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Review Article

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REGULATORY REQUIREMENTS FOR MARKETING AUTHORIZATION OF GENERIC DRUG PRODUCT IN BOTSWANA

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ABSTRACT

Immediately after independence in 1966, the pharmaceutical sector became a priority for the Government, and for many years Botswana pioneered numerous areas of pharmaceutical policy, receiving international recognition for this work. The Botswana pharmaceutical market is growing rapidly. It is heavily driven by imports. The majority of pharmaceutical sales in the country are from prescription drugs. There are two procedure by which a marketing authorization in Botswana can be obtained, Registration of Medicine through General format (MH 2048) and Registration of Medicines through CTD & SADC format. These both procedure are applicable to innovator and generic medicines. Branded medicines play an important role in medications, but generic medicines are their cost effective alternatives. Generic Medicines are similar to branded drugs in terms of efficacy, purity and are perceived to be safer as compared to new drug molecules, as they likely to be older and time tested. This review article attempts an insight on the recent regulatory aspects and marketing authorization procedures in Botswana by giving a detailed overview of the both General format and CTD-SADC format for pharmaceutical applicants to make proper marketing applications and market or place their pharmaceutical generic products in the Botswana.

KEYWORDS: Generic drug product in Botswana, CTD & SADC format, Marketing authorization.

INTRODUCTION

Regulatory Affairs[1]

Regulatory Affairs is a new profession which has developed from the desire of government to protect public health by controlling the efficacy, safety of products in areas include pharmaceuticals, medical devices, veterinary medicines, pesticides, cosmetics, complementary medicines and agro chemicals.

Regulatory Network[2]

Regulatory Affairs regulate the pharmaceutical business through designing appropriate laws and enforce the same so that the drugs meeting the maximum values of Quality are brought into the Global Trade.

Rules and regulations are being prepared in view of Regional, Global and National pharmaceutical trade as well as need of the drugs based on patient population.

Most of the national guidelines for drug growth and marketing authorization application are defined based on Regional and Global Harmonized guidelines.

- Global Regulatory Network:- WHO, ICH.
- Regional Regulatory Network:- EU, ASEAN, GCC, SADC.
- National Regulatory Network:- DCGI, USFDA, MHLW, MCC.

Marketing Authorization[3]

The process of assessing and reviewing the dossier of a pharmaceutical product containing its detailed data like administrative, chemistry, preclinical, clinical and the permission granted by the Regulatory Agencies of a country with a view to support its marketing approval in a country is called as the Marketing Authorization or Marketing Approval.

It is commonly called as the New Drug Application (NDA) in the USA or Marketing Authorization Application (MAA) in the European Union (EU) or simply Registration Dossier.

Generic Drug[4]

A generic drug is a drug defined as "A drug product that is comparable to a brand- reference listed drug product in strength, dosage form, performance characteristics, quality and

intended use. It is also been defined as a term which referring to any drug marketed under its chemical name without promotion.

Advantages of Generic Drugs

- Generic drugs usually sold for lower prices compare to the branded drugs.
- Lower price of generic drugs is due to competition increases between generic drugs manufacturers after innovative drugs are not longer protected by patents.
- Generic drugs manufacturer spend fewer costs in making drugs which includes cost of manufacturer (rather than entire cost of testing and development) & are maintain the profit at lower prices.
- The prices of generic drugs are low enough for users in many less-developed countries to afford them.
- Generic drug manufacturers may also take the benefit of the prior marketing efforts of the branded name drug company, presentations by drug representatives, including media advertising and distribution of free samples.

Introduction to Southern African Development Community (SADC)[5-14]

Regulatory Authority of SADC

Table.no.1: Overview of Regulatory Authority of SADC.

No.	COUNTRY	REGULATORY AUTHORITY
1	Angola	Ministry of Health
2	**Botswana**	Ministry of Health
3	Congo	Ministry of Health
4	Lesotho	Ministry of Health and Social Welfare
5	Madagascar	Ministry of Health
6	Malawi	Ministry of Health
7	Mauritius	Mauritius Institute of Health
8	Mozambique	-
9	Namibia	The Namibia Medicines Regulatory Council (NMRC)
10	Seychelles	Ministry of Health
11	South Africa	Medicine Control Council
12	Swaziland	The Government of the kingdom of the Swaziland
13	Tanzania	Tanzania Food and Drugs Authority
14	Zambia	Ministry of Health
15	Zimbabwe	Medicines Control Authority of Zimbabwe

Regulation of Botswana[15-18]

The broad policy of the Ministry of Health (MOH) aims at ensuring that all drugs manufactured, exported or imported and sold in Botswana are of acceptable safety, quality

and efficacy. The process of drug registration forms an important basis for evaluating and assure drug quality, safety and efficacy. Therefore, all drugs manufactured, exported/ imported, and sold in Botswana should be registered.

The registration of drugs, medicines and related substances in Botswana is governed by the provisions and requirements of the Drugs and Related Substances Act, 1992 and the Regulations, 1993.

Under MOH Pharmaceutical Department (PD) is responsible for the drug registration and regulation. Two units help the regulation and registration procedure which are

A. Drug Advisory Board (DAB)
B. Drug Regulatory Unit (DRU)

A. 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.
- DAB develop and issues the guidelines for drug registration for MOH and other guidelines which helps applicant to register their pharmaceutical products in to the Botswana.
- The Clinical Trials Sub-Committee under DAB is responsible for the evaluation of drug registration applications for clinical trials/studies.

B. Drug Regulatory Unit

- A committee of the Board or the DRU (Drugs Regulatory Unit) evaluates applications for registration.
- The recommendations about generic drug registration application are submitted to the Board for the final resolution.
- The inspection of manufactures plants are responsibility of DRU.

Dossier Evaluation Flow Chart

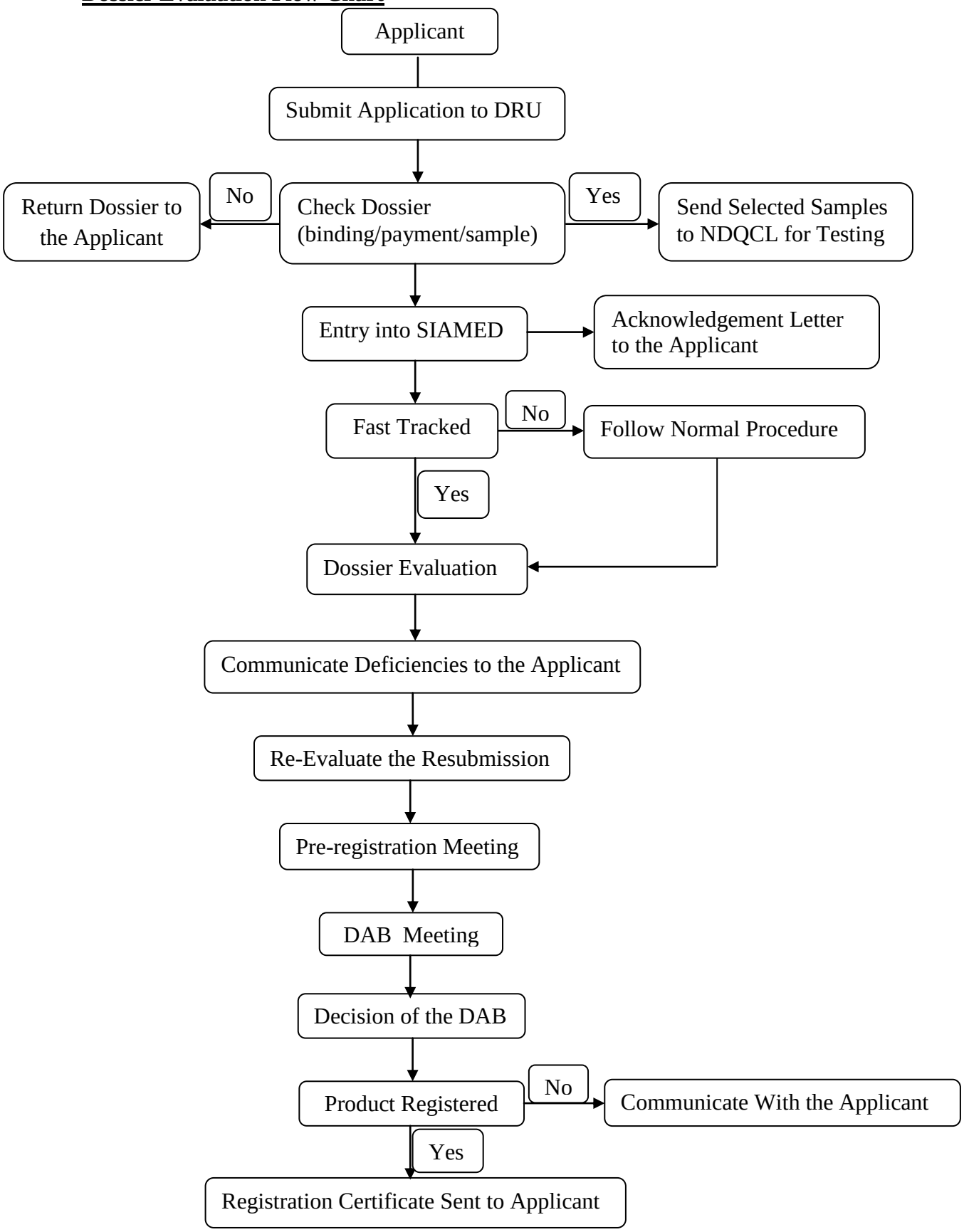

Fig.no.1: Dossier Evaluation Flow Chart of Botswana

Botswana follows **2 sets** of guidelines for drug registration which are,

1. Registration of Medicines through General format (MH 2048)
2. Registration of Medicines through CTD & SADC format

1. Registration of Medicine through General format (MH 2048)

- Application for registration of medicines is made on **MH-2048**, which consists of **7 parts**. This application form requires information on safety, efficacy and quality of the product applied for.
- It is required that MH-2048 should be completed and signed by a registered pharmacist (Applicant).
- The product pre-registration/evaluation report should be completed for all submissions. Submitting registered pharmacist should signs the Pre-Registration/Evaluation Report.
- All documents of submitted dossier must be in English.

MH-2048 Application Part For Registration Of Drug

The application comprises of 7 part,

1. Application for registration of a Drug (Applicant and Drug Particulars)
2. Composition
3. Package insert
4. Container specification and control
5. Pharmaceutical documentation
6. Pharmacological and clinical documentation
7. Registration status and other information

1. Application For Registration Of A Drug

A. Applicant Details	a) Details of Applicant b) Details of Manufacturers
B. Medicines Details	a) The Proprietary Name of the product b) Dosage form and Strength c) Color d) Package Size e) Pharmacological Classification (ATC) f) Route of Administration of product g) Container/closure and administrative devices g) Proposed Shelf Life of the product in each of the different package type and sizes
C. Signatory	i) A registered pharmacist in the company who submitting the application must sign the application. ii) A notarized proof of registration of the pharmacist

	in the resident country should be attached with the application. iii) A declaration should be made by the applicant or a responsible person nominated by the applicant and who must have the required skills and necessary qualifications. iv) 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. v) False and misleading declarations will lead to rejection of application or prosecution.

2. Composition

A.Development Pharmaceutics	(i) Explanation with regard to the choice of the composition, formulation, container and ingredients, supported if compulsory, by data on development pharmaceutics. (ii) The overage, with justification thereof. (iii) Tests carried out during pharmaceutical development must be described in detail. (iv) Reasons for the choice of the primary packaging must be given.
B. Unit Formula	i) The composition of dosage unit. ii) 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. iii) The purpose of each inactive raw material must be stated briefly. If the excipient is used for multiple purpose in the formulation than each purpose must be stated. iv) Flavoring and coloring agents should describe in their main constituents only and with their chemical identification and characterization. v) The presence of alcohol in the product must be declared, and concentration stated, on the label, the package insert and in the patient information leaflet. vi) Solution added to adjust pH must be described in terms of composition and strength (normality, morality).
C. Schedule of Ingredients	
a. For Active Ingredients	1) Approved or INN name 2) IUPAC chemical name 3) Molecular and structural formulas 4) Physico-chemical property specification or reference of specification 5) Quantity in dosage unit or other appropriate unit of mass or of volume of the drug

b. For Inactive Ingredients	1) Approved or Compendial name 2) Chemical name 3) Molecular formula 4) Reference of specification or specification 5) Quantity in dosage unit or other appropriate unit of mass or of volume of the drug 6) Purpose for inclusion in the formulation

3. Package Insert

A. Package Insert	1) Schedule Status 2) Proprietary Name & Dosage Form 3) Composition 4) Pharmacological Classification 5) Pharmacological & Mechanism of Action 6) Indication 7) Contraindication 8) Warning 9) Dosage and Direction for Use 10) Side Effects and Special Precaution 11) Drug Interaction 12) Known symptoms of over-dosage and particulars of treatment 13) Conditions of registration 14) Identification 15) Presentation 16) Storage Instruction 17) Registration Number 18) Name and addresses of applicant 19) Date of Publication
B. Patient Information Leaflet (PIL)	The PIL should be in accordance with the summary of product's characteristics. 1) The dosage form and total quantity of product in the package shall be stated 2) Pharmaco-therapeutic group 3) Name and address of the holder of a registration 4) Warning and precautions 5) Therapeutic indications 6) Contraindications 7) Interaction with other medicines 8) Special warnings 9) Instruction for use 10) Special precautions 11) A description of undesirable effects 12) The date on which the leaflet was last revised
C. Summary of Product Characteristics (SmPC)	1) Proprietary name of medicines 2) Approved Generic Name 3) Quantitative & Qualitative Composition 4) Dosage Form 5) Clinical Particulars

	6) Pharmacological Properties 7) Pharmaceutical Particulars 8) Administrative Data

4. Immediate Container Specification and Control

A. Specifications and routine tests	(i) Type of material (ii) Construction (iii) Quality specifications (routine tests) and test procedures
B. Scientific data	(i) Batch analysis results (ii) Release criteria detailing acceptable limits (iii) Sampling method

5. Pharmaceutical Documentation

A. Raw Material Specification, Analytical and Control Procedure	
1. Active Pharmaceutical Ingredients (API) **i. Route of synthetic including impurities**	
a) Scientific Data	1) Nomenclature 2) INN 3) Chemical name 4) Other non proprietary name 5) Chemical abstract service register number 6) Description 7) Physical form 8) Structure formula indicating conformational data for macromolecules 9) Molecular formula 10) Relative molecular mass 11) Chirality
b) Manufacture	(1) Names and addresses of manufacturing source (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
c) Quality Control During Manufacture	(1) Starting materials (2) Control test on intermediate product
d) Development Chemistry	(1) Evidence of chemical structure (2) Potential isomerism (3) Physiochemical characterisation (4) Full characterisation of primary reference material (5) Analytical validation and comments on the choice or routine test and standard e.g. working standard
e) Impurities	(1) Potential impurities originating from the route of synthesis (2) Potential arise throughout the production and purification (degradation products) (3) Analytical test procedure & their limits of detection

f) Batch Analysis	(1) Date of manufacture, place of manufacture, batch size, and use of batches tested including batches used in pre clinical in pre clinical and clinical testing (2) Results of tests (3) Analytical results of reference materials, primary and others
ii. Specification and Release Criteria Tests	
a) Active substance described in the pharmacopoeia, a copy of the monograph of the said pharmacopoeia should be presented.	
b) Active substances which not described in the pharmacopoeia. - Characteristics - Identification tests - Purity tests (including limits for total, named, other single, unidentified single & total impurities)	
c) Most recent certification of analyte of the API	
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.	
2. Excipients	
a) Specifications and Routine tests	(1) Characteristics (2) Identification tests (3) Purity tests (4) Other tests (5) Assay and or evaluations
b) Additional tests	Any additional tests done on the excipients must be indicated.
c) Scientific Data	(1) Nomenclature (2) International non-proprietary name (INN) (3) Chemical name (4) Other names (5) Laboratory name (6) Physicochemical properties (7) Potential and actual isomerism (8) Specifications (9) Safety Data
3. Intermediate Products	
a) Identification of intermediate product	
b) Specification of the intermediate product	
c) Justification for the tests and the control tests in detail	
B. Summarized Details of Final Product Specifications and Release Criteria	
a) Specification and routine tests	(1) Pharmacopoeial monograph copy (2) In-house supply details (3) Quality specifications routine tests procedures with detailed methods to allow repetition of tests by another laboratory
b) Justification for tests	
c) Analytical validation of	Comment on the choice of routine tests and standards

methods	
C. Stability Tests on Finished Products	
(i) Quality specification for the proposed shelf-life (ii) Characteristics to be tested and the explanation thereof (iii) Batches type and sizes tested (iv) Packaging material and sizes where applicable (v) Real-time and accelerated conditions (vi) Results of tests, including initial results and reference to degradation products (vii) Validation of stability indicating tests (viii) Conclusion and shelf life claim is expected in relation to the results (ix) Discussion of the results must be done	
D. Methods of Preparation for Finish Product	
(i) Batch manufacturing formula including details of batch size. (ii) Site of manufacture in which name and address of each manufacturing facility, GMP certificate for each site, manufacturing licence from the regulatory authority must be confirmed.	
(iii) Manufacturing Process	(1) Detailed manufacturing procedure including equipment, in process control, processing conditions and packaging procedure must be presented. (2) A flow chart of entire manufacturing process (3) Validation of the process, experimental data showing manufacturing process. (4) A copy of master formula (5) Batch production records (BPR) corresponding to the sample for at least 2 batches must be submitted. (6) A certificate of analysis for all raw materials (7) Batch certificates for all vaccines and biological products

6. Pharmacological and Clinical Documentation

A. Bioavailability and Bioequivalence	(i) Sufficient evidence of efficacy and safety for all multisource (generic) products in the form of appropriate in vivo bioequivalence studies should be submitted with each (except biological) application for the registration of a medicine. (ii) It is apply to dosage forms intended for oral administration. It is also generally applicable to non-orally administered medicine products where reliance on systemic exposure measures is suitable to document BA and BE (e.g. transdermal delivery systems and certain rectal and nasal medicine products). (iii) BA/BE study are necessary for the product as follows, Solutions Suspension Immediate Release Product- Tablets, Capsules Modified Release Products Miscellaneous Oral Dosage Forms Fixed Dose Combinations

	(iv) BE study conducted on Human subjects and study is conducted for six months and design of the study is single dose studies and steady state studies.. (v) GMP, GLP and GCP standards should be followed during the study. (vi) Pharmacokinetic parameters used to estimate the rate of absorption are the Cmax and Tmax & parameter that is used to estimate the extent of absorption is the AUC (Area Under Curve).
B. Safety and Efficacy	
a) 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. Categories D and E drugs require in depth investigation of efficacy and safety. These types of applications frequently involve massive volumes of clinical data and are time consuming.	
b) Summary of Toxico-Pharmacological Documentation	The principle finding from the toxicological 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 indicated
c) 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.
d) 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.
e) 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.
f) 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 toxico kinetics evaluation) (iv) Other systems
g) 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
h) Pharmacodynamic	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.
i) 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.
j) 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.
k) Other Toxicity studies	(i) Immunotoxicity (ii) Antigenicity (iii) Studies on metabolites (iv) Dependence (v) Studies on impurities (vi) Other studies
l) Discussion and Conclusions	Discuss the toxicological evaluation and the significance of any issues that arise. Tables or figures summarising this information are recommended.
C. Summaries of Clinical Studies	
a) Human Pharmacology	
1. Product Development Rationale	(i) Identify the pharmacological class of the medicinal product. (ii) Describe the particular clinical/pathophysiological condition that the medicinal product is intended to treat, prevent, or diagnose. (iii) Briefly summarise the scientific background that supported the investigation of medicinal product for the indication. (iv) Briefly describe the clinical development programme of the medicinal product including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the programme. (v) Briefly describe plans for the use of foreign clinical data.
2. Summary Of Biopharmaceutical Studies and Associated	(i) Background and Overview (ii) Summary of results of Individual Studies (iii) Comparison and Analyses of Results Across

Analytical Methods	Studies
3. Summary of Clinical Pharmacological Studies	(i) Background and Overview (ii) Summary of Results of Individual Studies (iii) Comparison and Analyses of Results Across Studies (iv) Special Studies
b) Clinical Documentation	
1. Summary of Clinical Efficacy	(i) Background and Overview of Clinical Efficacy (ii) Summary of results of Individuals Studies (iii) Comparison and Analyses of Results Across Studies
2. Summary of Clinical Safety	(i) Exposure to the Medicine (ii) Adverse Events (iii) Narratives (iv) Clinical Laboratory Evaluations (v) Vital Signs, Physical Findings, and other observations Related to Safety (vi) Safety in Special Groups and Situations

7. Registration Status and Other Information

A. Registration Status in Other Countries	(i) Information on registration status in ICH and SADC Member States and in Other Countries (not more than five) and other foreign countries where the drug is registered should be submitted with certified copies of certificates. (ii) If the marketing authorisation for the drug has been refused, rejected and 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	(i) A WHO type certificate, in the latest format, prepared from the country of origin of the drug should be submitted together with the application. (ii) Free Sale Certificates will be accepted only from countries not subscribing to the WHO Certification Scheme. (iii) 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	(i) The label should have all the information specified under this section. (ii) 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. (iii) Label information includes name of active ingredients, quantity of each per dosage unit, pharmaceutical dosage form, specific excipients and content, route of administration, storage instruction, special warning, date of manufacture of the medicines, expiry date, name and address of holder of registration, name and address of manufacturer, registration number of medicine in market, batch number, pack size of the medicines e.g. 100 capsules, 100 ml etc. Outer Packing Label (i) There should be no promotional material included in the text.

	(ii) For outer packing of medicines proprietary name of a medicine followed by generic name (INN), name of active ingredient and the quantity of each per dosage unit, dosage form, specific excipients and contents, route of administration, storage instruction, special warning, date of manufacture of medicine, expiry date, name and address of holder of registration, registration number of a medicine, manufacturing batch number, pack size for medicine . (iii) The outer packaging may include symbols or pictograms, designed to clarify certain information 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. (iv) Promotional or advertising materials should also be attached to the submission.
G. Additional Requirements	
a) Number of Copies of Applications	(i) Two copies of the registration application (dossiers) shall be submitted. (ii) A covering letter must be attached to each MH 2048 document submitted. (iii) 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.
b) Application Fees and Payment	(i) Subject to the amendment of the Act and Regulations there under, the fees payable in respect of drug registration are, • BWP (Pula) 800.00 for a drug which imported. • BWP 400.00 for a drug which is partially locally manufactured. • BWP 200.00 for a drug which is totally locally manufactured. (ii) An appropriate fee must accompany the application of each drug and is non-refundable. (iii) All payments shall be made in Pula to the Ministry of Health Headquarters, Botswana revenue office.
c) Samples	(i) Sealed samples, from at least two (2) batches, in the actual distribution container along with certificates of analysis shall be submitted. (ii) Reasonable amount of raw material sample or about 10 g of standardized active raw material accompanied by a certificate of analysis shall be submitted.
d) Pre Registration Evaluation Report	The pre-registration evaluation report is a self checking mechanism for the evaluation of MH-2048 application. It should be attached to each drug registration application.

2. Registration of Medicines through CTD & SADC Format: According to the CTD format, each application is a collection of documents, grouped into 5 modules.

The guideline provides information on the contents of the Botswana CTD Module 1: Administrative Information and describes the format and organisation of the Summaries, Quality, Non-clinical, and Clinical modules and Modules 2 to 5, respectively.

The CTD guidelines, together with the Botswana Registration Guidelines provide detailed information about the contents of an application. The CTD format apply to applications to register medicines and all related variations.

In line with Botswana National Drug Policy (BNDP) of August 2002 and Article 29 of the SADC Protocol on Health, harmonization of medicines regulatory systems was identified as a critical component within the context of public health and access to medicines, to achieve the regional common agenda on health.

In 2013, SADC Health Ministers and Ministers responsible for HIV and AIDS approved the adoption of the Common Technical Document (CTD)to facilitate harmonization in the SADC region.

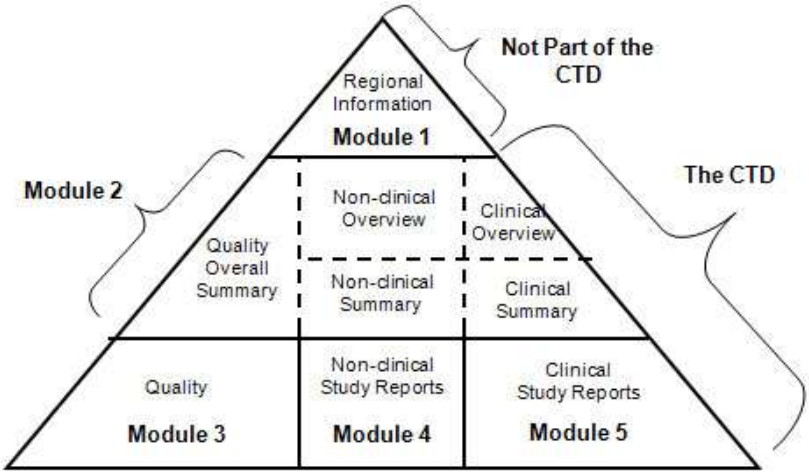

Fig.no.2: CTD Triangle

1. MODULE 1 - Administrative Information and Prescribing Information

1.0	**Cover Letter**	A copy of cover letter should be placed at beginning of module-1.
1.1	**Comprehensive Table of Content**	It includes a complete list of documents provided in the application by module.
1.2	**Application**	It includes application form and annexes to application form which includes proof of payment, LOA, electronic copy declaration, C.V of person responsible for pharmacovigilance, drug substance, copy of EMA certificate for a vaccine antigen master file, copy of EMA certificate of PMF, copy of certificate of suitability of European pharmacopoeia (CEP), copy of confirmation of API prequalification document, letter of access from CEP holder, quality information summary (QIS).
1.3	**Labelling and Packing**	It includes package insert, PIL & labels (outer and inner labels).
1.4	**Information About the Experts**	Experts must provide detailed reports of the documents and particulars, which constitute module 3,4 and 5. A declaration

		signed by the experts should also included.
1.5	**Specific Requirements for Different types of Application**	Studies and data of generic product showing pharmaceutical and biological availability of the product should be include.
1.6	**Environmental Risk Assessment**	An application should be accompanied by an environmental risk assessment, evaluating any potential risks of the medicinal product to the environment should be included.
1.7	**Details of Screening**	A copy of the completed screening checklist must be include.
1.8	**GMP**	Date of last inspection of each site, inspection reports, GMP certificate for API and FPP manufacturers, copy of manufacturing licence, registration of responsible pharmacist, confirmation of submission of sample, certificate analysis of sample.
1.9	**Individual Patient Data-Statement of Availability**	Include a statement that raw clinical and pre-clinical data have been removed from the application and that individual patient data are available on request by MRA.
1.10	**Foreign Regulatory Status**	List of countries in which an application for the same product as being applied for has been submitted, approved rejected or withdrawn, WHO-type Certificate of a Pharmaceutical product, Registration certificates or marketing authorisation, Foreign prescribing and patient information, Data set similarities.
1.11	**Bioequivalence Trail Information**	Information regarding bioequivalence trail should be included in this section.
1.12	**Pediatric Development Program**	State the pediatric development program for applied medicine if any.
1.13	**Information Relating to Pharmacovigilance**	A plan of phamacovigilance and risk management should be submitted in this section.
1.14	**Electronic Review Document**	Electronic copies of product information, BTIF, Botswana-OQS and Biowaiver application forms should be included in this section.

2. MODULE 2 – CTD Summaries

2.1	**CTD Tables of Contents**	**Table of content of module 2 to 5 are included in this section.**		
2.2	**Introduction**	General introduction to the pharmaceuticals including pharmaceutical class, mode of action, proposed clinical use are included in this section.		
2.3	**Quality Overall Summary (QOS)**	**2.3 S QOS-Introduction**	**2.3 P QOS-Drug Product/FPP**	**2.3 A QOS-Appendices**
		General information	Product (name ,dosage form)	Facilities and equipment (name, manufacturer)
		Manufacture name	Pharmaceutical development	Adventitious agent safely evaluation
		Characterization	Manufacturer (name, dosage form)	Excipients
		Control of API	Control of excipients	

		References standards Container closure system	Control of Product	
		Stability (name, manufacturer)	Reference standards (name, dosage form)	
		Container closure system	Container closure system (name, dosage form)	
			Stability (name, dosage form)	

3. MODULE-3 Quality

3.1	**Table of Content Module-3**		
3.2.S	**Drug substances/ Active Pharmaceutical Ingredient (Name, Manufacturer)**	3.2.S.1	Drug Substances/API (Name, Manufacturer)
		3.2.S.2	Manufacturer (Name, Manufacturer)
		3.2.S.3	Characterization (Name, Manufacturer)
		3.2.S.4	Control of API (Name, Manufacturer)
		3.2.S.5	Reference Standards (Name, Manufacturer)
		3.2.S.6	Container Closure System
		3.2.S.7	Stability (Name, Manufacture)
3.2.P	**Drug Product/ Pharmaceutical Product (Name, Dosage form)**	3.2.P.1	Description & Composition of product
		3.2.P.2	Pharmaceutical Development
		3.2.P.3	Manufacture
		3.2.P.4	Control of Inactive Pharmaceutical Ingredient
		3.2.P.5	Control of Pharmaceutical Product
		3.2.P.6	Reference Standards or Materials
		3.2.P.7	Container Closure System
		3.2.P.8	Stability
3.2.A	**Appendices**	3.2.A.1	Facilities & Equipment (Name, Manufacturer)
		3.2.A.2	Adventitious Agents Safety Evaluation (Name, Dosage form, Manufacturer)
		3.2.A.3	Excipients
3.2.R	**Regional Information**	3.2.R.1	Production Documentation
		3.2.R.2	Analytical Procedures and Validation Information
		3.2.R.3	Bioequivalence Trail Information (BTIF)
3.3	**Literature References**		

4. MODULE-4 Non Clinical Study Report

4.1	**Table of Content of Module-4**		
4.2	**Study Reports**	4.2.1	Pharmacology
		4.2.2	Pharmacokinetics
		4.2.3	Toxicology
4.3	**Literature References**		

5. MODULE-5 Clinical Study Reports

5.1	**Table of Contents of Module-5**		
5.2	**Tabular Listing of All Clinical Studies**		
5.3	**Clinical Study Reports**	5.2.1	Reports of Bio-pharmaceutics Studies
		5.2.2	Reports of Studies Pertinent to Pharmacokinetics using Human Participants
		5.2.3	Reports of Human PK studies
		5.2.4	Reports of Human PD Studies
		5.2.5	Reports of Post-marketing Experience
		5.2.6	Reports of Safety and Efficacy Studies
		5.2.7	Case Report forms & Individual Patient Listings
5.4	**Literature References**		

CONCLUSION

Discussion between the industry and regulatory bodies is going on till date regarding the requirements for submission of generic drug application. The aim of this article have to examine how a generic drug product can be approved in Botswana using a both Registration of Medicine through General format (MH 2048) and Registration of Medicines through CTD & SADC format. After this article will be helpful to understand the requirements for the dossier for marketing authorization in Botswana for generic pharmaceutical product.

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