines and dosage forms provide bioequivalence studies data corroborated with literature review.

4.18 PRESENTATION OF SAFETY STUDIES

All toxicity studies shall be properly presented including the following:
(i) Objectives
(ii) Experimental protocol including methodology and materials
(iii) Summarized results and related statistical analysis
(iv) Discussions and conclusions
(v) Proposed measures to minimize potential toxicity during use of the product

5.1 MODULE 5: EFFICACY DATA

This section shall only be applicable to new chemical entities. For generic preparations, literature references of published studies will suffice. Original efficacy data will be required for all veterinary medicinal products containing new chemical entities (NCE) whether when mono or in fixed dose combination with another NCE or a well-known medicine substances. A summary of well presented, controlled blinded clinical trials conducted in target animals investigating the pharmacological and therapeutic properties, and adverse reactions is required. Pharmacological studies are only required if the biological studies were not done in target animals. The principles of Good Veterinary Clinical Practice (GVCP) should be adhered to during the study.

5.2 PHARMACODYNAMIC STUDIES (TARGET ANIMALS)

Describe the study protocol including the study design, pharmacological or biochemical response measured, measuring instruments used results, statistical methods used and their justification. Tabulation and graphical illustration of results and conclusion.

Notes:
a) A cross-over design is preferred and where it is not appropriate a parallel design is acceptable. The study design must consider the pathology and natural history of the condition.
b) Studies should be done in healthy animals or in sick animal if the disease affects the actions/responses studied.
c) Inclusion/exclusion criteria must be stated and non-responders should be identified and excluded prior to the study commencement
d) Measured pharmacological response should be relevant to the claimed therapeutic uses where there are more than one therapeutic use studies should be done to demonstrate the therapeutic use for each indication.
e) Measurement of responses should as far as possible be quantitative, measured under double blind conditions and be recorded in an instrument producer/instrument recorded fashion. The methodology
must be validated for precision, accuracy, reproducibility and specificity.
f) Where possible the effect can be graphically illustrated using the area under the effect time curve, maximum effect and time of maximum effect.

In using pharmacodynamic methods, the following requirements must be satisfied:
a) The response can be measured precisely over a reasonable range
b) The response can be measured repeatedly to obtain time-course from the beginning to end of the response

5.3 PHARMACOKINETICS AND BIOAVAILABILITY OF THE MEDICINE IN TARGET ANIMALS

The summary should outline;
a) Particulars of principal investigators (name, curriculum vitae, affiliation and signature)
b) Medicine and medicine product information, batch details, batch number, manufacturing site and date, expiry date, specifications. The Medicine product must be identical to the intended commercial product in every respect; same manufacturing site and same

composition (qualitative and quantitative). Samples should be from commercial scale production

c) Protocol and study design; (objectives, animal selection, conduct of the study, medicine administration, food intake, sample collection, storage, bio-analytical methods and validation results, pharmacokinetics parameters measured and results. Justifications for the chosen design (e.g. cross over or replicated design), measures taken to minimize intra and inter-animal variability and elimination of bias must be stated. All possible factors that may influence the product pharmacokinetics must be standardized e.g. fluid intake, food intake, exercise, etc.

d) Population

Population size of 12 – 24 (sample size shall depend on the animal
co-efficient of variation CV if low say < 15%; n = 14,
> 30% ; n = 44) healthy young animals

e) The results, data and statistical procedures should be detailed enough to allow for repeat analysis if necessary.

5.4 EFFICACY CLINICAL END POINT STUDIES IN TARGET SPECIES

Describe in detail the study protocol, which should, include:

a) the title of the study

b) particulars of principal investigator(s), location, justification and objectives, dates, time, duration, observation periods and justification thereof,

c) study design (randomization methods description of design e.g. cross-over or parallel etc), inclusion, exclusion, criteria, animal housing and feeding, methods and treatments, dosage used, concurrent treatments,

d) specification of test medicine and placebo,

e) response variables – clinical endpoints measured, and recording clinical response (scoring system for endpoints).

f) analysis of results including statistical methods used and their justification.

g) Discussions and conclusions on efficacy and safety, including but not limited to: adverse reactions observed and their relationship with the administered dose.

5.5 RESIDUE STUDIES

This section provides guidance for situations or conditions under which waivers of the drug residue depletion studies could be granted. It also describes conditions under which the relevant studies will be required. Overall, the information submitted on residues should be sufficient to confirm or establish that the withdrawal period / withholding time of the generic drug product is identical to that of the reference product. Requests for waiver of the residue depletion studies will be considered on a case-by-case basis. When an applicant requests a waiver for residue depletion study requirements, an assessment of the dossier is conducted to determine whether the generic drug product is identical to the reference product. When a waiver cannot be granted, the residue depletion studies to confirm or establish that the withdrawal period of the generic product is the same as approved for the reference product will be required.

5.5.1 Situations and Conditions When the Residue Data Requirements Could

Be Waived

For certain products for which the waivers of pharmaceutical equivalence and bioequivalence study requirements have been granted, residue data to confirm the withdrawal period assigned to the reference product will not be necessary. As described in Subsection 5.5.2 of this document, there are situations where an abbreviated depletion study (see Subsection 5.5.3 below) may be required even after granting pharmaceutical equivalence and bioequivalence of the generic products.

If bioequivalence is granted based on blood-level studies, which should cover the absorption, distribution, and elimination phases of the active ingredients vs. the time profile, and the assay method used is sensitive enough to measure the residue levels in blood for the entire withdrawal period established for the reference product, the residue depletion data requirements may be waived provided that the correlation data between the depletion of drug residue from plasma and target tissue is known. The waiver of residue data requirements may be granted to medicated premix products or soluble powder oral dosage forms that are pharmaceutically equivalent to the reference product.

5.5.2 Situations and Conditions When the Residue Data Requirements Cannot Be Waived

In various situations, the residue depletion data requirements cannot be waived.

The descriptions below specify the situations where applicants must submit the data from an abbreviated residue depletion study (see Subsection 5.5.3) or a comprehensive residue depletion study (see Subsection 5.5.4 below). In general, when the waivers for pharmaceutical equivalence or bioequivalence cannot be granted, a waiver for the residue depletion study requirements will also not be considered. In most cases, data from an abbreviated residue depletion study will be required to confirm the withdrawal period of the generic products. An abbreviated residue depletion study is generally required in food-producing animals for the following product formulations:

- Non-aqueous products for injection by subcutaneous and/or intramuscular routes;
- Intra-mammary infusion in dry cows;
- Pour-on formulations;
- Implants; and
- Intra-ruminal devices.

For products where the formulation (e.g., pH, vehicle, excipients, etc.) differs from that of the reference product, and concerns about residue depletion are evident, data from residue depletion studies to confirm the withdrawal period may still be required even though the generic product is considered to be pharmaceutically equivalent and the waiver of bioequivalence study requirements has been granted. Some generic drug products may have the same plasma disposition profile as the reference product at the concentrations used in bioequivalence studies, but may have very different tissue disposition kinetics when followed out to the withdrawal period for the reference product. In these cases the submission must include data from the residue depletion study. Similarly, differences in the location of injection sites or evidence of significant injection site tissue reaction might lead to altered tissue residue depletion pattern, which may result in the submission requiring data from an abbreviated residue depletion study. In generic drug submissions where residue depletion studies are not waived, and when the reference is indicated for use in more than one food-producing species, an abbreviated tissue residue depletion study will generally be required for

each major food-producing species on the label. This is because the data derived from one animal species generally cannot be extrapolated to another species due to possible species differences in drug partitioning or binding in tissues. These differences could magnify a small variation in the rate and extent of drug absorbed into a large variation in marker residue concentrations in the target tissue.
For a reference product approved for use in major and minor species, data from a residue depletion study from a major species on the label is generally sufficient for confirmation of withdrawal periods for all related minor species on the label.
In all cases where no residue data are available on file for the reference product, the submission must contain data from the tissue residue depletion studies to meet the current standards of the guidelines. An applicant seeking a shorter withdrawal period for the generic product must provide the data from a comprehensive residue depletion study to support the proposed shorter withdrawal period.

5.5.3 Residue Depletion Study

The purpose of a residue depletion study is to confirm the withdrawal period of a generic version of the reference product. This study should be conducted in a minimum of 6 animals (evenly mixed by sex) for large and medium sized animals (e.g., cattle, swine, sheep, etc.), 12 birds for poultry, 15-20 for fish, and 20 lactating dairy animals (e.g., cows, goats, and sheep), treated with the product at the same dose and using the same route and frequency of administration as recommended for the reference product. The study should include a control (nontreated) animal. The concentration levels of the marker residue or residues in the target tissue, if known, at the recommended withdrawal period for the reference product, will need to be determined by using the validated analytical method (regulatory method). A single-point statistical procedure will be used to determine the upper tolerance limit of residue concentrations with 95% confidence for 99% of the animal population, which should be below the established maximum residue limit (MRL) at the established withdrawal period for the reference product. In case the residue levels in target tissue, if known, at the established withdrawal period for the reference product, exceed the established MRL, data from a comprehensive residue depletion study.

5.5.4 Comprehensive Residue Depletion Study

The purpose of a comprehensive residue depletion study is to establish a withdrawal period for the generic drug product. This study should be conducted in a minimum of 20 animals, divided into either four or five groups of four or five animals each. The study should include at least one control (non-treated) animal. Groups of animals are slaughtered at each of either four or five appropriately distributed and pre-selected time point intervals following the last administration of the test article. Edible tissues are then collected for marker residue analysis. For the purpose of establishing the withdrawal period, only marker residue in the target tissue, if known, would be analyzed.

A statistical procedure will be used to calculate the withdrawal period. The upper tolerance limit residue concentrations with 95% confidence for 99% of the animal population will be determined, which should be below the established MRL. It is noted that to meet the current standards of the guidelines, data from a comprehensive residue depletion study in all the edible tissues may be requested where the MRL in tissues other than the target tissue are not available.

5.5.5 Analytical Methodology

When choosing analytical methods to determine marker residue concentration levels, applicants should consider the approved method. If an analytical method other than the approved method of analysis is used, the applicants of the generic products should provide method validation data with consideration of the analytical methodology requirements.

ANNEX I

CONFIDENTIAL MEDICINES CONTROL AUTHORITY
MEDICINES AND ALLIED SUBSTANCES CO NTROL ACT [CHAPTER 15:03]
APPLICATION FOR REGISTRATION OF A MEDICINE
(To be submitted in duplicate)
To be sent to the Director – General, Medicines Control Authority, P.O. Box UA 559, Union Avenue, Harare or to be lodged at the offices of the
Director – General, Medicines Control Authority, 106 Baines Avenue, Harare.
Samples and printed matter to be forwarded by post or by other means and carriage, customs duty and clearance to be paid and effected by the
applicant in all instances.
Particulars of Applicant:
Name ……
Business address
……
Postal address ……
Telephone number
……
Particulars of medicine:
Approved name (if any) (1)
……...
Proprietary name (Trade mark), if any (2)
……..
Title of patent (registered in terms of the Patent Act *[Chapter 202]* if any
……
Name of proprietor of patent
……
Number of Patent
……
Is the patent still in force? YES/NO*
The form in which the medicine is presented, and the colour thereof (3)
……..
Name and address of principal
……
Name and address of manufacturer
……
Country of origin
……
The strength of the medicine
……
Classification (4)
……
Will the medicine be manufactured, partially manufactured, repacked or relabeled in Zimbabwe?
……
State who will complete the process of manufacture
……
State address at which the certificate will be kept
……
I enclose the fee of
……
I, the undersigned, hereby declare that all the information contained herein and in the appendices is correct and true.
Date …….. …….*Signature of applicant*
**Delete the inapplicable*_____
Notes I. 2. 3 and 4
GENERAL INFORMATION
1. If no name has been allocated to the medicine by an appropriate international body, the name which has been or will be submitted for approval
must be mentioned here.
2. Medicines which are not identical in composition or strength are not regarded as the same medicine, but application for registration of medicines which vary only in strength may be made on the same form.
3. The form of preparation, i.e. capsules, ear drops, emulsions, eye drops, injections, ointments, solutions, suppositories, suspensions, tablets, etc.
and the colour thereof must be mentioned here.
4. The classification of the medicine as described in the Fifth Schedule of the Medicines and Allied Substances Control (General) Regulations,
1991.

ANNEX I

APPENDIX I

Name of medicine

……...

Name of applicant

……

The form in which the medicine is presented and the colour thereof

……...

The following is a schedule of the —

(a) Active ingredients, giving their approved names, chemical names, structural formulae, specification and quantity in a dosage unit of the medicine;

(b) Inactive ingredients giving specifications and quantity and reason for inclusion, e.g., preservative, antioxidant;

(c) Specification of any raw materials used in the manufacturing process and not present in the finished medicine; and

(d) Specification of packaging material in immediate contact with the medicine.

Approved name	Chemical name (1)	structural formula	Quantity per dosage unit	Active or non-active Specifications (2)	Reason for inclusion of ingredient

Specifications of additional raw material (if any) (2) used in the manufacturing process and not in the final product

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……
……
……
……

Specification of packaging material (3)

……

NOTES

1. The chemical name must, where possible, be given in terms of the published list of an appropriate international body.
2. Reference to the following publications will, where applicable, be acceptable:

(a) British Pharmacopoeia;

(b) European Pharmacopoeia;

((c) Pharmacopoeia of the United States of America;

(d) Pharmacopoeia of Japan;

(e) International Pharmacopoeia;

(f) such other works of reference as may be approved by the Authority.

3. Where no specifications for raw materials and packaging materials exist this must be mentioned.

ANNEX I

APPENDIX II

Name of applicant

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Name of medicine

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The form in which the medicine is presented and the colour thereof

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(a) A summary of the manufacturing procedure

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(b) The analytical control procedures performed on raw materials including the microbial status where applicable.

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(c) The analytical control procedures performed during the manufacturing process

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(d) The analytical control procedures used to determine the compliance with specifications

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(e) The full specifications of the medicine including microbial limits

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(0 Data and reasoning on which the stability of the medicine is predicted (minimum of three batches is required)

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(g) The shelf life claim

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(h) Copies of all records and batch data relating to a particular batch (preferably that of the sample submitted). This includes raw material analytical reports, manufacturing and packing master sheets, in process control records, final product analytical report and authorization for release and any other appropriate records.

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Where appropriate, references to the publications mentioned in the notes to Appendix I, will be acceptable

ANNEX I

APPENDIX III
Name of applicant
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Name of medicine
……
The form in which the medicine is presented and the colour thereof
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……..
1. (a) Has the medicine been registered in the country of origin? YES/NO* [If YES a valid certificate of registration in respect of such medicine issued by the appropriate authority established for the registration of medicines in the country of origin must accompany misapplication.]
(b) Has an application for the registration of the medicine been made in any other country? YES/NO*
If YES, state details ……..
……
……
(c) Has the registration of the medicine been rejected, refused, deferred or cancelled in any country? YES/NO*
If YES, state full details
……
……
..
Do you intend to advertise the medicine? YES/NO*
If YES, state how and give details of proposed advertising and promotional materials ……
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……
.
2. Under what category do you envisage distributing the medicine? ……
…...
……
**Delete the inapplicable*

ANNEX I

APPENDIX IV

Name of applicant

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Name of medicine

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The form in which the medicine is presented and the colour thereof

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(a) The following particulars refer to the lexicological trials undertaken.

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(b) The following particulars refer to therapeutic effects of the medicine

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(c) The following particulars refer to the tests which have been performed on animals regarding the efficacy of the medicine and the purposes for
which it will be promoted, with special reference to the dosage and method of administration (pharmacological trials)

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(d) The following particulars refer to the tests which have been performed as in (c) above on humans:

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(e) The following are particulars of the purpose, mode of action, side effects, contra-indications of the medicine:

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(f) The following data relating to the pharmacokinetics and the bioavailability of the medicine in humans and animals is attached.

(g). State details of medicine residue in species intended for human consumption

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(h) State details of withdrawal periods for species intended for human consumption

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ANNEX I

APPENDIX VI

Name of applicant

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Name of medicine

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The form in which the medicine is presented and the colour thereof

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(a) The following are references to literature about the medicine:

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(b) The attached are relevant documents concerning the medicine:

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(c) Twenty copies of the package inserts or draft package inserts and twenty labels or copies of packages are attached:

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(d) All proposed advertising and promotional material is attached:

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(e) Samples have been submitted by registered post/by hand* to the Director - General:

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*Delete the inapplicable__

ANNEX II SCREENING CHECK LIST FOR SUBMISSION OF A DOSSIER FOR REGISTRATION OF A VETERINARY MEDICINAL PRODUCT

Section		DOCUMENTS	Submitted?			
			Yes	No	Location (Page numbers)	Critical or non-critical
2.1		**MODULE 1 ADMINISTRATIVE INFORMATION**				
	2.1.2	**Comprehensive Table of Contents** ~Include a complete list of all documents provided in the product dossier by module ~The location of each document should be located by the module number				NC
	2.1.3	**Completed, signed and dated MC8 form**				C
	2.1.6	**Proof of payment of appropriate fees**				C
	2.1.7	**Manufacturing and Marketing Authorization(s)**				C
	2.1.8	**Summary of Product Characteristics (SMPC) and Package Insert**				NC
	2.1.9	**Labelling**				NC
2.2		**MODULE 2**				
	2.2.1	**Quality Overall Summary – Product Dossiers (QOS – PD)**				NC
	2.2.2	**Quality Information summary**				NC
3		**MODULE 3**				
3.2.S		**ACTIVE PHARMACEUTICAL INGREDIENT (API)**				
	3.1	**Approved API source(s)**				
		DMF[1]				C
		CEP[2] with annexes				
	3.2.S.2.1	**Manufacturer(s) name and address**				C
	3.2.S.2.2	**Description of Manufacturing Process and Process Controls**				C
	3.2.S.2.3	**Control of Materials**				NC
	3.2.S.2.4	**Controls of Critical Steps and Intermediates**				C
	3.2.S.2.5	**Process Validation and/or Evaluation** ~ Must be submitted for sterile APIs and NCEs				NC
		*: For applications with DMF, sections S2.3, S2.4, S2.5 and S2.6 are included in the closed part of DMF				

3.2.S.3	CHARACTERISATION				
Section	DOCUMENTS	Submitted?			
		Yes	No	Location (Page numbers)	Critical or non-critical
3.2.S.3.1	Elucidation of Structure and other Characteristics				C
3.2.S.3.2	Impurities				C
3.2.S.4	CONTROL OF DRUG SUBSTANCE				
3.2.S.4.1	API Specifications				C
3.2.S.4.2	Analytical Procedures				C
3.2.S.4.3	Validation of Analytical Procedures *: Can be waived for methods that reference compendial methods				C
3.2.S.4.4	Batch Analysis				C
3.2.S.5	REFERENCE STANDARDS				NC
3.2.S.6	CONTAINER CLOSURE SYSTEM				
	Specifications and Test Methods				C
3.2.S.7	Stability				C
3.2.P	FINISHED PHARMACEUTICAL PRODUCT (FPP)				
3.2.P.1	Description of the Drug Product				C
3.2.P.2	Pharmaceutical Development				C
3.2.P.3	Manufacture				
3.2.P.3.1	Manufacturer(s)				C
3.2.P.3.2	Formulae				NC
3.2.P.3.3	Manufacturing Process				C
3.2.P.3.4	Process validation ~For three consecutive batches				C
3.2.P.4	Control of Excipients				
3.2.P.4.1	Specifications				C
3.2.P.4.4	Excipients of Human or Animal Origin *: BSE / TSE free certification				NC
3.2.P.4.5	Novel excipients *: Provide information provided as per full API Section				C
3.2.P.5	Control of FPP				
3.2.P.5.1	Finished Product Specifications				C
3.2.P.5.2	Analytical Procedures				C
3.2.P.5.3	Validation of Analytical Procedures				C
3.2.P.5.4	Batch Analyses				C
3.2.P.6	Reference Standards				NC
3.2.P.7	Packaging/Container Closure System				
3.2.P.7.1	Specifications and Test Methods				C
3.2.P.8	Stability				C
3.2.R	REGIONAL INFORMATION/ REQUIREMENTS				
3.2.R.1	Batch Manufacturing Records				C
Section	DOCUMENTS	Submitted?			

		Yes	No	Location (Page numbers)	Critical or non-critical
4.1	**MODULE 4 NON-CLINICAL PHARMACO-TOXICOLOGICAL DATA**				
5.1	**MODULE 5 EFFICACY DATA**				
	REGISTRATION DETAILS				
	Certificate of pharmaceutical product specific for Zimbabwe				**C**
	List of countries where product is registered				**NC**
	Proof of registration countries with stringent regulation (VICH)				
	Sample of FPP				**C**

[1] DMF Drug Master File

[2] CEP Certificate of Pharmaceutical Suitability

C Critical

NC Non Critical

NCE New Chemical Entity

VICH International Cooperation on Harmonisation for Technical Requirements for Registration of Veterinary Medicines

ANNEX III: INGREDIENTS GAZETTED AS UNDESIRABLE IN PHARMACEUTICAL PREPARATIONS BY THE MCAZ

CURRENT LIST

Astemizole
Benoxaprofen
Chlormezanone
Clioquinol (in medicines for oral administration)
Dipyrone
Lead and lead salts
Nimesulide
Oxyphenbutazone
Phenacetin
Phenformin
Phenolphthalein
Ponceau 4r
Practolol
Rofecoxib
Zomiperac
Chloroform (in liquid oral medicines or preparations)
Tartrazine (in medicines intended for oral use).
Chlorofluorocarbons (CFC)/halocarbons as propellants in aerosol inhalation products

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