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Review Article

COMPARATIVE STUDY OF REGULATORY REQUIREMENTS AND MARKETING AUTHORIZATION FOR MEDICINAL PRODUCTS IN EUROPEAN UNION AND ZIMBABWE

RAJU KAMARAJ, LINDA M BURUWE*

Department of Regulatory Affairs, SRM College of Pharmacy, SRM Institute of Science and Technology, Tamil Nadu, India.
Email: mklindana@gmail.com

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ABSTRACT

The aim of this study is to evaluate the requirements for marketing authorization procedures of new drugs, generic medicines in developed countries such as Europe and to compare these procedures with those in developing countries such as Zimbabwe. Medicines control authority of Zimbabwe (MCAZ) grants the marketing authorization for medicinal products in Zimbabwe. However, there are still some gaps which need to be filled by the MCAZ to reach other bigger markets in the world. A comparative study of current MCAZ regulatory administration and practices with those of stringent regulators such as European Union will assist in the identification of these loopholes. It also provides the need for improvement with regard to pharmaceutical industries compliance with the relevant standards. This study will give a tremendous reassurance that the MCAZ regulatory affairs acquiescence is being met and gap analysis will systematically challenge the MCAZ regulatory requirements and procedures by comparing them to the European medicines agency regulatory guidelines, which will provide MCAZ with an insight into areas that have room for improvement. The study provides MCAZ with an insight into areas that have room for improvement. Current GMP Supervision of Manufactures and Inspections need to be upgraded; however, currently in Zimbabwe, there is inadequate internal audits, inadequate quality departments to do the validation and self-inspection in pharmaceutical industries. The comparison results obtained showed grey areas needed to be enhanced by MCAZ.

Keywords: Marketing authorization, Medicines control authority of Zimbabwe, European medicines agency, Gap analysis, European medicines agency guidelines.

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INTRODUCTION

Zimbabwe is a landlocked country located in the southern part of Africa. It is categorized under the low-to-middle income countries in the world. The national and health-care products in Zimbabwe are regulated by the medicines control authority of Zimbabwe (MCAZ). The MCAZ authority was first established in 1969 as the drug control council. Under the act of parliament, medicines and allied substances act (Chapter 15:03), the MCAZ became a successor of the Drug Control Council and Zimbabwe Regional Medicines Control Laboratory in 1997. The MCAZ reports to the Minister of Health and Child Welfare, but it has a 100% funding derived from fees collected for services. The MCAZ is responsible for ensuring that all medicines available for sale to the public of Zimbabwe are safe, effective, and of good quality. This authority will ensure that every medicinal product that needs to be marketed in Zimbabwe is registered first before it is distributed to the public. The evaluation and registration division (EVR) is designated to assess the applications for medicinal products [1].

The MCAZ is one of Africa's triumph stories regarding the regulation of medicines and many other health products. In 2012, the MCAZ received a certification from the WHO prequalification program which has led to the expansion and improvement of MCAZ serves in the chemistry laboratory. The quality testing of medicinal products at MCAZ has proved to meet international standards. The MCAZ has supplementary advanced into a service provider for a number of countries in the African region such as Tanzania, Zambia, Ethiopia, Mozambique, and several others [2].

The MCAZ is one of the founding member states of the Southern African Development Committee (SADC) which is known as ZAZIBONA. This is a centralized procedure in which the objective is to provide access to safe, effective, and quality medicines by work sharing in the analysis of applications for registration. This centralized procedure allows inspection of manufacturing testing facilities. The aim is to allow a region which issues good-quality medicines to the public all the time and to significantly decrease the time taken for the approval of marketing authorization in individual countries. They also guarantee efficient utilization of resources within the regional regulatory by sharing their work and evaluations.

However, MCAZ still has a long way to go to meet the world international market of medicinal products. Stringently regulated countries such as the European Union (EU) have set a standard for the marketing and authorization of medicinal products in the world. EU is a giant in the drug regulating markets; it has very stringent requirements for drug development, drug processing, and drug approval. The Medicines Agency (EMA) is a decentralized body of EU which is in charge for the safety and promotion of public health and animal health, through the evaluation and supervision of medicines for human and veterinary use. The EMA was established in 1995 and has worked across EU and globally to facilitate public and animal health assessing medicines to severe scientific standards and by providing partners with independent science-based data. The main objective of the EU pharmaceutical legislation is to safeguard public health while protecting free movement of medicinal products [3].

The EMA is accountable for the assessment of applications for European marketing authorization for medicinal products (centralized procedure). In this centralized procedure, companies must succumb a single marketing authorization application to the EMA which will constantly monitor the safety of medicines through a pharmacovigilance program.

The EMA will take appropriate action if adverse drugs report suggests changes to the benefit-risk balance of a medicinal product [3].

MATERIALS AND METHODS

Registration requirements in EU

For a medicinal product to be placed on the market in Europe, a marketing authorization has to be issued by the competent authorities

Table 1: Comparison for EMA and MCAZ

Contents	EU	Zimbabwe
Authority	**EMA**	**MCAZ**
Committees	1.Committee for human medicinal products 2.Pediatric committee 3.Committee on herbal medicinal products 4.Pharmacovigilance risk assessment committee 5.Committee for advanced therapies 6.Committee for orphan medicinal products 7.Committee for medicinal products for veterinary use	1.Evaluation and registration committee 2.Licensing and advertising committee 3.Legal committee 4.Pharmacovigilance and clinical trials 5.Laboratory committee 6.Veterinary committee
Types of registration procedure	1.Centralized procedure 2.Decentralized procedure 3.Mutual recognition procedure 4.National procedure	1.National procedure 2.The WHO collaborative procedure 3.ZAZIBONA procedure
Types of application	1.Full dossier application 2.Generic product application 3.Hybrid application 4.Biosimilar application 5.Bibliographic application 6.Fixed dose application 7.Informed consent application	1.New chemical entity application (biological and biosimilar medicines are included under this group) 2.Generic drug application 3.Line extension application
CTD presentation	eCTD	Paper CTD
eCTD year implemented	2005	Not yet
Fees structure marketing authorization application	€282,100 for the whole process	$3000 for NCE registration $2 500 generics $1 500 line extensions
Stability requirements		
Number of batches	2	3
Climatic zone	Northern Europe Zone I Southern Europe Zone II	Zone II
Storage conditions long-term intermediate accelerated	25°C±2°C/60% RH±5% RH or 30°C±2°C/65% RH±5% RH 12 months 30°C±2°C/65% RH±5% RH 6 months 40°C±2°C/75% RH±5% RH 6 months	25°C±2°C/60% RH±5% RH or 30°C±2°C/65% RH±5% RH 12 months 30°C±2°C/65% RH±5% RH 6 months 40°C±2°C/75% RH±5% RH 6 months
Container closure system	Testing to be conducted on the dosage form packaged in a container closure system proposed for marketing	Testing is done in dosage form packaged in the container closure system for marketing
Quality personnel certification	Required	May not be necessary
Bioequivalence requirements		
Clinical research organization	Audited EMA	Audited MCAZ
Fasted/fed	As recommended by EMA	As recommended by MCAZ
Number of subjects	Minimum 12	Minimum 12
1. Acceptance criteria for bioequivalence	90% confidence interval	
2. Acceptance criteria for bioequivalence for special class drugs	80–125% Cmax Narrow therapeutic index drugs 90% confidence interval 90.00–111.11% Highly variable drugs 69.84–143.19%	80–125% Cmax 80–125% 75–133%
Supporting documents	ICH E3 Guidelines	ICH E3 Guidelines
Manufacturing and control requirements		
Number of batches	3	3
Packaging	A minimum of 100,000 units	100,000
Batch size	A minimum of 100,000 units	100,000
Finished product control requirements		
Color identification	Required	needed
Disintegration	Required	Required
Water content	Not required	Required
Supporting documents	ICH Q6A	WHO TRS 95,2009

EMA: European medicines agency, MCAZ: Medicines control authority of Zimbabwe

Table 2: Summary of key national differences

EU	MCAZ
i. Administrative information such as cover letter specified for the particular country, application form applicable in that country, exclusivity statement, proof of payment to clinical investigators, proof of establishment of the applicant in EEA	Administrative information correspondence table of contents (M1–5) administrative information product information specific requirements proof of payment and regional summaries
ii. A4 (8.27×11.69 inches) paper size is used for the dossier preparation with font size 12 in Times New Roman	Similar to EU
iii. 1.3 Product information SPC (summary of product characteristic) is provided about the drug product in labeling	SPC, package inserts, patient information leaflet are provided in the labeling braille labeling not required
iv. 1.3.1. Mock-ups and specimens of labels and cartons sent with the application as appropriate. Braille is used for the labeling conditions on the labels	
v. 1.4 Information about experts who sign the module 2 summaries. A qualified personnel is selected	Any member of the MCAZ is selected
vi. 1.5 Specific requirements for different kinds of applications (summary to support generics, hybrid, bibliographic, extension)	No specific requirements biowaiver request is provided in module 1 in 1.2.8
vii. Request for waiver is not provided in module 1.	
viii. 1.6 Environ risk certification 21 is given with the information for GMO or Non-GMO. The fresh/new certificate is provided	No GMO or Non-GMO certification
ix. 1.7 information relating to orphan market exclusivity	Evidence linking to an orphan drug is not required in this section
x. 1.8 Data associated with pharmacovigilance. A separate additional section is provided for the pharmacovigilance system for surveying and controlling the post-approval undesired effects of the drug	No information related to pharmacovigilance required in this module
xi. 1.9 Information relating to clinical trials	Most generic drugs are registered in Zimbabwe. Clinical trials information is obtained from MCAZ
Module 2: It is the same for EU and MCAZ	
Module 3: Quality	
i. 3.2. S drug substance data may be submitted as an EU part DMF (open part to be reproduced in 3.2. S) or as a reference to pharmacopeia European certificate of suitability, for an EU monograph substance	Drug substance data are submitted to the MCAZ in the form of DMF and QIS with reference of the pharmacopeias used. A complaint has been already raised.
i. 3.2.S 7 stability storage requirements to be stated in accord with CHMP guideline	1.2 S7 stability Storage requirements as per MCAZ quality guidelines
ii. 3.2. *P* description and composition colors to be on the European permitted list. Excipients to be designated as conforming to European national pharmacopeia where there is a monograph 3.2 *P* 4 excipients to conform to European national pharmacopeia if described in a monograph.	3.2 *P* Reference may be in DMF supplied directly to MACZ by excipient and container closure manufacture 3.2 *P* 1 Description and composition. Colors to be on MCAZ permitted list. Excipients to be designated as confirm to monograph. 1.3 P 4 Excipients to confirm to MCAZ guidelines
iii. 3.2.P 5 Control of drug product	3.2 *P* 5 control of drug product
Assay limits to be `5% unless justified. A different manufacturer and shelf-life specification may be required for products to conform to the general monograph of the European.	Assay±10%. A single regulatory shelf specification is allowed
iv. 3.2 *P* 7 Container closure system	3.2.P 7 Container closure system
Name of the manufacturer not required unless a product is critical (e.g., parental).	As per MCAZ quality guidelines
v. 3.2 *P* 8 Stability	3.2 *P* 8 Stability
Storage requirements in accord with CHMP guidelines	Stability storage requirements to be in accord with MCAZ requirements
Module 4: There are no major differences in this module.	
Module 5	Module 5
Module 2.3 quality overall summary and module 2.5 clinical overview summarize this module	It also includes a summary of module 2.3 quality overall summary and module 2.5 clinical overview.

MCAZ: Medicines control authority of Zimbabwe, EU: European Union

of the member state to the applicant. The legal requirements and procedures for making an application for a marketing authorization are outlined in Directive 2001/83/EC and in Regulation (EC) No726/2004. There are four marketing authorization procedures in EU which are the centralized procedure, decentralized procedure, mutual recognition, and national procedure. The centralized procedure is the authorization of medicines, whereby a single application, a single assessment and a single approval throughout the EU. This type of procedure enables the applicant to market the medicinal product and make it available to patients and health-care professionals all over Europe because of a single marketing authorization [4].

Mutual recognition procedure is when the applicant gets marketing authorization in several member states where the medicinal product in question has already received a marketing authorization from one of the member state at the time of application. After the first marketing

Table 3: Summarized comparison of the Biowaiver requirements for EMA and MCAZ

Criteria	EMA		MCAZ (WHO BA/BE guidelines)		
API	**BCS Class I**	**BCS Class III**	**BCS Class I**	**BCS Class II**	**BCS Class III**
Excipients	Excipients that might affect bioavailability and qualitatively are the same	Same excipients that might affect the bioavailability and qualitative	An exhibit that the excipients are well established for use in products with API and will not lead to any differences with respect to process affecting the absorption or which may lead to interactions that affect the pharmacokinetics of API		
Drug type	It is not for narrow therapeutic index drugs		Both indication and therapeutic index are important in determining the biowaiver based BCS can be applied		
Dissolution formulation	Very rapid (>85% within 15 min) Rapid dissolution (85% within 30 min)	Very rapid dissolution (>85% within 15 min)	Rapid dissolution (NLT 85% in 30 min)	Dose solubility ratio of<250 ml at pH 6.8 and rapid dissolution : (NTL 85% in 30 min) at pH 6.8	Very rapid dissolution (>85% in within 15 min)
Comparative *in vitro* dissolution test	pH 1–6.8 (at least pH 1.2,4.5, and 6.8) no surfactant enzymes for gelatin only		pH 1.2, 4.5, and 6.8		
Equivalence acceptance criteria	Similarity (f2 calculation 50–100) or other appropriate statistical methods		Similarity (f2 calculation 50–100) or other appropriate statistical methods, provided that the same criterion is used for acceptance(maximum 10% differences between the profiles)		
FDC	FDC products might be acceptable if all API belong to BCS - Class I or III		FDC product with Class I, II, and III APIs meeting the dissolution criteria as specified above		

FDC: Fixed dose combination, EMA: European medicines agency, MCAZ: Medicines control authority of Zimbabwe

authorization in the community is granted, the marketing authorization holder may request one or more member state to recognize an authorization granted by the reference member state by submitting an application in accordance with article 28 of Directive 2001/83/EC. The reference member state will provide a list of documents to the concerned member state and applicant which will be validated in 90 days. The documents to be submitted include the assessment report, summary product of characteristics, labeling, and package leaflet. The concerned member state shall assess and approve these documents and inform the reference member state (Kumar, 2015).

The decentralized procedure is whereby an applicant obtains a marketing authorization in several member states where the medicinal product in question has not yet received a marketing authorization in any member state at the time of application. A national procedure is the starting point for mutual recognition and decentralized procedure, this procedure is when an applicant submits an application to an individual competent member state authority of the EU.

Centralized procedure in EU

Flowchart of centralized procedure show in Fig. 1.

Flowchart: Mutual recognition procedure show in Fig. 2.

Flowchart of decentralized procedure show in Fig. 3.

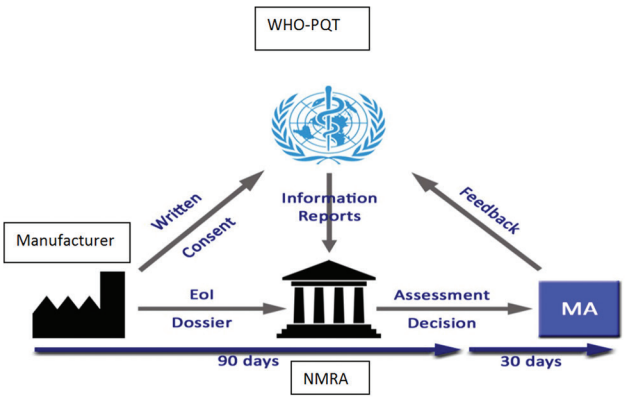
MCAZ

To obtain approval to market, sell, and distribute the medicinal product for human or animal use in Zimbabwe, an applicant should register with the Medicine Control Authority of Zimbabwe. The EVR of MCAZ is designated to assess the applications of medicinal products. This division is responsible for reviewing the safety, quality, and efficacy of medicines intended for marketing, sale, and distribution in Zimbabwe. There are three ways of obtaining marketing authorization in Zimbabwe. One is through the national procedure by MCAZ, second is by the WHO Collaborative Procedure, and third is by The ZAZIBONA procedure.

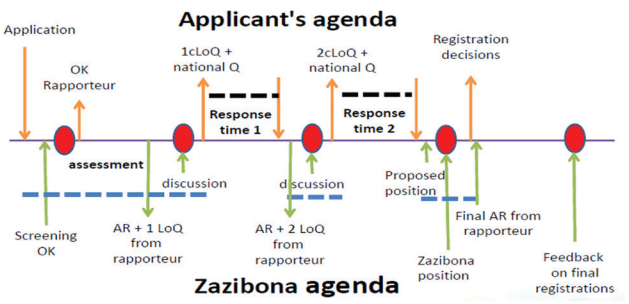
The WHO Collaborative Registration Procedure serves to expedite and fast-track registration of products which have already been assessed and prequalified by the WHO Prequalification team. In the ZAZIBONA process, it is a collaborative registration initiative among four national medicines regulatory authority in Zambia, Zimbabwe, Botswana, and Namibia. The objective of this procedure is to assist in the provision of good quality medicines through work sharing in the assessment of applications for registration and inspection of manufacturing and testing facilities. Medicinal products that pass the evaluation are then provided with an approval for marketing authorization in the participating countries in which applications for registration would have been submitted [5].

Flowchart medicinal product registration by MCAZ Show in Fig. 4.

A schematic overview of the collaborative registration procedure [6].



Zazibona process design



KEY:-

- AR……..assessment report
- Loq……..List of questions.

RESULTS AND DISCUSSION

Comparison of CTD modules.

The Table 4 gives detailed information about procedures and timelines for variations in EU and Zimbabwe [7,8,9 and 10].

This study systematically challenges MCAZ regulatory requirements and procedures by comparing them with the EU standard drug regulations. It helps process improvement in Zimbabwe drug regulatory system [11]. This will enable the MCAZ to determine what actions are necessary for them to be in compliance with the new EU guidelines and requirements. The study provides MCAZ with an insight into areas that have room for improvement [12, 13, 14,15]. Current GMP Supervision of Manufactures and Inspections need to be upgraded. However, currently, in Zimbabwe, there are inadequate internal audits, inadequate quality departments to do the validation and self-inspection in pharmaceutical industries [16-40]. The MCAZ can resolve this by ensuring that pharmaceutical industries implement frequent inspections determined on risk-based approach as done in EU [41-56].

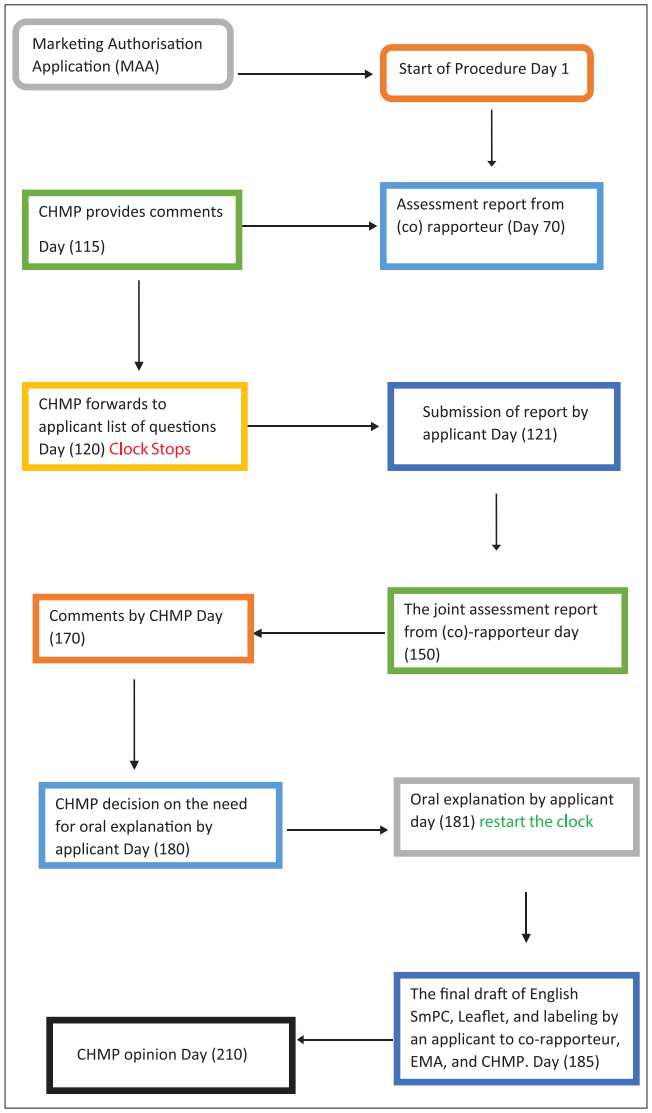


Fig. 1: Centralized procedure

Braille requirement

In Zimbabwe, the MCAZ lacks in the area of braille labeling on drugs primary package. It can harmonize the braille requirements with that of EMA and address applicants to implement these necessities on the carton of a medicinal product [57-73].

Pharmacovigilance

A very big gap in this area underreporting of ADR due to common phenomenon of technical and psychological issues.

- Lack of knowledge and understanding regarding the adverse drug reactions reporting system.
- Fear of negative competence among health-care professionals.
- In most hospitals, there is an underestimation of the true size of a problem resulting in ignorance for ADR reporting.

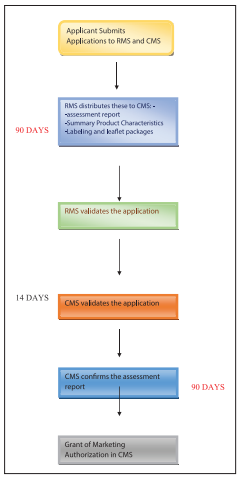


Fig. 2: Mutual recognition procedure

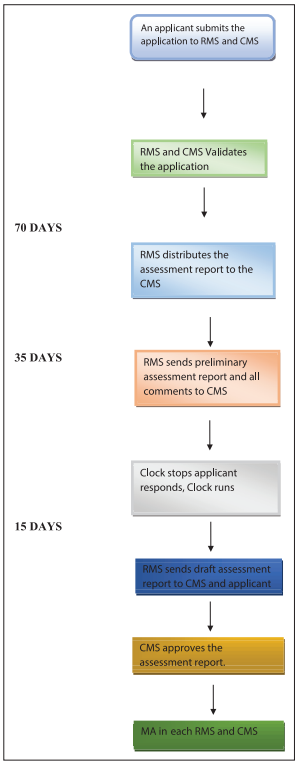


Fig. 3: Decentralized procedure

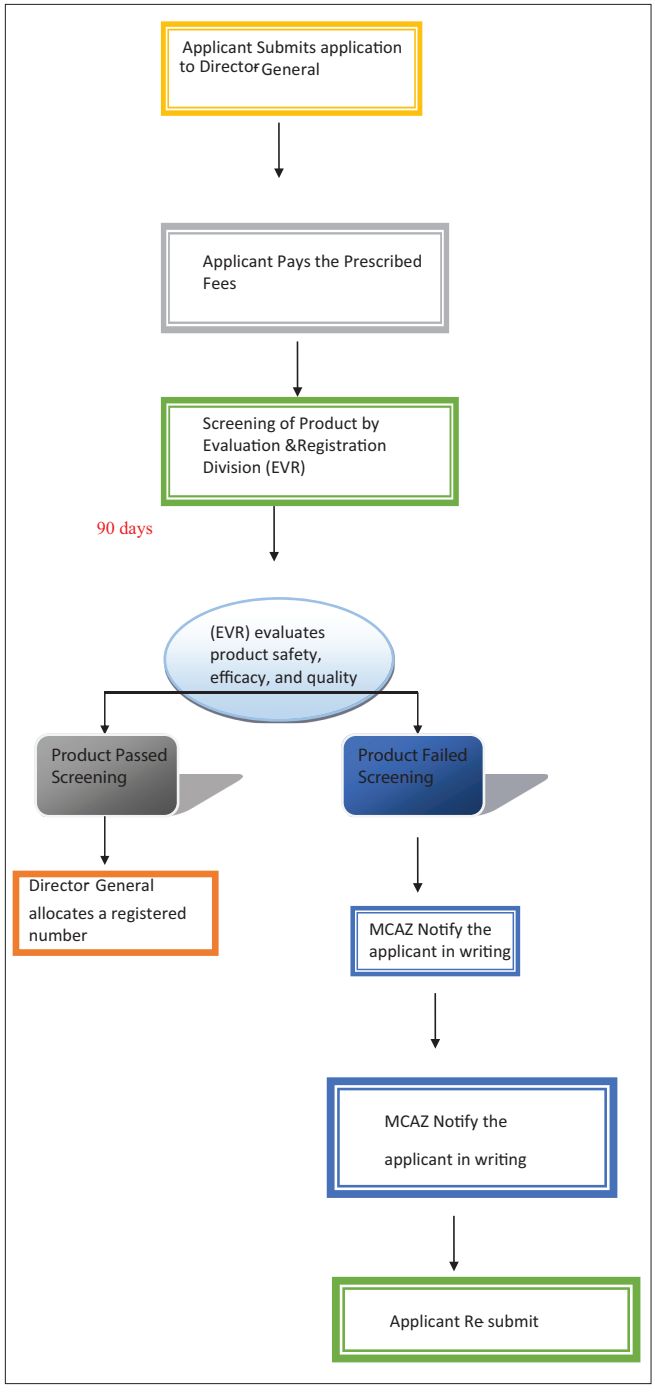


Fig. 4: Medicinal product registration by MCA

Thus, to stimulate the reporting system in Zimbabwe, there should be easy access to reporting forms and other means of reporting. There should be public education regarding adverse drug reaction reporting as this is done in EU, it helps the public to be aware of ADR. (ATUL KHURANA, 2014) MCAZ PVCT team can establish a mobile application in which health-care professionals and consumers can report ADR.

Digitalization

There is a huge gap in the online application for a marketing authorization in Zimbabwe by the regulatory authority of MCAZ. MCAZ should harmonize their webpage with that of EMA. All important documents should be easily accessed on the website, for example, the GMP guidelines must be available on the website

Table 4: Comparisons of variations in EU and Zimbabwe

Europe (EMA)		
Type of variation	**Procedure**	**Timeline**
1.Type IA	Notification. "Do&Tell" and do not require prior approval	Notify within 30 days after implementation.
a.Type IA-IN		Notify with immediate effect, within 2 weeks of implementation
2.Type IB	"Tell, Wait and Do"	Agency will give a response within 30 days
3.Type II	Require approval before implementation and the variation has an effect on safety, efficacy, and quality.	Assessment period is 60 days it may be reduced or extended up to 90 days, based on the urgency of the matter
4.Extensions	These notifications will be evaluated as an initial MAA.	It may be considered as a new MA. Assessment may take 60–90 days.
Zimbabwe (MCAZ)		
Type of application	Procedure	Timeline
1.Minor variation	The applicant submits an application to MCAZ	Within duration subject to MCAZ response
2.Major variation.	MCAZ evaluates	Within duration subject to MCAZ response

EMA: European medicines agency, MCAZ: Medicines control authority of Zimbabwe, EU: European Union

rather than to let an applicant visit the MCAZ premises to collect the guidelines. The website must be updated on a daily bases. There is a gap in the capacity of assessing and registering new products and to carry clinical trials of new drugs for neglected diseases that are necessary to establish safety and efficacy in Zimbabwe. The SADC has pursued harmonization of registration procedures with a mutual recognition process akin to that of Europe. There is still a gap in the effort put by SADC in relation to focus on NCEs. The SADC should put more effort to harmonize formulation of NCEs rather than on generic products only [74-81].

CONCLUSION

EU with its communal and mutual recognition procedures to enable one dossier to oblige for all is a well-established exemplary for harmonization of drug registration. Thus, the MCAZ and SADC should correspond with EU guidelines to enable improvement of a common scientific framework for assessing medicines and safeguarding the legislation which is enacted to support the assessments. Harmonization of EU and SADC documentation will enable manufacturers to prepare the same dossier for each authority, although there are still country-specific requirements such as the product information documents. Registration of medicines needs to be vigorously embarked on by the MCAZ. Factors responsible for the small number of registered medicines need to be determined so that remedial action can be taken. Subsequently, Zimbabwe is resource constrained, allocation of information, and facilities to register medicines in the subregion must be stimulated. To address the human resources, restraints for MCAZ investment in the training of the human capital for efficient implementation of various functions of regulation should be mandatory. To ensure greater value for harmonization and benefits, the MCAZ and Zazibona member states should build capacity

for better sharing of resources. To strengthen WHOPQP programs, tolerable funding is required to support operations and regional activities. Consequently, Government should offer an adequate grant to support program implementation by MCAZ; the manufacturing pharmaceuticals should access and use most of the industry fees for production of new drugs.

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Dr. R. Kamaraj is my guide and has reviewed this article.

CONFLICTS OF INTEREST

None.

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