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REVIEW ARTICLE

Comparative Study of Generic Drug Registration Requirements for Dossier Submission in African Region-Kenya, Ghana, Nigeria, and Botswana

Nandini Warier and Priti Mehta*

Program of Regulatory Affairs and Quality Assurance, Department of Pharmaceutical Analysis, Institute of Pharmacy, Nirma University, Ahmedabad- 382481, Gujarat, India

Priti Mehta

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Abstract: ***Background*:** Regulation of drugs across the world has been a crucial component in providing quality products around the globe. Henceforth different drug administrative powers are moving forward for initiating better regulatory framework which will lead to easier differentiation of superior medicinal products to that of sub-standard ones. For this purpose legitimate dossier preparation becomes essential so that a worthy drug gets registered with better evaluation process instead of getting rejected due to various hindrances. The pharmaceutical markets are established all around the world depending upon the qualitative and complexity of the regulations implied and as a result it has been divided into regulated and emerging markets. Amongst the emerging markets, Africa is considered as long term opportunity for pharmaceutical investment, with GDP of $ 2.9 trillion. This article provides a detailed comparative study of the specifications to be noted during generic drug registration documentation in African region emphasizing more on Kenya, Ghana, Botswana, and Nigeria. Hence this article will ultimately lead to a clearer view of dossier registration variations within these regions and will help in systematic acceptance of essential medicines for more prominent purposes in near future.

***Conclusion*:** Comparative finding of regulatory requirements in African countries provide with the understanding of variations which are to be considered during drug registration in such countries despite the fact that harmonization is taking place at an extensive pace. It can also be concluded that African countries are rapidly developing their regulatory needs for compliance with stringent authorities with concern of procuring better health products.

Keywords: Africa, quality, sub-standard, pharmaceutical investment, emerging market, dossier, regulatory.

1. INTRODUCTION

Emerging disease challenges across Africa has put extraordinary weight on the pharmaceutical business to deliver quality medications at lower and reasonable expenses. Getting this open door, Indian pharmaceutical industry has been in the front line in the production of generic medications to the world. Among all, African nations are the best recipients from the Indian producer. African Pharmaceutical industry has evolved from $ 4.7 billion to $ 20.8 billion in 2013 within a decade and it is further expected to expand up to $65 billion by 2020 [1]. This provides a wide opportunity for drug sales and export to such semi-regulated markets and hence specific requirements for their drug registration are essential to be evaluated.

*Address correspondence to this author at the Department of Pharmaceutical Analysis, Institute of Pharmacy, Nirma University, Ahmedabad-382481, Gujarat, India; Tel: +91-9537936304/+91-9898335567;
E-mail: drpritimehta@nirmauni.ac.in

2. PHARMACEUTICAL MARKET SCENARIO IN AFRICA

According to Council for Health Research and Development, Switzerland only 37 countries out of 54 in African Union (AU) has the capacity to produce their own pharmaceutical products and out of these South Africa has the most established pharmaceutical market and systematic regulation [2]. Africa contains 25% of world's disease problems with about only 1% expenditure on health sector [3]. As for current situation India, China, and Innovative Multinational companies (MNCs) are the major business investors in Africa. Amongst the principal MNCs which entered African market were Abbott (South Africa), Sanofi-Aventis (Morocco), Novartis (Egypt), Pfizer(Morocco),GSK (Nigeria).Indian Manufactures players who achieved to enter this mainland through NGOs & government tenders were Cipla, Serum Institute, Ranbaxy and Dr. Reddy's. Domestic manufacturers like Aspen (South Africa), EIPICO (Egypt), and

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Table 1. Pharmaceutical Market Sales based on disease prevalence in Africa [5-7].

Country	Disease Prevalence (% Morbidity)	Market Sales (%)	Drugs Being Imported.
Sub Saharan African Region.	HIV/AIDS (16%-28%), Malaria (11%), Tuberculosis are the most prevalent diseases causing maximum morbidity. Others diseases like Neglected Tropical Diseases, Cardiovascular (10%), Respiratory (14%), and Diarrheal (7%), CNS (4.4%) are also observed.	Anti-Infectives (25.8%) OTC drug Products (34.7%) Cardiovascular products (11.9%) Diabetes (6.2%) Respiratory drugs (5.6%) Oncology products (3.5%)	Majority of Anti-malarial drugs supplies include Artemisinin Combination Therapy (ACT)-Arthemether /Lumefantrine Combination Tablets, Quinine Hydrochloride, Arthemether, Artesunate Injections, Sulphadoxine / Pyrimethamine tablets. Tuberculosis treatments include FDC of Rifampicin, Isonazid, Pyrazinamide, and Ethambutol (RHZE) using DOTS therapy. Anti-Retrovirals (ARVs) are first line treatments for AIDS. For E.g.: FDCs of Stavudine + Lamivudine (FDC-30), Triple FDC (Stavudine + Lamivudine+ Nevirapine), Tenofovir, Abacavir tablets.

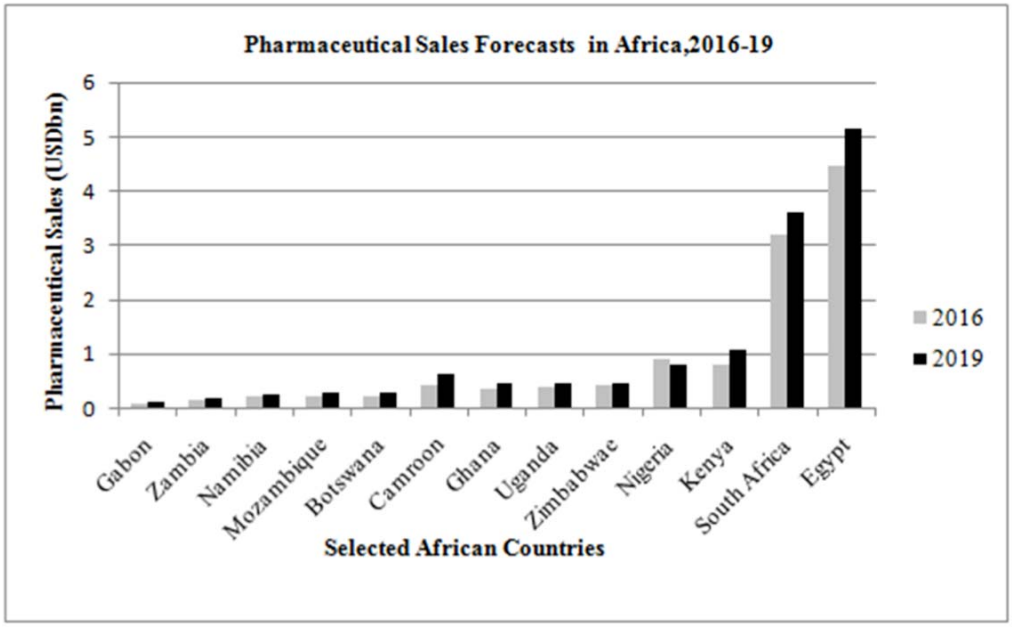

Fig. (1). Pharmaceutical Sales Forecasts in Africa, 2016-19.

Saidal (Algeria) exist in African market but yet at the same time face real issues of high cost APIs and execution of GMP to ensure quality of product [4].

Export of drugs by these established organizations widely depends on disease prevalence and drug urgency in such countries which are depicted in Table **1** and rise in pharmaceutical market sales in near future due to imported medicinal products for these diseases is given in Figure **1** [8-20].

3. AFRICAN DRUG REGULATORY ADVANCES

Initially Africa had different regulatory processes and requirements which caused difficulty in regulation of drugs. Factors such as specific drug registration requirements, GMP inspection fees, country-specific labeling, and difference in registration costs, country specific format for dossiers were the key issues in providing hindrance in drug registration process. Moreover it extended the time duration for approval of drugs across entire Africa. Hence various regulatory harmonization initiatives have been established for easier procedures [21].

Africa has established NEPADs (New Partnership for Africa's Development) Agency which facilitates implementation of programs, projects, partnerships. RECs (Regional Economic communities) support NEPAD by providing a platform for virtualization of such harmonization initiatives. In 2009 NEPAD and PAP (Pan African Parliament) organized a conference with stakeholders were they discussed about emergence of AMRH [22]. Later on, In 2011 AMRH (African Medicinal Regulatory Harmonization) became effective by collaboration of various stakeholders like NEPAD, RECs, WHO, NMRA, who played a major role in

collaborating RECs regulatory agencies to provide patients with superior medicines through transparent registration techniques [23].

Major RECs working on adapting AMRH includes:

1). Arab Maghreb Union (AMA//UMA)

2). Community of Sehel-Saharan States (CEN-SAD)

3). Common Market for Eastern and Southern Africa (COMESA)

4). Inter-Governmental Authority on Development. (IGAD)

5). Economic Community of Central African States (CEEAC-ECCAS)

6). East African Community (EAC)

7). Economic Community of Western African States (ECOWAS-WAHO)

8). Sothern African Development Community (SADC)

Amongst these EAC, SADC, ECOWAS member countries has implemented the proposal by AMRH for harmonized registration process by implementing ICH-CTD format. The process is still under progress as all member countries have not yet established this proposal.

In East African region, a scheme named "East African Community-Medicines Regulatory Harmonization" (EAC-MRH) was established including six NMRAs of Burundi, Kenya, Rwanda, Uganda, Zanzibar and Tanzania. It established Technical Working Groups(TWGs) to harmonize guidelines, requirements and standards for Medicines Evaluation and Registration (MER) by Tanzania, Good Manufacturing Practice (GMP) by Uganda, Information Management System(IMS) by Rwanda and Quality Management System (QMS) by Kenya, as approved by the EAC Council till 2014.EAC-MRH project is still working towards implementation of national authorization procedures, joint dossier assessment procedures for essential medicines and WHO collaborative procedures for WHO prequalified pharmaceutical products [24].Access to affordable healthcare products for communicable and non-communicable diseases in EAC partner states is a major challenge due to inadequate local production and over reliance on imported products, as a result EAC has implemented "EAC-Regional Pharmaceutical Manufacturing Plan of Action" (EAC-PMPOA) a strategic approach with an aim to reduce imports and increase the quality of medicines produced by domestic manufactures in EAC countries [25].

4. PRE-REGISTRATION MANUFACTURING INSPECTIONS AND RAW MATERIAL SOURCING

GMP inspections of manufacturing sites are the primary requirements of all the African countries to ensure quality of manufacturer's product before product registration. Each NMRA's undertake GMP inspections even though they are within same economic community. All the foreign manufacturing units are to be inspected every 3 years by NMRA's of Africa. Site Master File, Master Batch Records (MBRs) and Executed Batch Records (EBRs) are the key documents which are evaluated during inspections. Certificate of recognition are required by SGS Nigeria for their compliance with GMP standards. If the GMP inspection has already been done by SRA or PIC/S member country and if valid GMP certificate occurs, then GMP inspection is exempted by NMRAs. Africa is now encouraging risk based assessment and joint inspections to reduce duplication of GMP inspections by individual African countries [26].

In context to raw material sourcing about 95% of African manufacturers rely on foreign exporters from China and India for API and excipients due to high costs for supreme quality of APIs and lack of resources occurring within Africa. As a consequence domestic formulators are continuously pushed towards lower API prices because of price and quality competitions with that of foreign finished product importers [27]. Local firms import plant, equipment and machinery from India and China, whereas analytical equipment is sourced from developed countries like Germany [28].South Africa, Egypt and Ghana are the leading areas which has a better API production in comparison to other African region. Sub-Saharan Africa faces challenges due to incredible price pressures, loose regulatory framework, supply chain rigidity which make them more willing to risk APIs from less established companies [29].

5. DRUG REGISTRATION PROCEDURE IN AFRICA

ICH-CTD (M4) guidelines have been established to provide a structured format to produce all the documents necessary for drug registration. Although due to harmonization Africa has started adopting ICH-(M4) CTD guidelines but variations across drug registration process of ECOWAS, EAC, SADC has been observed. In 2013 EAC Partner States, National Medicinal Regulatory Authorities (NMRAs), Tanzania Food and Drug Authority (TFDA) coordinated to propose "EAC Compendium of Medical Evaluation and Registration for Medical Regulation" to accelerate registration of needed products by adapting Common Technical Document (CTD), Good Manufacturing Practices (GMP) and Quality Management System (QMS) [30]. SADC later followed EAC's path in adapting similar strategies. The countries under study in this article include Kenya, Ghana, Nigeria and Botswana as shown in (Table **2**).

5.1. Pharmaceutical Dossier Submission Requirements

Pharmaceutical dossier is integral part of marketing authorization and it mainly contains of administrative, quality, nonclinical and clinical sections. Administrative section varies according to different country requirements and so it is not considered as part of pharmaceutical documented evidence. The differences seen in administrative requirements, technical quality and clinical documentation requirements of generic drug registration are summarized in (Table **3** and Table **4**) respectively.

6. CURRENT STATUS OF PHARMACOVIGILANCE IN AFRICA

Adverse Drug Reactions, medication errors, circulation of poor quality of medicines have huge impact on healthcare system and is increased due to import of medicinal products and this call for an established post-surveillance pharma-

Table 2. Comparative Study of Drug Registration Specifications of Individual African Countries [31-36].

No.	PARAMETERS	KENYA	GHANA	BOTSWANA	NIGERIA
1.	African Committee	EAC	ECOWAS	SADC	ECOWAS
2.	Regulatory Authority	Pharmacy Poison Board (PPB).	Food and Drug Authority (FDA-Ghana).	Ministry of Health (MOH)-Drug Regulatory Authority (DRU) responsible for reviewing application.	National Agency of Food and Drug Administration Control(NAFDAC)
3.	Dossier Format followed	ICH CTD	ICH-CTD	ICH-CTD	Country Specific.
4.	Timelines				
a.	Fast Track Registration	Available for local manufacturers and priority medicines only (90 working days).	90 working days.	120 working days.	Not yet Available
			Available for priority medicines, WHO prequalified drugs, Products approved in SRA.		
b.	Application Approval	Within 12 months + 6 months, if additional data requested.	Within 6 months + 12 months, if additional data requested.	9-12 months	100 working days.
5.	Validity of Registration Certificate	5 years	3 years	5 years	5 years
6.	Fees: Generics				
a.	Imported Drugs	1000 USD	3600 USD + 20,000 USD for GMP inspections.	71.58 USD according to DRSA Regulation. Current fees for generic drug applications are 1500 USD which has not been amended in latest guidelines.	1,500 USD
b.	Renewal	500 USD	-	-	1,255 USD
c.	Variation	200 USD	-	-	-

Table 3. Comparison of Administrative Documents Requirements [31, 32, 34, 37-42].

No.	PARAMETERS	KENYA	GHANA	BOTSWANA	NIGERIA
1.	Application Form	Required	Required	Required	Required
2.	Brand Name clearance	Evidence from Kenya Industrial Property Institute (KIPI) trademarks required.	N/A	N/A	Evidence of trade mark approval of brand name from Federal Ministry of Commerce Nigeria.
3.	Pre-Registration Analysis and Sample requirement.	Before dossier submission, samples along with COA are sent to DARU or any WHO prequalified labs in Kenya and EAC, for sample analysis.	Samples required along with dossier according to FDA sample schedule. E.g.- Minimum 40 tablet/capsules required.	Samples from two batches essential for at-least three complete monograph tests + 10 gm raw material with its Certificate of Analysis.	Three vetting samples along its respective COAs and import permit for analysis purpose.

Table 3. contd…

No.	PARAMETERS	KENYA	GHANA	BOTSWANA	NIGERIA
4.	GMP certificate/GMP Inspection	GMP inspection done for plant approval by PPB (Pharmacy Poison Board).	Pre-Licensing inspections required by Ghana Pharmacy Council.	Certificate Not older than 3 years+ Date of last inspected site+ Inspection Reports+ Sample documents.	GMP certificate authenticated by Nigerian Embassy in country of origin or any ECOWAS country commission.
5.	Manufacturing Certificate	Required.	Mfg certificate with supporting documents from drug authority for manufacturing license code.	Required.	Manufacturing License authenticated by Nigerian Embassy in country of origin (For India and China only).
6.	Free-Sale Certificate/COPP	COPP as per WHO certification scheme.	COPP as per WHO certification scheme and Free Sale Certificate.	COPP as per WHO certification scheme.	
7.	PIL/Package Inserts/Labels	PIL should be written in English or Kiswahili language.	Labels and artwork of respective commercial batch pack should only be sent. -4 copies of PIL/PI/Labels required.	-BOT number is mandatory on Package Inserts. -PI and PILs should contain scheduling status allotted by DAB. -Braille Labeling is essential for future use.	-Provision of NAFDAC registration number is to be made on labels.
		Excipients like lactose, gluten, metabisulfites, parabens, ethanol, tartrazine should be on secondary label with safety concern.			
8.	Bioequivalence Trial Information Form(BTIF)	N/A	N/A	Required to be filled and submitted in MS-Word format.	N/A
9.	Environmental Risk assessment	N/A	N/A	Details about existence of genetically modified organisms (GMO) and non-genetic organisms.(Non-GMO)	N/A
10.	VAMF/PMF/ASMF/CEP	CEP required if product is already registered in EU or complete API details to be added.		CEP, VAMF, PMF required if applicable.	N/A
11.	SmPC	Mandatory	Mandatory	Mandatory	Mandatory
a.	Expert reports	N/A	N/A	Required	N/A
b.	Foreign Regulatory Status	Required	Required	Required	Required

covigilance system to maintain the quality and safety of products. In Africa although PV is not as systematic as US and Europe, but at least 34 countries have an organized PV structure with 18 countries having proper national guidelines available. Pharmacovigilance in Africa is managed by WHO Uppsala Monitoring Centre using data software "VigiFlow" and "VigiBase" a WHO database for ADR reports [46]. The current reporting system in Kenya incorporates use of electronic "Suspected Adverse Drug Reaction Notification Form" (Yellow Form) and "Poor Quality Medicinal Product Reporting Form" (Pink Form) for institutes and health care professionals, to alert PPB. Patient Alert Card on the other hand alerts health care professionals about serious ADRs detected by PPB. Additional to this PPB publishes biannual newsletters to update the safety alerts [47].

Ghana has provided Marketing Authorization holder(MAH) with "Adverse Reaction Reporting Form" or and "Consumer Reporting Form (Blue Form)" for consumers, to report suspected ADRs to FDA-Ghana. MAH are responsible to submit Ghana Specific Risk Management Plan,

Table 4. Technical Documents Requirements [31, 32, 34, 43-45].

No.	PARAMETERS	KENYA	GHANA	BOTSWANA	NIGERIA
1.	Drug Master File	Required (open part)	Required (open part)	Require both open and closed part.	Not required.
2.	TSE/BSE Certificate.	Applicable	Applicable	Required along with Letter of Attestation to ensure that the API and starting material are free from TSE/BSE.	Not required.
3.	Quality Overall Summary (QOS)	Applicable	Applicable	Quality Information template (QIS) subset of QOS, to be submitted with application, which are required for screening of applications during renewals, variations, or GMP Inspection.	Country specific format do not contain QOS.
4.	Structural Elucidation and characterization	Applicable-To confirm chemical structure of API- IR, U.V, NMR, XRPD, and DSC carried out according to that described in official pharmacopeias.			N/A
5.	Manufacture	Applicable	Applicable	Applicable	Applicable
a.	Process Validation Protocol and Reports	Required	Required	Required	N/A
b.	Validation of Analytical Procedures.	Validation of In-House methods only required.		Validation of In-House methods only required and the equivalence between In-house and compendia methods should be demonstrated.	Analytical Test procedures of each ingredient occur. Validation of in-house method provided on request.
c.	Reference Standards	List of Reference Standards and their respective Certificate of Analysis (COA), Standard Test procedure (STP) and Technical Specification.			N/A
d.	Container Closure System Data	Technical Specifications, Standard Analytical Procedure (STP), Certificate Analysis (COA) of all packaging components used is demanded.			
e.	Pharmaceutical Development	Formulation development, overages calculations, microbial attributes, compatibility between proposed excipients and APIs, choice of container closure system to be used for further formulation development are included along with manufacturing development data.			N/A
6.	Regional Information				
a.	Production Documents	Batch Manufacturing Records (BMR) required to be submitted 6 months before submission of application.	Production Documentation including Executed and Master production documents should be provided.	Production documentation including-Executed and master production documents, Analytical procedures and Validation information, Bioequivalence Trial Information.	N/A
7.	Stability Requirements				
a.	Climatic Zone	IVa	IVb	III	IVb
b.	Accelerated Condition	40± 2˚C 75± 5% RH	40±2 ˚C 75±5% RH	40±2 ˚C 75±5% RH	40±2 ˚C 75±5% RH
c.	Long Term Conditions	30± 2˚C 65± 5% RH	30± 2˚C 75± 5% RH	30± 2˚C 65± 5% RH	30± 2˚C 65± 5% RH

Table 4. contd…

No.	PARAMETERS	KENYA	GHANA	BOTSWANA	NIGERIA
d.	Commercial Batch Requirements	3 Batches (one from production scale and two from pilot scale)			
e.	Stability Test Requirements	Minimum 6 months accelerated studies and 12 months long term stability data required. (Stability commitment given if complete long term stability is not available).			Complete accelerated and long term stability data required for registration
8.	Clinical Data Requirements				
a.	Clinical Overview	Short representation of bio-pharmaceutics studies, product developments rationale and in-vitro dissolution report summary data			N/A
b.	Tabular Listing of Clinical study	Applicable. Tabular briefings of study reference number, objective, design, treatment, analyte measured and Pharmacokinetics parameters are provided.			N/A
c.	Clinical Study Report	Only Bioequivalence and In-Vitro Dissolution Reports Required.			Includes clinical and toxicological data.
9.	Bioequivalence Study Requirements				
a.	Preferred Study Design	Randomized two periods, two sequence single dose crossover design.			Bioequivalence Reports are Optional
b.	Test Product Quantity	$1/10^{th}$ of production scale or 1, 00,000 units.			
c.	Innovator Reference Product	N/A	N/A	Reference Product Labeling + Data invoice from distributor + method of shipment and storage conditions	
d.	Selection of Subjects				
	Age	18-50 years	18 years of age or older	18-55 years	
	Number of Subjects	Minimum 12 patients for BE study.	Minimum 24 patients for BE study	Minimum 12 patients for BE study	
	BMI Index	$18.5\text{-}30 kg/m^2$			
	Fed Conditions	According to SmPC of originator product.			
e.	Regulatory Acceptance Criteria for BE				
	90% confidence interval for test/reference ratio for single and modified dosage forms				
	AUC-Ratio and C_{max} Ratio	80-125%			
	Narrow Therapeutic index drugs				
	AUC-Ratio and C_{max} Ratio	90-111%			
	Highly Variable Drugs				
	AUC-Ratio and C_{max} Ratio	75-133%	69.84-143.19%		
f.	Bioequivalence study in Foreign Country.	Acceptable			N/A
g.	Comparative In-Vitro Dissolution	12 units from first three batches of Test sample versus Innovator product registered within ICH, SADC countries. In-Vitro Equivalence test should include at least three media: pH 1.2, pH 4.5 and pH 6.8.			Applicable

Table 5. Time Frame for Safety Reporting.

Country	Type of Safety Reports	Time Frame for Reporting
Kenya	Suspected Adverse Drug Reaction (Yellow Form)	-
Ghana	Serious unexpected and expected adverse reaction	7 days
	Non serious expected and unexpected adverse reactions	28 days
	PSUR/PBRERs:	Immediately on Authority Request 6 months for first two years after MA. Annually for 3 years. During Renewal (at 3 years interval)
Nigeria	Serious(expected and unexpected)	15 days
	Non serious(unexpected)	15 days
	Non serious (expected)	90 days
	PSURs:	
	New Drug Molecules	6 months for first two years after MA. Annually for 3 years. During Renewal (at 5 years interval)
	For drugs registered in other country	Existing PSURs not later than 30 days after submission of MA dossier in Nigeria.
	For listed drugs with provisional registration.	Every 6 months for 2 years listing period.
Botswana	Adverse Reaction Reporting Form.	-

PSUR/PBRER and additional PMS Studies with updated data at regular intervals [48].

PV system in Nigeria has improved significantly during past years. It required a well formatted Pharmacovigilance System Master File (PSMF) from MAH and QPPV within the Nigeria. Furthermore to communicate safety information, the National Pharmacovigilance Centre (NPC) issues quarterly newsletters, safety alerts and public announcement on NAFDAC site [49]. Additional provisions provided includes direct ADR reporting to NPC by consumers, using short messaging system called "Pharmacovigilance Rapid Alert System for Consumer Reporting" (PRASCOR) [50].

Drug Regulatory Unit (DRU) in Botswana is responsible for regulating PV system. Botswana has policy and legal frames for PV but the roles and responsibilities of stakeholders are not fully coordinated as compared to that of Nigeria and Ghana and hence Pharmacovigilance guidelines provide a brief discussion about reporting an ADR. Although all these countries have PV activities, limited capacities occur to ensure quality and safety of medicines. These countries should further develop strategies to coordinate PV amongst various stakeholders and should provide more rigorous legislations [51]. Timelines provided for safety reporting in different regions is summarized in (Table **5**).

7. KEY CHALLENGES IN DRUG REGISTRATION IN AFRICAN COUNTRIES

1). Reduced human resources to evaluate the dossier documents within stipulated time-frame.

2). Lack of transparency in guidelines, insufficient resources to evaluate and monitor safety, efficacy and quality of health products, compared to stringent authorities in developed countries can be considered as major drawback.

3). Specific plant approval inspections and expensive inspection fees from different National Authorities of Africa are demanded, because different African regions contain varied GMP guidelines and lack a joint GMP inspection system.

4). Lack of Pre-Submission meetings which can guide the applicants towards better dossier compilation.

5). Difference in the structure, evaluation process and requirements of regulatory dossier within African countries. For E.g. South Africa contains well established regulatory framework which follows South African CTD that is "ZA-eCTD" for dossier submission whereas other regions like Kenya, Uganda, Ghana, Botswana follows paper CTD format and rest other countries like Mozambique, Cameroon, Congo has specific country format registration.

6). Corruption acts as a barrier in accessing quality medicines across Africa and hence a more stringent regulatory system should be established.

7). Sample analysis timeline in Kenya can be considered as a challenge as they require the samples to be tested in their two specific laboratories that is Drugs Analysis and Research Unit (DARU) and National Quality

Control laboratory (NQCL) in order to obtain product license.

8). As regulatory harmonization is occurring over Africa this is a period of drastic change in regulatory guidelines from country specific format to ICH M4Q CTD guidelines. Hence constant revision and changes in documentation is observed.

9). Nigeria has started accepting dossier in CTD format which further proves the development of regulatory perspectives in such emerging markets and this can pose a challenge to applicants during this changing period.

CONCLUSION

Comparison of regulatory requirements in African countries has been carried out to provide a broader view of specific detailing required for easier evaluation of dossier. Clearer regulatory strategies should be made for drug approval in such regions since minor variations occur in each regulatory authority system and therefore, in-order to prevent any deferral letters these specifications are essential to be adapted. Although harmonization has been established, the regulatory authorities being different, there is wide range of diversity in guidelines, process and assessment techniques unlike in stringent regulatory authority areas like US-FDA,EMA,TGA,PMDA wherein typical procedures are established along the whole region. Moreover increased adaptation of WHO prequalified dossier assessment and NQCL quality assessment will aid in faster drug registration time period along with better quality health products. As a result it can be noted that Africa being an emerging pharmaceutical market has incredibly accentuated on better regulation which will tremendously impact the pharmaceutical business within Africa as well as international agencies attempting to market their products here, to provide better safer and effective medicines.

LIST OF ABBREVIATIONS

ADR	=	Adverse Drug Reactions
AMRH	=	African Medicinal Regulatory Harmonization.
ASMF	=	Active Substance Master File
AU	=	African Union
BOT	=	Botswana Identification Number
CEP	=	Certificate of Suitability to the monographs of European Pharmacopeia
COPP	=	Certificate of Pharmaceutical Product
CTD	=	Common technical Document
DAB	=	Drug Advisory Board
DARU	=	Drug Analysis Research Unit, of School of Pharmacy, University of Nairobi
DOTS	=	Directly Observed Treatment Short course
DRSA	=	Botswana Drug and Related Substance Act 18-1992
DSC	=	Differential Scanning Calorimetric
FDC	=	Fixed Dose Combination
GMP	=	Good Manufacturing Practices
ICH	=	International Council of Harmonization
NEPAD	=	New Partnership for Africa's Development
NMR	=	Nuclear Magnetic Resonance Spectroscopy
NMRA	=	National Medicinal Regulatory Authority
PAP	=	Pan African Parliament
PI	=	Package Insert
PIL	=	Package Information Leaflets
PMF	=	Plasma Master File
PPB	=	Pharmacy Poison Board
PV	=	Pharmacovigilance System
QMS	=	Quality Management System
QPPV	=	Qualified Person for Pharmacovigilance
RECs	=	Regional Economic Communities
SmPC	=	Summary of Product Characteristics
SRA	=	Stringent Regulatory Authority
TFDA	=	Tanzania Food and Drug Authority
TSE/BSE	=	Transmissible spongiform encephalopathy/Bovine spongiform encephalopathy
VAMF	=	Vaccine Antigen Master File
XRPD	=	X-ray Power Diffraction

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Company. Available from: http://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/africa-a-continent-of-opportunity-for-pharma-and-patients [Accessed on: 3/18/2016].

[2] Coetzee G. Generic drugs are vital for a healthy Africa. The M & G Online. Available from: http://mg.co.za/article/2012-10-06-generic-drugs-are-vital-for-a-healthy-africa/. [Accessed on: 3/16/2016].

[3] Making medicine in Africa - the untapped possibilities that could save millions of lives. MG Africa 2015. Available from: http://mgafrica.com/article/2015-02-17-manufacturing-

pharmaceuticals-in-africa-the-untapped-opportunity-that-could-save-countless-lives [Accessed on 5/15/2016].

[4] Africa: A ripe opportunity: Understanding the pharmaceutical market opportunity and developing sustainable business models in Africa. Available from: http://www.fullertreacymoney.com/system/data/files/PDFs/2014/April/29th/IMS_Africa_Opportunity_Whitepaper.pdf [Accessed on 5/17/2016].

[5] Pharmaceutical Industry in Ghana and Nigeria-A Ripe Business Opportunity for Big Pharma and Generic Pharma Companies. Available from: https://www.frost.com/sublib/display-report.do?csqnc=1463142256485&id=MA49-01-00-00-00 [Accessed on 5/14/2016].

[6] Pharmaceutical Sector Profile: Nigeria. UNIDO-United Nations Industrial Development Organization. Available from: https://www.unido.org/fileadmin/user_media/Services/PSD/BEP/Nigeria_Pharma%20Sector%20Profile_032011_Ebook.pdf [Accessed on 5/14/2016].

[7] Pharmaceutical Sector Profile: Kenya Global UNIDO Project: Strengthening the local production of essential generic drugs in the least developed and developing countries. Available from: https://www.unido.org/fileadmin/user_media/Services/PSD/BEP/Kenya_Pharma%20Sector%20profile_TEGLO05015_Ebook.pdf [Accessed on 5/14/2016].

[8] Gabon Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/gabon-pharmaceuticals-healthcare-report.html [Accessed on: 3/16/2016].

[9] Zambia Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/zambia-pharmaceuticals-healthcare-report.html [Accessed on: 3/16/2016].

[10] Namibia Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/namibia-pharmaceuticals-healthcare-report.html [Accessed on: 3/16/2016].

[11] Mozambique Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/mozambique-pharmaceuticals-healthcare-report.html [Accessed:3/16/2016].

[12] Botswana Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/botswana-pharmaceuticals-healthcare-report.html [Accessed on: 3/16/2016].

[13] Cameroon Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/cameroon-pharmaceuticals-healthcare-report.html [Accessed on: 3/16/2016].

[14] Ghana Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/ghana-pharmaceuticals-healthcare-report.html [Accessed on: 3/16/2016].

[15] Uganda Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/uganda-pharmaceuticals-healthcare-report.html. [Accessed on: 3/16/2016].

[16] Zimbabwe Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/zimbabwe-pharmaceuticals-healthcare-report.html [Accessed on: 3/16/2016].

[17] Nigeria Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/nigeria-pharmaceuticals-healthcare-report.html [Accessed on: 3/16/2016].

[18] Kenya Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/kenya-pharmaceuticals-healthcare-report.html [Accessed on: 3/16/2016].

[19] South Africa Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/south-africa-pharmaceuticals-healthcare-report.html [Accessed on: 3/16/2016].

[20] Egypt Pharmaceuticals & Healthcare Report. Available from: http://store.bmiresearch.com/egypt-pharmaceuticals-healthcare-report.html. [Accessed on: 3/16/2016].

[21] Narsai K, Williams A, Mantel-Teeuwisse AK. Impact of regulatory requirements on medicine registration in African countries – perceptions and experiences of pharmaceutical companies in South Africa. South Med Rev. 2012 Jul 23; 5(1):31–7.

[22] WHO support for medicines regulatory harmonization in Africa: focus on East African Community. (WHO Drug Information Vol. 28 No. 1, 2014). Available from: www.who.int/medicines/.../drug information/DI_28-1_Africa.pdf [Accessed on: 3/6/2016].

[23] The African Medicines Regulatory Harmonization (AMRH) Initiatives. Available from: http://www.who.int/medicines/areas/quality_safety/regulation_legislation/PL2_3.pdf [Accessed on: 3/17/2016].

[24] Notice To Applicants: East African Community's Procedure for Marketing Authorization of Medicinal Products. East African Community-Medicines Regulation and Harmonization. Available from: http://mrh.eac.int/wp-content/uploads/2016/04/VERSION-II-EAC-MA-PROCEDURE-2016.pdf [Accessed on 5/19/2016].

[25] East African Community Regional Pharmaceutical Manufacturing Plan of Action (2012 - 2016). Available from: http://feapm.com/fileadmin/user_upload/documents/EAC_Regional_Pharmaceutical_Manufacturing_Plan_of_Action.pdf [Accessed on 5/20/2016].

[26] Good Manufacturing Practice Inspections and the Provision of Batch Records1 in Sub-Saharan Africa.-April 2016.IFPMA. Available from: http://www.ifpma.org/wp-content/uploads/2016/04/GMP-Inspections-and-the-Provision-of-Batch-Records-in-Sub-Saharan-Africa.pdf [Accessed on 5/20/2016].

[27] Fortunak J, Ngozwana S, Gebre-Mariam T, Ellison T, Watts P, Emeje M, et al. Raising the Technological Level: The Scope for API, Excipients, and Biologicals Manufacture in Africa. In: Mackintosh M, Banda G, Tibandebage P, Wamae W, editors. Making Medicines in Africa. Palgrave Macmillan UK; 2016 p. 122–43. (International Political Economy Series).Available from: http://link.springer.com/chapter/10.1007/978-1-137-54647-0_8 [Accessed on 5/27/2016].

[28] Mackintosh M, Banda G, Wamae W, Tibande bage P. Making Medicines in Africa: The Political Economy of Industrializing for Local Health. Springer; 2016. 383 p.

[29] Exploratory Study on Active Pharmaceutical Ingredient Manufacturing for Essential Medicines. Available from: http://apps.who.int/medicinedocs/en/d/Js17509en/ [Accessed on 5/25/2016].

[30] Compendium of Medicines Evaluation and Registration for medicine regulation harmonization in the East African Community. East African Community. Available from: http://mrh.eac.int/wp-content/uploads/2013/10/MER_Compendium.pdf [Accessed on: 3/16/2016].

[31] Pharmacy and Poison Board Kenya, Drug Registration- Guidelines for submission of applications, pp. 1-94, 2010. http://pharmacyboardkenya.org/?page_id=401 [Accessed on: 3/17/2016].

[32] Food and Drug Authority. Guidelines for Registration of Allopathic Drugs. Available from: http://www.fdaghana.gov.gh/images/stories/pdfs/downloads/drugs%20guidelines/GUIDELINES%20FOR%20REGISTRATION%20OF%20ALLOPATHIC%20DRUGS%20(HUMAN%20&%20VETERINARY)%20%E2%80%93%20CTD%20FORMAT.pdf. [Accessed on: 3/17/2016].

[33] Ministry of Health Botswana. Additional Requirements For Products Registered In Stringent Regulatory Authority, pp. 1-6, June 2011. Available from: http://www.moh.gov.bw/Publications/drug_regulation/Additional%20Requirements%20for%20Products%20Registered%20in%20Stringent%20Regulatory%20Authorities%20082011.pdf [Accessed on: 3/17/2016].

[34] National Agency of Food and Drug Administration and Control, Guidelines for Registration of Imported Drug Products in Nigeria, pp. 1-7. Available from: http://www.nafdac.gov.ng/images/GUIDELINES/DRUG%20GUIDELINES/IMPORTS/GUIDE32_GUIDELINES%20FOR%20REGISTRATION%20OF%20IMPORTED%20DRUG%20PRODUCTS%20IN%20NIGERIA.pdf [Accessed on: 3/17/2016].

[35] Food and Drug Authority- Approved Fees Schedule. Available from: http://www.fdaghana.gov.gh/images/stories/pdfs/Quick%20links/APPROVED%20FEES%20SCHEDULE.pdf [Accessed on: 3/17/2016].

[36] Pawar N, Shah D, Maheshwari D. Regulatory Requirements for marketing authorization of Generic Drug product in Botswana. Eur J Pharm Med Res Med Res. 2015;2(4):693–8.

[37] Ministry of Health Botswana, Common Technical Document for Registration of Pharmaceuticals for Human Use, pp. 1-14, April 2015. Available from: http://www.moh.gov.bw/Publications/drug_regulation/CTD/Botswana%20CTD-Format%20April%202015.pdf. [Accessed on: 3/17/2016].

[38] Food and Drug Authority Ghana, Sampling Schedule for Registration and Re-registration of products. pp. 1-3, Available from: http://www.fdaghana.gov.gh/images/stories/pdfs/Quick%20links/SAM-PLE%20SCHEDULE%20FOR%20REGISTRATION%20AND%20RE.pdf [Accessed on: 3/17/2016].

[39] Ministry of Health Botswana, Guidelines on Drug Registration Applications in Botswana, pp. 1-29, 2000. Available from: http://www.moh.gov.bw/Publications/registration%20guidelines.pdf [Accessed on: 3/18/2016].

[40] G.RMR, Venkatesh MP, M PKT. Regulatory perspectives of pharmaceutical products in ghana. 2014;2(2):7–15.

[41] Food and Drug Authority Ghana, Application Form for Registration of a Drug [Human and Veterinary], pp.1-12. Available from: http://www.fdaghana.gov.gh/images/stories/pdfs/downloads/drugs%20application%20forms/THE%20REGISTRATION%20OF%20A%20DRUG%20HUMAN%20AND%20VETERINARY].pdf [Accessed on: 3/18/2016].

[42] Food and Drug Authority Ghana, Template Labeling, pp. 1-4, 2013.Available from: http://www.fdaghana.gov.gh/images/stories/pdfs/downloads/drugs%20guidelines/TEMPLATE%20LABELLING.pdf. [Accessed on: 3/18/2016].

[43] Ministry of Health Botswana, Guidance for Submission of Applications for Registration in Common Technical Document Format, Drug Regulatory Unit, pp. 1-52, April 2015. Available from: http://www.moh.gov.bw/Publications/drug_regulation/CTD/Botswana%20Registration%20Quality%20Guideline%20April%202015.pdf. [Accessed on: 3/18/2016].

[44] Food and Drug Authority Ghana: Guidelines for Conducting Bioequivalence Studies-2013 Available from: http://www.fdaghana.gov.gh/images/stories/pdfs/downloads/drugs%20guidelines/GUIDELINES%20FOR%20CONDUCTING%20BIOEQUIVALENCE%20STUDIES.pdf [Accessed on 5/26/2016].

[45] Ministry of Health Botswana, Drug Regulatory Unit: Guidelines of Bioavailability and Bioequivalence-April 2015. Available from: http://www.moh.gov.bw/Publications/drug_regulation/CTD/Botswana%20Guideline%20in%20BA%20&%20BE%20April%202015.pdf [Accessed on 5/23/2016].

[46] Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance. USAIDS-US Agency for International Development. Available from: http://apps.who.int/medicinedocs/documents/s19152en/s19152en.pdf [Accessed on 5/13/2016].

[47] Pharmacy and Poison Board. Guidelines for National Pharmacovigilance System In Kenya-2009.Available from: http://pharmacyboardkenya.org/?page_id=401 [Accessed on 5/13/2016].

[48] Food and Drug Authority Ghana. Guidelines for Reporting Adverse Drug Reaction. 2016 Available from: http://www.fdaghana.gov.gh/images/stories/pdfs/downloads/drugs%20guidelines/SafetyMonitoring/Guidelines%20for%20Adverse%20Reaction%20Reporting.pdf [Accessed on 5/13/2016].

[49] National Agency for Food and Drug Administration and Control: NAFDAC Good Pharmacovigilance Practice Guidelines 2016. Available from: http://www.nafdac.gov.ng/images/GUIDELINES/DRUG%20GUIDELINES/NAFDAC_GOOD_PHARMACOVIGILANCE_PRACTICE_GUIDELINES_2016_V13_NEW.pdf [Accessed on 5/13/2016].

[50] Olowofela A, Fourrier- Réglat A, Isah AO. Pharmacovigilance in Nigeria: An Overview. Pharm Med. 2016 Jan 19; 30(2):87–94.

[51] Ministry of Health Botswana: Drug Regulatory Unit-Pharmacovigilance Guidlines-2009 Available from: http://www.moh.gov.bw/Publications/drug_regulation/Pharmacovigilance%20guidelines%20Nov%202009.pdf [Accessed on 5/13/2016].