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Regulatory Requirements for Registration of Multi Source Anti Retro Viral Medicinal Products in Zimbabwe

Pasumarthy N V Gopal[1], Lakshmi T*[2], P Anusha[2], M V Nagabhushanam[2], D Nagarjuna Reddy[2]

1. Departments of Pharmaceutical Biotechnology, Hindu College of Pharmacy, Guntur, AP, India-522002.

2. Departments of Pharmaceutical Management and Regulatory Affairs, Hindu College of Pharmacy, Guntur, AP, India-522002.

ABSTRACT

In 2013 world health organization concluded that approximately around 35.0 million people have been infected with HIV and about 1.5 million people have died of AIDS. Most of the people infected with HIV particularly African regions. World health organization continuous to bear the burnt of HIV epidemic in sub Saharan African region like Zimbabwe. This country is experiencing one of the harshest HIV/AIDS epidemics in the world .So according to performance of ART program estimated that percentage of eligible adulates 76.9% and children's around 46.12 % in 2013. The statistical information about Global economic environment in ARV business has continued to grow in the generic-accessible market. So it is an essential need for quality assured ART's with proper regulatory control and evolution procedures. In this paper work it involves how will the Anti Retroviral generic drugs filing have been processed based on Medicinal Control Authority of Zimbabwe [MCAZ].

Keywords: HIV/AIDS, ART, MCAZ.

*Corresponding Author Email: lakshmirajput65@gmail.com

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INTRODUCTION

HIV defined as human immune deficiency virus that infects cells of the immune system, destroying or impairing their function. As the infection progresses, the immune system becomes weaker, and the person becomes more susceptible to infections. The most advanced stage of HIV infection is acquired immunodeficiency syndrome (AIDS). It can take 10-15 years for an HIV-infected person to develop AIDS. Antiretroviral drugs can slow down the process even further. HIV is transmitted through unprotected sexual intercourse (anal or vaginal), Transfusion of contaminated blood, sharing of contaminated needles and between a mother and her infant during pregnancy, childbirth and breastfeeding.[1] According to Global summary of the AIDS epidemic 2013 information given below. [1]

No. of people living with HIV 2013

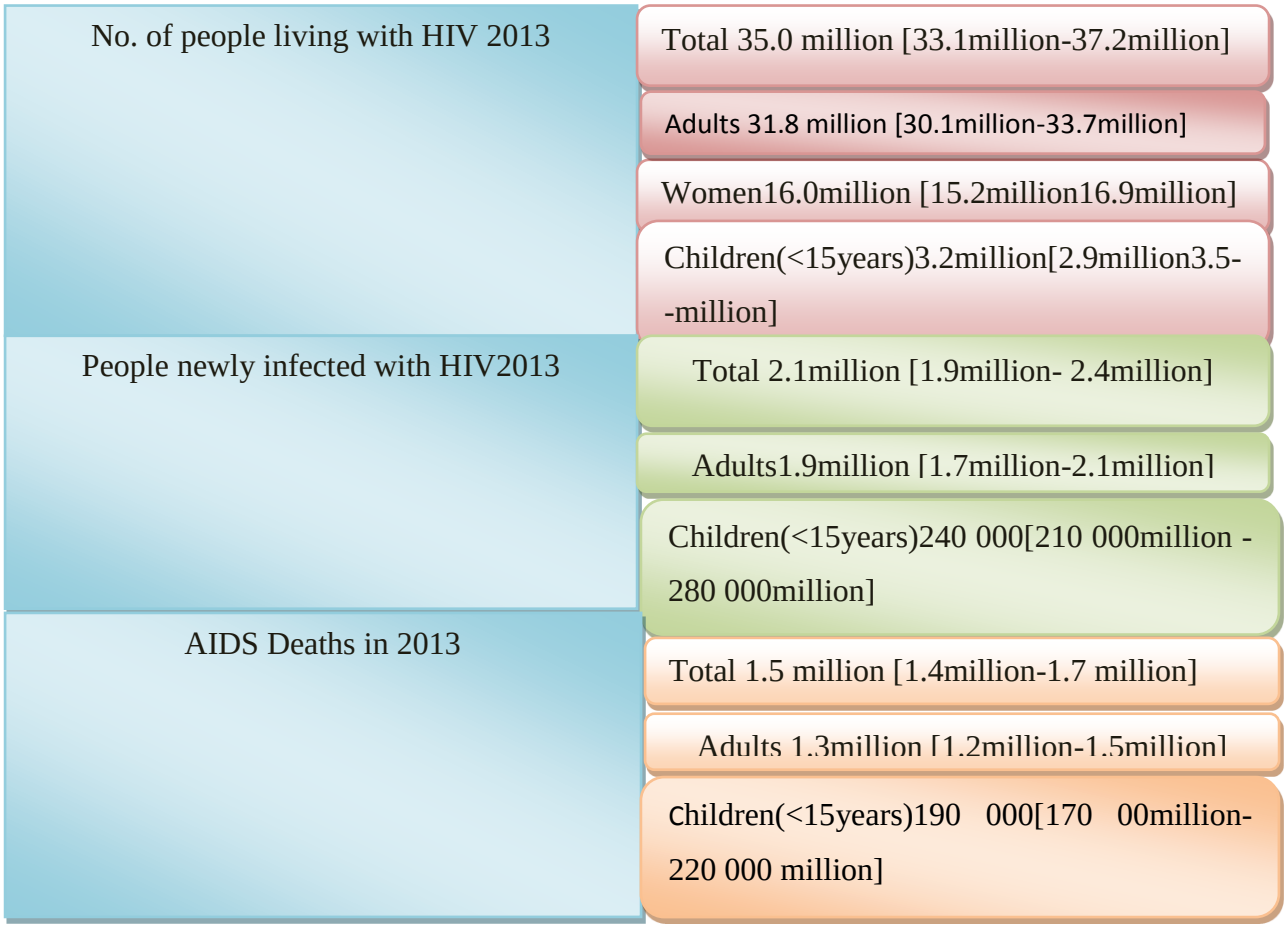

Figure 1: Global summary of HIV/AIDS epidemic in 2013 report [2]

Classification of Countries

According to WHO region and regional patent office's classified as

Classification of Member States by WHO Region[3,4]

WHO regions contain 144 countries which comes under low income and middle income countries and categorized into six groups. They are WHO African Region (n = 45); WHO Region of the Americas (n = 29); WHO Eastern Mediterranean Region (n =16); WHO European Region (n = 22); WHO South- East Asia Region (n = 11); and WHO Western Pacific Region (n = 21). Zimbabwe comes under low income countries of WHO sub-Saharan African region.[3]

Classification of Regional Patent Offices

- African regional intellectual property organization (ARIPO)
- Organization of de la property intellectually (OAPI)
- Eurasian patent organization (EAPO) countries

Zimbabwe comes under ARIPO member of countries.

Table.1.Anti Retro Viral Therapy among Adults and Children In Zimbabwe With A High Burden Of HIV Infection 2007, 2009, 2012 and 2013[6]

Year	2007	2009	2012	2013
Percentage of eligible adults currently receiving Antiretroviral therapy.	31.3%	62 %	85%	76.9%
Percentage of eligible Children currently receiving Antiretroviral therapy	9.7%	22%	43%	46.12%

Table 1 describes the percentage of people in Zimbabwe receiving ART in the years 2007, 2009, 2012 and 2013 which includes both Adults and Children.

Drugs Used in Treatment of HIV And AIDS[7]

There are six major types of drugs used to treat hiv/aids called anti retro virals

- Multi class combination products eg. Lamivudine and Zidovudine
- Nucleoside reverse transcriptase inhibitors (NRTIS) eg, Tenofovir disoproxil Fumarate and Emtricitabine, Stavudine, d4T
- Non nucleoside reverse transcriptase inhibitors eg . Rilpivirine, Etravirine
- Fusion inhibitors, eg. Darunavir, indinavir, IDV,
- Entry inhibitors CCR5 corepots antagonist eg. Maraviroc
- Hiv integrase standard transfer inhibitors eg. Raltegravir, Dolutegravir

Approved anti retro viral drugs by zimbabwe[8]

Company name	Drugs approved by MCAZ
CAPS private limited	Acyclovir, Nevirapine
PLUS FIVE pharmaceuticals private limited	Acyclovir
VARICHEM pharmaceuticals	lamivudine+zidovudine Lamiveudine + nevirpine+stavudine Rifampacin

Table.2. Overview of Patents by Anti Retroviral[5]

Drug	Patent status	Licensing status	Combinations
Abacavir Recommended by WHO .These are First line & second line treatment for infants &children	It was Expired in 2010, other patents on forms & formulations are hemi sulfate salt will expire in 2018. 1.This patent was granted to Argentina ARPO member countries 2.paediatric oral solution.: will expire in 2019 & it was granted in Argentina ,ARPIO,EAPO member countries	The patent holder has committed to licensing abacavir to the interested ARV manufacturers to all low income countries, least developed countries and sub-Saharan Africa. A license on abacavir pediatric formulations has been granted by the patent holder directly to one manufacturer.	Abacavir have been developed with lamivudine & zido vudin. These are sold by several generic manufacturers including ARIIPO, EAPO, OAPI member countries.
Darunavir (DRV) Recommended by world health organization	Expired in august 2013 Patents on the pseudo polymorph and/or on the combination with ritonavir have been granted in Albania, ARIPO member countries, China, EAPO member countries, Mexico, Philippines, South Africa ,brazil	A commitment not to enforce patents on darunavir in sub-Saharan Africa and least-developed countries has been announced by the patent holder. In addition, a license was granted to one manufacturer for sale of the medicine in India.	Ritonavir clinical trial are ongoing for DRV/COBI and DRV/TAF/FTC/COBI combinations
Cobicistat(COBI) it was approved by the United States Food and Drug Administration in 2012	Expire in 2027. It has been granted in OAPI member countries and in Ukraine. It is pending in Argentina, ARIPO member countries, Brazil, China, EAPO member countries, India, Indonesia, Mexico, South Africa, Thailand and Viet Nam	Voluntary licenses on cobicistat have been granted in relation to 112 countries (nine of them on a semi-exclusive basis to three different companies). The license granted to the MPP, it covers 103 countries and has so far been sub licensed to six companies.	Cobicistat has been developed as part of the combination TDF/FTC/EVG/COBI and is currently under development as a booster for at azanavir and darunavir In the combinations with TAF/FTC/DRV/COBI and TAF/FTC/EVG/COBI.
Efavirenz(EFV) Recommended by WHO first-line treatment regimens for adults and as a component of first- and second-line treatment regimens for children over	expired in august 2013 the compound patent was in force in Argentina, China, Dominican Republic, Indonesia, Mexico, Pakistan (process patent only), South Africa, Thailand and Ukraine	Pursuant to a complaint filed with the Competition Commission of South Africa, a number of South African manufacturers have obtained a license for production of efavirenz	Combinations of Efavirenz with TDF/FTC and with TDF/3TC Bristol-Myers Squibb and Gilead Sciences jointly own patents, and patent applications on the combination with TDF/FTC, which have been granted in EAPO member

three years of age.	but it is likely to have expired in most of these countries.	in South Africa and sale to 10 neighboring Countries. Compulsory licenses on efavirenz have been issued in Brazil, Indonesia and Thailand.	states, South Africa and Turkey are also pending in Argentina, Brazil, China, India, Mexico, Thailand and Venezuela

The following countries are covered by this report

ARIPO member countries are: Botswana, Gambia, Ghana, Kenya, Lesotho, Liberia, Malawi, Mozambique, Namibia, Rwanda, Sierra Leone, Somalia, Sudan, Swaziland, Uganda, United Republic of Tanzania, Zambia and Zimbabwe.

EAPO member countries are: Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Republic of Moldova, Russian Federation, Tajikistan and Turkmenistan.

OAPI member countries are: Benin, Burkina, Faso, Cameroon, central African republic, chad.

Anti Retro Viral Market[9]

The statistical information for Global economic environment in ARV business has continued to grow in generic-accessible market. The Generic ARV market growth rate is faster than most other segments of the pharmaceutical market as evident in given below.

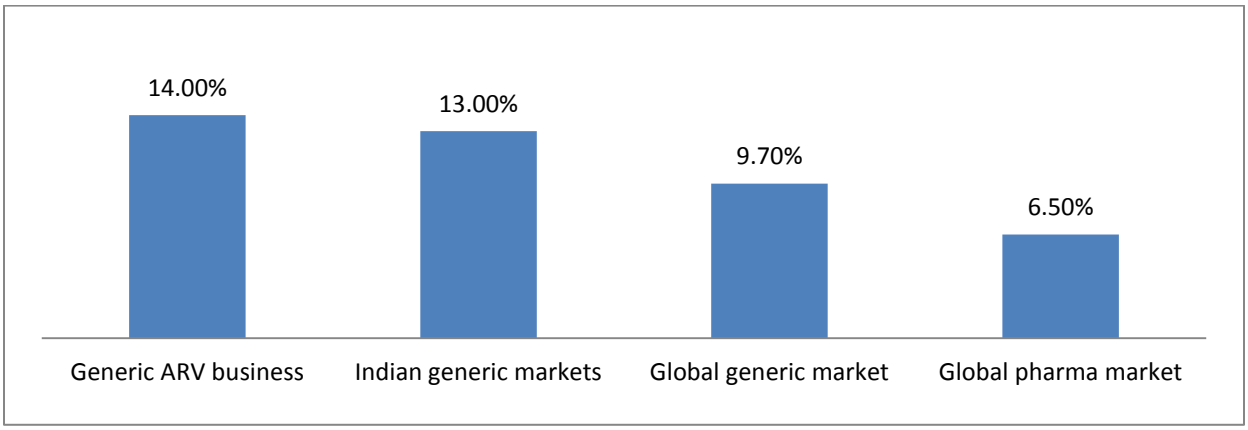

Figure 2: Estmated Cumulutative Growth Rate for Pharmaceutical Industry Segments 2011-216

Low and Middile Income Countries Technical Reports[10]

According to statistical information at the end of 2013, more than 11.7 million people were received antiretroviral therapy (ART) in low- and middle-income countries (LMICs). The 2013 World Health Organization (WHO) antiretroviral (ARV) guidelines are designed to extend these benefits more widely and will increase potential number of people eligible for antiretroviral therapy (ART) to an estimated 28.6 million. WHO collates information on the cost of ARVs in the

Global Price Reporting Mechanism (GPRM) on public procurement of ARVs in collaboration with GFATM, PEPFAR and international procurement organizations In the GPRM database, this covers around 75% of all ARV use in LMICs, but which has limitations in recording procurement by upper middle income countries. First line ART annual cost is varied from US$ 117 in 2011 to US$ 115 per patient per year (ppy) in 2013. The price of second-line and third-line ART Documented in GPRM also decreased, but less than first-line treatment. LMICs which can access generic drugs for second-line treatment paid approximately US$ 330 ppy in 2013. The price of the most commonly used first-line ART regimen in LMICs between 2004 and 2013 has decreased considerably over the past decade Figure

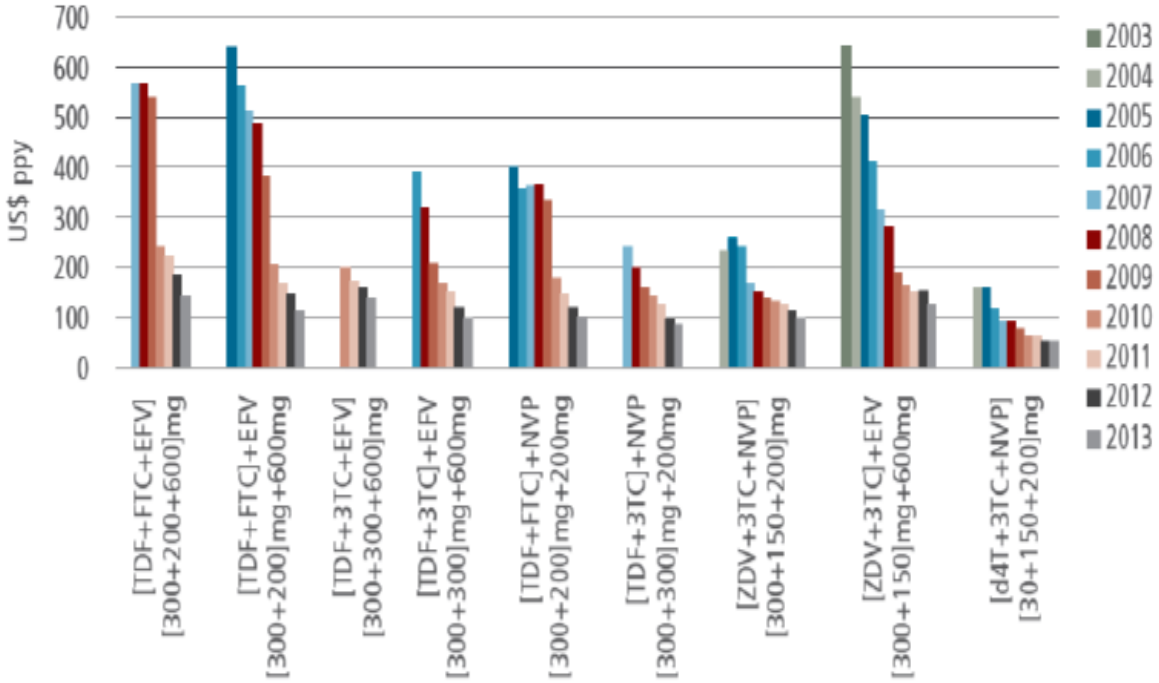

Figure 3: Price of First Line ART Regimens in Low Middle Income Countries Between 2004 And 2013

Regulatery status of anti retro virals in low middle income countries[10]

The WHO ARV drug regulatory database records regulatory approvals in place for all ARVs (5). The database is updated annually with information contributed on a voluntary basis by WHO-prequalified or US FDA tentatively approved manufacturers. While not exhaustive, the database gives a fairly comprehensive view of the extent to which drug regulatory approvals have been obtained, for which drugs, by which manufacturers, and in which countries. Figure 4 shows the percentage of 139 LMICs with regulatory approvals on record in the 2013 update of the WHO ARV drug regulatory database for at least one producer of the 14 most commonly used ARV

formulations. On an average, only 36% of ARVs were on record as having at least one manufacturer with drug regulatory approval in place.

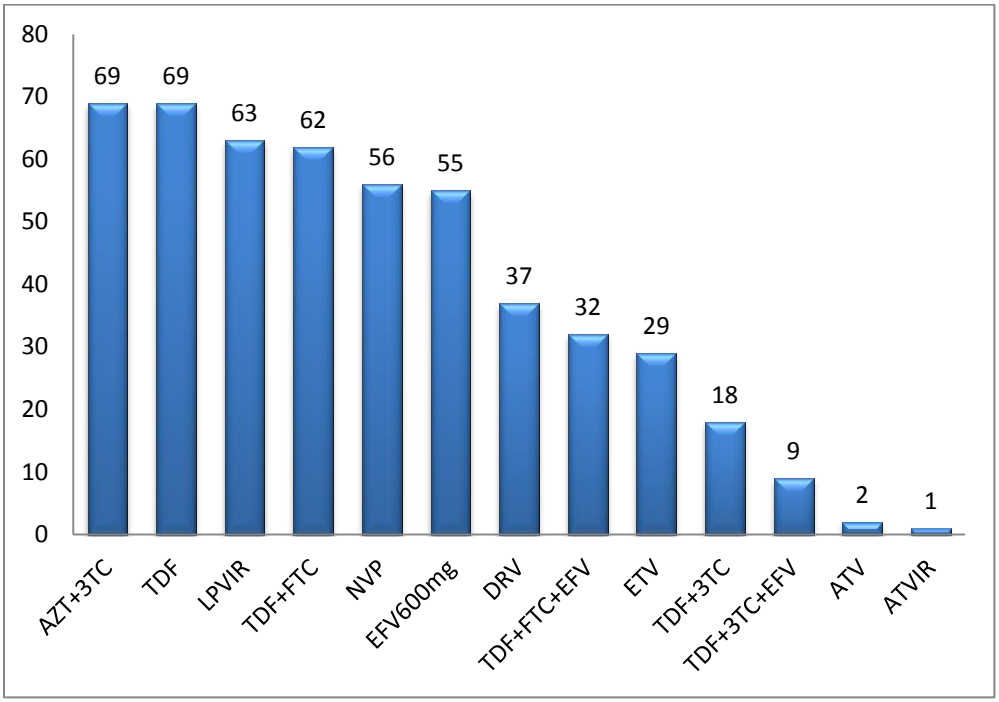

Figure 4: Percentage of 139 Countries with a Least Registered Producer of Key Adult ARV Formulation 2013

DISCUSSION[11]

Dossier requirements vary, many countries accept the Common Technical Dossier (CTD) format but few countries still require local format dossiers. Zimbabwe is also requires specific format for dossier submission. Zimbabwe Regulatory Authority:

MCAZ

MEDICINES CONTROL AUTHORITY OF ZIMBABAWE

Figure logo of MCAZ

The Mandate of MCAZ is to protect public health ensuring that medicines and medical devices on the market are safe, effective and of good quality[11].

Area of action:

- Medicines and allied substances
- Pharmacovigilence centers

- Narcotics
- Medical devices
- Laboratories
- Medicine Bioavailability/Bioequivalence Centers
- Dangerous drugs.
- Anti retro viral drugs
- Veterinary medicines

MCAZ

Medicines control authority of Zimbabwe

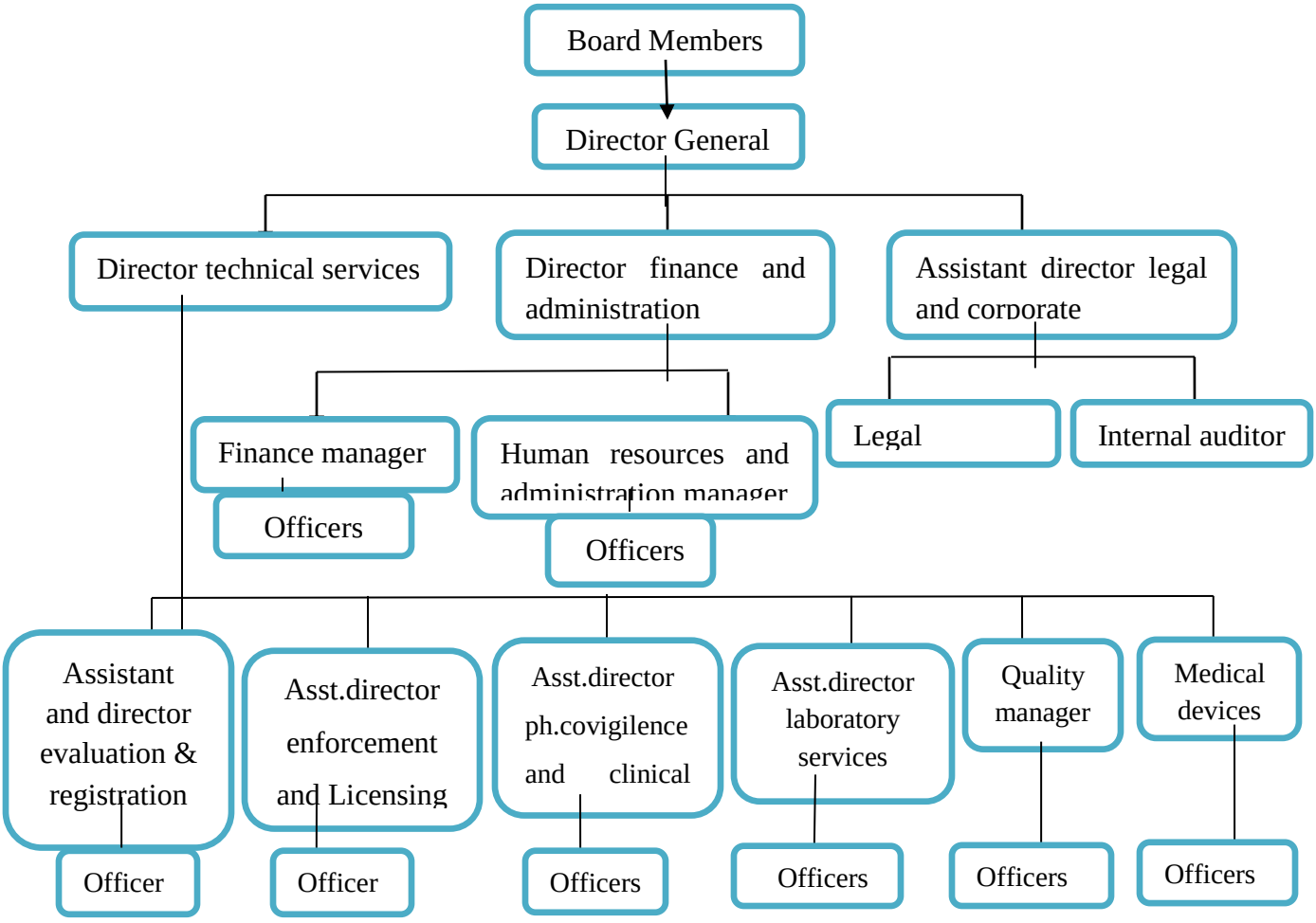

Figure 5: Organogram of Medicinal Control Authority of Zimbabwe[12]

Registration Procedure[13,14]

First applicant should submit all documents to the director general of medicinal control

authority of Zimbabwe within a period specified by the Authority, which shall not be less than fourteen days. Authority will start the screening **it takes nearly 3months and after that evolution was started they will check all aspects of drug information it takes around 6 months. If all documents submitted comply with the specifications of authority then the product get approval within 12 months**

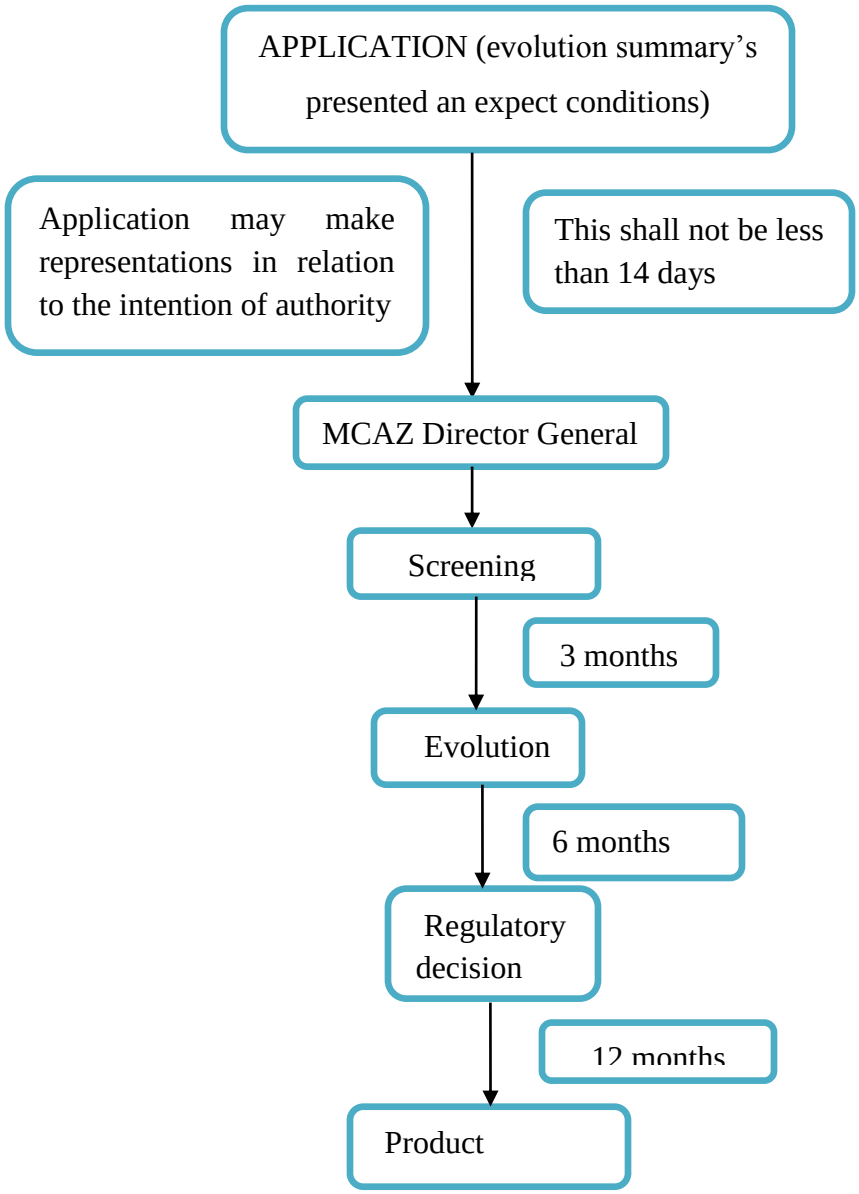

Figure 6: Registration Procedure for Approval of Generic Drugs in Zimbabwe

Table.3.Registration Requirements for Anti Retro Viral Drugs in Zimbabwe[14, 15, 16]

ADMINISTRATIVE INFORMATION	
REQUIRMENT	ZIMBABWE
Application	MC8(generic)
Documents	Cover letter, screening check list, proof payment appropriate

	fees, WHOCPP, CEP, cGMP, SMPC certificates and QOS,QIS, Certificate of analysis ,bioequivalence application form, biowaiver application form.
Copies	2 (one hard copy & one electronic copy)
Approval time	12 months
Pharmacovigilence	Required
MANUFACTURING AND CONTROLE	
REQUIRMENT	ZIMBABAWE
Bach size	One tenth that of full production scale or 1 lack units
Packaging	24,30,60,90,120,500.1000 (tablets, capsule)
Process validation	Required
Product sample	2 sample product in market container
STABILITY REQUIRMENT	
REQUIRMENT	ZIMBABAWE
No. of batches	2
Date and submission	3 months long term and 3 months accelerated
FEES U$	
Generic drug (in case of medicine imported in to Zimbabwe as a finished product)	2500,00
Resubmission of application	600,00
In case of expedited review of generic medicine	4000,00

CONCLUSION

Global economic environment in ARV business has continued to grow in the generic-accessible market. ARV market growth rate is faster than most other segments of the pharmaceutical market. Percentage of adults and children receiving that anti retroviral therapy is increasing from year to year in Zimbabwe. So Zimbabwe government should need to increase guidelines and regulations to get approval to manufacture of ARV drugs. It should conduct thorough inspections and audits to ensure quality of drugs. If necessary it should increase the import of anti retroviral to meet the patient requirements. It needs to conduct HIV/AIDS awareness programs.

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