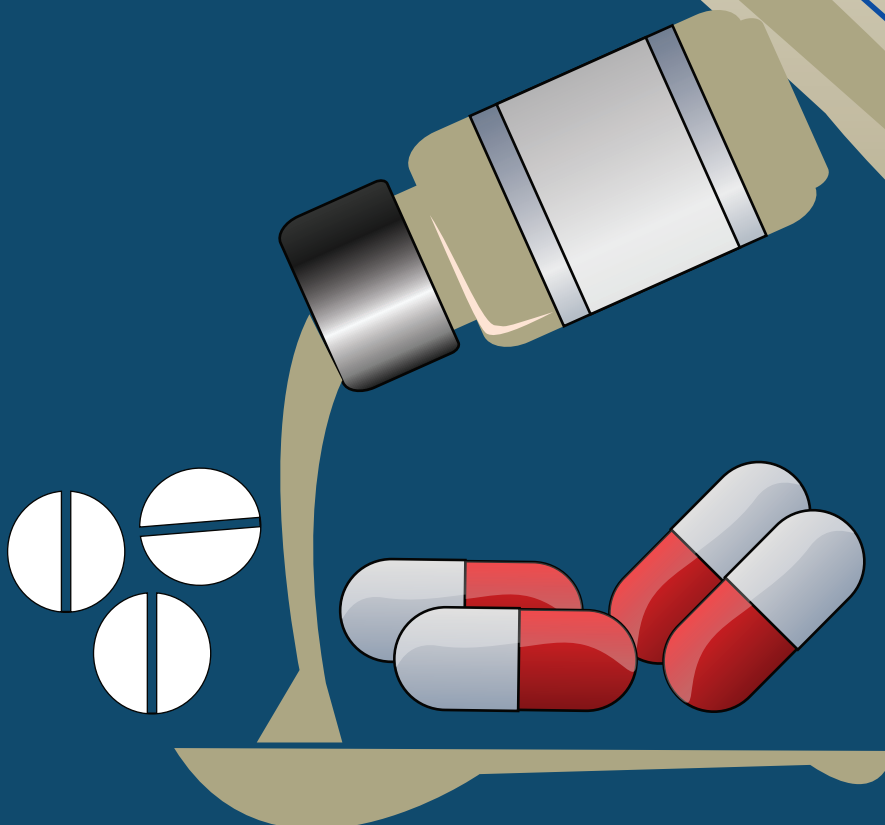




Republic of Botswana

# GUIDELINES ON DRUG REGISTRATION APPLICATIONS IN BOTSWANA



First Revised Edition

March 2000

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

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REPUBLIC OF BOTSWANA

## **DRUGS ADVISORY BOARD**

C/O Drugs Regulatory Unit

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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. Fax: 312001. Tel: 353202 at a small fee.

The Drugs Advisory Board 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 Form 1 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 Ministry of Health 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 until March 2000.

## **B. DEFINITIONS**

For the purpose of these guidelines the following definitions shall apply.

- 1) **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.

- 2) **Act:** The Drugs and Related Substances Act, 1992 and as subsequently amended.
- 3) **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”.
- 4) **Regulations:** Drugs and Related Substances Regulations, 1993 and as subsequently amended.
- 5) **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.
- 6) **Stability:** The capacity of an active ingredient or drug or dosage form to remain within specifications established to maintain its identity, purity, strength and other critical physico-chemical, microbiological and organoleptic properties during its shelf-life.
- 7) **Storage Condition:** The storage condition which shall guarantee the maintenance of the quality of the product in relation to its safety, efficacy and acceptability through out the shelf-life as may be predicted from the stability studies. The described conditions shall indicate temperature or temperature range in degrees Celsius, humidity, light and other relevant conditions.
- 8) **Tentative Shelf Life:** A provisional shelf life predicted from results of accelerated stability studies.

## II. REGISTRATION GUIDELINES

### A. GENERAL INFORMATION

- 1) Application for registration is made on MH 2048 form, (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 “FORM MH 2048 - APPLICATION FOR REGISTRATION OF A DRUG” Section II. D.
- 2) Prospective applicant's attention is drawn to the reverse side of every page of the MH 2048 form, 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 Form 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 (especially active ingredients and the quantities thereof) and 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 to, advise applicants on the opinion of the DAB as to whether the product should be registered.
- 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 it is *imperative* that a registered pharmacist signs the Pre-Registration/Evaluation Report.
- 9) All documents submitted must be in, or translated into 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 is a statutory body appointed by the Minister of Health, and it is responsible for the registration of drugs of acceptable safety, efficacy and quality and in the interest of the public.

### **1. Application evaluation**

- 1) A committee of the Board or the Drugs Regulatory Unit evaluates applications for registration. The recommendations are submitted to the Board for the final resolution;
- 2) Board meetings are at intervals of approximately six to eight weeks;
- 3) Applicants are notified in writing about Board resolutions regarding their applications.

### **2. DAB Clinical Trials Sub-Committee**

The Clinical Trials Sub-Committee is responsible for the evaluation of drug registration applications for clinical trials/studies, for approval by the DAB. Refer to Guidelines for Drug Registration Applications for Clinical Trials.

## **C. 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 Drugs Advisory Board may determine.

The following is a description of the categories:

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

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

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

These are drugs with safety and efficacy record well documented in standard textbooks. Registration of these drugs may be based on all parts except Page 6 of the application information. Appropriate references on Page 6 information should be made to the latest editions of the standards textbooks and reference material.

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

These are drugs exempted under Regulation 4 of the Drugs and Related Substances Regulations, 1993. The Board may be 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.

Additional Page 5 and limited Page 6 information from Form 1 MH 2048 may be requested to supplement that already documented.

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

These are new drugs for which detailed pharmaceutical, pharmacological and clinical documentation evaluation is necessary.

## ***D. FORM MH 2048 - 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. Additional items like need and cost may only be used to move an application faster through the queue but not as a basis for authorising the drug into the market.

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

This part requires general information about the applicant, the drug and the manufacturer (the applicant may or may not be the actual manufacturer). The name and address (both postal and physical) of the applicant should be provided.

### b) Drug details

The details of the drug should include:

- the drug name (both approved or non-proprietary and proprietary or trade-name);
- dosage-form;
- colour;
- strength per dosage unit;
- package size(s) and corresponding ex-factory price(s);
- pharmacological classification (anatomic, therapeutic and chemical classification);
- country of origin where the principal manufacturer or owner of the drug is located;
- Name and address of all the manufacturers.

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.

All the various package sizes intended for marketing should be presented accompanied by ex-factory price of each. 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.

The pharmacological classification of the drug should give the anatomical, therapeutic and chemical (A.T.C. WHO Collaborating Centre, Uppsala, Sweden) groupings of the drug, e.g.:

Clotrimazole: Anatomical = dermatological (D); therapeutic = anti-fungal for dermatological (D01) topical use (D01A); chemical = imidazole derivative (D01AC); and drug = Clotrimazole (D01AC01).

Other classifications may be used, but they must show both the code and corresponding description of the drug.

### c) Signatory

A registered pharmacist of high ranking in the company must sign the application. Proof of registration of the pharmacist should be attached.

**NOTE:** ALL PARTS HEREAFTER SHOULD INDICATE THE NAME OF THE DRUG, THE APPLICANT AND THE DESCRIPTION OF THE DRUG (DOSAGE FORM AND STRENGTH).

## 2. Composition (Page 2 of 7)

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

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

**a) For active ingredients**

- 1) approved name;
- 2) chemical name;
- 3) molecular formula (structural formula);
- 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.

**b) For inactive ingredients**

- 1) approved 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) 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 Drugs Advisory Board). Specifications not documented in the above references should be fully substantiated with copies of the specifications attached to the applications.

**3. Package Insert (Page 3 of 7)**

The Board will approve the information intended for either the consumers or health workers in the package insert. The Board will issue some of the items required in the insert while the applicant would provide the rest.

The Board shall issue the following information:

- 1) Scheduling status - Allocated by the Board according to Section 9 of the Act:
  - a) Schedule 1A drug - a (narcotic) drug which is highly liable to abuse and which may be dispensed only on a written prescription; Schedule 1B - a (psychotropic) drug which is also liable to abuse though not as highly liable as a Schedule 1A drug, and which may be dispensed only on a written prescription; Schedule 1C - a (psychotropic) drug which, though widely used therapeutically, is liable to some, but relatively minor, abuse in comparison with a Schedule 1A or a 1B drug, and may be dispensed only on prescription.; Schedule 1D - a drug (containing a habit forming drug) which is unlikely to produce dependence or cause harm is misused, and may be dispensed without prescription<sup>1</sup>;

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<sup>1</sup> Text in parenthesis is not quoted from the Act.

- b) Schedule 2 drug - a drug, not being or containing a habit forming drug, which may be dispensed only on written prescription;
  - c) Schedule 3 drug - a drug which may be sold from a pharmacy without prescription;
  - d) Schedule 4 drug - a drug that may be sold over the counter by any licensed trader.
- 2) **Conditions of registration:** These include sales category, public advertising status, distribution restrictions, etc., as may be decided by the Board.
  - 3) **Registration number:** The number allocated by the Board.
  - 4) **Date of publication:** Date of approval of the package insert by the Board.
  - 5) **Proprietary name:** The proprietary name(s) used for different strengths or dosage forms shall be distinguished by at least the corresponding strengths and dosage forms.
  - 6) **Composition:** This includes approved name and quantity per dosage unit (suitable mass or volume) of active and inactive ingredient(s), preservative(s), colorant(s), alcohol and any sugar included. Excipients shown on the package insert may be listed without specifying quantities.
  - 7) **Pharmacological classification:** The classification according to anatomical, therapeutic and chemical groupings as discussed under “Drug details”, Section I. D. 1. b)).
  - 8) **Pharmacological and mechanism of action:** A brief description of the pharmacological actions and pharmacokinetics of the drug shall be mentioned.
  - 9) **Indications:** Indications for the drug applied for shall be supported by appropriate clinical information given under “Pharmacological and Clinical Documentation (**Page 6 of 7**)”, Section I. C. 6.
  - 10) **Contraindications:** Both absolute and relative contraindications shall be mentioned.
  
  - 11) **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.
  - 12) **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.
  - 13) **Side effects and special precautions:** Side effects should be mentioned by order of occurrence. Special precautions necessary for the safe use of the drug shall be mentioned. Drug interactions form part of the special precautions.
  - 14) **Known symptoms of over-dosage and particulars of treatment:** Signs and symptoms of over-dosage and recommended treatment must be mentioned.
  - 15) **Storage instructions:** Conditions should quote a suitable temperature or temperature range in degree Celsius. Refer to “GUIDELINES FOR STABILITY TESTING OF DRUGS - PRE-REGISTRATION” Section IV.
  - 16) **Identification:** The physical appearance and characteristics of the drug shall be described.

17) **Presentation:** All the types of packaging and pack sizes shall be mentioned.

#### **4. Container Specification and Control** (Page 4 of 7)

- 1) The container-closure system shall be described.
- 2) The immediate container, i.e., the container-closure system in immediate contact with the drug, should be subjected to similar controls like all other raw materials. The container-closure system is likely to interact with the contents in various ways including chemical reaction with the drug, leaching properties of the system, adsorbent properties in relation to specific contents, moisture penetration, air tightness, etc. All these have important implications on the quality of the drug or its acceptability.
- 3) Specific container-closure system release criteria detailing acceptable limits and the sampling method should be mentioned.
- 4) Immediate container specifications should include the type, nature, size, grade, method of closure, method of use, etc.

#### **5. Pharmaceutical Documentation** (Page 5 of 7)

- 1) Information required in the pharmaceutical documentation should indicate details of the following:
  - a) Specification;
  - b) analytical control procedures;
  - c) release criteria for both raw materials control and finished products;
  - d) manufacturing procedures and in-process controls;
  - e) Stability studies (see “GUIDELINES FOR STABILITY TESTING OF DRUGS - PRE-REGISTRATION”, Section IV).
- 2) Specifications should include:
  - a) title;
  - b) limits;
  - c) criteria of acceptance of all physical and chemical characteristics;
  - d) identification;
  - e) purity;
  - f) assay/potency;
  - g) Microbiological parameters, where applicable.
- 3) Manufacturing procedures should give detailed summaries of all stages of manufacturing, packaging and labelling in a sequence adopted, describing the type of equipment used and all in-process control steps.
- 4) Batch manufacturing records for submitted samples should be attached.
- 5) Where other companies are involved in undertaking other tasks in the manufacturing process, packaging, labelling, quality control, etc., such companies should be mentioned and tasks be specified with reference made to underlying agreements.

**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)

Relevant details of pharmacological and clinical information about the drug or reference of the latest existing editions of textbooks or articles on the specific subjects should be submitted for new chemical entities or well known products, respectively, as may be determined by the Board.

### ***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.

For these and other applications where clinical data are involved, a synopsis of clinical studies should be submitted.

The following information should be provided:

- 1) pre-clinical toxicological information - acute toxicity, estimated average lethal dose, teratogenicity, carcinogenicity and other studies on the safety of the product;
- 2) information on efficacy, dosage and method of administration, mode or mechanism of action, indications, adverse reactions, precautions and contraindications as may be observed in both humans and other test models;
- 3) details of pharmacokinetic properties, metabolism, metabolic products and their fate; and
  
- 4) Studies confirming bioavailability, biological equivalence and/or the clinical interchangeability of pharmaceutically equivalent drugs.

## **7. Registration Status and Other Information** (Page 7 of 7)

### ***a) Registration status in other countries***

- 1) Information on registration status (marketing authorisation) in three other 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.

***b) Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce***

- 1) A W.H.O. 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) General requirements***

- 1) A table of contents showing all items in the application should be submitted.
- 2) 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.
- 3) The information supporting the application should be summarised by the use of tables and graphs. Each application should not exceed 100 pages, where practicable.
- 4) Copies of all technical agreements relevant to the application should be submitted.

***d) Label text matter***

- 1) A sample label as would appear on the immediate container should be attached bearing information included under Regulation 8 of the Drugs and Related Substances, Regulations, 1993:
  - a) Approved name (international non-proprietary name);
  - b) brand name, if any;
  - c) contents of the container;
  - d) quantity of the active ingredient per dosage unit;
  - e) batch identification;
  - f) expiry date;
  - g) storage conditions;
  - h) warnings and precautions;
  - i) directions for use;
  
  - j) statutory or cautionary label (see Regulation 8(5));
  - k) Manufacturer's name and address.
- 2) In the case of small containers items (a) or (b), (d), (e) and (f) should be provided. This and the rest of the information should be provided in an outer container.
- 3) Promotional or advertising materials should also be attached to the submission.

## **E. ADDITIONAL REQUIREMENTS**

The following guidelines are meant to supplement MH 2048 Form 1, Application for Registration of a Drug and assist applicants to adhere to the requirements with regard to the submission of new applications.

### **1. Number of copies of applications**

Three (3) copies of the registration application dossiers and additional documents required 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 diskettes or CD may facilitate the evaluation of the package insert, labelling information as well as assist in application pre-registration evaluation. The computers at DRU run on Microsoft Office. *This request is not binding to applicants.*

### **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) P(Pula)800.00 for a drug which imported;
- 2) P400.00 for a drug which is partially locally manufactured; and
- 3) P200.00 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 to the Ministry of Health, Botswana Government. Payment should be made in Botswana Pula through a bank draft or money order. Where cash is used, an appropriate amount shall be paid at Central Medical Stores Revenue Office. The receipt should be submitted to the DRU along with the application.

Where it is impractical and impossible to obtain Botswana Pula, a direct deposit may be made into a Botswana Government Account as follows.

- 1) Credit the Government of Botswana Bank Remittance Account No. BoB 016/00/20001, Bank of Botswana, Private Bag 154, 18 Khama Crescent, Gaborone Botswana. Tel.: (267) 3606000, Fax: (267) 313890 or 372984.
- 2) Advise Bank of Botswana to credit vote 112-503-01 - Drug Registration and Licensing, Technical Support Services, Ministry of Health.
- 3) Advise the DRU that a transfer has been made and provide details. ***Please note that the DRU will not be in a position to know whether payment was made until confirmation is received from the Accountant General.***

### **3. Multiple manufacturing sites**

The applicant shall mention all possible manufacturers of the drug applied for, and shall assure that all the manufacturers are registered with the Drugs Regulatory Unit by completing the Company Registration Form for each. GMP certificates for each manufacturer should be attached. A copy of a company registration application form that has been submitted to Botswana Central Medical Stores is acceptable. (Attach to Page 1 of 7 of MH 2048 Form 1, "Application for Registration of a Drug")

#### **4. Storage conditions**

Storage conditions shall reflect actual storage temperatures with or without descriptive phrases and NOT descriptive phrases only. For example, “Store at room temperature below 30 °C” NOT “Store at room temperature”. Also refer to “GUIDELINES FOR STABILITY TESTING OF DRUGS - PRE-REGISTRATION”, Section IV. (Attach to Page 3 of 7 of MH 2048 Form 1, “Package Insert”)

#### **5. Immediate container**

The immediate container shall include the primary container in direct contact with the drug and any other secondary container or closure system whose presence is vital to product integrity. (Attach to Page 4 of 7 of MH 2048 Form 1, “Container Specification and Control”)

#### **6. Samples**

Sealed samples, of at least two (2) batches, in the actual distribution container and accompanied by certificates of analysis shall be submitted. The quantities of each sample should be enough to allow for at least three complete monograph tests (according to specifications) to be performed.

#### **7. 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.

#### **8. Batch production records and release certificates**

- 1) 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;
- 2) Include certificates of analysis for all raw materials;
- 3) Batch Certificates shall be submitted for all vaccines, biological and biotechnology products. (Attach to Page 5 of 7 of MH 2048 Form 1, “Pharmaceutical Documentation”)

#### **9. Stability Studies (Refer to “GUIDELINES FOR STABILITY TESTING OF DRUGS - PRE-REGISTRATION”, Section IV)**

- 1) A detailed report of studies from at least three (3) batches shall be submitted (Attach to Page 5 of 7 of MH 2048 Form 1, “Pharmaceutical Documentation”).
- 2) For all products of complete foreign manufacture, only real time studies, at recommended storage conditions, shall be accepted.

#### **10. WHO Type Certificates and Free Sale Certificates**

Only the certificates corresponding to the **latest format** of the World Health Organisation Certification Scheme on the Quality of Products Moving in International Commerce will be accepted as Product Certificates. Free Sale Certificates will NOT be accepted from countries subscribing to the WHO certification scheme. See D. 7. b) 2. “Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce”, above. (Attach to Page 7 of 7 MH 2048 Form 1, “Registration Status and Other Information”)



**11. Promotional material**

Copies of existing and proposed promotional material shall be submitted. (Attach to Page 7 of 7, MH 2048 Form 1, "Registration Status and Other Information")

### 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 (for official use only):	
Date of evaluation (for official use only):	
Evaluator (for official use only):	

	Remarks <sup>1</sup>	For official use only	
		Yes	No
<b>A. GENERAL INFORMATION</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			

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

English)					
11) Is payment or proof of payment attached?					
12) Is there a table of contents or index?					
Conclusion:					

	For official use only		
	Yes	No	Remarks <sup>1</sup>
<b>B. COMPOSITION</b>			
1) Is the full composition stated?			
2) Are storage conditions for the active ingredient given?			
3) Are specifications or references stated?			
4) Are copies of in-house specifications included in Pharmaceutical Documentation?			
Conclusion:			

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

<b>C. PACKAGE INSERT</b>		Yes	No		
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>		Yes	No		
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>	<b>Remarks<sup>1</sup></b>	
1)	Are real-time stability data included for at least: a) 6 months at the storage temperature recommended in the package insert? b) 3 months accelerated conditions?			N/A	RH %
				N/A	RH %
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	PROD	BOTH	
4)	Were accelerated studies performed with trial or production batches or both?	TRIAL	PROD	BOTH	
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.

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		Yes	No		
<b>G.</b>	<b>PHARMACEUTICAL AND BIOLOGICAL AVAILABILITY</b>			Remarks <sup>1</sup>	
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:					



				For official use only		
		Yes	No	Remarks <sup>1</sup>	Yes	No
<b>H. PHARMACOLOGICAL AND CLINICAL DOCUMENTATION</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?						
3) Has there been an audit performed at the manufacturer and/or laboratory by quality assurance personnel conversant with good clinical trial practice (GCP) requirements?						
4) Are written reports available for the above inspection?						
Conclusion:						

				For official use only	
<b>I. REGISTRATION STATUS</b>				Yes	No
1) State in which of the following countries the drug (formulation applied for) is registered. Give registration number and the date of registration.				Yes	No
Country	Registration Number	Date of Registration	Remarks <sup>1</sup>	Yes	No
a) USA					
b) UK					
c) Netherlands					
d) Sweden					
e) New Zealand					
f) Australia					
g) Canada					
h) EU					
i) Malaysia					
j) South Africa					
k) Egypt					
l) Norway					
m) Denmark					
n) Other (Specify)					

Conclusion:

**J. DECLARATION**

I, ..... am a Registered Pharmacist, and I ..... declare that the information given above is correct.

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: Yes	<input type="checkbox"/>	No	<input type="checkbox"/>						
Priority: 1 Government Tender	<input type="checkbox"/>	2 Local manufactured	<input type="checkbox"/>	3 Specific health need	<input type="checkbox"/>	4 Other (specify)	<input type="checkbox"/>	5 Normal	<input type="checkbox"/>

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

## **IV. GUIDELINES FOR STABILITY TESTING OF DRUGS - PRE-REGISTRATION**

### **A. INTRODUCTION**

These stability studies should aim to establish that the dosage form conforms to the critical specifications during the estimated shelf life. The stability characteristics of the ingredients, the nature of the product/dosage form, the type of packaging and the environmental conditions under which the product will be marketed and used, all have great influence on the study design and the type of tests to be performed.

### **B. STABILITY STUDIES**

Stability studies are carried out to provide information necessary for predicting problems likely to be encountered during storage, establishing storage conditions and establishing a shelf life for the drug.

- 1) Stability studies should investigate:
  - a) the stability of the drug in unopened packs;
  - b) stability of the drug following manipulation necessary prior to administration (e.g., re-constitution or dilution);
  - c) Stability of the drug during use, e.g., the effects of opening and closing of the container-closure system.
- 2) The packaging used during stability studies should be the one intended for marketing, in all respects including the relative size.
- 3) Both accelerated and real-time stability studies must be carried out in at least two batches. The batch number, date of manufacture and the size of each batch should be mentioned.
- 4) All methods of analysis for stability testing should be fully described and all analytical methods used to determine degradation products should be submitted with the results.
- 5) Data should be presented in a summarised, legible form. Where possible tables and graphs should be used. The submission of large volumes of undigested data shall not be encouraged. Statistical analyses may be used where appropriate at specified confidence limits.
- 6) Results should be discussed and a conclusion (shelf life) drawn from the studies. Differences within and between batches should be explained. The effects of the storage at temperature and the inferred shelf life should be summarised.
- 7) Shelf life predictions should be based on available data.

#### **1. Accelerated stability studies**

These studies should be performed in the proposed container-closure system and be utilised to determine the tentative shelf life of a drug. The following exaggerated conditions are recommended.

- 1) Temperatures: Low (2-8 °C ) and high (37-40 °C ), at least two;
- 2) Relative humidity of 75% and/or combined temperature/humidity;
- 3) Exposure to light (natural or artificial), air and chemical agents (particularly for liquids);
- 4) At least 3 months to be indicative of shelf life of 2 years.

Accelerated studies should be paralleled by real-time studies at room temperature controlled to 30 °C or a stated maximum storage temperature in the case of heat labile products.

Accelerated stability studies shall not be acceptable for the items on the market for at least 2 years before application for registration is received.

## **2. Real-time stability studies**

Real-time stability studies shall simulate recommended storage conditions, at the maximum storage temperature for the full term proposed.

- 1) Maximum storage temperature, e.g., 30 °C, if maximum recommended temperature is 30 °C ;
- 2) Relative humidity of 45% - 60%;
- 3) At least 9 months testing results shall be indicative of 2 years shelf life.

## **3. Extension of shelf-life**

Where studies have not been carried out on full-scale production batches, on-going studies may be required to substantiate shelf-life extension.

- 1) The shelf life may be extended on the basis of real-time stability studies carried out for the full shelf life period. An extension may never be based on accelerated studies. Stability tests intended to substantiate an increase in shelf life shall be performed at reasonable intervals.
- 2) The shelf life of a product may not exceed five (5) years.

## **4. Stability indicating properties**

- 1) Stability studies should monitor properties included in finished product specification and any other properties which happen to be stability indicating, including the following:
  - a) chemical stability of the active ingredient and any essential excipients (e.g., preservatives and antioxidants);
  - b) degradation product(s) levels;
  - c) Physical properties (e.g., particle size, dissolution rate, hardness, viscosity, re-suspendability, etc.);
  - d) packaging interactions and integrity;
  - e) microbiological stability (including anti-microbial preservative efficacy on fresh and old drug);
  - f) Organoleptic properties (odour, taste, palatability, etc.)
- 2) Validation studies should be carried out to support the stability indicating claims:

## ***C. CHANGES REQUIRING STABILITY TESTING***

Stability testing results may be required in all applications for drug registration and in the following circumstances, before the drug is re-marketed:

### **1. Change of formulation**

Where a drug (originally stability tested with proven) shelf-life undergoes a change that may affect its stability, e.g., change in formulation, container or closure, system, manufacturing procedure or environment conditions, and manufacturing process of the active ingredient raw material.

### **2. Re-packaging**

Where a drug manufactured at one site undergoes re-packaging at a different site, unless approved by the Board.

### **3. Change of manufacturer**

Where there has been a change of manufacturer, unless approved by the Board.

**N. B.** Stability studies conducted according to the guidelines issued by the International Conference on Harmonisation (ICH) will be accepted.

# GUIDELINES ON DRUG REGISTRATION APPLICATIONS IN BOTSWANA

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