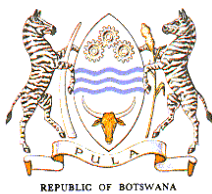


# **GUIDELINES ON DRUG REGISTRATION APPLICATIONS IN BOTSWANA**

**Fourth Revised  
Edition**

**JULY 2014**



## **DRUGS ADVISORY BOARD**

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# **I. INTRODUCTION**

## **A. BACKGROUND**

The broad policy of the Ministry of Health aims at ensuring that all drugs manufactured, imported or exported, distributed or sold in Botswana are of acceptable quality, safety and efficacy. The process of drug registration forms an important basis for evaluating and assuring drug safety, efficacy and quality. Therefore, all drugs manufactured, imported/exported, distributed or sold in Botswana should be registered.

The registration of drugs and related substances in Botswana is governed by the provisions and requirements of the Drugs and Related Substances Act, 1992 and the Regulations, 1993. Copies of these may be obtained from the Government Printers Private Bag 0081 Gaborone, Botswana. Tel: 3953202/3914441 .Fax: 3959392 at a small fee.

The Drugs Advisory Board (DAB) has developed these guidelines to guide applicants when applying for drug registration.

Section I covers the introductory background and definitions as they apply to the guidelines.

Section II of these guidelines provides general guidance on the kind of information to be submitted as part of completing MH 2048 Application for Registration of a Drug.

Section III provides the applicant with a self-checking mechanism that also serves as an evaluation report. Accurate completion of the table in Section III is expected to expedite the processing and evaluation of applications. It should therefore be attached to each MH 2048 submitted.

Section IV provides a specific guidance to manufacturers/applicants on stability data as considered desirable and acceptable by the DAB in supporting the stability hence the shelf life of the various dosage forms. It is the responsibility of the manufacturer to ensure that stability studies are carried out in accordance with the guidelines.

This set of guidelines replaces all previous guidelines on drug registration distributed by the Drugs Regulatory Unit (DRU) until October 2007.

## **B DEFINITIONS**

**Absorption:** Process whereby an active pharmaceutical ingredient is transported unchanged from the site of administration across a bio membrane to the general circulation.

**Accelerated Stability Studies:** Studies designed to simulate the rate of chemical and/or physical degradation of active ingredient or dosage form or product, under exaggerated storage conditions. The purpose is to determine the kinetic parameters, if possible and/or predict a tentative shelf life.

**Act:** The Drugs and Related Substances Act 1992 and as subsequently amended

**Active Pharmaceutical Ingredient (API)/Intermediates:** A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound.

**Adverse drug reaction (serious):** An adverse drug reaction which is fatal, life-threatening, permanently or significantly disabling, require or prolongs hospitalisation, causes congenital anomaly or requires intervention to prevent permanent impairment or damage.

**Analytical method:** A detailed description of the procedures to be followed in performing tests for conformity with specification/specifications.

**Analytical procedure:** It is detailed description of steps necessary to perform each analytical test including but not limited to sample, reference standard and reagent preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation.

**Analytical validation:** This is a demonstration with documentary evidence that an analytical procedure leads to the expected results.

**Anatomic-Therapeutic Chemical Classification(ATC):** This is a classification of drugs according to site of action (anatomical), therapeutic indication and chemical group. Synonymous with pharmacotherapeutic classification

**Applicant:** The company that applies for registration, licensing or marketing authorisation of a new pharmaceutical product or an update or variation to an existing marketing authorisation

**Approved name:** A non proprietary name of a medicinal product containing specified API approved by Medicine Regulatory Authorities (MRA) in SADC member states.

**Assay method:** Quantitative method for determination of percentage purity of a drug substance or content of active ingredients in a preparation or crude drug.

**Authorisation holder:** A company (Applicant) in whose name the marketing authorisation has been granted.

**Authorised person:** Is an appointed person with qualification, knowledge and sufficient experience in the area of application.

**Batch (or lot):** A defined quantity of starting material, packaging material or bulk, intermediate or finished product that is intended or purported to be homogeneous in character and quality, and which has been produced during a defined cycle of manufacture.

**Batch certificate:** A document which provides information on quality of a particular batch.

**Batch manufacturing record/Executed batch record:** A document stating the materials used and the operations carried out during the processing of a given batch, including details of in-process controls and packaging information.

**Batch number (lot number):** A distinctive combination of numbers and/or letters which specifically identifies a batch or lot and permits its history to be traced.

**Bioavailability:** The extent and rate at which an active ingredient or active moiety is delivered to the general circulation from a particular dosage form or for medicines not intended to be absorbed into the bloodstream, bioavailability reflects the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

**Bioequivalence:** Bioequivalence is defined as the lack of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutically equivalent or pharmaceutical alternative medicines become available in the general circulation or at the site of drug action, when administered at the same molar dose, under similar conditions and in an appropriately designed study, such that their effects can be expected to be essentially the same.

**Biological:** A medicinal product prepared from biologic material of human, animal, plant or microbiologic origin (such as blood products, vaccines, insulin).

**Business address:** It is used interchangeably with physical address to describe a place or location where a given activity such as manufacturing is carried out.

**Carcinogenic:** A substance which is capable of causing uncontrollable/malignant proliferation of cells in animal or human body.

**Categorisation for distribution purposes:** Listing or placing of medicinal products in different groups in accordance with level of control when being dispensed.

**Certificate of analysis:** A documented testimony issued by an authorised person showing conformity or non-conformity to the specifications.

**Clinical trial:** A systematic study on pharmaceutical products in human subjects in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism, and excretion of one or more investigational medicinal products with the objective of ascertaining their efficacy and safety.

**Collaborative studies:** Studies conducted jointly by two or more people or parties for the purpose of sharing resources and information.

**Common name:** The non-proprietary name/brand name which is widely and internationally used e.g. Aspirin, Antepar etc.

**Comparator Product:** A pharmaceutical product for which efficacy, safety and quality have been fully established with which a new product is intended to be interchangeable in clinical practice.

**Composition:** List of ingredients, their specification and their respective quantitative content.

**Container-closure system:** The sum of packaging components that together contains and protects the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product.

**Container labelling:** All information that appears on any part of a container, including that on any outer packaging.

#### **Contract manufacture, analysis or servicing**

Manufacture (or partial manufacture), analysis or service work ordered by one person or organisation (the Contract Giver) and carried out by a separate person or organisation (the Contract Acceptor).

**Contra-indication:** Situation in which the drug should not be used because of the risk of use which outweighs any possible beneficial effects.

**Country of origin:** A country where a medicinal product has been released for marketing into destination market.

**DAB:** The Drug Advisory Board which is the legislative body that registers products applied for

**DRU:** Drug Regulatory Unit

**Delivery system:** A system which enables a pharmaceutical active ingredient to be available at the site of administration or absorption.

**Dosage form:** The form of a pharmaceutical product intended for accurately and convenient delivery of active ingredient to the site of action e.g. tablets, suppositories.

**Drug:** According to the Act, a drug is "Any substance or mixture of substances used or purporting to be suitable for use, or manufactured or sold for use in the diagnosis, treatment, alleviation, modification or prevention of disease, illness, abnormal physical or organic condition or the symptoms thereof, or restoring, correcting or modifying any somatic or psychic or organic condition, and shall include a related substance and, to the extent that it complies with the above definition, a habit forming drug".

**Drug interactions:** An act of two or more drugs affecting each other pharmacodynamically and pharmacokinetically.

**Drug master file:** A drug master file (DMF) is a master file that provides a full set of data on an API or an excipients or a component of a product such as a container.

**Embryo toxicity:** The causation of harm to the developing embryo.

**Essential drugs:** Essential drugs are medicinal substances identified by a given country that satisfy the health care needs of majority of population in a given country.

**Evaluation report:** A critical summary and interpretation and conclusions prepared by or on behalf of the drug regulatory authority on quality, safety and efficacy of data submitted in a drug registration application.

**Excipient / Inactive pharmaceutical ingredient (IPI):** Any component of a finished dosage form other than the claimed therapeutic ingredient or ingredients.

**Expert:** A person who has undergone specialised training and has accumulated a body of experience in a particular field and is considered as having sufficient knowledge to interpret issues related to that field.

**Expert report:** A report prepared by an independent expert on behalf of the drug registration applicant on quality, safety and efficacy of data submitted in a drug registration application.

**Expiry date (Expiration date):** A date placed on the container or label of a product designating the time during which a batch of the product is expected to remain within the approved shelf-life specifications, if stored under defined conditions and after which it should not be used.

**Finished pharmaceutical product (FPP):** (*synonyms finished product (medicinal product)*) A medicinal product which has undergone all stages of production, including packaging in its final container and labelling, intended for marketing.

**Fixed dose combination (FDC):** A medicinal product consisting of two or more active ingredients co-formulated into a single product or two or more separate medicinal products in their final dosage forms co-packaged together for the purposes of being administered together in a fixed ratio.

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

**Formula (pharmaceutical Product):** A list of all ingredients, their specifications and respective quantities that are composed in a dosage form.

**Formula:** The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

**General sale:** Any drug whose use does not need the direction or prescription by a medical practitioner or dentist.

**Generic name:** International non-proprietary name recommended by the World Health Organization.

*Alternatively you can check one of these definitions:*

- **The chemical name of drug**
- **A term referring to the chemical make up of a drug rather than to the advertised brand name under which the drug is sold.**
- **A term referring to any drug marketed under its chemical name without advertising.**
- **The name of the active ingredients as distinct**

**Generic products:** A pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights.

**Good Clinical Practice (GCP):** Quality standard for designing, conducting, performing, monitoring, auditing, recording, analysis, and reporting of clinical trials in ethical manner that provides assurance that data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

**Holder of a registration certificate:** A person or company under whom a medicinal product has been registered.

**Inactive pharmaceutical ingredient (IPI):** A substance or compound that is used in the manufacture of a pharmaceutical product and does not contribute to the therapeutic effect of the product, but is intended to enhance the consistency, appearance, integrity, stability, release characteristics, or other features of the product. (Synonymous with Excipient.)

**Indications of the product (synonymous with therapeutic Indication):** Is a narrative identification of a well defined disease state, syndrome or clinical applications of a pharmaceutical product.

**Innovator pharmaceutical product:** A pharmaceutical product which was first authorised for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to requirements at the time of the authorisation).

**In-process control:** Tests, checks and measurements made during the course of manufacture (including packaging) to ensure that the resultant product will comply with its specification and to provide feedback to production for process adjustment. The control of the environment or equipment may also be regarded as a part of in-process control.

**Interactions:** An effect of one substance being changed by the presence of another substance or by some environmental chemical agent

**Interchangeable medicine:** Medicines are said to be clinically interchangeable if they are both bioequivalent and therapeutically equivalent.

**Intermediate product:** A partly processed material which must undergo further processing before it becomes a bulk or finished product.

**International Non-proprietary Name:** A generic name, publicly owned internationally, that identifies active ingredient (s)/substance(s) of pharmaceutical product in existence worldwide.

**In vitro test:** Test done outside a living animal or human body usually it involves isolated tissues, or organ or cell preparation. It is done in artificial environment such as a test tube or culture medium.

**Artificial :** This means outside the natural environment.

**In vivo test:** Test done/performed on or in a living body or organism.

**Labelling:** Is a process of putting information on the immediate or outer package.

**Licence:** A legal document which authorises an individual or any entity to perform a given operation.

**Light testing (photo stability testing):** A test done to elucidate intrinsic stability characteristics of a substance when subjected to specified light intensity.

**Linearity:** An ability of analytical procedure within a given range, to obtain test results which are directly proportional to the concentration of analyte in the sample.

**Local tolerance:** A characteristic of a medicinal product to cause tolerable adverse effect at its site of administration such as skin.

**Long-term (Real-time) testing:** Stability evaluation of the physical, chemical, biological, and microbiological characteristics of a product and its API, which covers the expected duration of the shelf-life, and retest period, that are claimed in the application for registration, and which will appear on the label.

**MH-2048 Form 1:** The application for medicine registration form

**Manufacture (manufacturing, manufacturer):** All operations of purchase of materials and products, production and packaging, quality control, release, storage, shipment of finished pharmaceutical product and related controls.

**Manufacturing process validation:** The documented evidence that the procedure or process operated within established parameters can perform effectively and reproducibility, based on the approved process method and product specification

**Manufacturing process protocol:** Document which explaining in a stepwise manner how to implant a given manufacturing process.

**Marketing authorisation:** An official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It normally contains product particulars, information on which authorisation is based, approved product information` and address and name of the holder of the authorisation, and the period of validity of the authorisation.

**Market leader :** Synonymous with innovator product



**Master document:** A master document is a formally authorised source document relating to specifications and/or manufacturing/analytical methods, which is protected from unauthorised access or amendment.

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

**Medicine:** Any preparation for human or veterinary use containing one or more active pharmaceutical ingredients, with or without pharmaceutical excipients or additives that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

**Medicinal product:** See pharmaceutical product

**Multisource (Generic) pharmaceutical product:** Multisource pharmaceutical products are pharmaceutically equivalent medicines available from different and sometimes unrelated manufacturers.

**Narcotic substance:** A natural or synthetic substance referred to in the single Convention on Narcotic Drugs of 1961 intended for medical and scientific purposes

**New chemical entity (NCE) / New molecular entity / New API:** An active pharmaceutical substance not previously contained in any medicinal product registered with the national or regional authority concerned.

**New medicine:** Any drug that does not match the definition of well established drugs (see below).

**New pharmaceutical product:** A pharmaceutical product that contains a new API, a new combination of marketed APIs, or a new multisource (generic) product.

**Oncogenic agent:** Virus or any other living organism, physiological process or biological event capable of causing uncontrolled/malignant proliferation of cell in animal or human. For example, tobacco is said to be carcinogenic while virus causing gene mutation might be oncogenic.

**Outer packaging:** Container into which a primary receptacle and secondary packaging together are placed.

**Package insert:** Package insert means a leaflet containing information for the prescriber, the dispenser and the end user.

**Packaging:** All operations, including filling (except sterile filling) and labelling, which a bulk product has to undergo in order to become a finished product.

*Note:* Sterile filling would not normally be regarded as part of packaging – the bulk product being the filled, but not finally packaged, primary container.

**Packaging material:** Any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment. The packaging material may either be primary (immediate) packaging materials, those that come in contact with the product or secondary (outer) packaging materials which are those which the immediate packaging is placed.

**Package size:** A defined amount of a finished product in a unit pack

**Patient information leaflet (PIL):** Patient information leaflet (PIL) means a leaflet containing information for the patient

**Pharmaceutical alternatives:** Medicinal products that contain the same active moiety but differ in chemical form (e.g. salt, ester) of that moiety or in the dosage form or strength.

**Pharmaceutical development:** All stages and processes in discovery, evaluation, and formulation of a new pharmaceutical product, until it reaches the market

**A pharmaceutical dosage form:** A pharmaceutical product formulated to produce a specific physical form (e.g. tablet, capsule, solution) suitable for administration to human and veterinary subjects.

**Pharmaceutical equivalence:** Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same API(s) in the same dosage form, if they meet the same or comparable standards and if they are intended to be administered by the same route.

**Pharmaceutical product:** Any preparation for human or veterinary use containing one or more active pharmaceutical ingredients, with or without pharmaceutical excipients or additives that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

**Pharmaco-dynamic properties:** Biochemical and physiological effects of medicinal products and the mechanisms or mode by which they are brought about.

**Pharmacokinetic properties:** The processes of bodily absorption, distribution, metabolism and excretion of medicines.

**Pharmacy only (Drugs):** Drugs authorised to be dispensed only in licensed pharmacies under the supervision of registered pharmacists on a non-prescription basis either on his advice or patient self-selection.

**Pharmacopoeia:** Regulatory compendium containing list of medicinal and pharmaceutical ingredients/products with their description and formulae, specifications and methods of quality control

**Pictogram:** Graphical presentation that includes a symbol plus other graphic elements, such as a border, background pattern or colour that is intended to convey specific information.

**Power of attorney:** A legal right of a separate person to act on behalf of the market authorization holder in matters related to a registered product.

**Precaution(s) for use:** Special care to be exercised by prescriber and patient in the use of a medicinal product

**Precaution(s) for storage:** Special care to be taken into consideration to prevent contamination and deterioration of a medicinal product in relation to the effects of atmosphere, moisture, heat and light.

**Precision:** The precision (usually expressed as the variance, standard deviation or coefficient of variance of a series of measurements) of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.)

**Preclinical safety data:** Data on safety studies done in animals or cells to determine the relative freedom from harm or damage resulting from adverse reactions or physical, psychological, or behavioural abnormalities that might occur as a result of use of a medicine.

**Prescription Only Medicine:** Means a medicinal product required to be dispensed upon presentation of written direction issued by a lawfully recognized medical practitioner.

**Procedures (manufacturing):** Description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly to the manufacture of a medicinal product.

**Processing stages:** The separate operations (or groups of related operations) involved in the manufacture of a medicinal product.

**Product information:** A document defining information that may be supplied with or about a pharmaceutical product by or on behalf of the marketing authorisation holder.

**Product profile:** See product information

**Proprietary name:** A name that is unique to a particular medicinal product by which it is generally identified, which may be either invented, common or scientific, which in case of a registered medicinal products, is the name approved by that regulatory authority in respect of that specific medicinal product, together with a trade mark or the name of the manufacturer.

**Qualified person:** An authorized person with the requisite knowledge and experience to perform a given task.

**Qualitative composition:** Means list of ingredients in a medicinal product.

**Quality assurance:** Is the sum total of all organised arrangements made with the object of ensuring that medicines are of the quality required for their intended use.

**Quality control:** Is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are, in fact, carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

**Quantitative composition:** The amount of each ingredient in a medicinal product.

**Raw materials:** Means all substances which are used to make up a finished product.

**Reference standards:** A drug, chemical or dosage form of specified properties used as the basis for quantitative comparison with other materials of qualitatively similar properties, but the same identity

**Register:** A document maintained by the drug regulatory authority consisting of a list of all the pharmaceutical products authorised for marketing in a particular country.

**Registration certificate:** See marketing authorization.

**Registration number:** A number assigned to a medicinal product after being given marketing authorization.

**Registration status:** Means either of 'registered', 'pending', 'rejected', 'withdrawn', 'suspended' or 'revoked'

**Regulations:** Drugs and Related Substances Act 1993 and as subsequently amended

**Release specification:** The combination of physical, chemical, biological, and microbiological test requirements that determine whether a product is suitable for release at the time of its manufacture.

**Reproducibility:** Reproducibility expresses the precision between the same test, different analysts and between different laboratories (collaborative studies, usually applied to standardisation of methods)

**Reproduction studies:** Safety studies carried out in animals to determine the effect of a particular drug substance on reproduction.

**Renewal:** See periodic review and retention fee.

**Responsible person:** A local person who may be an individual or body corporate incorporated in and fully resident in a country and authorized to handle all issues related to a registered pharmaceutical product in the country.

**Retention fee (for marketing authorisation):** A fee paid annually to maintain marketing authorisation of a medicine.

**Route of administration:** The site or area where a medicinal product is introduced into the human or animal body from where it is absorbed and or transported to its site of action; such as; oral, intravenous, intramuscular, subcutaneous, intravaginal, rectal, intradermal, topical, etc.

**SADC Member states:** Includes Angola, Botswana, Democratic Republic of Congo, Lesotho, Malawi Mozambique, Namibia, South Africa, Swaziland, Tanzania, Mauritius, Zambia and Zimbabwe.

**Shelf life:** The period that product is expected to remain within specifications, as predicted from stability studies. The expiry date of an individual batch is based on the known shelf life.

**Shelf life specification:** The combination of physical, chemical, biological and microbiological test requirements that an API should meet up to at its retest date or a product should meet throughout its shelf-life.

**Shelf life (after first opening of container):** The time interval that a product is expected to remain within the approved shelf-life specifications, provided that it is stored under the conditions defined on the label in the proposed container and closure system after first opening of the container.

**Shelf life (after reconstitution):** The time interval that a product is expected to remain within the approved shelf-life specifications, provided that it is stored under the conditions defined on the label in the proposed container and closure system after reconstitution.

**Shelf-life (expiry dating period):** The time interval that a product is expected to remain within the approved shelf-life specifications, provided that it is stored under the conditions defined on the label in the proposed container-closure system.

**Source of APIs:** Means a manufacturer or supplier of APIs

**Special warnings:** A statement that inform in advance about a possible danger or unpleasant condition that is likely to happen when using a medicinal product.

**Specification:** A document giving a description of a starting material, packaging material, intermediate, bulk or finished product in terms of its chemical, physical and microbiological characteristics. A specification normally includes descriptive clauses and numerical clauses, the latter stating standards and permitted tolerances.

**Specification – release:** The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

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

**Specificity:** Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. These might include impurities, degradants, matrix, etc. Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedures.

**Stability-indicating assay method(s):** Analytical method(s) that will quantitatively differentiate between the API and all known degradation products and/or related impurities.

**Stability:** The capacity of an API or dosage form to remain over a period of time within specifications established to assure its identity, purity, strength, microbiological, biopharmaceutical and physico-chemical characteristics.

**Stability tests (protocol):** A series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf-life and utilisation period under specified packaging and storage conditions.

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

**Storage conditions (storage condition tolerances):** An acceptable variation in temperature, light and relative humidity under which an API or medicinal product may be stored for the duration of the shelf life while retaining its characteristics.

**Strength:** 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.

**Tentative shelf-life:** A provisional shelf-life determined by projecting results from less than full term data (such as “accelerated studies”) and storage under maximum recommended conditions for a period motivated by the applicant using the dosage form to be marketed in the proposed container-closure system.

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

**Therapeutic indication:** Approved use of medicinal product by a qualified authority in the treatment, prevention, or diagnosis of disease, or condition.

**Tolerance:** A decrease in response to a drug dose that occurs with continued use i.e. increased drug doses are required to achieve the effect originally produced by lower doses.

**Toxicology:** Science of substances as causes of adverse or undesired effects and diseases in man, including sources, appearance, chemical composition, properties, biological actions, detection and method of treatment (antidotes).

**Toxico-pharmacology:** Part of pharmacology dedicated to the identification of mechanisms, pathways and site for toxic manifestation.

**Unit Formula:** Is the list of ingredients and their quantities per unit dose.

**Unregistered drug products:** Pharmaceutical products that do not have a marketing authorisation.

**Validation:** The demonstration, with documentary evidence, that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

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

**Well-established active pharmaceutical ingredients):** Are APIs which have:

- been marketed for at least five years in countries that undertake active postmarketing monitoring;
- been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- the same route of administration and strength, and the same or similar indications as in those countries.

**Well-established drug combinations:** Combinations of drugs which have:

- been marketed for at least five years in countries which undertake active post marketing monitoring;
- been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- the same route of administration and strength, and the same or similar indications as in those countries.

**Well-established drug products:** Pharmaceutical products which contain well established drugs, and which have:

- been marketed for at least five years in countries that undertake active post-marketing monitoring;
- been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- the same route of administration and strength, and the same or similar indications as in those countries.

**WHO-type certificate:** A certificate of pharmaceutical product of the type defined in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (see WHO Manual for DRA Authorisation Annex 2).

**Withdrawal:** Implies the total removal of the product from the market.

## **II. REGISTRATION GUIDELINES**

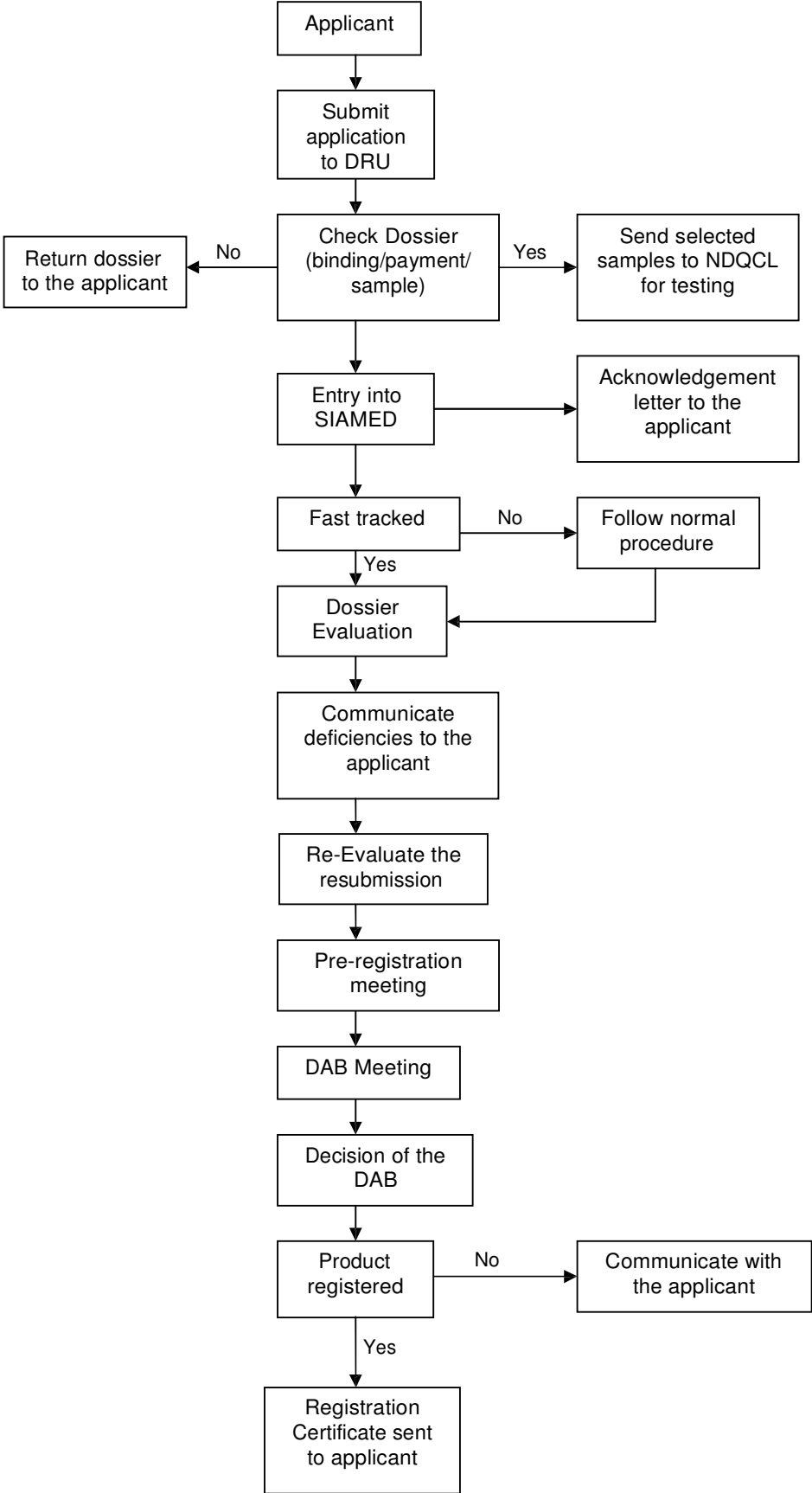
### **A. GENERAL INFORMATION**

- 1) Application for registration is made on MH 2048, (attached to these guidelines) which consists of 7 parts. This application form requires information on safety, efficacy and quality of the product applied for. Refer to "MH 2048 FORM 1 - APPLICATION FOR REGISTRATION OF A DRUG" Section II. C.
- 2) Prospective applicant's attention is drawn to the reverse side of every page of the MH 2048, where explanations are provided.
- 3) Manufacturing plants and distribution facilities are subject to inspections by the DRU prior to the issuing of a registration certificate.
- 4) It is required that MH 2048 be completed and signed by a registered pharmacist
- 5) Where applicants are unsure whether a product falls within the definition of a drug in terms of the Drugs and Related Substances Act, 1992 the following information should be forwarded to the DAB:
  - a) The proposed name of the product;
  - b) The composition including active and inactive ingredients and the quantities thereof and the formulation of the product;
  - c) The intended use/indications;
  - d) The intended marketing/promotional strategy and material.
- 6) A written reply, based on the information submitted, will be issued.
- 7) The product pre-registration/evaluation report should be completed for all submissions (See "APPLICATION PRE-REGISTRATION/EVALUATION REPORT" Section III.
- 8) Please note that the submitting registered pharmacist signs the Pre-Registration/Evaluation Report.
- 9) All documents submitted must be in English.
- 10) Do not hesitate to contact DRU for further clarification and information on specific aspects.

### **B. THE DRUG ADVISORY BOARD**

The Drug Advisory Board (DAB) is a statutory body appointed by the Minister of Health with the approval of the Cabinet, and it is responsible for the registration of drugs of acceptable safety, efficacy and quality and in the interest of the public.

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## **DRUG CATEGORIES**

Depending on the degree of identified risks relating to specific products and/or formulations the drugs may be organised into five broad categories.

The information required for product registration will vary between and within categories as the DAB may determine.

The following is a description of the categories:

### **1. Category A: Low risk drugs**

These are drugs of low risk or over-the-counter drugs mostly intended for self-medication, as may be decided by the DAB.

### **2. Category B: Established drugs**

These are drugs with safety and efficacy record well documented in standard textbooks such as Martindale, Goodman and Gilman, USP-DI, etc.

### **3. Category C: Exempted drugs**

These are drugs exempted under Regulation 4 of the Drugs and Related Substances Regulations, 1993. The DAB may request additional information, as the drug continues to be used. A completed Application for Registration Exemption form shall be submitted.

### **4. Category D: Drugs requiring selected areas of evaluation**

Drugs under this category may include:

- 1) New combination drugs;
- 2) First line generic drug;
- 3) Established drug with new indication(s);
- 4) New formulation of an established drug;
- 5) Any other drug as the DAB may decide.

### **5. Category E: New products and Biologicals**

These are New Chemical Entities, New Formulation and all biological products. For these detailed pharmaceutical, pharmacological and clinical documentation must be submitted. Applicants may also be requested to submit evaluation reports from ICH member states including Canada, Australia and Switzerland.

## ***C. MH 2048 FORM 1 - APPLICATION FOR REGISTRATION OF A DRUG***

The following guidelines are intended to familiarise the applicants with the type of information to be submitted with applications for drug registration.

Drugs and related substances will be evaluated on at least three main accounts - safety, efficacy and quality. Evaluation process of some products may be fast-tracked due to a public health need or some other reason as the DAB may identify

In order to substantially address these areas the application form comprises of:

- Page 1, Application for registration. (Applicant and Drug Particulars);
- Page 2, Composition;
- Page 3, Package insert;



- Page 4, Container specification and control;
- Page 5, Pharmaceutical documentation;
- Page 6, Pharmacological and clinical documentation;
- Page 7, Registration status and other information.

## 1. APPLICATION FOR REGISTRATION OF A DRUG (Page 1 of 7)

### a) Applicant Details

#### Details of Applicant

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

#### 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 of manufacturing process performed should also be indicated for each site. The details of any contract company used at development of the formulation, bioavailability or bioequivalence trials should be indicated.

### b) Medicine details

The details of the medicine should include:

- The proposed proprietary name of the product should not infringe on the INN stem. It should not imply superiority over other products. It should not be the same or similar to the name of another medicine so as to cause confusion.
- Dosage-form and Strength: The dosage-form should be specific to the formulation being applied for, e.g. solution, suspension, eye-drop, emulsion, ointment, powder, suppository, capsule, injection, etc. Injections should specify presentation, i.e., whether a vial, ampoule, dental cartridge, etc. and the contents thereof, e.g., powder, solution, etc.
- Colour:
- Package size(s): All the various package sizes intended for marketing should be presented. Any distinguishing unique characteristics of each package should be described. A sample label bearing all the labelling information as would appear on the immediate container should be attached to the application (**Cross-reference with page 30-32 from no. 5**)
- Pharmacological classification (anatomic, therapeutic and chemical classification): The pharmacological classification of the drug should give the anatomical, therapeutic and chemical (ATC) groupings of the drug (WHO Collaborating Centre, Uppsala, Sweden), e.g. Clotrimazole: Anatomical = dermatological (D); Therapeutic = anti-fungal for dermatological (D01) topical use (D01A); Chemical = imidazole derivative (D01AC); and Drug = Clotrimazole (D01AC01)
- Route of administration: This should be clearly indicated e.g. Oral, I/M, Rectal
- Container/closure and administrative devices
- The proposed shelf life of the product in each of the different package type(s) and sizes :
  - (i) The proposed shelf life after first opening of container where applicable:
  - (ii) The proposed shelf life after reconstitution where applicable

Storage condition

**c) Signatory**

A submitting registered pharmacist in the company must sign the application. A notarised proof of registration of the pharmacist in the resident country should be attached.

**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.

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.

- The current edition of the Botswana Guideline on “**Good Manufacturing Practice for Pharmaceutical products**”, and/or the SADC guideline, is applied in full in all premises involved in the manufacture of this medicine.
- The formula per dosage form correlates with the master formula and with the batch manufacturing record.
- the manufacturing procedure is exactly as specified in the master formula and batch manufacturing record.
- 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.
- All batches of the active pharmaceutical ingredient (s) (raw materials) are obtained from the source(s) specified in the accompanying documentation.
- No batch of active pharmaceutical(s) will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.
- Each batch of the container/closure system is tested and certified against the full specifications in the accompanying documentation and complies fully with those specifications before it is released for manufacturing purposes.
- Each batch of the finished product is tested and 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.
- The person releasing the product is an authorized person as defined by the SADC guideline “**Good Manufacturing Practices: Authorized person - the role, functions and training**” and /or an equivalent national guideline.
- The procedures for control of the finished product have been validated. The assay method has been validated for accuracy, precision, specificity and linearity.
- The holder of the registration is obliged to follow national requirements for handling adverse reaction on its products.
- The holder of the registration is obliged to follow national requirements for handling batch recalls of its products.
- Clinical Trials including Bioavailability or Bioequivalence studies were conducted in accordance with Good Clinical Practice.
- All the documentation referred to in this application is available for inspection.

Name:

Qualification:

Position in the company:

## 2. COMPOSITION (Page 2 of 7)

### a) Development Pharmaceuticals

Refer to the Guidelines on Pharmaceutical Development for this section.

- 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 immediate packaging must be given.

### b) Unit Formula

- 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” are 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.
- x. The specific composition of the product should be calculated by the pack size applied for e.g the schedule of ingredients for 20g ointment must be given per 20gas well as the schedule of ingredients for 100g if both are applied for

***d)Schedule of ingredients***

The bulk of this part should be presented in tabular form.

The specific composition of the product should be calculated by the pack size applied for e.g the schedule of ingredients for 20g ointment must be given per 20gas well as the schedule of ingredients for 100g if both are applied for

The specific composition of the drug taken to be the master formulation of the drug should be provided:

***For active ingredients***

- 1) Approved or INN name;
- 2) IUPAC chemical name;
- 3) molecular and structural formulas);
- 4) physico-chemical properties specification or reference of specification;
- 5) quantity in a dosage unit or other suitable unit of mass or of volume of the drug;

***For inactive ingredients***

- 1) Approved or Compendial name;
- 2) chemical name;
- 3) molecular formula;
- 4) specification or reference of specification;
- 5) quantity in a dosage unit or other suitable unit of mass or of volume of the drug;
- 6) purpose or reasons for inclusion in the formulation.

Specifications and the fate of any other raw materials used in the manufacturing process, whether or not present in the final product shall be included.

All specifications should be at the levels documented in the latest editions of the approved references (the BP, USP, International Pharmacopoeia, European Pharmacopoeia and others approved by the DAB).

### 3. PACKAGE INSERT (Page 3 of 7)

#### A. Package insert

The DAB will approve the information intended for either the consumers or health workers in the package insert.

The Package Insert shall contain:

- 1) Scheduling status - Allocated by the DAB according to Section 9 of the Act:
- 2) **Proprietary name and dosage form:** The proprietary name(s) used for different strengths or dosage forms shall be distinguished by at least the corresponding strengths and dosage forms.
- 3) **Composition:** This includes compendial or approved name and quantity per dosage unit (suitable mass or volume) of active and inactive ingredient(s). Excipients shown on the package insert may be listed without specifying quantities.
- 4) **Pharmacological classification:** The classification according to ATC groupings as discussed under "Medicine details".
- 5) **Pharmacological and mechanism of action:** A brief description of the pharmacological actions and pharmacokinetics of the drug shall be mentioned.
- 6) **Indications:** Indications for the drug is applied for shall be supported by appropriate clinical information given under "PHARMACOLOGICAL AND CLINICAL DOCUMENTATION (Page 6 of 7)".
- 7) **Contraindications:** Both absolute and relative contraindications shall be mentioned.
- 8) **Warnings:** Warnings should include any applicable statutory label in Regulation 8 (5). All forms of contraceptives, except condoms, shall bear the following warning statement: **"This product helps prevent unplanned pregnancy, if used properly. It does NOT prevent the transmission of the human immuno-deficiency virus (HIV) or sexually transmitted diseases (STD). A condom must be used to prevent HIV or STD transmission."** Child warnings should be indicated where applicable.
- 9) **Dosage and directions for use:** Dosage and directions for use should take into account the use of the drug in special groups like elderly and children and disorders like impaired renal and/or hepatic function, asthma, diabetes, heart disease, etc. Child dosages should be indicated where applicable.
- 10) **Side effects and special precautions:** Side effects should be mentioned by order of occurrence.
- 11) Special precautions necessary for the safe use of the drug shall be mentioned.
- 12) **Drug Interactions**
- 13) **Known symptoms of over-dosage and particulars of treatment:** Signs and symptoms of over-dosage and recommended treatment must be mentioned.
- 14) **Conditions of registration:** These include sales category, public advertising status, distribution restrictions, etc., as may be decided by the DAB.
- 15) **Identification:** The physical appearance and characteristics of the drug shall be described.
- 16) **Presentation:** All the types of packaging and pack sizes shall be mentioned.
- 17) **Storage instructions:** Conditions should quote a suitable temperature or temperature range in degree Celsius. Refer to "GUIDELINES FOR STABILITY TESTING" .
- 18) **Registration number:** The number allocated by the DAB.

19) **Applicant:** Name and addresses of applicant must be submitted

20) **Date of publication:** Date of approval of the package insert by the DAB.

## ***B. Patient Information leaflet***

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

A medicine shall not be dispensed without a Patient Information Leaflet unless all the information required in these rules by point 12.(i) is conveyed on the outer packaging or on the immediate packaging;

- (i) 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 medicine
  - (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 and/or per dosage unit ;
  - (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 in millimoles;
  - (g) For dosage forms, where the active ingredient is presented as a powder for reconstitution, 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 rate of release per releasing surface shall be stated on the outer and immediate package;
  - (i) For aerosols the content of the active ingredient per puff shall be stated;
- (ii) The dosage form and the total quantity of the product in the package shall be stated . (e.g. 100 tablets, 100mls, 10 ampoules, 10g, 200 puffs)
- (iii) The pharmaco-therapeutic group
- (iv) Type of activity in words easily comprehensible for the patient
- (v) The name and address of the holder of a registration; in case the manufacturer is not the holder of a registration, both shall be stated
- (vi) Warnings and Precautions
  - (a) "Please read this Leaflet carefully before taking your medicine. If you need some more information, consult your doctor or pharmacist"
  - (b) For prescription only medicines, additionally: "Do not give this medicine to other persons, even if their symptoms seem similar to yours";
  - (c) Any other product specific warnings.
- (vii) Therapeutic indications - a list of conditions or diseases for which the medicine may be used.
- (viii) Contraindications – a list of conditions or circumstances under which the medicine should not be used. (remark: "Inform your doctor before taking medicine if you have any of the before-mentioned conditions");
- (ix) Interactions with other medicines and other forms of interactions (e.g. alcohol, tobacco, foodstuffs) which may affect the action of a medicine; (remark: " Inform your doctor, if you are taking other medicines");

- (x) 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;
- (xi) Instructions for use:
  - (a) The dosage; (if the medicine may be administered to newborn, infant, under-3 years old, the doses must be specified per one kg of body weight per day;
  - (b) The detailed instructions for appropriate use of the medicine (e.g. should be swallowed intact, masticated, dissolved, sucked)
  - (c) The frequency of administration, specifying if necessary the appropriate time at which the product may or must be administered;
  - (d) 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";
  - (e) 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";
  - (f) If appropriate, the information about the risk of withdrawal effects;
  - (g) If appropriate, the course of action to be taken when one or more doses has been skipped.;
- (xii) A description of the undesirable effects which can occur under normal use of the product and, if necessary, the action to be taken.  
Remark: "Inform your doctor about the development of undesirable effects which are not mentioned in this leaflet
- (xiii) A statement indicating that the medicine should not be used after the expiry date. . (xiv) Where appropriate, special storage precautions (e.g. protect from light, humidity, heat or freezing)
- (xv) If necessary, a warning against certain visible signs of deterioration
- (xvi) The date on which the leaflet was last revised
- (xvii) Special particulars:
  - (a) The leaflet may include symbols or pictograms designed to clarify information compatible with the summary of the product's characteristics.
  - (b) The leaflet shall be written in English and/or other official languages (except the name of a medicine) and shall be legible and clearly comprehensible. The information should be the same in all languages used
  - (c) Promotional material should not be included in the insert

**Note: The Drug Regulatory Unit may decide that certain therapeutic indications shall not be mentioned in the leaflet, where dissemination of such information might have serious disadvantages for the patient.**

### ***C. Summary of Product Characteristics (SmPC)***

#### **Summary of Product Characteristics (if not identical to package insert)**

##### **a) Proprietary name of a medicine**

The name given by the registration holder to distinguish the product from others containing the same API (s)

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

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

##### **c) 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.

#### **d) Dosage form**

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

#### **e) 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.

#### **f) 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 – brief summaries of studies done in animals to indicate the safety of the active ingredient(s) in humans should be included.

#### **g) 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 of the appropriate use of the product should be indicated. Any special features to be carefully observed should be indicated
- vii. Restriction on sale / distribution

#### **h) Administrative data**

- i. Name and address of holder of a registration. The name and address ( business and postal) of the registration holder should be indicated
- ii. Registration number. The registration number of the product as issued by the Regulatory Authority should be indicated
- iii. Date of first registration/renewal of a registration certificate. 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 Regulatory Authority should be indicated



#### 4. IMMEDIATE CONTAINER SPECIFICATION AND CONTROL (Page 4 of 7)

- (i) Specifications and routine tests:
  - (a) Type of material;
  - (b) Construction;
  - (c) Quality specifications (routine tests) and test procedures
  
- (ii) Scientific data:
  - (a) Batch analysis results;
  - (b) Release criteria detailing acceptable limits
  - (c) Sampling method

#### 5. PHARMACEUTICAL DOCUMENTATION (Page 5 of 7)

##### 1) Raw material Specification, Analytical and Control procedures

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

- (i) Route of synthesis including impurities
  - (a) Scientific data:
    - (1) Nomenclature;  
International Non-proprietary Name (INN);  
Chemical name;  
Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN); British Approved Name (BAN)  
Chemical Abstracts Service (CAS) registry number
    - (2) Description;  
Physical form;  
Structural formula including conformational data for macromolecules;  
Molecular formula;  
Relative molecular mass;  
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) 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 and clinical testing;
  - (2) Results of tests;
  - (3) Analytical results of reference material, primary and others
- (ii) Specifications and Release Criteria Tests:
  - (a) Active substance(s) described in the pharmacopoeia; a copy of the monograph 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.
- (iii) Most recent certificates of analysis of the API
- (iv) Analytical validation for the test methods used for the analysis of the API should be submitted
- (v) Stability data for the API should be generated and presented as per stability guidelines

### **Excipient(s)**

- (i) Specifications and Release criteria tests:
  - (a) Excipient(s) described in a pharmacopoeia; a copy of the relevant Pharmacopoeial monograph 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
  - (i) Safety data (as evidence of acceptability for use in humans)

### **Intermediate Products(where applicable)**

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

## **2) Summarized details of final product specifications and release criteria**

- (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 of routine tests and standards (e.g. working standards).

## **3) Stability Tests on finished Products**

- (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 pack 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
- (ix) Conclusion and shelf life claim is expected in relation to the results

The stability testing must be done in accordance with the Drug Regulatory Unit guidelines on stability testing.

## **4) Methods of Preparation for 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 Regulatory Authority must be submitted
- (iii) For domestic companies supply the current license number issued by a regional or national regulatory authority.
- (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) Batch Production Records (BPR) corresponding to the samples (Refer to "Samples" above) for at least two batches shall be submitted. These shall reflect all entries made during the manufacturing process. Cancellations on the BPR shall be counter-signed and shall remain legible. The use of correcting fluid is NOT acceptable. Where the skeleton of the entry form is not in English, then a translation of the corresponding record shall be submitted. Photocopied materials shall be acceptable only when they are legible;
- (f) Include certificates of analysis for all raw materials;
- (g) Batch Certificates shall be submitted for all vaccines, biological and biotechnology products.

*N.B.: FOR PRODUCTS PREPARED UNDER ASEPTIC CONDITIONS, STERILE PREPARATIONS, VACCINES AND BIOLOGICALS, A DETAILED DESCRIPTION OF THE PRODUCTION PROCESS SHOULD BE SUBMITTED. SUMMARIES OF THE STERILISATION PROCESSES AND CONTROLS SHOULD BE PROVIDED. A PLAN FOR THE SITES OF MANUFACTURE SHALL BE SUBMITTED*

## **6. PHARMACOLOGICAL AND CLINICAL DOCUMENTATION (Page 6 of 7)**

### **I. Bioavailability & Bioequivalence**

Refer to the Guidelines on Bioavailability/Bioequivalence and Bio-analytical method validation for information to submit this part.

### **II. Safety and Efficacy**

#### **a. Category B drugs**

For Category B drugs proof of efficacy of the formulation being applied for registration will be required. Proof of efficacy could be comparative dissolution/bio-availability data, acid neutralising capacity, inhibition zones, etc.

#### **b. Categories D and E drugs**

Categories D and E drugs require in depth investigation of safety and efficacy. These types of applications frequently involve massive volumes of clinical data and are time consuming.

### **Summary of Toxicopharmacological Documentation**

#### **Preamble:**

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.

#### **Single Dose Toxicity**

The data should be summarised by species and by route. In some cases it is helpful to provide the data in a tabular form.

#### **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.

### **Reproduction studies**

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

- (i) Mating behaviour, fertility and early embryonic development
- (ii) Embryo-foetal 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.

### **Genotoxicity**

Summary if 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

### **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 dose range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- (ii) Short or medium-term studies (including dose range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- (iii) Other Studies

### **Pharmacodynamics**

Summary in order by species, by route, and by dose giving brief details of the major and minor pharmacological effects of the medicine including pharmacodynamic interactions with other medicines

### **Pharmacokinetics**

Summary in order by species, by route, giving brief details of the rate and extent of absorption, distribution, metabolism and excretion of the medicine highlighting important findings Including factors e.g. those that influence these parameters, interactions with other drugs etc.

### **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.

### **Other Toxicity studies** (where appropriate)

- (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.

## **III. Summary of Clinical Studies**

### **A. Human Pharmacology**

#### **1 Product Development Rationale**

The discussion of the product development rationale should:

- (i) Identify the pharmacological class of the medicine

- (ii) Describe the particular clinical/pathophysiological condition that the medicine is intended to treat, prevent, or diagnose.
- (iii) Briefly summarise the scientific background that supported the investigation of medicine for the indication(s).
- (iv) Briefly describe the clinical development programme of the medicine 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 Biopharmaceutical 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 biopharmaceutical studies should be provided, together with narrative descriptions of all relevant features, outcomes of individual studies that provided in vitro or in vivo data and information relevant to BA/BE as well as 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 be summarised in text and tables taking into consideration the following:
  - (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 medicines. 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 or intrasubject variability for each formulation in a comparative BA study.

## **3 Summary of Clinical Pharmacological studies**

- (i) **Background and Overview:**

This section should provide data from clinical studies performed to evaluate PK, PD and in vitro studies with human cells, tissues or related materials that are pertinent to PK processes. Studies of permeability (e.g. intestinal absorption, blood brain barrier passage), protein binding, metabolism and metabolic-based drug-drug interactions are particularly relevant. This should be followed by a brief overview of clinical studies that were carried out to characterise PK and PD of the medicine, 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 study design 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 study 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 provide 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 medicines. 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 medicines, in vitro studies to characterise the spectrum of activity. Studies that evaluate findings as patterns of in vitro susceptibility of strains of bacteria from different parts of the world would be included here.

## **B 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. Justification must be provided for the type of study used e.g. placebo or no placebo controlled etc.

The design of controlled studies that were conducted to evaluate efficacy should be described. 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. These studies include dose-response, comparative efficacy, long-term efficacy and efficacy studies in population subsets

(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 of important studies. Provide 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 whether it supports or does not support the hypothesis. Any major inconsistencies in the data regarding efficacy should be addressed and 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 supports dosage and administration, dose interval recommended, evidence pertinent to individualisation of dosage and need for modifications of dosage for specific patient populations (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, should be provided.

(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 study analyses of efficacy in specific populations should be summarised in this section. The purpose of these comparisons is to 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 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 should clearly be 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 as follows:

(i) Exposure to the Medicine;

The extent of exposure (dose, duration, number of patients, type of patients) should be examined to determine the degree to those which safety can be assessed from the database.

(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 generated safety information, this section should include data of studies that considered 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 the 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 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 such as:

- (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, particularly 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 indicated.

(ii) Adverse Events:

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.

(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 for data from studies that are of similar design e.g. similar in dose, duration, methods of determining adverse events and population to be presented together
- (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 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-term 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 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 should be presented. 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. Potential 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, particularly for medicines that may be used chronically. Potential relationship to the factors listed under “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 under “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 or system so that they may be considered in the context of potentially related events including laboratory abnormalities.

(iii) Narratives:  
The allocation 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. 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 studies 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 de-challenge, positive re-challenge. 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 also be given to studies that were designed to evaluate specific safety issues, e.g. studies of the QT interval prolongation.

(vi) 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, 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 in children. Analysis of the impact of such factors on safety outcomes should have been presented in the particular 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 vents when analyses of such groups have been carried out.
- (b) **Extrinsic Factors:**  
This section should summarise data pertinent to individualising therapy or patient management on the basis of factors defined as extrinsic ethnic factors. These factors are 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 be 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:**  
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 factors that would result in diminished ability to drive or operate machinery or that would impair mental ability should be summarised. This includes 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:  
Data on safety of the medicine after initial registration in any market should be presented.

## 7 REGISTRATION STATUS AND OTHER INFORMATION (Page 7 of 7)

### A. Registration status in other countries

- 1) Information on registration status (marketing authorisation) in ICH or PIC/S (not more than five) and not more than five other foreign countries where the drug is registered should be submitted with certified copies of certificates attached.
- 2) If the registration or marketing authorisation for the drug has been rejected, refused, deferred or cancelled then this information and reasons for such action should be submitted.
- 3) Registration Status for this Medicine in the SADC Member States and in Other Countries

Registered:	Countries:	Date of registration: Proprietary name:
Pending:	Country:	Date of submission: Ref. No:
Rejected:	Country:	Date of rejection: Ref. No: Reason for rejection:
Withdrawn By applicant before registration	Country:	Date of withdrawal: Reason of withdrawal: Proprietary name:
Withdrawn By applicant after registration	Country:	Date of registration: Date of withdrawal: Reason for withdrawal:
Suspended ( revoked/cancelled)	Country:	Date of withdrawal: Reason for withdrawal: Proprietary name:

### B. Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

- 1) A WHO type certificate, in the latest format, prepared from the country of origin of the drug should be submitted together with the application. With a few exceptions, only drugs suitable and licensed for marketing in the country of origin would be considered for registration
- 2) Free Sale Certificates will be accepted only from countries not subscribing to the WHO Certification Scheme. However, the Free Sale Certificates should have the same information as that of the WHO-type certificate and should be accompanied by a Good Manufacturing Practice (GMP) certificate.

**C.** A list of references mentioned in the application should be submitted. Where reference is made to journals and internal records, relevant copies of these should be attached.

**D.** A table of contents showing all items in the application should be submitted.



**E.** The information supporting the application should be summarised by the use of tables and graphs.

**F. 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 medicine followed by a generic name (INN). where a medicine contains only one active ingredient. Where a medicine 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 medicine; the name of the medicine shall differ from the names of the previously registered medicines by at least two letters;
- (ii) The name of active pharmaceutical ingredient and the quantity of each per dosage unit.
- (iii) The pharmaceutical dosage form e.g. tablet, suspension etc
- (iv) Specific excipients and content e.g. preservatives, ethyl alcohol and anti-oxidants
- (v) The route of administration e.g. oral use, for vaginal use etc.
- (vi) Storage Instructions
- (vii) Special warnings, if necessary, for the medicine;
- (viii) Date of manufacture of the medicine
- (ix) Expiry date (month/year ) for the product according to the shelf life granted by the Regulatory Authority
- (x) The name and address of the holder of a registration..
- (xi) Name and address of the manufacturer
- (xii) The registration number of a medicine 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 medicine;
- (xv) The pack size for the medicine e.g. 100 capsules, 100 ml etc.

**Exceptions**

- (i) 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
- (ii) The following particulars at least shall appear on small units (5 ml containers):
  - (a) Name of a medicine 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;

**Outer packaging label**

There should be no promotional material included in the text.

The following particulars shall appear on the outer packaging of a medicine;

- (i) The proprietary name of a medicine followed by a generic name (INN). where a medicine contains only one active ingredient. Where a medicine 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 medicine; the name of the medicine shall differ from the names of the previously registered medicines by at least two letters;

- (ii) The name of active pharmaceutical ingredient and the quantity of each per dosage unit.
- (iii) The pharmaceutical dosage form e.g. tablet, suspension etc
- (iv) Specific excipients and content e.g. preservatives, ethyl alcohol and anti-oxidants
- (v) The route of administration e.g. oral use, for vaginal use etc.
- (vi) Storage Instructions
- (vii) Special warnings, if necessary, for the medicine;
- (viii) Date of manufacture of the medicine
- (ix) Expiry date (month/year ) for the product according to the shelf life granted by the Regulatory Authority
- (x) The name and address of the holder of a registration..
- (xi) Name and address of the manufacturer
- (xii) The registration number of a medicine 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 medicine;
- (xv) The pack size for the medicine e.g. 100 capsules, 100 ml etc.
- (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 ;

Promotional or advertising materials should also be attached to the submission.

#### **D. ADDITIONAL REQUIREMENTS**

##### **1) Number of copies of applications**

Two (2) copies of the registration application( dossiers) shall be submitted. A covering letter must be attached to each MH 2048 document submitted. To expedite unpacking of documents the covering letter should itemise the contents of the submission. In addition to printed copies, submission of MH 2048 information on flash-disk or CD(compatible with windows 2000 to date) may facilitate the evaluation of the package insert, labelling information as well as assist in application pre-registration evaluation.

##### **2)Application fees and payment**

Subject to the amendment of the Act and Regulations there under, the fees payable in respect of drugs shall be as follows:

- 1) BWP (Pula)800.00 for a drug which imported;
- 2) BWP400.00 for a drug which is partially locally manufactured; and
- 3) BWP200.00 for a drug which is totally locally manufactured.

An appropriate fee must accompany the application of each drug and is non-refundable.

All payments shall be made in Pula to the Ministry of Health Headquarters, Botswana revenue office.

##### **4. Samples**

Sealed samples, from at least two (2) batches, in the actual distribution container along with certificates of analysis shall be submitted. The required quantities of each sample are given in the Table 1, below

##### **5. Raw material sample**

A reasonable amount or about 10g of standardised active raw material accompanied by a certificate of analysis shall be submitted, if practicable.

<b>Table 1. DRU Drug Application Sample Submission Requirements</b>
---

<b>CAPSULES, TABLETS, CHEWABLE TABLETS</b>	
Submit three unopened containers containing 100 or more dosage units. If less than 100 dosage units per container, collect the appropriate number of containers to equal at least 300 dosage units	
<b>SMALL VOLUME PARENTARALS (&lt;100ML)</b>	
Pack size	Quantity
1 x 5	20
1 x 10	10
1 x 20	5
1 x 50	4
1 x 100	2
<b>LARGE VOLUME PARENTARALS (100ML &amp; ABOVE)</b>	
Pack size	Quantity
100ml – 1 L	6
> 1 L	4
<b>DRY POWDERS FOR RE-CONSTITUTION (PARENTARALS)</b>	
Weight	Quantity
100mg	50 vials
> 100mg	30 vials
> 500mg – 1g	20 vials
Multi dose depot preparations	5 vials
<b>TOPICAL APPLICATIONS (CREAMS, LOTIONS, OINTMENTS, ETC.)</b>	
Pack size	Quantity
10g	12
15g	12
20g	12
50g	12
100g	12
500g	6
> 500g	4
<b>EYE/EAR PREPARATIONS</b>	
Pack size	Quantity
1 – 5ml	50
10 – 20ml	30
> 20ml	20
<b>INHALATION PREPARATIONS</b>	
10 packs	
<b>COSMETICS</b>	
Volume	Quantity
< 100ml	10
1 x 100ml	6
1 x 150ml	6

1 x 200ml	6
1 x 250ml	6
1 x 500ml	6
1 x 1000ml	2
1 x 2L	2
1 x 4.5L	2
<b>Pack size</b>	<b>Quantity</b>
10g	6
15g	6
20g	6
50g	6
100g	6
200 – 400g	6
500g	2
>500g	2
<b>HOUSEHOLD CHEMICALS</b>	
<b>Volume</b>	<b>Quantity</b>
< 100ml	10
1 x 100ml	6
1 x 150ml	6
1 x 200ml	6
1 x 250ml	6
1 x 500ml	6
1 x 1000ml	2
1 x 2L	2
1 x 4.5L	2
<b>Pack size</b>	<b>Quantity</b>
1 x 10g	12
1 x 15g	12
1 x 20g	12
1 x 50g	12
1 x 100g	12
1 x 500g	6
> 500g	4
<b>MEDICAL DEVICES</b>	
<b>Product type</b>	<b>Quantity</b>
Disposable syringe & needle	50 per fill volume
Plasters	6
Surgical gloves	50 pairs
Giving sets	10
IV cannula	10
Cotton wool < 200g	6
Cotton wool >200g	4
Gauzes/Bandages	10
Sanitary pads/mop up towels etc.	6 packets per variety
Sutures	20 packets per variety
Blood bags	10 per fill volume
P.O.P	5
Feeding Tubes/umbilical cord clamps	6
Mucus extractors, Oxygen masks etc.	2
Thermometers	2
Condoms	1,500 pieces per batch

Diagnostic test kits for proteins, sugar, etc	2 per type
HIV test kits	2 packs
<b>All products should be in a final package ready for the market. The above list notwithstanding where necessary. The board may request for samples more than quantities stated above</b>	

## ANNEXURE I

### RECOMMENDED WORDINGS OF WARNINGS ON PACKAGES

- (i) *May cause drowsiness*  
On packages of preparations for children containing antihistamine substances or other substances where point (ii) and the warning against consumption would not be appropriate.
- (ii) *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) *Causes 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 which 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) *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 where ingestion of antacids would cause premature dissolution of the coating at an alkaline pH. The warning applies to ketoconazole and other medicines where the absorption is significantly decreased when administered together with antacids. The interval between administrations of the two medicinal products should at least be 2-4 hours.
- (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 2 hours.*  
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 2 hours.
- (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 over a long period (the effect is also apparent only after a long period of use), e.g. antituberculosis preparations. It also applies to preparations for which withdrawal of therapy can be hazardous. Concerning glucocorticosteroids, 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 very rare cases 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 a medicine which, in the 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 sulphapyrazone 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 30 days 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 causes 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 is s harmful for people with phenylketonuria. Phenylmercuric salts (acetate, borate, nitrate) are 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 cause stomach upset and diarrhoea. The vapour from it can irritate eyes and nose If present in topical products: *'known to cause allergy'*
- (v) Fructose : *"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 : *"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 : *" This medicinal product contains...g of glucose" When taken according to the dosage recommendation search dose supplies up to ...g of glucose.*
- (viii) Glycerol : *"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 : 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 of injection or phlebitis
- (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) Sodium the quantity in the maximum daily dose exceeds sodium may be harmful to people on a low sodium diet
- (xiii) Wheat starch may be harmful to people with coeliac disease
- (xiv) Organic mercury compounds :can cause kidney damage



- (xv) 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*
- (xvi) 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.
- (xvii) Polyethoxylated castor oils :  
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
- (xviii) Propylene glycols, its salts and esters
- (xix) Sorbic acid and its salts E200-E203 always irritant: Can cause dermatitis
- (xx) 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.
- (xxi) 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.
- (xxii) Sulphites (metabisulphites) E220-E228 : Can cause allergic-type reactions, including anaphylactic symptoms and bronchospasm in susceptible people, especially those with a history of asthma or allergy.
- (xxiii) Tartrazine and other azo colouring agents E120 E110 E122-E124 E151 : Can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.
- (xxiv) Urea:

For products given I.V:- may cause venous thrombosis or phlebitis. Topical application: May be irritant to sensitive skin

III. APPLICATION PRE-REGISTRATION/EVALUATION REPORT

<i>To be attached to each MH 2048 submitted.</i>	
Name of applicant:	
Proprietary name of the drug:	
Approved name of the drug:	
Strength and dosage form:	
Pharmacological classification (ATC):	
Description:	
Country of origin:	
Manufacturer:	
Date of submission:	
Application Number <b>(for official use only)</b> :	
Date of evaluation <b>(for official use only)</b> :	
Evaluator <b>(for official use only)</b> :	

<b>A. GENERAL INFORMATION</b>	<b>Yes</b>	<b>No</b>	<b>Remarks<sup>1</sup></b>
1) Is the signatory a registered pharmacist?			
2) Are the following included?			
a) Manufacturing Site and/or Packaging Site Master Files for biologicals and vaccines.			
b) Completed Company Registration form for all manufacturing sites.			
c) WHO type Certificate (latest format >1992).			
d) Batch certificate for biologicals and vaccine.			
e) Registration Certificate from country of origin.			
f) GMP approval from country of manufacture.			
g) Confirmation of contract between applicant and third party manufacturer/ laboratory/ packer.			
3) Are samples of at least two batches of the drug included?			
4) Are samples labelled in accordance with Regulation 8 of the Regulations?			
5) Are batch manufacturing records of the samples included?			
6) Are certificates of analysis of the samples included?			
7) Is a copy of the permit for manufacture of Schedule 1 drugs in the Act included?			
8) Are copies and/or reasonable English translations of the package inserts, from three countries where the drug is registered, included? (In English)			
9) Are copies of labels and/or English translations, from three countries where the drug is registered, included?			
10) Are copies of registration certificates and/or reasonable English translations, from three countries where the drug is registered, included? (In English)			
11) Is payment or proof of payment attached?			
12) Is there a table of contents or index?			
Conclusion:			

<b>B. COMPOSITION</b>	<b>Yes</b>	<b>No</b>	<b>Remarks<sup>1</sup></b>
1) Is the full composition stated?			
2) Are storage conditions for the active ingredient given?			

<sup>1</sup> Remarks may include cross-referencing, reasons for not submitting any document requested, or other observations.

<sup>1</sup> Remarks may include cross-referencing, reasons for not submitting any document requested, or other observations.

3) Are specifications or references stated?			
4) Are copies of in-house specifications included in Pharmaceutical Documentation?			
Conclusion:			

<b>C. PACKAGE INSERT</b>	<b>Yes</b>	<b>No</b>	
1) Is all required information provided?			
2) Are statements included in the package insert substantiated by the information in pharmacological and clinical documentation submission?			
3) State the reference documents used:			
a) Martindale			
b) Goodman & Gilman			
c) USP DI			
d) Other (Specify)			
Conclusion:			

<b>D. CONTAINER SPECIFICATION</b>	<b>Yes</b>	<b>No</b>	
1) Are all the container specifications given?			
2) Are all the container release criteria given?			
3) Are directions for use provided?			
Conclusion:			

<b>E. PHARMACEUTICAL DOCUMENTATION</b>	<b>Yes</b>	<b>No</b>	
1) Are relevant certificates of analysis of the raw materials included?			
2) Are manufacturing procedures submitted?			
3) Is the manufacturing flow diagram included?			
4) Are in process controls included?			
5) Is there proof that process validation has been carried out?			
6) Are the in-house methods validated?			
7) Are master documents completed for the specific drug?			
8) Is the certificate of analysis of the final product included (samples)?			
9) Does the drug meet all the final product specification and release criteria?			
Conclusion:			

<b>F. STABILITY STUDIES</b>	<b>Yes</b>	<b>No</b>			
1) Are real -time stability data included for at least:					
a) 12 months at the storage temperature recommended in the package insert?			N/A	°C	
b) 6 months accelerated conditions?			N/A	°C	
2) Are stability studies conducted in at least three batches?			N/A		
3) Were real-time stability studies performed with trial or production (PROD) batches or both?	TRIAL	PRO D	BOT H		
4) Were accelerated studies performed with trial or production batches or both?	TRIAL	PRO D	BOT H		
5) Is the stability data derived from the same manufacturing site as applied for?					
6) Is the stability data derived from the same container system as applied for?					
7) Are degradation patterns outlined?					
8) Are degradation products given?					
9) Do the studies support the claimed shelf life and storage conditions?					
10) State the address where development and stability data can be verified.					
Conclusion:					

<sup>1</sup> Remarks may include cross-referencing, reasons for not submitting any document requested, or other observations.

<b>G. PHARMACEUTICAL AND BIOLOGICAL AVAILABILITY</b>	<b>Yes</b>	<b>No</b>	<b>Remar</b>
1) State the method used to prove efficacy of the formulation: bioavailability, dissolution, acid neutralising capacity, inhibition zones, clinical trial, etc.)			
2) Is the drug used in the efficacy study the same as the one applied for with regards to:			
a) Formulation?			
b) Site of manufacture?			
c) Method of manufacture?			
3) State the product used as the comparator.			
4) State the country of origin of the comparator.			
5) Is the comparator registered in Botswana?			
6) Does the bioavailability study comprise of at least 12 subjects for a conventional product or 20 subjects for a controlled release product?			
7) Does the study contain as adequate statistical analysis of the results?			
8) State the address where the data, used as proof of efficacy of the drug, can be verified.			
Conclusion:			

<b>H. PHARMACOLOGICAL AND CLINICAL DOCUMENTATION</b>	<b>Yes</b>	<b>No</b>	<b>Remarks<sup>1</sup></b>
1) Pre-Clinical and clinical documentation:			
a) Is each section preceded by a comprehensive table of contents comprising, e.g. chapters, volumes and page numbers?			
b) Is an expert report included?			
c) Is a synopsis of each study presented?			
d) Is all data presented in English?			
e) Are the formulations used in the studies clearly identified?			
2) Do the studies support the indications, side effects, etc?			



Signed: ..... Date:

.....

**K. FOR OFFICIAL USE**

Category: A	<input type="checkbox"/>	B	<input type="checkbox"/>	C	<input type="checkbox"/>	D	<input type="checkbox"/>	E	<input type="checkbox"/>
Accelerate: Ye	<input type="checkbox"/>	No	<input type="checkbox"/>						
Priority: 1 Government Tender	<input type="checkbox"/>	2 Local manufacture	<input type="checkbox"/>	3 Specific	<input type="checkbox"/>	4 Other (specify)		5 Normal	<input type="checkbox"/>

**NB. This evaluation report must be attached to each drug registration application (MH 2048) submitted**