



**ZAMBIA MEDICINES REGULATORY AUTHORITY**

**GENERAL GUIDELINES FOR  
SUBMITTING APPLICATIONS  
FOR REGISTRATION OF A  
MEDICINE**

**First Edition**

## Table of Contents

1. Foreword.....	3
2. Acknowledgements.....	4
3. Definitions and Interpretations.....	5
4. Abbreviations and Acronyms.....	7
5. Introduction.....	10
6. General Information.....	13
7. Product Profile.....	16
8. Bioavailability / Bioequivalence data.....	21
9. Expert reports.....	22
10. Chemical and Pharmaceutical Information.....	22
PART IIIA    Composition	
PART IIIB    Development Pharmaceutics	
PART IIIC    Control of the starting materials	
Active pharmaceutical ingredients (API)	
Excipient(s)	
PART IIID    Packaging material (immediate packaging)	
PART IIIE    Control tests on intermediate products (if	
necessary)	
PART IIIF    Control tests on the finished product	
PART IIIG    Method of preparation for the finished product	
PART IIIH    Stability tests on the finished product	
11. PART IV      Summary of toxico-pharmacological documentation of a medicine	
Brief summary.....	27
PART IVA    Single dose toxicity	
PART IVB    Repeat dose toxicity	
PART IVC    Reproduction studies	
PART IVD    Genotoxicity	
PART IVE    Carcinogenicity	
PART IVF    Pharmacodynamics	
PART IVG    Pharmacokinetics	
PART IVH    Local tolerance	
PART IVJ    Other toxicity studies (if available)	
(i)      Antigenicity	
(ii)     Immunotoxicity	
(iii)    Dependence	
(iv)    Studies on metabolites	
(v)     Studies on impurities	
(vi)    Other studies	
Discussions and Conclusions	
12. PART V      Summary of clinical studies.....	27
PART VA      Human pharmacology	
(i)      Pharmacodynamics	
(ii)    Pharmacokinetics	
Summary of clinical pharmacology studies.....	27
Product Development Rationale .....	27

Summary of Bio pharmaceuticals (BC) studies and associated analytical methods.....	27
PART VB Clinical documentation.....	29
Summary of clinical efficacy.....	29
Summary of clinical safety.....	32
ANNEX I Recommended wordings of warnings on packages.....	38
Other warnings.....	40
ANNEX II Colours permitted in medicinal products.....	42
ANNEX III ATC.....	43
ANNEX IV Application form.....	54

## **Foreword**

The Pharmaceutical Act (No. 14) of 2004 requires that medicinal products intended to be marketed in Zambia meet acceptable standards of quality, safety and efficacy and at the same time be assessed to have been manufactured in facilities which comply with current Good Manufacturing Practices (cGMP).

One of the means for ensuring that medicinal products meet the required standards of quality, safety and efficacy is by conducting product specific pre-marketing assessments to determine whether the product should be registered.

These guidelines have been prepared to provide information to applicants who intend to register medicinal products for human use in Zambia.

This document has been developed by the Pharmaceutical Regulatory Authority (PRA) to provide guidance to applicants on the content and format of the dossier in respect of products submitted for registration. These guidelines also indicate the order of the material to be submitted and the minimum requirements for product registration.

Compliance to these guidelines in the submission of applications will facilitate the speedy processing and evaluation of the applications and subsequent registration of the products. This will enable the product prospective licence holders to market their products on time and make them available to the consumers in a timely manner.

It is therefore my sincere hope that these guidelines will provide the necessary information in preparing and submitting documents for registration of medicinal products for human use in Zambia.

Finally, I wish to urge our esteemed readers and applicants to read this first edition of guidelines carefully and make as many suggestions as possible so that we have a version of the guidelines that are commensurate with current practices.

Dr S.K. Miti  
**PERMANENT SECRETARY**  
**Ministry of Health**

## **Acknowledgements**

The Ministry of Health (MoH) and the Pharmaceutical Regulatory Authority (PRA) wish to acknowledge the immense contributions of individuals and organizations that constituted the Technical Working Group in developing these guidelines. The principal contributors for this guidance document were:

1. Mr D.M. Ng'uni:       Pharmaceutical Society of Zambia
2. Ms Esnat Mwape:     Director General, PRA
3. Dr G. Chishimba:    Medical Practitioner, National AIDS Council
4. Ms Anne Zulu:        Pharmacist, Medical Stores Limited
5. Dr K Choongo:        Lecturer, UNZA School of Veterinary Medicine
6. Ms Loyce Lishimpi:  National Profession Officer, WHO
7. Mrs Bernice C. Mwale: Director-Product Registration, PRA,
8. Mr. Felix P. Chizu:  Regulatory Officer, PRA
9. Dr Zuma Munkombwe:  Regulatory Officer, PRA
10. Mr. Pelekelo Mangisha: Assistant Regulatory Officer, PRA

The MoH and PRA would further like to thank the World Health Organisation (WHO) for providing financial and technical support to the development of these guidelines.

Ms E. Mwape  
**DIRECTOR-GENERAL**  
**Pharmaceutical Regulatory Authority**

## Definitions & Interpretations

**Active pharmaceutical ingredient (API)** means a substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

**Authority** Means the Pharmaceutical Regulatory Authority established under Section 4 of the Pharmaceutical Act No 14 of 2004.

**Bio-equivalence** Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or alternatives and their bio-availabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be expected to be essentially the same.

**Composition** Composition in relation to a medicinal product means the ingredients of which it consists, proportions, degree of strength, quality and purity in which those ingredients are contained.

**Container** Means a bottle, jar, box, packet, sachet or other receptacle which contains or is to contain in it, not being a capsule or other article in which the product is or is to be administered or consumed, and where any such receptacle is or is to be contained in another receptacle, includes the former but does not include the latter receptacle.

### **Container labelling**

Means all information that appears on any part of a container, including that on any outer packaging such as a carton.

### **Medicines, Medicinal or Pharmaceutical product**

"Medicine" means any substance or mixture of substances which is used or is manufactured, sold or represented as suitable for use in the diagnosis, treatment, mitigation or prevention of disease or abnormal physical or mental state or the symptoms thereof in man, or in animal; or restoring, correcting or modifying any physical, mental or organic function in man or in animals.

### **Established active pharmaceutical ingredient**

Means APIs which are subject of the current pharmacopoeias or those well documented in the literature and generally recognized as safe and effective for use as a medicine.

### **Excipient**

Means any component of a finished dosage form which has no therapeutic Value

### **Expert report**

Means a summary and interpretation of data, with conclusions, prepared by an independent competent person.

***Finished product***

Means a product that has undergone all stages of production, including packaging in its final container and labelling

***Formulation***

Means the composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

***General sale Medicines (GS)***

Means any Medicines whose use does not need the direction or prescription by a Veterinary surgeon or dentist.

***Generic products***

Means products that are pharmaceutical equivalents or alternatives to innovator or reference products and which are intended to be therapeutically equivalent and can therefore be used interchangeably with the innovator or reference product.

***Immediate release dosage form***

Means a dosage form that is intended to release the entire active ingredient on administration with or enhanced, delayed or extended release effect.

**Impurities** include by-product of synthesis arising from side reactions products in starting materials etc., residual solvents and reagents, trace elements arising from other sources and products of degradation

***Innovator (or pioneer) pharmaceutical product***

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

**Label** Means any tag, brand, mark, pictorial or other descriptive matter, written, printed, stenciled, marked, embossed or impressed on or attached to a container of any Medicines

**Manufacture** Means production, quality control, release and packaging of a product.

**Manufacturer** Means .a firm that is engaged in the manufacture of products

***Fixed dose combination***

Means a product containing Medicines in combinations (qualitative content and/or proportions) different from those products that are subject of current pharmacopoeias

**New active pharmaceutical ingredient** Means a Medicine (active ingredient), including its salts, esters, derivatives, etc. or biological agent, which is not a subject of current pharmacopoeias.

**Pharmacopoeia** Includes but not limited current edition of the British Pharmacopoeia, European Pharmacopoeia, United States Pharmacopoeia, International Pharmacopoeia and Japanese Pharmacopoeia.

**Pharmaceutical alternatives** Two or more medicinal products are said to be pharmaceutical alternatives if they contain the same active ingredients, but which may differ in salt, esters, dosage forms, strength and/ or route of administration.

**Pharmaceutical equivalents** Products are pharmaceutical equivalents means products that contain the same amount of the same active substance(s) in the same dosage form; if they meet the same or comparable standard; and if they are intended to be administered by the same route.

**Retention fee**

Means a fee paid annually to maintain product licence.

**Shelf life Specifications**

Means the combination of physical, chemical, biological and microbiological test requirements that an active ingredient should meet up to its retest date or a Medicines product should meet during its shelf life.

**Shelf Life**

Means the combination of physical, chemical, biological and microbiological test requirements that determine whether a Medicines product is suitable for release at the time of its manufacture

**Therapeutic equivalence**

Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

**WHO-type certificate**

Means a certificate of pharmaceutical product of the type defined in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

**Proprietary name**

Means the (trade or brand) name, which is unique to a particular Medicines and by which it is generally identified (and by which it is registered in the country of manufacture).

**Approved/ INN / generic name**

In relation to Medicines mean the internationally recognized non-proprietary name of such medicines.

**Dosage form**

Means the form in which the Medicines is presented, e.g. solution, suspension, eye drops, emulsion, ointment, suppository, tablet, capsule, etc. For injections, the type of presentation (e.g. vial, ampoule, dental cartridge, etc), and the type of content (e.g. powder for reconstitution, solution, suspension, oily solution, etc.) shall also be stated.

**Description of the product**

means a full visual description of the Medicines including colour, size, shape and other relevant features, e.g. 'black and red gelatin capsule with marks "Amp -250", 'pink film coated tablets with word "PAN" embossed on one side' etc.

**Commercial Presentation**

Means the final product pack as it will be presented in the market (e.g. 10 ampoules of 2ml each, 10 blister packs of 10capsules each, etc.)

**ATC Classification**



Means the Anatomical Therapeutic Chemical Classification system.

**Prescription Only Medicine (POM)**

The products in this category are available from pharmacies/dispensaries only.

All products in the above three categories are available upon presentation of a prescription from a prescriber to a licensed pharmacy/dispensary.

**Pharmacy Medicine (P)**

These products are available from licensed pharmacies only.

**General Sales Medicines (GS)**

Medicines in this category are available in pharmacies, dispensaries and all licensed trade supermarkets.

**Strength of the medicinal product**

Means the content of the active ingredient expressed quantitatively per dosage unit, per unit of volume or mass or weight according to the dosage form;

**Immediate packaging**

Means container or other form of packaging, which is immediately in direct contact with the medicinal product;

**Outer packaging**

Means the packaging into which is placed the immediate packaging;

**Labelling**

Means the information contained on the immediate or outer packaging;

**Package insert**

Means a leaflet containing information for the prescriber and the dispenser;

**Patient information leaflet**

Means a leaflet containing information for the patient;

**Product licence Holder** means a person or company under whom a medicinal product has been registered. This party is responsible for all aspects of the medicinal product including quality, safety, efficacy and compliance with conditions of registration.

# Abbreviations & Acronyms

**µg** Microgram  
**API** Active Pharmaceutical Ingredient  
**ATC** Anatomic Therapeutic Chemical classification  
**AUC** Area under the plasma concentration time curve  
**BE** Bioequivalence studies  
**BP** British Pharmacopoeia  
**CASR** Chemical Abstract Service Registry Number  
**cGMP** current Good Manufacturing Practices  
**CI** Confidence Interval  
**C<sub>max</sub>** Maximum plasma concentration  
**CV** Coefficient of Variation  
**e.c** Enteric coated  
**f.c Film** coated  
**FDC** Fixed Dose Combination  
**FP** Finished Product  
**GCP** Good Clinical Practice  
**GLP** Good Laboratory Practice  
**GMP** Good Manufacturing Practice  
**GS** General Sale  
**HPLC** High power Liquid Chromatograph  
**i.m** Intramuscular  
**i.v** Intravenous  
**INN** International Non-proprietary Name  
**IP** International Pharmacopoeia  
**IR** Infra red spectroscopy  
**IU** International Unit  
**IUPAC** International Union for Pure and Applied Chemistry  
**JP** Japanese Pharmacopoeia  
**M.R** Modified Release  
**mg** Milligram  
**ml** Millilitre  
**MRA** Medicines Regulatory Authority  
**P** Pharmacy  
**Ph. Eur** European Pharmacopoeia  
**POM** Prescription Only Medicines  
**PRA** Pharmaceutical Regulatory Authority  
**RF values**-Retention factors  
**RH** Relative Humidity  
**s.c** Sugar coated  
**SPC** Summary of Product Characteristics  
**SR** Sustained release  
**TE** Therapeutic Equivalence  
**TLC** Thin layer chromatography  
**T<sub>max</sub>** Time to reach maximum plasma concentration  
**USP** United States Pharmacopoeia  
**VICH** International Conference on Harmonization of Technical  
**WHO** World Health Organization

## **1 Introduction**

These guidelines are to assist applicants in completing application forms and preparing dossiers for submission to the Zambia they prescribe the format and content of registration dossier, number of samples, fees payable and labelling and package insert information requirements. Compliance to these guidelines in the submission of applications will facilitate the speedy processing and evaluation of the application and hence the product licensing. This will enable the prospective licence holders to market their products on time and make them available to the consumers. In view of this, applicants are advised to read these guidelines carefully and adhere in full to the prescribed instructions.

## **2 Applicants**

An application for registration of a medicine may be made by:

- (i) The prospective holder of the product licence, hereinafter referred to as the applicant.
- (ii) A nominee of the applicant who must submit evidence of empowerment of power of attorney

## **4 Application forms**

- (i) Each application for registration of a medicine must be submitted in accordance with the requirements of the Pharmaceutical Regulatory Authority (PRA).
- (ii) All forms are to be completed in English.
- (iii) Application forms are available from the PRA secretariat and all completed applications are to be submitted to the address below in person or by courier to: The Director General, Pharmaceutical Regulatory Authority, Plot No. 6903, Tuletaka Road, Rhodespark, P.O Box 31890, Lusaka, Zambia
- (iv) An application not submitted in the appropriate format or which is incomplete will be rejected.
- (v) Application for registration must be accompanied by:
  - (a) Two copies of a motivation letter of not more than 500 words as to why the product should be registered.
  - (b) Two copies of package inserts or drafts thereof and 2 labels or drafts thereof
  - (c) Copies of any literature in support of the application.
  - (d) A checklist indicating that all the sections of the application have been completed and the pages thereof.
  - (e) Two samples of the product in the smallest packaging.
- (vi) Each section of the dossier is to be marked by use of clearly annotated tabs.
- (vii) The documentation should be filed in accessible files. **Lever** arch files are not acceptable.

## **5 Application fees**

The application fees applicable are attached on statutory Instrument. Any remittance of fees should take into consideration bank charges. Applicants must ensure that the PRA will receive the correct amount. An application not accompanied by the appropriate fee will be rejected.

## **6 Confidentiality**

The confidentiality of information submitted to the PRA is preserved by legislation.

## **7 Same/Separate Applications**

### **7.6.1 Tablets/Capsules/Suppositories/Lozenges**

- (i) Different pack-sizes of the same strength and formulation will be considered as the same application
- (ii) Different strengths and/or formulations will be considered as separate applications.

### **7.6.2 Syrups/Liquids/Solutions (non parenterals)/Creams/intments**

- (i) Different container sizes of the same strength and formulation will be considered as the same.
- (ii) Same container size of different strengths and/or formulations will be considered as separate applications.

### **7.6.3 Ampoules, Vials and Large Volume Parenterals**

- (i) Ampoules containing identical solutions of the same strength but of different volumes will be considered as separate applications;
- (ii) Ampoules containing solutions of different strengths will be considered as separate applications;
- (iii) Ampoules and/or single dose vials containing dry powder, crystals etc, of different mass will be considered as separate applications;
- (iv) Ampoules and single dose vials containing the same respective masses of dry powder, crystals etc, will be considered as 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 be considered as the same application
- (vi) Dental cartridges containing fluids of different volumes will be considered as the same application;
- (vii) Ampoules containing "water for injection", but of different volume may be considered as 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, may be considered as the same application.
- (ix) Ampoules containing identical solutions of different volumes used only as a diluent in the reconstitution of a preparation for parenteral use, may be considered as the same application, depending on the relevant information being submitted;

- (x) Multi-dose vials of the same strength and formulation in different volumes may be considered as the same application, depending on the relevant information submitted (administered according to the same dosage schedule);
- (xi) Multi-dose vials and a single dose ampoule of the same formulation may be considered as separate applications, if the single-dose ampoule corresponds to the dose indicated for the multi-dose vial;
- (xii) Multi-dose vials containing dry powder of different mass and the same formulation, and having the same concentration when reconstituted may be considered as the same application;
- (xiii) A container of diluent to be used with any preparation in (iii), (iv) or (xii) will be considered as the same 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 may be considered as the same 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, may be treated as the same application, depending on the relevant information submitted;
- (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, shall be considered as separate applications;
- (xvii) Should a preparation, packed in plastic containers, be intended to be marketed in glass containers containing the same volume and the same formulation, it may be considered as the same application provided the following data are submitted :-
  - (a) characteristics of the rubber stopper;
  - (b) specifications for the glass;
  - (c) a comprehensive manufacturing process with particular reference to the washing and sterilization cycles and apparatus used;
  - (d) data on particulate matter (contamination);
  - (e) 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 be considered as 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 scheduling status, or different pharmacological classification or have any other restrictions imposed other than the original application, will require a separate registration.

## **8 Different applicants/proprietary names for same formula**

Same formulation applied under different proprietary names will be considered as separate applications.

## **PART IA GENERAL INFORMATION**

### **1 Details of Applicant**

The name and the addresses (both business and postal) should be indicated. The applicant is the future Product licence holder.

#### **1.1 Details of responsible person**

The full name and addresses of the responsible person are to be indicated for contact purposes. The person must submit evidence of power of attorney.

#### **1.2 Details of Manufacturers**

The name and addresses (physical and postal) for all the manufactures involved in the manufacture of the product are to be indicated. The steps(s) of manufacturing process performed should also be indicated for each site.

#### **1.3 Source (manufacturers) of Active Pharmaceutical Ingredient(s) (API)**

The manufacturer(s) of the API should be indicated. The details of any contract company used at development of the formulation, bioavailability or bioequivalence trials should be indicated.

### **2 Proprietary Name**

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 medicinal product so as to cause confusion. The generic name should also be defined.

#### **2.1 Name(s) of active pharmaceutical ingredient(s)**

The English INN of all the active ingredients and the strength in the formulation should be given.

#### **2.2 Pharmacotherapeutic classification**

The anatomical-therapeutic classification (ATC) system should be used to categorize a product.

### **3 Pharmaceutical dosage form**

It should be stated what form the product is e.g. tablet, solution, etc.

#### **3.1 Route of administration**

The route of administration e.g. oral, intramuscular (IM) injection, rectal, should be indicated

#### **3.2 Container, closure and administration devices**

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

#### **3.3 Package sizes**

The different package sizes are to be stated.

#### **3.4 Shelf life**

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

- (iii) the shelf life after reconstitution should be indicated
- 3.5 Storage conditions**  
The conditions under which the finished packaged product should be stored, e.g. store in a cool dark place at 15°C - 25°C, should be stated.
- 3.6 Categories for Distribution**  
The following categories apply to ensure the safe handling of medicinal products:
- (i) **Prescription Only Medicine (POM)**
  - (ii) **Pharmacy Medicine (P)**
  - (iv) **General Sales Medicines (GS)**
- 4 Registration in the country of original development**  
The details of registration in the country of original development are required. The country of origin is defined as the country in which the holder of the Product licence for the medicine is based. Reasons for non-registration should be stated if the medicine is not registered in the country of origin or country of manufacture.
- 5 Registration in other countries**  
Registration status in other countries should be indicated including any withdrawal, cancellations, suspension / revocations. The reasons for these should also be indicated.
- 6 Proposed indications**  
The uses for which the medicinal product is being registered should be indicated.
- 7 Unit (Master) Formulation**
- (i) The composition of dosage unit including coatings and capsule compositions should be indicated. The formula must show the approved (INN) names of all active raw materials and excipients including those that are removed during manufacture and do not appear in the final product. Ingredients that are not added to every batch e.g. acids/alkali should also be indicated. Special features for the ingredients should be indicated e.g. micronised, solubilised, emulsified etc.
  - (ii) A product may contain more than one active pharmaceutical ingredient provided that:
    - (a) Each active ingredient makes a contribution to the claimed indications;
    - (b) The effect of combining the active ingredients in one product does not decrease the safety, stability or efficacy of the product; and

- (c) The product provides rational concurrent therapy for a significant proportion of the target population.
- (iii) The purpose of each inactive raw material must be stated briefly. If the excipient is used for multiple purposes in the formulation, each purpose must be mentioned.
- (iv) Any overages for the active ingredient must be indicated and justified.
- (v) Where a potency adjustment for the active ingredient has to be made, a statement to the effect that the actual quantity of the active will depend on the potency, and the excipient(s) that will be used to adjust the bulk quantity must be mentioned, as well as the manner in which the adjustment will be made.
- (vi) Flavouring and colouring agents, because of their complexity in many instances, may be described in terms of their main constituents only, provided that appropriate chemical identification and characterisation for them is given in the relevant section. The Index Numbers of colourants must be included in the formula. The use of dyes, printing ink, coating materials, flavourants and organic solvents is subject to the same and quality requirements that apply to medicinal substances.
  
- (vii) The content of alcohol, if included, for oral and intravenous medicines must not exceed the stated maximum concentrations.
  - (a) The following maximum concentration limits will be allowed for ethyl alcohol as inactive ingredient in products intended for oral ingestion:
    - 1) 0,5 % v/v ethyl alcohol for children under 6 years of age
    - 2) 5,0 % v/v ethyl alcohol for children 6-12 years of age
    - 3) 10,0 % v/v ethyl alcohol for adults and adolescents over 12 years of age
  - (b) Minute dose preparations are exempted from this requirement.
  - (c) For products where higher concentration of alcohol are required, (e.g. plant extracts or where solubility or preservation might be problematic), exemption from ethanol concentration limits will be considered individually, provided that justification and motivation is submitted together with proof that the proposed dosage will not result in blood alcohol levels of 25mg/dl or higher.



- (d) The presence of alcohol in the product must be declared, and the concentration stated, on the label, the package insert and in the patient information leaflet.
- (viii) Where the vehicle is added up to the required volume or mass of the product, the actual or estimate quantity of that vehicle may be stated. However, expressions such as "add up to" and "qs" is acceptable. Solutions added to adjust the pH must be described in terms of composition and strength (normality, morality, etc.) but it is not necessary to state the actual quantity added as none may be added or only minute quantities may be needed.
- (ix) For biological medicines the details of any solution supplied by the manufacturer for the reconstitution before use of a dried biological medicine, which is offered for sale in a dried form, shall be supplied.

## **8 Declaration by an 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.

## **PART IB      PRODUCT PROFILE**

### **9.      Summary of product characteristics**

#### **9.1      Proprietary name of a medicinal product**

The name invented by the Product licence holder to distinguish the product from others containing the same API (s)

#### **9.2      Approved generic name(s)**

The INN by which the API(s) are known.

#### **9.3      Qualitative and quantitative composition**

The name of the ingredient (s) , their specifications e.g. BP , USP , EP etc and the quantities per dosage form are to be indicated for all the ingredients which are in the final product .

#### **9.4      Dosage form**

The form in which the product will be marketed is indicated e.g. tablet, syrup, injection

#### **9.5      Clinical particulars**

- (i)      Therapeutic indication(s) - the conditions for which the product is to be used as a medicine should be indicated.
- (ii)      Route of administration - the instructions for the administration of the medicine should be indicated e.g. for oral use, for external use only, for ophthalmic use etc.
- (iii)      Contra-indications- the situations in which the product should not be used are to be stated
- (iv)      Special warnings and precautions for use - the situations for which special attention and care should be exercised in the use of the product should be stated
- (v)      Interactions - all the known and possible interactions that may occur in the use of the product are to be indicated
- (vi)      Pregnancy and lactation - information should be given as to the suitability of the use of the product during pregnancy and lactation
- (vii)      Effects on the ability to drive and operate machinery - any effects on the ability to drive and operate machinery should be stated
- (viii)      Undesirable effects - any potential or known undesirable effects associated with use of the product should be indicated
- (ix)      Overdose - the particulars concerning the use of an excessive dose, the effects of this and its treatment should be indicated

#### **9.6      Pharmacological properties**

- (i)      Pharmacodynamic properties - the mode of action of the active ingredient (s) in the body should be discussed in detail
- (ii)      Pharmacokinetic properties - the absorption, distribution and excretion of the active ingredients should be discussed in detail .
- (iii)      Preclinical safety data - summaries of studies done in animals to indicate the safety of the active ingredient(s) in humans should be included.

#### **9.7      Pharmaceutical particulars**

- (i)      List of excipients - the common name of the excipients should be used in listing the excipients

- (ii) Incompatibilities - the incompatibilities of the excipients with each other , the active ingredient(s) and with the primary packaging
- (iii) Shelf-life - the shelf life of the product in the original unopened container and after reconstitution (where appropriate) should be indicated
- (iv) Special precautions for storage - the storage instructions should be indicated in terms of temperature and exposure to light should be indicated
- (v) Nature and composition of containers - the composition of the container and its properties should be indicated especially in respect of the protection of the product
- (vi) Instruction for use/handling - the instructions for the appropriate use of the product should be indicated Any special features to be carefully observed should be indicated
- (vii) Restriction on sale /distribution

### **9.8 Administrative data**

- (i) Name and address of holder of a Product licence. The name and address (business and postal) of the Product licence holder should be indicated
- (ii) Registration number. The registration number of the product as issued by the PRA should be indicated
- (iii) Date of first registration/renewal of a Product licence. The date when the product was approved / when the registration was renewed should be indicated
- (iv) Date of (partial) revision of the text. The date when the revised text was approved by the PRA should be indicated

### **9.9 Registration in a SADC member state**

The registration status in other SADC member states should be stated.

### **10 Package Insert**

The package insert should comply with the requirements of the summary of product characteristics. It should not contain any claims that cannot be substantiated by submitted information or any misleading statements.

### **11 Patient Information Leaflet (PIL)**

A medicinal product shall not be dispensed without a Patient Information Leaflet unless all the information required in these rules by point 11.1 is conveyed on the outer packaging or on the immediate packaging;

#### **11.1** The PIL shall be drawn up in accordance with the summary of the product's characteristics. For the identification of the product it shall include, in the following order, the following information:

- (a) The name of a medicinal product
- (b) A full statement of the active ingredient(s) and excipient(s) expressed qualitatively and a statement of the active ingredient(s) expressed

- quantitatively, using their common names; the content of the active ingredient shall be stated per dosage unit (e.g. tablet, capsule);
- (c) In the case of an active ingredient present in the form of a derivative (e.g. salt or ester), it shall be stated and the equivalent amount of active substance shall be stated;
  - (d) For liquids the content of each active ingredient shall be specified per one millilitre of the solution per dosage unit (e.g. drop, measuring spoon);
  - (e) For ointments, creams, gels the quantity of the active ingredient per one gram of the ointment, cream, gel shall be stated, or the content of the active ingredient per percentage of weight;
  - (f) For parenterals, for rehydration and dialysis solution containing inorganic salts, the quantity of the active ingredient (s) shall be additionally indicated also in millimoles;
  - (g) For dosage forms, where the active ingredient is presented as a powder for reconstitution and the quantity needed for single administration, the label shall state that the product contains x mg of the active ingredient per ml when reconstituted as recommended; the instructions for reconstitution are required on the label;
  - (h) For transdermal patches, the content of the active ingredient, the quantity-releasing surface shall be stated on the outer and immediate package;
  - (i) For aerosols the content of the active ingredient per one dose shall be stated;
  - (j) The dosage form and contents by weight/mass, by volume or by number of doses of the medicinal product, in the case of each presentation of the product, for multidose products, the quantity in the package (number of tablets, capsules, suppositories, ampoules) shall be stated. For liquids (e.g. mixtures suspensions) the total volume for the liquid shall be stated. For solutions for injection the amount of liquid per ampoule, vial shall be stated. For ointments, creams, gels the total quantity in grams shall be stated. For aerosols the number of doses and total volume shall be stated.
  - (k) The pharmaco-therapeutic group, or type
  - (l) type of activity in terms easily comprehensible for the patient
  - (m) The name and address of the holder of a Product licence, in case the manufacturer is not the holder of a Product licence, both shall be stated
  - (n) Warnings
    - (i) "Please read this Leaflet carefully before taking your medicinal product. If you need some more information, consult your doctor or pharmacist"
    - (ii) For prescription only medicinal products, additionally: "Do not give this medicinal product to other persons, even if their symptoms seem similar to yours";
  - (o) Therapeutic indications - a list of information that is necessary before the medicinal product is taken
  - (p) Contraindications, (remark: "Inform your doctor before taking medicinal product if you have any of the before-mentioned conditions");
  - (q) Precautions for use;
  - (r) Interactions with other medicinal product and other forms of interaction (e.g. alcohol, tobacco, foodstuffs) which may affect the action of a medicinal product; (remark: " Inform your doctor, if you are taking other medicinal products");

- (s) Special warnings, this list must take into account the particular condition of certain categories of users (e.g. children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions); mention if appropriate, potential effects on the ability to drive vehicles or operate machinery (drowsiness, decrease in reaction speed), a list of those excipients known to have a recognised action or effect;
- (s) Instructions for use:
  - (i) The dosage; (if the medicinal product may be administered to newborn, infant, under-3 years old, the doses must be specified per one kg of body weight per day;
  - (ii) The method of administration (whether it depends on mealtimes. whether it should be swallowed intact, masticated, dissolved, sucked, if one should drink water after ingestion and if necessary, route of administration (in case of a topical preparation a statement whether the product can be administered on mucous membrane; in case of an eye or ear preparation reference to aseptic procedures, method of administration);
  - (iii) The frequency of administration, specifying if necessary the appropriate time at which the product may or must be administered;
  - (iv) If appropriate, the duration of treatment; when it should be stopped; may the treatment be stopped when the patient feels better? Remark: "Consult your doctor, if symptoms persist";
  - (v) If appropriate, the action to be taken in the case of an overdose (e.g. symptoms. Emergency procedures), recommended remarks: "In case of overdose, contact your doctor immediately". For topical preparations: "In case of accidental swallowing, contact your doctor immediately";
  - (vi) If appropriate, the information about the risk of withdrawal effects;
  - (vii) If appropriate, the course of action to be taken when or more doses has not been taken;
- (t) A description of the undesirable effects which can occur under normal use of the product and, if necessary, the action to be taken in case, the patient should be invited to consult his/her doctor  
Remark: "Inform your doctor about the development of undesirable effects which are not mentioned in this leaflet
- (u) A reference to the expiry date indicated on the label, with a warning against using the product after this date
- (v) Where appropriate, special storage precautions (e.g. protect from light, humidity, heat or freezing)
- (w) If necessary, a warning against certain visible signs of deterioration
- (x) The date on which the leaflet was last revised
- (y) Special particulars:
  - (i) The leaflet may include symbols or pictograms designed to clarify information compatible with the summary of the product's characteristics, to the exclusion of any promotional material

- (ii) The leaflet shall be written in English and/or other official languages (except the name of a medicinal product) be legible and clearly comprehensible. The information should be the same in all languages used
- (iii) Promotional material should not be included in the insert

## **12A Immediate Container Label**

The label should have all the information specified under this section. In addition the statements "Not for resale", "Professional sample", "For State use only" may be included as appropriate. The actual label or draft thereof should be submitted.

- (i) The proprietary name of a medicinal product followed by a common name where a medicinal product contains only one active ingredient and if its an invented name; where a medicinal product is available in several pharmaceutical dosage forms and/or several strengths, the pharmaceutical dosage form and/or strength shall be expressed in the name of a medicinal product; the name of the medicinal product shall differ from the names of the previously registered medicinal products by at least two letters;
  - (ii) INN in English
  - (iii) The name of active pharmaceutical ingredient and quantity of each
  - (iv) The pharmaceutical dosage form e.g. tablet, suspension etc
  - (v) Specific excipients and content e.g. preservatives, ethyl alcohol and anti-oxidants
  - (vi) The route of administration e.g. oral use, for vaginal use etc
  - (vi) Storage Instructions
  - (vii) A special warning, if necessary, for the medicinal product;
  - (viii) Date of manufacture of the medicine
  - (ix) Expiry date (month/year ) for the product according to the shelf life granted by the PRA
  - (x) The name and address of the holder of a Product licence; in the case the manufacturer of the holder of a Product licence, both shall be stated;
  - (xi) Name and address of the manufacturer
  - (xii) The registration number of a medicinal product on the market;
  - (xiii) The manufacturer's batch number;
  - (xiv) In the case of a General sales medicine, instruction (indications and dosage ) on the use of the medicinal product;
  - (xv) The following particulars shall appear on blister packaging
    - (a) Proprietary name
    - (b) Name and address of manufacturer
    - (c) Storage instructions
    - (d) Name of licence holder
    - (e) Expiry date
    - (d) Batch number
  - (xvi) The following particulars at least shall appear on small units (5 ml containers):
    - (a) Name of a medicinal product and if necessary, the strength and route of administration;
    - (b) Method of administration;
    - (c) Expiry date
    - (d) Batch number;
    - (e) Contents by weight/mass, by volume or by units;

## **12B Outer packaging label**

There should be no promotional material included in the text.

The following particulars shall appear on the outer packaging of a medicinal product, or where there is no outer packaging, on the immediate packaging:

- (i) The proprietary name, if any of a medicinal product followed by a generic name where a medicinal product contains only one active ingredient and if it is an invented name. Where a medicinal product is available in several pharmaceutical dosage forms and/or several strengths, the pharmaceutical dosage form and/or strength shall be expressed in the name of a medicinal product; the name of the medicinal product shall differ from the names of the previously registered medicinal products by at least two letters;
- (ii) A statement of the active ingredients expressed qualitatively and quantitatively, using common names and the dosage form. If a medicinal product contains only one active ingredient, the content of the latter shall appear together with the name of that medicinal product. If a medicinal product contains more than one active ingredient, the content of each ingredient shall be stated per one dose. In the case of an active ingredient present in the form of a derivative (salt or ester), it shall be stated on the label and the equivalent amount
- (iii) The pack size for the medicine e.g. 100 capsules, 100 ml etc.
- (iv) A list of those excipients known to have a recognised action or effect and included in the guidelines. However, if the product is injectable, or a topical or eye preparation, specific excipients must be stated.
- (v) The method of administration, if not for oral use, the route of administration;
- (vi) A special warning that the medicinal product must be stored out of reach of children;
- (vii) A special warning, if this necessary, for the medicinal product;
- (viii) The expiry date in clear terms (month/year);
- (ix) The date of manufacture in clear terms (month/year);
- (x) Storage requirements and necessary precautions
- (xi) Special precautions for disposal of an unused medicinal product or waste materials derived from such products, when applicable;
- (xii) The name and address of the holder of a Product licence; in the case the manufacturer of the holder of a Product licence, both shall be stated;
- (xiii) The registration number of a medicinal product on the market;
- (xiv) The batch number;
- (xv) In the case of a General sales medicine instruction on the use of the medicinal product;
- (xvi) The outer packaging may include symbols or pictograms, designed to clarify certain information mentioned in paragraph 1 and other information compatible with the summary of the product characteristics, which is useful for health education , to the exclusion of any element of a promotional nature ;

## **PROPOSED PACKAGING, PACKAGE INSERT, PATIENT INFORMATION LEAFLET AS WELL AS LABELLING**

- (i) A replica of both the outer and immediate container packaging must be presented with the artwork design and full colour as it will be on the market with a clearly label, package insert and patient information leaflet text.
- (ii) All further amendments to the summary of product characteristics and package inserts must first be brought to the PRA for evaluation and approval.
- (iii) The summary of a product's characteristics may only be distributed after approval by the PRA.
- (iv) The package insert as well as the patient information leaflet and the instruction for use of an GS must be based on the approval by the PRA summary of the product's characteristics.
- (v) Legibility of the labels and the package insert:
  - (a) Print size and type: The particulars appearing on the label and on the package leaflet , of all medicinal product should be printed in characters of at least 7 points Didot (or of a size where the lower case x is at least 1.4mm in height ) and leaving a space between lines of at least 3.2mm . The type of print chosen should be such as to ensure maximum legibility
  - (b) Print colour: Readability is not only determined by print size. The characters may be printed in one or several colours allowing them to be clearly distinguished from the background. A different colour may be used for headings.
  - (c) Syntax: Sentences should be avoided as far as possible. It should be ensured that the lines of a length exceeding 70 characters are not used. Different fonts for upper and lower cases to be used. Length of words, number of clauses per sentence and length of sentences can all influence readability.

## **PART IIA BIOAVAILABILITY / BIOEQUIVALENCE DATA**

Data about the bioavailability must be presented concerning the medicinal products acting systemically, which are administered enterally and which have not been registered before.

If the medicinal product acting systemically with same active ingredient with similar pharmacokinetic properties for enteric administration has been registered before, the data about bioequivalence studies where the reference preparation is generally accepted or the medicinal product acting systemically with the same active ingredient with similar pharmacokinetic properties for enteric administration registered previously in the SADC region or any other must be presented.

The reference product chosen for the bioequivalence studies must be brought in concordance with the PRA. For enterally administered



modified release medicinal products acting systematically the steady-state bioavailability studies must be presented. Bioavailability and Bioequivalence studies refer to Bioavailability Guideline.

## **PART IIB EXPERT REPORTS**

The expert reports should be submitted as per the requirements under this section. Clinical and Pharmaceutical information:

- (i) Chemical and pharmaceutical documentation
- (ii) Toxicological and pharmacological documentation
- (iii) Clinical documentation

## **PART III CHEMICAL AND PHARMACEUTICAL INFORMATION**

### **PART IIIA COMPOSITION**

#### **1 Composition of the medicinal product**

- (i) The formula for the dosage unit in terms of ingredients (Active and Non Active), contents, reference standards and reason for inclusion

#### **2 Container /packaging**

- (i) Nature of container materials
- (ii) Qualitative composition
- (iii) Method of closure
- (iv) Method of opening

#### **3 Clinical trial formula(e) for new chemical entities**

### **PART IIIB DEVELOPMENT PHARMACEUTICS**

- (i) Explanation with regard to the choice of formulation, composition, ingredients and container, supported if necessary, by data on development pharmaceuticals
- (ii) The overage, with justification thereof
- (iii) Tests carried out during pharmaceutical development must be described in detail e.g. in vitro dissolution studies for solid pharmaceutical forms must be stated.
- (iv) Reasons for the choice of the primary packaging must be given.

### **PART IIIC CONTROL OF THE STARTING MATERIALS**

#### **1 Active pharmaceutical ingredients (API)**

- (i) Route of synthesis including impurities

- (a) Scientific data:
  - (1) Nomenclature;
  - (2) International Non-proprietary Name (INN);
  - (3) Chemical name;
  - (4) Other names;
  - (5) Laboratory code;
  - (6) Description;
  - (7) Physical form;
  - (8) Structural formula including conformational data for macromolecules;
  - (9) Molecular formula;
  - (10) Relative molecular mass;
  - (11) Chirality.
- (b) Manufacture:
  - (1) Name (s) and address(es) of manufacturing source (s);
  - (2) Synthetic or manufacturing route, including flow chart for the process;
  - (3) Description of process, including in-process control;
  - (4) Analysts, also data about solvents, reagents, auxiliary materials;
  - (5) Purification stages, including reprocessing criteria for purification steps supported by data.
- (c) Quality control during manufacture:
  - (1) Starting materials;
  - (2) Control tests on intermediate products (where appropriate);
- (d) Development chemistry:
  - (1) Evidence of chemical structure (synthetic route, key intermediates, elemental analysis, mass spectrum, NMR, IR, UV, other);
  - (2) Potential isomerism;
  - (3) Physicochemical characterisation (solubility, physical characteristics, polymorphism, pKa and pH values, other);
  - (4) Full characterisation of primary reference material;
  - (5) Analytical validation and comments on the choice or routine tests and standards, e.g. working standard;
- (e) Impurities:
  - (1) Potential impurities originating from the route of synthesis;
  - (2) Potential arising during the production and purification (degradation products);
  - (3) Analytical test procedures and their limits of detection;
- (f) Batch analysis:
  - (1) Date of manufacture, place of manufacture, batch size, and use of batches tested including batches used in pre clinical in pre clinical and clinical testing;
  - (2) Results of tests;
  - (3) Analytical results of reference material, primary and others

- (ii) Physical and chemical characteristics  
The physicochemical properties of the API should be presented.
- (iii) Specifications and routine tests:
  - (a) Active substance(s) described in the pharmacopoeia; a copy of pages of the said pharmacopoeia should be presented.
  - (b) Active substance(s) not described in the pharmacopoeia:
    - (1) Characteristics;
    - (2) Identification tests;
    - (3) Purity tests (including limits for named, total, other single, unidentified single and unidentified total impurities):
  - (c) Physical, chemical, other tests.
- (iv) Certificates of analysis of the API
- (v) Analytical validation for the test methods used for the analysis of the API should be submitted
- (vi) Stability data for the API should be generated and presented as per stability guidelines

## **2 Excipient(s)**

- (i) Specifications and routine tests:
  - (a) Excipient(s) described in a pharmacopoeia; a copy of the pharmacopoeia is acceptable
  - (b) Excipient(s) not described in the pharmacopoeia;
    - (1) Characteristics;
    - (2) Identification tests;
    - (3) Purity tests, including limits for named, total, other single and unidentified single and unidentified total impurities: physical chemical;
    - (4) Other tests;
    - (5) Assay(s) and/or evaluations, where necessary.
- (ii) Additional tests  
Any additional tests done on the excipients must be indicated here
- (iii) Scientific data (excipients used for the first time in a medicine )
  - (a) Nomenclature
  - (b) International non-proprietary name (INN)
  - (c) Chemical name
  - (d) Other names
  - (e) Laboratory name
  - (f) Physicochemical properties
  - (g) Potential and actual isomerism
  - (h) Specifications

**PART IIID PACKAGING MATERIAL (IMMEDIATE PACKAGING)**

- (i) Specifications and routine tests:
  - (a) Type of material;
  - (b) Construction;
  - (c) Quality specifications (routine tests) and test procedures
- (ii) Scientific data:
  - (a) Development studies on packaging materials;
  - (b) Batch analysis results;

**PART IIIE CONTROL TESTS ON INTERMEDIATE PRODUCTS (IF NECESSARY)**

- (i) Identification of intermediate product e.g. powder mix or granules ready for compression
- (ii) Specification of the intermediate product
- (iii) Justification for the tests and the control tests in detail

**PART IIIF: CONTROL TESTS ON THE FINISHED PRODUCT**

- (i) Specifications and routine tests:
  - (a) Pharmacopoeial (include copy of the monograph);
  - (b) In-house (supply details)
  - (c) Quality specifications (routine tests) and test procedures. The detailed methods should be submitted to allow repetition of the tests by another laboratory
- (ii) Justification for tests must be given
- (iii) Analytical validation of methods and comments on the choice routine test and standards (e.g. working standards).

### **PART III G    METHOD OF PREPARATION FOR THE FINISHED PRODUCT**

- (i) Batch manufacturing formula including details of batch size
- (ii) Site of manufacture
  - (a) The name and business address of each manufacturing facility where any aspect of manufacture occurs including activity performed in each site
  - (b) GMP certificate for each site and the manufacturing licence from the DRA must be submitted
- (iii) For domestic companies supply the current license number issued by a regional or national DRA.
- (iv) Manufacturing process
  - (a) Detailed manufacturing procedure including equipment, in process controls, processing conditions and packaging procedure must be presented.
  - (b) A flow chart of the entire manufacturing process (including packaging and labelling) must be presented
  - (c) Validation of the process when a non-standard method of manufacture is used or it is critical for the product. Experimental data showing that the manufacturing process, using materials of the stated quality and the types of manufacturing equipment specified, is a suitable one and will consistently yield a product of the desired quality, which is described in the finished product specification.
  - (d) A copy of the Master formula should be presented
  - (e) Copy of the batch manufacturing record including the ingredient analytical reports, in process control tests reports, intermediate product test reports, reconciliation records and a certificate of analysis for the batch must be presented.

### **PART III H    STABILITY TESTS ON THE FINISHED PRODUCT**

- (i) Quality specification for the proposed shelf-life
- (ii) Characteristics to be tested and the justification thereof
- (iii) Batches types and sizes tested
- (iv) Packaging material and the sizes where applicable
- (v) Real-time and accelerated conditions
- (vi) Validation of stability indicating tests
- (vii) Results of tests, including initial results and reference to degradation products
- (viii) Discussion of the results must be done
- (ix) Conclusion and shelf life claim is expected in relation to the results

## **PART IV SUMMARY OF TOXICO-PHARMACOLOGICAL DOCUMENTATION OF A MEDICINE**

### **BRIEF SUMMARY:**

The principal findings from the toxicology studies should be summarised. The scope of evaluation should be described in relation to the proposed clinical use. A comment on the GLP status of the studies should be included.

### **PART IVA SINGLE DOSE TOXICITY**

The data should be summarised by species, by route. In some cases it is helpful to provide the data in the form of table.

### **PART IVB REPEAT DOSE TOXICITY**

Studies should be summarised by species, by route and by duration, giving brief details of methodology and highlighting important findings e.g. nature and severity of the target organ toxicity, dose (exposure)/response relationships, no observed adverse effect, levels, etc.

### **PART IVC REPRODUCTION STUDIES**

Summary of the following order, giving details of the methodology and important findings:

- (i) Fertility and early embryonic development
- (ii) Embryo-fetal development
  - (iii) Prenatal and post natal development, including maternal function
  - (iv) Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted.

### **PART IVD GENOTOXICITY**

Summary of the studies in the following order:

- (i) *in vitro* non-mammalian cell system
  - (ii) *in vitro* mammalian cell system
  - (iii) *in vivo* mammalian system (including supportive toxicokinetics evaluation)
- (iv) other systems

### **PART IVE CARCINOGENICITY**

A rationale on the studies that were chosen and the basis for high dose selection individual studies should be summarised in the following order:

- (i) Long-term studies (by species, including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- (ii) Short or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- (iii) Other studies

### **PART IVF PHARMACODYNAMICS**

## **PART IVG PHARMACOKINETICS**

Summary in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings, if local tolerance studies have been conducted.

## **PART IVH LOCAL TOLERANCE**

Summary in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings, if local tolerance studies have been conducted.

## **PART IVJ OTHER TOXICITY STUDIES (if available)**

- (i) Antigenicity
- (ii) Immunotoxicity
- (iii) Dependence
- (iv) Studies on metabolites
- (v) Studies on impurities
- (vi) Other studies

## **DISCUSSION AND CONCLUSIONS**

Discuss the toxicologic evaluation and the significance of any issues that arise. Tables or figures summarising this information are recommended.

## **PART V SUMMARY OF CLINICAL STUDIES**

### **PART VA HUMAN PHARMACOLOGY**

- (i) Pharmacodynamics
- (ii) Pharmacokinetics

### **1 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES**

#### **Product Development Rationale**

The discussion of the product development rationale should:

- (i) Identify the pharmacological class of the medicinal product
  - (ii) Describe the particular clinical/pathophysiological condition that the medicinal product is intended to treat, prevent, or diagnose.
  - (iii) Briefly summarise the scientific background that supported the investigation of medicinal product for the indication(s).
  - (iv) Briefly describe the clinical development programme of the medicinal product including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the programme.
- (v) Briefly describe plans for the use of foreign clinical data.

### **2 SUMMARY OF BIOPHARMACEUTIC (BC) STUDIES AND ASSOCIATED ANALYTICAL METHODS**

- (i) Background and Overview

The general approach and rationale in developing bioavailability (BA), comparative BA, bioequivalence (BE), in vitro dissolution profile. Reference should be made to any guidelines or literature used in planning and conducting the studies. This section should also provide performance characteristics of assay validation (e.g. linearity range, sensitivity, specificity) and quality control (e.g. accuracy and precision).

(ii) Summary of results of Individual Studies

A tabular listing of all BCS studies should be provided, together with narrative descriptions of all relevant features and outcomes of each individual studies that provided in vitro or in vivo data and information relevant to BA and BE. And any individual results and any differences among studies. References should be included in the narratives.

(iii) Comparison and Analyses of Results Across Studies

This section should provide a factual summary of all in vitro dissolution, BA and comparative BA studies carried out with the medicinal substance or drug product, with particular attention to differences in results across studies. Findings should summarised in text and tables. And the following should be considered:

- (a) Evidence of the effects of formulation and manufacturing changes on in vitro dissolution and BA and conclusion regarding BE. When manufacturing or formulation changes are made for products containing complex medicinal substances (e.g. protein), PK studies comparing the product before and after changes may be performed to ensure that the PK characteristics have not changed as a result of product changes. Note also that PK studies alone may not be sufficient to assure similarity between such medicinal products. In many situations, PD studies or clinical trials may be necessary. In addition antigenicity data may also be needed. Results of these other studies, when they are needed, can be reported in the appropriate sections in the dossier.
- (b) Evidence of the extent of food effects on BA and conclusions regarding BE with respect to meal type or timing of the meal (where appropriate).
- (c) Evidence of correlation between in vitro dissolution and BA, including the effects of pH on dissolution, and conclusions regarding the dissolution specifications.
- (d) Comparative BA, including BE conclusions, for different dosage form strengths.
- (e) Comparative BA of the clinical study formulations (for clinical studies providing substantial evidence of efficacy) and formulation to be marketed.
- (f) The source and magnitude of observed inter-intrasubject variability for each formulation in a comparative BA study.



### 3 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

- (i) **Background and Overview**

This section should provided clinical studies performed to evaluate PK, PD and in vitro studies with human cells, tissues or related materials that are pertinent to PK processes. Studied of permeability (e.g. intestinal absorption, blood brain barrier passage), protein binding, and hepatic metabolism. And metabolic-based drug-drug interactions are particular relevant. This should be followed by a brief overview of clinical studies that were carried out to characterise PK and PD of the medicinal product, including studies on PK/PD relationship in healthy subjects and patients, and relevant effects of intrinsic and extrinsic factors on PK and PK/PD relationships. Critical aspects of design studies and data analysis should be noted e.g. choice of PD endpoints, and whether a traditional approach or a population approach was used to collect and analyse data to assess PK or PD.
- (ii) **Summary of Results of Individual Studies**

A tabular listing of all clinical pharmacology studies should generally be provided, together with a narrative description of the relevant features and outcomes of each critical individual studies that provided in vitro and in vivo data and information relevant to PK, PD and PK/PD relationships. Summary of dose-response or concentration response (PK/PD) studies with PD endpoints should be included.
- (iii) **Comparison and Analyses of Results Across Studies**

This section should provide the results of all in vitro, and PK, PD and PK/PD studies to characterise the PK, PD and PK/PD relationships of the medicine. Results related to the inter and intra-individual variability and the intrinsic and extrinsic factors affecting these PK relationships should be discussed. This section should provided a factual presentation of all data across studies with the use of text and tables:

  - (a) *In vitro* drug metabolism and in vitro drug-drug interaction studies and their clinical implications.
  - (b) Human PK studies, including estimates of standard parameters and sources of variability. The focus should be on evidence supporting dose and dose individualisation in the target patient population and in special population e.g. paediatric or geriatric or patients with renal or hepatic impairment.
  - (c) Comparison between single and repeated-dose PK.
  - (d) Population PK analyses, such as results based on sparse sampling across studies that address inter-individual variations in the PK or PD of the active medicinal substances that may be due to extrinsic or intrinsic factors.
  - (e) Dose-response or concentration response relationship. The discussion should highlight evidence of selecting dosages and dose intervals studies in the clinical trials. In addition information that supports the dosage instructions in the proposed labelling.

- (f) Major inconsistencies in the human biomaterial, PK or PD database.
  - (g) PK studies that were performed to determine foreign clinical data could be extrapolated to the new region. The results of the studies and analysis of the similarity of the PK data between regions or races should be summarised.
- (iv) **Special Studies**  
This section should include studies that provide special types of data relevant to specific types of medicinal products. For immunogenicity studies and other studies in which data may correlate with PK, PD, safety, and/or efficacy data, explanations of such correlations should be summarised here. E.g.:
- (a) **Immunogenicity**  
For protein products and other products to which specific immunological reactions have been measured, data regarding immunogenicity should be summarised. Assays used should be briefly described and information about their performance (e.g. sensitivity, specificity, reliability, and validity) should be summarised; the location in the application of the detailed information should be cross-referenced. Data regarding the incidence, titre, timing of onset and duration of antibody responses should be summarised for each type of antibody assay used. Relationship of antibody formation to underlying diseases, concomitant medication, dose, duration, regimen and formulation should be explored and summarised. For medicines intended to be given as chronic, continuous therapy, any data on the impact of interruptions of therapy on antigenicity should be analysed and summarised.
  - (b) **Clinical microbiology**  
For antimicrobial or antiviral medicinal products, in vitro studies to characterise the spectrum of activity. Studies that evaluate findings as pattern of in vitro susceptibility of strains of bacteria from different parts of the world would be included here.

## **PART VB CLINICAL DOCUMENTATION**

### **1 SUMMARY OF CLINICAL EFFICACY**

- (i) **Background and Overview of Clinical Efficacy**  
This section should describe the programme of controlled studies and other pertinent studies in the application that evaluated efficacy specific to indication(s) sought. The design of controlled studies that were conducted to evaluate efficacy. These studies include dose-response, comparative efficacy, long-term efficacy and efficacy studies in population subsets. Critical features of study design should be discussed e.g. randomisation, blinding, choices of control treatment, choice of patient population,

unusual design features such as crossover or randomised withdrawal designs, use of run-in periods other methods of "enrichment", study endpoints, study duration and pre-specified plans for analysis of the study results.

(ii) Summary of results of Individuals Studies

A table listing all studies that provided (or were designed to provide) information relevant to product efficacy should be provided. Together with narrative descriptions for important studies. Narratives of any bridging studies using clinical endpoints, i.e. certain studies intended to evaluate the ability to extrapolate certain types of foreign clinical data to the new region. An analysis of the results together with other information that addresses the ability to extrapolate the efficacy and safety results of foreign studies, should be performed if necessary.

(iii) Comparison and Analyses of Results Across Studies

Summary of all available data that characterise the efficacy of the medicine. This summary should include analyses of all data, irrespective of their support of the relevant studies, do or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed any areas needing further exploration should be identified. This section utilises two kinds of comparison namely comparison of results of individual studies, and analysis of data combined from various studies. Data that support dosage and administration section of the label, dose interval recommended, evidence pertinent to individualisation of dosage and need for modifications of dosage for specific b (e.g. paediatric or geriatric subjects or subjects with hepatic or renal impairment) and data relevant to dose-response or concentration response (PK/PD) relationship).

(a) Study populations

The demographic and baseline characteristics of patients across all efficacy studies should be described. The following should be included:

- The characteristics of the disease (e.g. severity, duration) and prior treatment in study subjects, and study inclusion/exclusion criteria.
- Differences in baseline characteristics of the study populations in different studies or groups of studies.
- Any differences between populations included in critical efficacy analyses and the overall patient that would be expected to receive the medicine when it is marketed should be noted.
- Assessment of the number of patients who dropped out of the studies, time of withdrawal (a defined study day or visit during treatment or follow-up period), and reasons for discontinuation.

(b) Comparison of Efficacy Results of All Studies

An analysis of the similarity of efficacy in subjects between regions, as well as any other information that may support

extrapolation of the efficacy data to the new region, should be summarised. The results from all studies designed to evaluate the medicine's efficacy should be summarised and compared, including studies with inconclusive or negative results. Important differences in study design such as endpoints, control group, study duration, statistical methods, patient population and dose should be identified.

Confidence intervals for treatment effects should be given to aid interpretation of point estimates. If differences are shown between placebo and test medicines in the change from baseline, the baseline values and the magnitude of effect in all treatment groups, including placebo and active controls, should be presented in the table or text accompanying a figure. If the objective of an active control trial was to show equivalence or non-inferiority, the difference or the ratio of outcomes between treatments should be given with confidence interval. The results should be evaluated by using the predefined criteria for defining equivalence or non-inferiority and the rationale for the criteria and support for the determination that the study had assay sensitivity should be provided.

Important differences in outcomes between studies with a similar design should be delineated and discussed. Cross-study comparisons of factors that may have contributed to differences in outcomes should be described.

If a meta-analysis of the clinical studies is performed, it should be clear whether this analysis is conducted according to a predefined protocol or a post hoc exercise. Any differences in trial designs or populations, or in efficacy measurements between trials should be described to allow assessment of the relevance and validity of the results and conclusions.

(c) **Comparison of Results in Sub-populations**

The results of individual studies analyses of efficacy in specific populations should be summarised in this section. The purpose of this comparisons should be show whether the claimed treatment effects are observed consistently across all relevant sub-populations, especially those where there are special reasons for concern.

Given the limited sample sizes in individual studies, analyses across multiple studies should be performed to evaluate effects of major demographic factors (age, sex, and race) and other predefined or relevant intrinsic and extrinsic factors (e.g. disease severity, prior treatment, concomitant illness, concomitant medicines, alcohol, tobacco, and body weight) on efficacy. Factors of special interest may arise from general concerns e.g. the elderly or from specific issues that are related to the pharmacology of the medicine or that have arisen during medicinal development.

Efficacy in the paediatric population should be routinely analysed in applications for a proposed indication that occurs in children.

(d) Analysis of Clinical Information Relevant to Dosing recommendations

This section should provide an integrated summary and analysis of all data that pertain to dose-response or blood level-response relationship of effectiveness (including dose-blood level relationship), and thus have contributed to dose selection and choice of dose interval. The individual study results and any cross-study analyses that will be used to support dosing recommendations (including the recommended starting and maximal doses, the method of dose titration, and any other instructions regarding individualisation of dosage) should be summarised here. Any other deviations from relatively simple dose-response or blood-level response relationships due to non-linearity of PK, delayed effects, tolerance, enzyme induction etc should be described.

Any evidence of differences in dose-response relationships that result from patient's age, sex, disease or other factors should be described. Any evidence of different PK or PD responses should be discussed. The way in which such differences were looked for, even if no differences were found should be described (e.g. specific studies in subpopulations, analysis of efficacy results by subgroups, or blood level determinations of test medicines).

(e) Persistence of Efficacy and/or Tolerance Effects

Available information on persistence of efficacy over time should be summarised. The number of patients for whom long-term efficacy data are available, and the length of exposure should be provided. Any evidence of tolerance (loss of therapeutic effects overtime) should be noted.

The primary focus should be on controlled studies specifically designed to collect long-term efficacy data, and such studies be clearly differentiated from other, less rigorous, studies such as open extension studies. In long term efficacy studies, the effect of premature discontinuation of therapy or switching to other therapies upon the assessment of results should be considered.

## 2 SUMMARY OF CLINICAL SAFETY

The display of safety-related data should be considered at three levels:

- The extent of exposure (dose, duration, number of patients, type of patients) should be examined to determine the degree to which safety can be assessed from the database.
- The more common adverse events and changes in laboratory tests should be identified and classified, and their occurrence should be summarised.
- Serious adverse events and other significant events should be identified and their occurrence should be summarised. These events should be

examined for frequency over time, particularly for medicines that may be used chronically.

(i) Exposure to the Medicine

(a) Overall Safety Evaluation Plan And Narratives of Safety Studies

The overall safety evaluation plan should be described briefly, including special considerations and observations concerning the non-clinical data, any relevant pharmacological class effects, and sources of the safety data controlled trials, open studies, etc). A tabular listing of all clinical studies that provided safety data, grouped appropriately, should generally be provided. In addition to studies that evaluated efficacy and safety and uncontrolled studies that generate safety information, this section includes that consider special safety issues. Examples would include studies to compare particular adverse event rates for two therapies, to assess safety in particular demographic subsets, to evaluate withdrawal, or rebound phenomena, or to evaluate particular adverse events (e.g. sedation, sexual function, effects on driving, absence of a class adverse effect). Narrative description of these studies should be provided here, except that narrative descriptions for studies that contributed both efficacy and safety data should be included in section of "Summary Results of Individual Studies" and cross-referenced here. The methods used and the extent of safety monitoring of subjects enrolled in the individual's studies should be provided. If some studies are analysed separately but are grouped for safety analysis, that should be noted, and a single narrative description can be provided.

(b) Overall Extent of Exposure

A table should be generated and appropriate text should be generated to summarise the overall extent of medicinal exposure from all phases of the clinical study development programme. This table should indicate the numbers of subjects exposed in studies of different types and at various doses, routes and duration. If a large number of different doses and/or durations of exposure were used, these can be grouped in a manner appropriate for the medicine. In some cases it may be appropriate to identify diagnostic subgroup and/or groups receiving specific concomitant therapies deemed particular relevant to safety assessment in the intended use.

The dose levels used for each subject in this presentation could be maximum dose received by that subject, the dose with longest exposure and/or mean daily dose, as appropriate. In some cases, cumulative dose may be pertinent. Dosage may be given as actual daily dose or on a mg/kg or mg/m<sup>2</sup> basis as appropriate. If appropriate medicinal concentration data (e.g. concentration at the time of an adverse event, maximum plasma concentration, area under curve) may be helpful in individual subjects for correlation with adverse events of changes in laboratory variables.

It is assumed that all subjects who were enrolled and received at least one dose of the treatment are included in the safety analysis, if that is not so, an explanation should be provided.

- (c) **Demographic and Other Characteristics of Study Population**  
A summary should be provided with an overview of the demographic characteristics of the population that was exposed to the medicine during the development. If the relative exposure of the demographic groups in the controlled trials differed from overall exposure, it may be useful to provide separate tables. In addition one or more tables should show relevant characteristics of the study population as such:
- (1) Severity of the disease
  - (2) Hospitalisation
  - (3) Impaired renal function
  - (4) Concomitant illness
  - (5) Concomitant use of particular medications
  - (6) Geographical location

The text accompanying the tables should mention any imbalances between the medicine and placebo and/or comparator regarding any of the above demographic characteristics, particular if they could lead to differences in safety outcomes. If certain subjects were excluded from studies (concomitant illness, severity of illness, concomitant medications), this fact should be noted.

- (ii) **Adverse Events**
- (a) **Analysis of Adverse Events**  
Data on the frequency of adverse events should be described in text and tables. All adverse events occurring or worsening after treatment has begun (treatment emergent signs and symptoms, those adverse events not seen at baseline and those that worsened even if present at baseline) should be summarised in tables. In cases where differences in safety data are apparent, it is more appropriate to present data by study. The following issues should be considered:
- (1) It is most appropriate data from studies that are of similar design e.g. similar in dose, duration, methods of determining adverse events and population
  - (2) If the incidence for a particular adverse event differs substantially across the individual studies in a pool, the pooled estimate is less informative.
  - (3) Any study with an unusual adverse event pattern should be presented separately.
  - (4) The appropriate extent of analysis depends on the seriousness of the adverse event and the strength of evidence of medicine causation. Differences in rates of

drug-related, serious events or events leading to discontinuation or dosage change deserve more investigation, whereas rates of other adverse events do not merit elaborate analysis.

(5) Examination of which subjects experience extreme laboratory value abnormalities may be useful in identifying subgroups of individuals who are at particular risk for certain adverse events.

(6) Groups of studies that could be used in pooled safety analyses include:

- All controlled studies or subsets of controlled studies, such as all placebo-controlled studies, studies, studies with any positive control, studies with a particular positive control, or studies of particular indications (and thus carried to in different populations). These groupings are considered the best source of information about the more common adverse events and can distinguish drug-related events from spontaneous events. Rates in control and treatment groups should be compared.

- All studies, excluding short-terms studies in healthy subjects. This grouping is most useful for evaluating rarer events.

- All studies using a particular dose route or regimen, or particular concomitant therapy.

- Studies in which adverse event reports are elicited by checklist or direct questioning, or studies in which events are volunteered

- Pools of studies by region

When a decision is made to pool data from several studies, the rationale for selecting the method used for pooling should be described. If substantial differences are seen between clinical trials in the rates of adverse events, these differences should be noted and possible reasons should be discussed (e.g. relevant differences in study populations, in dose administration, or in methods of collecting adverse event data).

(b) Common Adverse Events

It is usually useful to examine more closely the common adverse events that seem to be drug related (e.g. those that show that a dose-response and/or a clear difference between medicine and placebo rates) for relationship to relevant factors including:

(1) dosage mg/kg or mg/m<sup>2</sup> dose

(2) dose regimen



- (3) duration of treatment
- (4) total dose
- (5) demographic characteristics such as age, **sex**, race
- (6) concomitant medication use
- (7) other baseline features such as renal status
- (8) efficacy outcomes
- (9) medicine concentration, where available

It is not all necessary that all such analyses are presented in this report. When the safety analyses are too extensive to be presented in detail in this report, they may be presented in a separate report.

(c) Deaths

A table listing all deaths occurring while on study (including deaths that occurred shortly following treatment termination, e.g. within 30 days or as specified in the protocol, as well as other deaths that occurred later but may have resulted from process that began during studies. Only deaths that are clearly disease -related per protocol definitions and not related to the investigational product, either in studies of conditions with high mortality such as advanced cancer or in studies where mortality from disease is primary study endpoint, should be excepted from the individual study reports. Even these deaths should be examined for any unexpected patterns between study arms, and further analysed if unexplained differences are observed. Deaths should be examined individually and analysed on the basis of rates in individual trials and appropriate pools of trials, considering both total mortality and cause-specific deaths. Potentially relationship to the factors listed under “Common Adverse Events” should be considered.

(d) Other Serious Adverse Events

Summary of all serious adverse events (other than death but including the serious adverse events temporally associated with or preceding the deaths) should be displayed. Serious adverse events that occurred after the medicine was discontinued should be included in this section. The display should include major laboratory abnormalities, abnormal vital signs and abnormal physical observations that are considered serious adverse events. Results of analyses or assessments of serious adverse events across the studies should be presented. Serious adverse events should be examined for frequency over time, particular for medicines that may be used chronically. Potential relationship to the factors listed “Common Adverse Events” should also be considered.

(e) Other Significant Adverse Events

Marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to a substantial intervention (premature discontinuation of study medicine, dose reduction of substantial additional

concomitant therapy), other than those reported as serious adverse events should be displayed. Reasons for premature discontinuation should be discussed and rates of discontinuations should be compared across studies and compared with those of placebo and/or control treatment. In addition the study data should be examined for any potential relationships to factors listed “Common Adverse Events”

(f) **Analysis of Adverse Events by Organ System or Syndrome**  
Assessment of the causality of, and risk factors for, deaths, other serious events, and other significant events is often complicated by the fact that they are uncommon. As a result, consideration of related events as a group, including less important events of potentially related pathophysiology, may be of critical value in understanding the safety profile. E.g. the relationship to treatment of an isolated sudden death may become much clearer when considered in the context of cases of syncope, palpitations and asymptomatic arrhythmias. It is thus generally useful to summarize adverse events by organ system so that they may be considered in the context of potentially related events including laboratory abnormalities.

(iii) **Narratives**

The allocations in the application of individual narratives of patient deaths, other serious adverse events, and other significant adverse events deemed to be of special interest because of clinical importance should be referenced here. The narratives themselves should be part of the individual reports, if there is such a report. Narratives should not be included here, unless an abbreviated narrative of particular events is considered critical to the summary assessment of the medicine.

(iv) **Clinical Laboratory Evaluations**

This section should describe changes in patterns of laboratory tests with medicine use. Marked laboratory abnormalities and those that led to a substantial intervention should be reported in Serious or Significant Events. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate and as comparable with study size. In addition normal laboratory ranges should be given for each analysis. Where possible laboratory values should be given in standard international units.

A brief overview of the major changes in laboratory values across the clinical studied should be provided. Laboratory data should include haematology, clinical chemistry, urinalysis and their data as appropriate. Each parameter at each time over the course of the study (e.g. at each visit) should be described at the following three levels:

- (a) The central tendency i.e. the group mean and median values
- (b) The range of values, and the number of subjects with abnormal values or with abnormal values of a certain size (e.g. twice the upper limit of normal, 5 times the upper limit; choices should be

explained). When data are pooled from centres with differences in normal laboratory ranges, the methodology used in pooling should be described. The analysis of individual subject changes by treatment group can be shown with a variety of approaches (e.g. shift tables).

- (c) Individual clinically important abnormalities, including those leading to discontinuations. The significance of the laboratory changes and the likely relation to the treatment should be assessed (e.g. by analysis of such features as relationship to dose, relation to medicine concentration, disappearance on continued therapy, positive dechallenge, positive rechallenge. and the nature of concomitant therapy). Potential relationships of other factors listed under “Common Adverse Events” should also be considered.

(v) Vital Signs, Physical Findings, and other Observations Related to Safety

The manner of presenting cross study observations and comparison of vital signs (e.g. heart rate, blood pressure, temperature, respiratory rate) weight and other data (e.g. electrocardiograms, X-rays) related to safety should be similar to that for laboratory variables. If there is evidence of a medicinal effect, any dose-response or medicine concentration-response relationship or relationship to individual variables (e.g. disease, demographics, concomitant therapy) should be identified and the clinical relevance of the observation described. Particular attention should be given to changes not evaluated as efficacy variables and to those considered to be adverse events. Particular attention should be given to studies that were designed to evaluate specific safety issues, e.g. studies of the QT interval prolongation.

(vi)b Safety in Special Groups and Situations

(a) Intrinsic Factors

This section should summarize safety data pertinent to individualizing therapy or patient management on the basis of demographic and other factors defined as intrinsic ethnic factors. These factors include age, sex, and height, weight. Lean body mass, genetic polymorphism; body composition, other illness and organ dysfunction. Safety in the paediatric population should be routinely analysed in applications for a proposed indication that occurs in children. Analysis of the impact of such factors on safety outcomes should have been presented in those sections but should be summarised here, together with pertinent PK or other information e.g. in-patients with renal or hepatic disease. If sufficiently large number of subjects with a given co-morbid condition such as hypertension, heart disease, or diabetes was enrolled, analyses should be carried out to assess whether the co-morbid condition affected the safety of the medicine under study. Cross-reference should be made to the tables or description of adverse events when analyses of such groups have been carried out.

(b) Extrinsic Factors

This section should be s data pertinent to individualising therapy or patient management on the basis of factors defined as extrinsic ethnic factors. These factors associated with patient environment. Examples are medical environment, use of medicines, use of tobacco, use of alcohol and food habits.

- (c) **Medicine Interactions**  
Studies on potential drug-drug or drug-food interactions should be summarised here. The potential impact on safety of such interactions should summarised based on PK, PD or clinical observations. Any observed changes in adverse event profile, changes in blood levels thought to be associated with risk, or changes in medicinal effects associated with other therapy should be presented here.
- (d) **Use in Pregnancy and Lactation**  
Any information on safety issues during pregnancy or breast-feeding that becomes available during clinical development or from other sources should be summarised here.
- (e) **Overdose**  
All available clinical information relevant to over dose, including signs/symptoms, laboratory findings and therapeutic measures/treatments and antidotes (if available) should be summarised and discussed. Information on the efficacy of specific antidotes and dialysis should be provided if available.
- (f) **Drug Abuse**  
Any relevant studies/information regarding the investigation of the dependence potential of new therapeutic agent in animals and in humans should be summarised and cross-referenced to the summary of toxico-pharmacology data. Particular susceptible patient populations should be identified.
- (g) **Withdrawal and Rebound**  
Any r or study results pertinent to rebound effects should be summarised. Events that occur, or increase in severity, after discontinuation of double-blind or active study medication should be examined to see if they are the result of withdrawal of the study medication. Particular emphasis should be given to studies designed to evaluate withdrawal and/or rebound.
- (h) **Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability**  
Safety data related to any impairment in the senses, co-ordination, or other factor that would result in diminished ability to drive or operate machinery or that would impair metal ability should be summarised. This included relevant adverse effects reported in safety monitoring e.g. drowsiness and specific studies concerning effects on ability to drive or operate machinery or impairment of mental ability.
- (i) **Post-marketing Data**

## ANNEX 1

### RECOMMENDED WORDINGS OF WARNINGS ON PACKAGES

- (i) *Warning. May cause drowsiness*  
On packages of preparations for children and containing antihistamine substances or other substances where point (ii) and the warning against consumption would not be appropriate.
- (ii) *Warning. May cause drowsiness. Avoid driving or operating machinery during the course of therapy. Avoid consumption of alcohol during the course of therapy.*  
To be used on preparations which can cause drowsiness and are intended for adults. Some preparations only cause drowsiness during the first day of treatment, others only cause drowsiness after administration of high doses. If this is the case, the patient must be informed that the warning applies until the effect of the medicinal product has worn off. The warning against consumption of alcohol is related to the enhanced effect of the substance, which inhibits the central nervous system when administered together with alcohol.
- (iii) *Warning. Cause drowsiness, which may extend to the following day. Avoid driving or operating machinery during the course of therapy. The warning applies to sleeping pills or other medicinal substances with a sedative effect with are administered in the evening. In exceptional cases, when a medicinal product is administered in the day time, (e.g. nitrazepam for epilepsy) the warning is not appropriate.*
- (iv) *Warning. Avoid consumption of alcohol during the course of therapy.*  
To be used in case of preparations which may cause flushing when consumed together with alcohol (e.g. metronidazole, chlorpropamide). Alcohol may enhance the hypoglycaemic effect of orally administered anti-diabetic medicinal products, however a warning is not necessary concerning those preparations.
- (v) *Do not take antacids at the same time of day as this medicinal product.*  
The warning applies to coated tablets and should prevent premature dissolution of the coating at an alkaline pH. The warning applies to ketoconazole where the absorption is significantly decreased when administered together with antacids. The interval between administrations of the two medicinal products should at least be 2-4hours.
- (vi) *Do not take iron preparations and /or antacids at the same time of day as this medicinal product. The interval between administrations of the two should at least be 2hours.*  
The warning applies to ciprofloxacin, doxycycline, minocycline and penicillamine. The absorption of medicinal products is reduced in the presence of iron and calcium ions. The interval between administrations of the two should at least be 2hours.
- (vii) *Do not take milk, iron preparations and /or antacids at the same time of day as this medicinal product.*

The warning applies to tetracyclines whose absorption is reduced in the presence of iron, calcium and magnesium ions. . The interval between administrations of the two should at least be 2 hours. Concerning doxycyclines and minocyclines, warning number 6 is sufficient as they are less liable to form chelates.

- (viii) *Do not stop taking this medicinal product except on your doctor's advice.*  
The warning applies to preparations, which must be administered during a longer period (the effect is also apparent only after a longer use), e.g. antituberculosis preparations. It also applies to preparations for which withdrawal of therapy can be hazardous. Concerning glyocorticosteroids, warning number 10 is more appropriate.
- (ix) *Take the medicinal product at regular intervals and at fixed times of day. Do not discontinue the prescribed course of treatment.* The warning applies to preparations whose long-time use helps avoid diseases relapse, the development of resistance, or failure of treatment. The preparations are orally administered antibiotics. In every rare case their use may cause the development of severe side-effects (e.g. pseudo-membranous colitis), in such a case the patient should discontinue the therapy and consult the doctor.
- (x) *Read the information leaflet in the package!*
- (xi) *Avoid direct sunlight or ultraviolet radiation during the course of treatment.*  
The warning applies to medicinal products which, in presence of ultraviolet radiation may give rise to phototoxic or photoallergic reaction. A number of medicinal products (including phenothiazines, sulphonamides) are likely to cause such reactions in sensitive patients.
- (xii) *Do not take acetylsalicylic acid while taking this medicinal product.*  
The warning applies to probenecid and sulphinyprazone whose effect is decreased by acetylsalicylic acid. Warning number eleven applies to anticoagulants.
- (xiii) *Dilute the medicinal product with water before taking.* Mix the medicinal product with water before taking.
- (xiv) *This medicinal product may change the colour of urine (e.g. phenolphthalein, triamterene, levodopa, rifampicin)*
- (xv) *Flammable*
- (xvi) *Administer the medicinal product under the tongue. Inhalation of the product is prohibited.*  
The warning applies to glyceryl nitrate (oral spray)
- (xvii) *Allow the medicinal product under the tongue. Keep the medicinal product in the original package and tightly closed. Discard eight weeks after opening.* The warning applies to glyceryl nitrate, the patient must not transfer the tablets to another package (e.g. a to a plastic container)
- (xviii) *Use within one month after opening.* To be used on the labelling of the package of eye drops.

- (xix) The maximum daily dose is...Applies to anti-migraine medicinal products not containing ergotamine (warning xx applies to ergotamine). The dose should be specified (number of tablets etc).
- (xx) *The maximum daily dose is..., the maximum weekly dose is...*  
Applies to anti-migraine medicinal products containing ergotamine. The dose should be specified (number of tablets etc).

#### **OTHER WARNINGS**

- (i) Dimethyl sulfoxide always can cause stomach upset, diarrhoea, drowsiness, and headache.
- (ii) The Ethanol % in the product should be stated on the label. If the single dose of the product contains more than 0,05g ethanol; "see the PIL" should be on the label. If the quantity in the maximum daily dose is between 0,05-3g, warning: *"This product contains...vol % of ethanol, Each dose contains up to ..g of alcohol. Harmful for those suffering from liver diseases, alcoholism, epilepsy, brain injury or diseases as well as for pregnant women and children. May modify or increase the effect of other medicinal products"*.  
If the quantity in the maximum daily dose exceeds 3g, warning: *"This product contains...vol % of ethanol. Each dose contains up...g of ethanol. Caution! This medicinal product must not be taken by children, pregnant women and people suffering from liver diseases, epilepsy and alcoholism and brain injury or disease. Reactions in road traffic and while operating machinery may be lowered. May modify or increases the effect of other medicinal products"*  
Topical products: *"Frequent applications to the skin produces irritation and dry skin"*.
- (iii) Phenylalanine always harmful for people with phenylketonuria.  
Phenylmercuric salts (acetate, borate, nitrate) always irritant to the skin.  
Topical application to the eyes has been associated with mercurialentis and atypical band keratopathy
- (iv) Formaldehyde the content of the unbound substance in the finished product exceeds 0,05% w/w.(?) If present in products taken internally it can caused stomach upset and diarrhoea. The vapour from it can irritate eyes and nose If present in topical products: *'known to cause allergy'*
- (v) Fructose always: *"This product contains...g of fructose. When taken according to the dosage recommendations, each dose supplies up to...g of fructose. Unsuitable in hereditary fructose intolerance.*  
Due to the possibility of not yet detected congenital fructose intolerance, *"This medicinal product should be given only to babies and infants after consultation with a physician"*.
- (vi) Galactose always: *"This medicinal product contains...g of galactose"*.  
*When taken according to the dosage recommendations each dose supplies up to ...g of glucose"*. Unsuitable for people with lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.

- (vii) Glucose always " *This medicinal product contains...g of glucose*" When taken according to the dosage recommendation search dose supplies up to ...g of glucose.
- (viii) Glycerol always " *For oral dosage form harmful in high doses. Can cause Headache and can cause stomach upset and diarrhoea.* If in sugar the quantity of the maximum daily dosage exceed 5g. The medicinal Product contains...g of glucose and ...g of fructose. When taken according to the dosage recommendations each dose supplies up to ...g of glucose and .g of fructose. Unsuitable for people with hereditary fructose intolerance.
- (ix) Potassium always Harmful to people on low potassium diet. Hyperkalaemia-can cause stomach upset and diarrhoea following oral administration. For products administered I.V: can cause pain at the site if injection or phlebitis
- (x) Chlorobutanol always
- (xi) Lactose the quantity in the maximum daily dose exceeds 5g. This medicinal Product contains...g of lactose. When taken according to the dosage recommendations each dose supplies up to ...g of lactose. Unsuitable for people with lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.
- (xii) Lanolin always
- (xiii) Mannitol always
- (xiv) Sodium the quantity in the maximum daily dose exceeds sodium may be harmful to people on a low sodium diet.
- (xv)Wheat starch always may be harmful to people with coeliac d
- (xvi)Organic mercury compounds always can cause kidney damag
- (xvii) Paraformaldehyde the content of the unbound substance in the medicinal product exceeds 0,5% w/w, if present in the products taken internally, can cause stomach upset and diarrhoea. The vapour is irritant to the eyes, and nose. If present in the topical products: *known to cause allergy'*
- (xviii) Parahydroxybenzoates and their esters E214-E219 the content of the unbound Substance in the medicinal product exceeds 0,5% w/w, Known to cause urticaria. Generally delayed type reactions, such as contact dermatitis. Rarely immediate reaction with urticaria and bronchospasm.
- (xix) Polyethoxylated castor oils always: warning for parenterals only:- Hypersensitivity-drop in blood pressure, inadequate circulation, dyspnoea, hot flushes Warning for oral dose forms: nausea, vomiting, colic, severe purgation (high doses)- Not to be given when intestinal obstruction is present. Polyols the content in the medicinal product exceeds 10% may cause diarrhoea
- (xx) Propylene glycols, its salts and esters always Salicylic acid always mild irritant- can cause dermatitis
- (xxi) Soya always
- (xxii) Sorb acid and its salts E200-E203 always irritant: Can cause dermatitis
- (xxiii) Sorbitol the quantity in the maximum daily dose exceeds 2g. This medicinal product contains...g of sorbitol. When taken according to the dosage recommendations each dose supplies up to...g of sorbitol.



- Unsuitable in hereditary fructose intolerance. Can cause stomach upset and diarrhoea.
- (xxiv) Sucrose (Saccharose) the quantity in the maximum daily dose exceeds 5g. This medicinal product contains...g of sucrose. When taken according to the dosage recommendations each dose supplies up to...g of sucrose. Unsuitable in hereditary fructose intolerance, galactose intolerance, malabsorption syndrome, or sucrase-isomaltase deficiency.
- (xxv) Sulphites (metabisulphites) E220-E228 always can cause allergic-type reactions, including anaphylactic symptoms and bronchospasm in susceptible people, especially those with a history of asthma or allergy.
- (xxvi) Tartrazine and other azo colouring agents E102 E110 E122-E124 E151 always can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.
- (xxvii) Urea always. For products given I.V:- may cause venous thrombosis or phlebitis. Topical application may be irritant to sensitive skin.
- (xxviii) Bovine aprotinin always

## **ANNEX II**

### **COLOURS PERMITTED IN MEDICINAL PRODUCTS**

Colour EC Number Common name Colour index number

Yellow E 100 Curmin 75 300

E 101 (i) Riboflavin

(ii) Riboflavin-5'-phosphate

E 102 Tartrazine 19 140

E 104 Quinoline Yellow 47 005

Orange E 105 Sunset Yellow FCF, Orange Yellow S 15 985

Red E 120 Carminic acid, Carmines, Cochineal 175 470

E 122 Azorubine, Carmoisine 14 720

E 123 Aamaranth 16 185

E 124 Ponceau 4R, Cochineal Red A 16 255

E 127 Erythrosine 45 430

E 129 Allura red AC 16 035

Blue E 131 Patent Blue V 42 051

E 132 Indigotine, Indigo carimine 73 015

E 133 Brilliant Blue FC 42 090

Green E 140 Chlorophylls and Chlorophyllins:

(i) Chlorophylls;

(ii) Chlorophyllins 75 810

75 815

E 141 Copper complexes of chlorophylls and Chlorophyllins (i) Copper

(ii) Copper complexes of chlorophyllins 75 815

E 142 Green S 44 090

Brown E 150a

E 150b

E 150c

E 150d Plain caramel

Caustic sulphite caramel  
Ammonia caramel  
Sulphite ammonia caramel  
E 151 Brilliant Black BN, Black PN28 440  
E 153 Vegetable carbon 77 266  
E 155 Brown HT20 285  
Various shades E 160a  
E 160c  
E 160d  
E 160e  
E 160f Carotenes:  
(i) Mixed carotenes  
(ii) Beta-carotene  
Paprika extract, capsanthin, capsorubin  
Lycopene  
Beta-apo-S'-carotenic acid (C30)  
75 130  
140800  
75 125  
40820  
40825  
E 161b Lutein  
E 162 Beetroot Red, betanin  
E 163 Anthocyanins  
E 170 Calcium carbonate 77 220  
E 171 Titanium dioxide 77 891  
E 172 Iron oxides and hydroxides 77 491  
77492  
77499

\* Identification number for additives in the EU that proves the additives complies with the criteria described in the specifications of JECFA (Joint WHO/FAO Expert Committee on Food Additives).

\*\*Colour index number according to the publication "Colour Index" 3<sup>rd</sup> Edition (1982), volume 1-7, 1315

### **APPENDIX III:**

#### **ANATOMIC THERAPEUTIC CHEMICAL CLASSIFICATION SYSTEM (ATC)**

The anatomical therapeutic chemical system serves as a basis for classifying Medicines according to therapeutic indications. It is made up of an alphabet, 2 numerals and ends with an alphabet. Example A01B and interpreted as shown below:

- A Anatomical main group
  - 01 - Therapeutic main group
- B Therapeutic subgroup

The main groups of the ATC classification system are:-

- A Alimentary tract and metabolism
- B Blood and blood forming organs
- C Cardiovascular system
- D Dermatologicals
- G Genito-Urinary System and Sex Hormones
- H Systemic hormonal preparations, excl. sex hormones
- J General anti-infectives, systemic
- L Anti-neoplastic and immunosuppressive Medicines
- M Musculo – skeletal system
- N Central nervous system
- P Anti-parasitic products
- R Respiratory system
- S Sensory organs
- V Various
- A. ALIMENTARY TRACT AND METABOLISM
  - A01 Stomatologicals, mouth preparations

- a. Stomatologicals, mouth preparations
- A02 Antacids, antiflatulents and anti-peptic ulcerants
  - a. Antacids and antiflatulents
  - b. Anti-peptic ulcerants
  - c. Others
- A03 Gastrointestinal antispasmodics and anticholinergics
  - a. Synthetics, incl. Papaverine
  - b. Belladonna and derivatives, pain
  - c. Antispasmodics in combination with psycholeptics
  - d. Antispasmodics in combination with analgesics
  - e. Other combinations
- A04 Antiemetics and anti-nauseants
  - a. Anti-emetics and anti-nauseants
- A05 Cholagogues and hepatic protectors
  - a. Bile therapy, cholagogues and cholagogues
  - b. Hepatic protectors, lipotropics
  - c. Cholagogues and lipotropics in combination
- A06 Laxatives
  - a. Laxative
- A07 Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents
  - a. Intestinal anti-infectives
  - b. Intestinal adsorbents
  - c. Electrolytes with carbohydrates
  - d. Antipropulsives
  - e. Intestinal anti-inflammatory agents
  - f. Antidiarrhoeal microorganisms
  - g. Various antidiarrhoeals
- A08 Anti-obesity preparations excl. diet products
  - a. Anti-obesity preparations, excl. diet products
- A09 Digestives, incl. Enzymes
  - a. Digestives, incl. Enzymes

- A10 Antidiabetic therapy
  - a. A Insulins and other parenterals
  - b. B Oral antidiabetics
  
- A11 Vitamins
  - a. A Multivitamins, combinations
  - b. B Multivitamins, plain
  - c. C Vitamin A and D, incl. combinations of the two
  - d. D Vitamin B1, plain and in combination with Vitamin B6 and B12
  - e. E Vitamin B – Complex incl. combinations
  - f. G Ascorbic acid (Vitamin C), incl. combinations
  - g. H Other plain vitamin preparations
  - h. J Other vitamin products, combination
  
- AB12 Mineral Supplements
  - a. A Calcium
  - b. B Potassium
  - c. C Other Mineral supplements
  
- A13 Tonics
  - a. Tonics
  
- A14 Anabolics, systemic
  - a. A Anabolic steroids
  - b. B Other anabolic agents
  
- A15 Appetite stimulants
  
- A16 Other alimentary tract and metabolism products

## **B BLOOD AND BLOOD FORMING ORGANS**

- B01 Anticoagulants

- a. Anticoagulants
  - B02 Antihaemorrhagics
    - a. Antifibrinolytics
    - b. Vitamin K and Others
  - B03 Antianaemic preparations
    - a. Haematinics, iron and all combinations
    - b. Vitamin B12 and folic acid
  - B04 Cholesterol reducers, antiatheroma preparation
    - a. Cholesterol reducers, antiatheroma preparations
  - B05 Plasma substitutes and perfusion solutions
    - a. Blood and related products
    - b. I.V. solutions
    - c. Irrigating solutions
    - d. Peritoneal dialytics
    - e. X I.V. solution additives
  - Z Haemodialytics
  - B06 Other haematological agents, incl. Fibrinolytics and hyaluronidase
- 53
- A Other haematological agents, incl. Fibrinolytics and hyaluronidase

## **C CARDIOVASCULAR SYSTEM**

- C01 Cardiac therapy
  - a. Cardiac glycosides
  - b. Antiarrhythmics
  - c. Antiadrenergic agents, ganglion – blocking
  - d. Arteriolar smooth muscle, agents acting on
  - e. Renin – angiotensin system, agents acting on
- K Other hypotensives
- L Hypotensives and diuretics in combination
- C02 Diuretics
  - a. Low – ceiling diuretics, thiazides

- b. Low – ceiling diuretics, excl. thiazides
- c. High – ceiling diuretics
- d. Potassium – sparing Medicines
- e. Diuretics and potassium – sparing Medicines in combination

C03 Peripheral vasodilators

- a. Peripheral vasodilators

C04 Vasoprotectives

- a. Antihemorrhoidals, topical preparations
- b. Antivaricose therapy
- c. Capillary stabilizing agents

C05 Beta blocking agents

- a. Beta blocking agents, plain

D DERMATOLOGICALS

D01 Antifungals, dermatological

- a. Antifungals, topical preparations
- b. Antifungals, systemic preparations

D02 Emollients and protectives

- a. Emollients and protectives

D03 Cicatrizants, excl. medicated dressings

D04 Antipruritics, incl. Antihistamines, Anaesthetics, etc.

- a. Antipruritics, incl. Antihistamines, Anaesthetics, etc.

D05 Coal tar, sulphur and resorcinol products

- a. Coal tar, sulphur and resorcinol products

D06 Antibiotics and chemotherapeutics, dermatologicals

- a. Antibiotics, topical preparations
- b. Chemotherapeutics, topical preparations
- c. Antibiotics and chemotherapeutics, combinations

D07 Corticosteroids, dermatological preparations

- a. Corticosteroids, plain

- b. Corticosteroids, combinations with antiseptics
- c. Corticosteroids, combinations with antibiotics

X Corticosteroids, other combinations

D08 Antiseptics and disinfectants

- a. Antiseptics and disinfectants

D09 Medicated dressings

- a. Medicated dressings

D10 Antiacne preparations

- a. Anti – acne preparations

D11 Other dermatological preparations

## **G GENITO-URINARY SYSTEM AND SEX HORMONES**

G01 Gynaecological anti-infectives and antiseptics

Antiinfectives, excl. combinations with corticosteroids

Antiinfectives and corticosteroids in combination

G02 Other gynaecologicals

Oxytocics

Topical contraceptives

Other gynaecologicals

G03 Sex hormones and stimulants of the genital system

Hormonal contraceptives, systemic

Androgens and combinations, excl. G03E

Estrogens and combinations, excl. G03E, G03F and anti-adrogens and estrogens

Progesterones and combinations, excl. G03E and G03F

Androgens and female sex hormones in combination

Progestogens and estrogens in combination



Gonadotrophins and other ovulation stimulants

Antiandrogens and combinations

X Other sex hormones

G04 Urologicals

Urinary antiseptics and antiinfectives

Other urologicals, incl. Antispasmodics

## **H SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES**

H01 Pituitary hormones

Anterior pituitary lobe hormones

Posterior pituitary lobe hormones

H02 Systemic corticosteroids

Systemic corticosteroids, plain

Systemic corticosteroids, combinations

Antiadrenal preparations

H03 Thyroid therapy

Thyroid preparations

Antithyroid preparations

Iodine therapy

H04 Pancreatic hormones

a. Glycogenolytic hormones

H05 Calcium homeostasis

Parathyroid hormones

Antiparathyroid hormones

**J GENERAL ANTIINFECTIVES, SYSTEMIC**

J01 Systemic antibiotics

- A Tetracyclines
- B Chloramphenicol
- C Penicillins with increases effect on Gram – negative bacilli
- D Cephalosporins
- E Trimethoprim, excl. combinations with sulphonamides
- F Macrolides
- G Streptomycins
- H Penicillins
- J Penicillin and streptomycin in combination
- K All other antibiotics

J02 Systemic antimycotics, excl. griseofulvin

- A Systemic antimycotics, excl. griseofulvin

J03 Systemic chemotherapeutics

- A Sulfonamides
- B Sulfonamides and antiinfectives in combination
- C Other chemotherapeutics

J04 Tuberculostatics, excl. streptomycin

- A Tuberculostatics, excl. streptomycin

J05 Systemic antivirals

- A Agents affecting the virus directly
- B Immunostimulating agents

- C Agents with immunostimulants and antiviral activity
- J06 Immune sera and immunoglobulins
  - A Immune sera
  - B Immunoglobulins
- J07 Vaccines
  - A Vaccines
- J08 Other antiinfectives, incl. Leprostatics
  - A Other antiinfectives, incl. Leprostatics.
- L. ANTI-NEOPLASTIC AND IMMUNOSUPPRESSIVE MEDICINES
- L01 Cytostatic Medicines
  - A Alkylating agents
  - B Antimetabolites
  - C Plant alkaloids and other natural products
  - D Cytotoxic antibiotics
  - X Various cytostatics
- L02 Hormone therapy
  - A Hormones
  - B Anti-hormones
- M MUSCULO – SKELETAL SYSTEM
- M01 Anti-inflammatory and anti-rheumatic products
  - A Anti-inflammatory and anti-rheumatic products pre – steroids
  - B Combinations with corticosteroids
- M02 Topical products for joint and muscular pain
  - A Topical products for joint and muscular pain

M03 Muscle relaxants

A Peripherally acting agents

B Centrally acting agents

C Directly acting agents

M04 Antigout preparations

A Antigout preparations

M05 Other Medicines for disorders of the musculo – skeletal system

A Other Medicines for disorders of the musculo – skeletal system

## N CENTRAL NERVOUS SYSTEM

N01 Anaesthetics

A Anaesthetics, general

B Local anaesthetics, excl. dermatologicals

N02 Analgesics

A Narcotics

B Other analgesics and antipyretics

C Anti-migraine preparations

N03 Anti-epileptics

A Anti – Parkinson Medicines

N04 Psycholeptics

A Neuroleptics

B Tranquilizers

C Hypnotics and sedatives

N05 Psychoanaleptics

- A Antidepressants
  - B Psychostimulants
  - C Psycholeptics and psychoanaleptics in combination
- N06 Other CNS Medicines, incl. Parasympathomimetics
- A Parasympathomimetics

## P ANTI-PARASITIC PRODUCTS

- P01 Antiprotozoals
- A Amoebicides and similar
  - B Antimalarials
  - X Other antiprotozoals
- P02 Anthelmintics
- A Schistosomicides
  - X Other anthelmintics
- P03 Ectoparasiticides, incl. Scabicides
- A Ectoparasiticides, incl. Scabicides

## R RESPIRATORY SYSTEM

- R01 Nasal preparations
- A Nasal decongestants, topical preparations
- R02 Throat preparations
- A Throat preparations
- R03 Anti-asthmatics
- A Bronchodilators and other anti – asthmatics, excl. R03B

- B Respiratory stimulants
- R04 Chest rubs and other inhalants
  - A Chest rubs and other inhalants
- R05 Cough and cold preparations
  - A Cold preparations without antiinfectives
  - B Cold preparations with antiinfectives
  - C Expectorants, excl. combinations with antitussives
  - D Antitussives, excl. combinations with expectorants
  - E Systemic nasal decongestants
  - F Antitussives and expectorants, combination
- R06 Antihistamines for Systemic use
  - A Antihistamines for systemic use

## S SENSORY ORGANS

- S01 Ophthalmologicals
  - A Antiinfectives
  - B Corticosteroids
  - C Corticosteroids and antiinfectives in combination
  - D Other ophthalmologicals
- S02 Otologicals
  - A Antiinfectives
  - B Corticosteroids
  - C Corticosteroids and antiinfectives in combination
  - D Other otologicals
- S03 Ophthalmological and otological preparations

- A Antiinfectives
- B Corticosteroids
- C Corticosteroids and antiinfectives in combination
- D Other ophthalmological preparations

## **V VARIOUS**

- V01 Allergens
  - A Allergens
- V02 Immunosuppressive Medicines
  - C Immunosuppressive Medicines
- V03 All other therapeutic products
  - A All other therapeutic products
- V04 Diagnostic agents
  - A Contrast media
  - B Urine tests
  - C Other diagnostic agents
- V05 Surgical antiseptics
- V06 General nutrients
  - A Slimming preparations
  - B Protein supplements
  - C Infant formulas
  - D Other nutrients
- V07 All other pre – therapeutic products
  - A All other pre – therapeutic product

**Annex IV**

**APPLICATION FORM**  
For registration of a medicine in Zambia

**PART 1A ADMINISTRATIVE INFORMATION**

<i>For official use</i>	
Date	Application number

*The Guidelines on registration of a medicine to be consulted in completing this form and preparing of dossiers for submission to the PRA*

<i>1 Details of Applicant (who must be the prospective holder of the product licence)</i>			
Name:			
Physical Address:			
Postal Address:			
Country:			
Phone:	Fax:	Mobile:	E-mail:
1.1 Details of a Distributor (who must be appointed by the applicant and submit evidence of power of attorney)			
Name:			
Physical Address:			
Country:			
Phone:	Fax:	Mobile:	E-mail:

1.2 Manufacturer(s), site(s) for the pharmaceutical dosage form			
NAME (each site involved in the manufacture of the dosage form)	ACTIVITY -Dosage form compounding (for each stage where applicable, including labelling)	SITE (Physical Address, Phone and Country)	



1.3 Source (s) (manufacturer(s) of Active Pharmaceutical Ingredient(s):

Name:

Physical Address:

Postal Address:

Country:

Phone:

Fax:

Mobile:

E-mail:

**2 Proprietary Name and dosage form**

**Generic (INN) name**

**Description**

2.1 Name of the Active Pharmaceutical Ingredient (s) (International Non-proprietary Name in English) and strength

2.2 Pharmacotherapeutic Classification (Anatomic-Therapeutic Classification system)

2.3 Dosage and Strength

**3 Pharmaceutical Dosage Form**

3.1 Dosage and Route of administration (in case of veterinary medicine, the dosage and route of administration for each species of animal for which the product is intended to be specified)

3.2 Container, closure and administration devices

3.3 Package sizes

3.4 Shelf life

(i) The shelf life of the product in each of the different package type(s) and sizes

(ii) The shelf life after first opening of container where applicable

(iii) The shelf life after reconstitution

3.5 Storage conditions

3.6 Categories for Distribution

Narcotic

Prescription only

Pharmacy only

	General Sales Medicines
Other information	

<b>4 Status of /Registration in the Country of Original Development and /Registration Number and Date, Where Applicable. Country of Manufacture</b>	
<b>5 Registration Status for this Medicine in the SADC Member States and in Other Countries</b>	
5.1 Registered:	Country: Date of registration: Proprietary name:
5.2 Pending:	Country: Date of submission: Application number:
5.3 Rejected:	Country: Date of rejection: Application number: Reason for rejection:
5.4 Withdrawn (by applicant before registration)	Country: Date of withdrawal: Reason for withdrawal: Proprietary name:
5.5 Withdrawn (by applicant after registration)	Country: Date of registration: Date of withdrawal: Reason for withdrawal: Proprietary name:
5.6 Suspended/ revoked/cancelled/Withdrawn by competent authority	Country: Date of withdrawal: Reason for withdrawal: Proprietary name:

<b>6 Therapeutic Indications for the Product (In case of a medicinal product for veterinary use, the target species are to be specified)</b>				
<b>7 Unit (Master) Formulation</b>				
Name (INN) of	Reason for inclusion	Quantity	Unit	Reference standards

-API				
1.				
2.				
3. etc.				
-Excipients:				
1.				
2.				
3. etc.				

**Declaration by an Applicant:**

I, the undersigned certify that all the information in this form and all accompanying documentation is correct. I further certify that I have examined the following statements and I attest to their accuracy.

- 8.1 The current edition of the WHO guideline on “**Good Manufacturing Practice for Pharmaceutical products**”, and/or equivalent national guideline, is applied in full in all premises involved in the manufacturer of this medicine.
- 8.2 The formulation per dosage form correlates with the master formula and with the batch manufacturing record.
- 8.3 the manufacturing procedure is exactly as specified in the master formula and batch manufacturing record.
- 8.4 Each batch of all starting materials is either tested or certified (in accompanying certificate of analysis for that batch) against the full specifications in the accompanying documentation and must comply fully with those specifications before it is released for manufacturing purposes.
- 8.5 All batches of the active pharmaceutical ingredient (s) (Raw materials are obtained from the source(s) specified in the accompanying documentation.
- 8.6 No batch of active pharmaceutical(s) will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.
- 8.7 Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications before it is released for the manufacturing purposes.
- 8.8 Each batch of the finished product is either tested, or certified (in an accompanying certificate of analysis for that batch), against the full specifications in the accompanying documentation and complies fully with release specifications before it is released for sale.
- 8.9 The person releasing the product an authorized person as defined by the WHO guideline “**Good Manufacturing Practices: Authorized person - the role, functions and training**” and /or an equivalent national guideline.
- 8.10 The procedures for control of the finished product have been validated for this information. The assay method has been validated for accuracy, precision, specify and linearity.
- 8.11 The holder of marketing authorization/Product licence is obliged to follow national requirements for handling adverse reaction on its products.
- 8.12 The holder of Product licence is obliged to follow national requirements for handling batch recalls of its products.
- 8.13 All the documentation referred to in this certificate is available for review during a GMP inspection.
- 8.14 Clinical Trials were conducted in accordance with Good Clinical Practice.

Name:

Qualification:

Position in the company:

Signature:

Date:

## **PART IB      PRODUCT PROFILE**

<p><b>9      Summary of Product Characteristics (if not identical to package insert)</b></p> <p>9.1    Proprietary name of the medicine</p> <p>9.2    Approved generic name(s) (use the INN if applicable)</p> <p>9.3    Qualitative and quantitative composition</p> <p>9.4    Dosage form</p> <p>9.5    Clinical particulars</p> <p>    5.1    Therapeutic indication (s)</p> <p>    5.2    Route of administration</p> <p>    5.3    Contra-indications</p> <p>    5.4    Special warnings and precautions for use (In case of veterinary medicine, include special precautions for each target species and precautions to be taken by the person administering the medicinal product to the animals, withdrawal periods for the various animals meant for food, including those for which withdrawal period is zero)</p> <p>    5.5    Interactions</p> <p>    5.6    Pregnancy and lactation ( Include lay for veterinary medicines)</p> <p>    5.7    Effects on the ability to drive and operate machinery</p> <p>    5.8    Undesirable effects</p> <p>    5.9    Overdose</p> <p>9.6    Pharmacological properties</p> <p>    6.1    Pharmacodynamic properties</p> <p>    6.2    Pharmacokinetic properties</p> <p>    6.3    Preclinical safety data</p> <p>9.7    Pharmaceutical particulars</p> <p>    7.1    List of excipients</p> <p>    7.2    Incompatibilities</p> <p>    7.3    Shelf-life</p> <p>    7.4    Special precautions for storage</p> <p>    7.5    Nature and composition of container</p> <p>    7.6    Instructions for use/handling</p> <p>    7.7    Restriction on sale/distribution</p> <p>9.8    Administrative data</p> <p>    8.1    Holder of a Product licence</p> <p>    8.2    Registration number</p> <p>    8.3    Date of first registration/renewal of a Product licence</p> <p>    8.4    Date of revision of the text</p> <p>9.9    Registration in a SADC member state</p>
<p><b>10    Package Insert</b></p>
<p><b>11    Patient Information Leaflet</b></p>

**12A Immediate Container Label**

1. Proprietary Name
2. Generic name in English
3. Name of active pharmaceutical ingredient, (INN) quantity of each
4. Pharmaceutical Dosage form and pack size
5. Scheduling status
6. Specific excipients
7. Dosage and route of administration (In case of veterinary medicines, include target species)
8. Store out of reach of children
9. Special warnings
10. Date of Manufacture
11. Storage Conditions
12. Expiry date (month/year)
13. Name and address of holder of marketing authorization/Product licence /registration number
14. Manufacturer's batch number
15. Manufacturer's name and Address
16. In the case of general sales products, indication for use (outer label will comply with the above as minimum)

In the case of veterinary medicines, the product label shall have the words 'for animal treatment only'

17. Blisters
  - Proprietary name
  - Name of manufacturer
  - Storage Instructions
  - Name of licence holder
  - Name and address of manufacturer
  - Expiry date (month/year)
  - Batch number

In the case of veterinary medicines, the product label shall have the words 'for animal treatment only'

16. Small units (5ml container)
  - Proprietary name
  - Method of administration
  - Batch number
  - Contents by mass/volume/units
  - Expiry Date

In the case of veterinary medicines, the product label shall have the words 'for animal treatment only'

12B Outer packaging label

1. The proprietary name of the medicine followed immediately below by the generic name of the API in equal print size where the medicine contains only one API. With the exception of multicomponent products
  2. Pharmaceutical dosage form and strength per unit dose.
  3. Pack size.
  4. A list of specific excipients.
  5. The route of administration.
  6. Store out of reach of children.
  7. Special warnings, if necessary for the medicine.
  8. The expiry date (monthly/year).
  9. Storage requirements and necessary precautions
  10. If appropriate, special precautions for disposal of unused medicine or waste materials derived from such medicine, for example cytotoxics and radiopharmaceuticals
  11. The name and address of the holder of marketing authorization/ Product licence
  12. The name and address of the manufacturer
  13. The registration number
  14. The manufacturers batch number
  15. In the case of General Sales products, instructions on the use of the medicines; (Not applicable to prescription medicines)
  16. Categorization for distribution purposes
  17. The outer packaging may include symbols or pictograms designed to clarify certain information mentioned in paragraph 1 and other information compatible with the summary of the product characteristics, which is useful for health education, to the exclusion of any element of a promotional nature.
- In the case of veterinary medicines, the product label shall have the words 'for animal treatment only'

**PART II BIOAVAILABILITY / BIOEQUIVALENCE DATA  
EXPERT REPORTS**

**Bioavailability and Bioequivalence Studies** (see Bioavailability Guidelines)

- |    |   |                  |
|----|---|------------------|
| 1. | Chemical and pharmaceutical documentation       | (No. of volumes) |
|    |   | (No. of pages)   |
| 2. | Toxicological and pharmacological documentation | (No. of volumes) |
|    |   | (No. of pages)   |
| 3. | Clinical Documentation                          | (No. of volumes) |
|    |   | (No. of pages)   |
- Add: Bioavailability / Bioequivalence data

**PART IIIA Composition**

1. Medicine
2. Container/packaging
3. Clinical trial formula(e) where applicable

**PART IIIB Development Pharmaceutics**

**PART IIIC Control of Starting Materials**

1. **Active Pharmaceutical Ingredients**
  - 1.1 Route of synthesis including impurities
  - 1.2 Physical and chemical characteristics
  - 1.3 Specifications
    - 1.3.1 API(s) described in the pharmacopoeia
    - 1.3.2 API(s) not described in the pharmacopoeia
  - 1.4 Certificate of Analysis (CoA)
  - 1.5 Analytical Validation
  - 1.6 Stability for the API(s) (NCEs only) flagged:
2. **Excipients**
  - 2.1 Specifications
 

2.1.1	Excipients described in the pharmacopoeia
2.1.2	Excipients not described in the pharmacopoeia
  - 2.2 Additional tests
  - 2.3 Scientific data (excipients used for the first time in a medicine)
    - 2.3.1 Nomenclature:

- 2.3.2 International non proprietary name (INN)
- 2.3.3 Chemical name
- 2.3.4 Other names
- 2.3.5 Laboratory code
- 2.3.6 Physiochemical Properties
- 2.3.7 Potential and actual Isomerism
- 2.3.8 Specifications

**PART IIID Packaging Material (Immediate Packaging)**

- 1. Type of material
- 2. Construction
- 3. Specifications
- 4. Development studies on packaging material
- 5. Batch analysis results

**PART IIIE Control Tests on Intermediate Products**

- 1. Identification of intermediate (e.g. powder mix, or granules ready for compression)
- 2. Specifications
- 3. Justification for tests

**PART IIIF Control Tests on Finished Product**

- 1. Specifications (a) pharmacopoeial (include copy of monograph)  
(b) in-house (supply details)
- 2. Justification for tests
- 3. Analytical validation

**PART IIIG Method of Preparation for the Finished Product**

- 1. Batch Formulation including details of batch size
- 2. Site of Manufacturer
  - 2.1 Name and business address of each facility where any aspect of manufacture occurs including activity performed in each site.
  - 2.2 GMP Certificate
- 3. For domestic companies supply the current license number issued by a regional or national PRA.
- 4. Manufacturing procedure
  - 4.1 Detailed manufacturing procedure including equipment, in-process controls, processing conditions and packaging procedure.
  - 4.2 Flow chart of the entire manufacturing procedure (including packaging and labeling)
  - 4.3 Manufacturing process validation protocol or report
  - 4.4 Copy of Master Formula
  - 4.5 Copy of batch manufacturing record

**PART IIHH Stability Testing of the Finished Product (See Stability Guidelines)**

- 1. Specifications
- 2. Characteristics to be tested
- 3. Batch sizes
- 4. Packaging material
- 5. Real time and accelerated conditions
- 6. Validation of stability-indicating tests
- 7. Tabulated results
- 8. Discussion
- 9. Conclusion

**PART IV: SUMMARY OF TOXICO-PHARMACOLOGY OF THE MEDICINE**

- Part IV A: Single dose toxicity
- IV B: Repeat dose toxicity
- IV C: Reproduction studies
  - 1. Fertility/general reproduction Performance
  - 2. Embryotoxicity
  - 3. Peri-/Post natal effects
- IV D: Mutagenic potential
  - 1. *In vitro*
  - 2. *In vivo*
- IV E: Oncogenic/Carcinogenic potential
- IV F: Pharmacodynamics
- IV G: Pharmacokinetics
- IV H: Local tolerance
- IV J: Other information



**PART V CLINICAL STUDIES**

V A: Human pharmacology

1. Pharmacodynamics
2. Pharmacokinetics

V B: Clinical Documentation

1. Clinical trials (Phase I, II and III)
2. Post marketing experience
3. Published and unpublished experience
4. Other relevant information