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Review Article

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Comparative Study of regulatory requirement for preparation of Dossier for Registration of Oral Solid Dosage form in Zimbabwe and Myanmar

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Abstract

The purpose of this research is to assess the requirements for generic medicine marketing approval procedures in developed nations such as Zimbabwe and Myanmar. The regulatory standards of many countries throughout the world differ. The regulatory agencies' work is to assure the quality, safety, and efficacy of medications in their respective countries. The Medicines Control Authority Zimbabwe (MCAZ) and Food and Drug Administration Myanmar (FDA) give marketing permission for healthcare products in Zimbabwe and Myanmar. The gap analysis will comprehensively assess the MCAZ and FDA regulatory requirements and procedures through comparison of them to the provided recommendations for guidance, and this study will give tremendous confidence that the MCAZ and FDA regulatory affairs agreement is being fulfilled.

Conclusions

Through this study it can be concluded that the drug registration procedure in any country is not similar and minor details cannot be missed. In detail knowledge is important of Drug Agency, its legislation, Approval pathways, dossier preparation process and dossier formats and other requirements which are required for dossier preparation and submission. This will make it easy for any drug to pass regulators eye with ease and fast. In this article will provide in depth knowledge about regulatory market and status for drug filling in given countries so that importance of drug registration in above countries can be understood. This study aims at making one understand the format and details of dossier preparation with important documentations needed. This will create impact for filling of drugs in above countries in future.

Keywords: Medicines Control Authority Zimbabwe (MCAZ), Food and Drug Administration (FDA), Certificate of pharmaceutical Product (COPP), Common Technical Document (CTD) Asian Common technical Document (ACTD) Summary of product characteristics (SmPC),Quality information summary (QIS)

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1. Introduction

Drug Regulatory Affairs is one that is always changing and expanding and it is also the one that is least affected by mergers and acquisitions as well as economic downturns. Global standardisation has resulted in a uniform approach to regulatory filings. The systematic formulation development serves as the framework for all export registration dossier preparation. (1)

It is challenging for any corporation to produce products for every location because the registration requirements vary by country. Because clusters in emerging markets are required for the filing of dossiers in formats like CTD and ACTD, we must take the majority of requirements into account while submitting technical data that will aid in export registration.

These activities are carried out by a variety of authorities, including member states and their national competent authorities, public health institutes and national technical institutes, including academia, and the European Commission in Brussels and the European Medicines Agency (EMA) in London. Another European agency, established in 2004 by Regulation (EC) No. 851/2004, is the European Commission.

1.1 Common Technical Document (CTD)

A Common Technical Document (CTD) is a supporting list of leaflets that must be given to the regulatory body with pharmaceutical registration applications to obtain market authorization. CTD mostly

describes the data format. It is customary for RA professionals to be aware of the documentation that must be provided when a medication product is approved. CTD, on the other hand, is primarily concerned with the orderly structure of information. CTD documents should be simple, straightforward, and transparent. (2)

CTD is an ICH-defined format that has been agreed upon and accepted by regulatory agencies in Europe, Japan, and the United States. The FDA defines the CTD as an information package containing clinical, non-clinical, manufacturing, and technical data that would be submitted for registration of novel pharmaceuticals in all three ICH regions, namely the United States, the European Union, and Japan. (3) Paper submission of ACTD and CTD format dossiers, as well as electronic submission of CD format dossiers, is used in semi-regulated markets such as ASEAN countries. (2)

- Module 1 Administrative and prescribing information.
- Module 2 Overall Summaries (Quality Overall summary)
- Module 3: Quality
- Module 4 Non-clinical study reports
- Module 5 Clinical Study Reports

1.2 ASEAN Common Technical Dossier (ACTD)

The Association of Southeast Asia (ASA), a grouping of the Philippines, Federation of Malaya, and Thailand, was established on July 31, 1961, and it predated ASEAN. The ASEAN Declaration was signed on August 8, 1967, by the foreign ministers of Indonesia, Malaysia, the Philippines, Singapore, and Thailand, thus founding ASEAN. (4, 5)

Brunei joined ASEAN as the sixth member in 1984, and Vietnam joined as the seventh member on July 28, 1995. Two years later, on July 23, 1997, Laos and Myanmar (Burma) joined [6]. Cambodia was supposed to join at the same time as Laos and Burma, but its accession was delayed owing to internal political strife in the nation. It later joined on April 30, 1999, once its administration had stabilized. (5)

The ACTD (Asian Common Technical Dossier) format is used by the ASEAN countries, which include Indonesia, Malaysia, the Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar, and Cambodia. (5)

The ACTD Format consists of four parts, including (4)

a) Part I: Table of Content, Administrative Information and Prescribing Information

b) Part II: Quality Document

c) Part III: Nonclinical Document

d) Part IV: Clinical Document

1.3 Generic Drug Market

A generic medicine is a pharmaceutical that is designed to be identical to an existing brand-name drug in dosage form, safety, and strength, mode of administration, quality, performance characteristics, and intended purpose. These commonalities serve to establish bioequivalence, which signifies that a generic drug operates in the same way as a brand-name medicine and delivers the same therapeutic benefit. In other words, you can use a generic drug in place of a brand-name medicine. (6)

The increasing prevalence of chronic diseases, diabetes, and cardiovascular diseases, growth in the geriatric population, increasing high demand for generic medicines, healthcare expenditure, and a large number of patent expired branded drugs is all significant factors driving the growth of the generic drugs market. However, strict regulatory controls and the detrimental effects of medications are projected to limit market growth. Rising need for newer versions of generic pharmaceuticals, various clinical trials, and a vast variety of licencing and partnership tactics used by important vendors to introduce new products all contribute to increasing demand for generic drugs. (7)

Table 1. Difference between CTD and ACTD

ICH CTD	ASEAN CTD	Description	Remarks
Module 1 Regional and Administrative Information	Part I	Administrative Document such as application forms, GMP, licences, labelling are included in the CTD.	Non-essential for generic drugs and new drug
Module 2 Overall Summary	Part II	This module provides an overview of Modules 3, 4, and 5. There are three parts: a non-clinical overview and summary, a clinical overview and summary, and a quality overall report. The summary gives the person conducting the review an overview of the documents included in the whole application.	Required for new drugs and generics. Only a summary of the Quality component is necessary for generics.
Module 3 Quality		This module contains the documentation relevant to the chemistry-based production and control of both drug substances and drug products.	Necessary for generics and New Drug
Module 4 Safety	Part III	Data on the pharmacologic, pharmacokinetic, and toxicological assessment of the pharmaceutical product are included in non-clinical study reports.	Not necessary for generics
Module 5 Efficacy	Part IV	Clinical Study Reports - This module provides a critical analysis of the clinical data and associated	Non-essential for generic drugs except

		reports.	Bioequivalence study

2. Difference between CTD & ACTD format

CTD format is a standardized format for pharmaceutical product registration in regulatory countries such as the EU, US, and Japan, but ACTD format is necessary for drug product registration in ASEAN Nation (Association for South East Asians Nation).

CTD Format contain 5 Module representing Module 1 for administrative Part, Module 2 for Quality Overall Summary, Module 3 for Quality, Module 4 for Non Clinical Studies, Module 5 for Clinical Part whereas ACTD format contains only 4 Parts namely Part 1 for administration, Part 2 for Quality and quality Overall Summary, Part 3 for Non Clinical Studies, and Part 4 for Clinical Part. (8)

3. General requirement and registration Process of Zimbabwe.

3.1 Administrative Document (9)

- Cover letter
- Table of Contents
- MC8 application form
- Declaration by the applicant
- Screening checklist
- Payment proof
- Certificate of pharmaceutical Product (COPP)
- Good Manufacturing Practices License
- Summary of product characteristics (SmPC)
- Labelling (primary and secondary packaging)
- Package insert and patient information leaflet
- Quality information summary (QIS)

3.2 Quality Document (9)

- Table of Contents
- Body of date
  - Drug Substance
  - Drug Product
- Literature references
- For Only Generic drug Bioequivalence study was Mandatory

3.3 Registration Process and Review Process Zimbabwe

Registration application submissions and regional marketing of goods can be done through various channels. There are three type of registration process

1. Expedited or "Fast-track" registration Process
2. WHO Collaborative registration procedure
3. ZAZIBONA (10)

The application evaluation process is outlined in Fig. 3 with timeframes and milestones. The map depicts the evaluation and approval of a product that moves from review to approval after one cycle. However, it often requires a minimum of three review cycles before the assessment is concluded. Additionally, the map excludes actions like submitting arguments to the administrative court to appeal against the denial of an application. (11)

4. General requirement and registration Process for Myanmar.

4.1 Administrative Document (12)

- Comprehensive Table of Contents
- Introduction
- Application
- Labeling, Package Insert and Patient Information Leaflet
- Approved Summary Product Characteristics (SPC) /Patient Information Leaflet (PIL)
- Assessment Report from Reference Agencies
- Description of Batch Numbering System
- Proof of Approval
- Authorization Letters
- GMP Certification/Proof of GMP Compliance
- Patent declaration
- Declaration on rejection, withdrawal and deferral
- Declaration for GDA verification
- Registration status in other countries

4.2 Quality Document

- Table of Contents
- Body of date
- Drug Substance
- Drug Master File (DMF)
- Certificates of Suitability (CEP)
- Stability Data of Drug Substance (3.2.S.7)
- Drug Product
  - ✓ Pharmaceutical Development (3.2.P.2)
  - ✓ Process Validation (3.2.P.3.5)
  - ✓ Control of Drug Product (3.2.P.5)
  - ✓ Container Closure System (3.2.P.7)
  - ✓ Stability Data of Drug Product (3.2.P.8)
  - ✓ Product Interchangeability (3.2.P.9)
  - ✓ Blank Production Batch Records
- Literature references

- For Only Generic drug Bioequivalence study was Mandatory. (4)

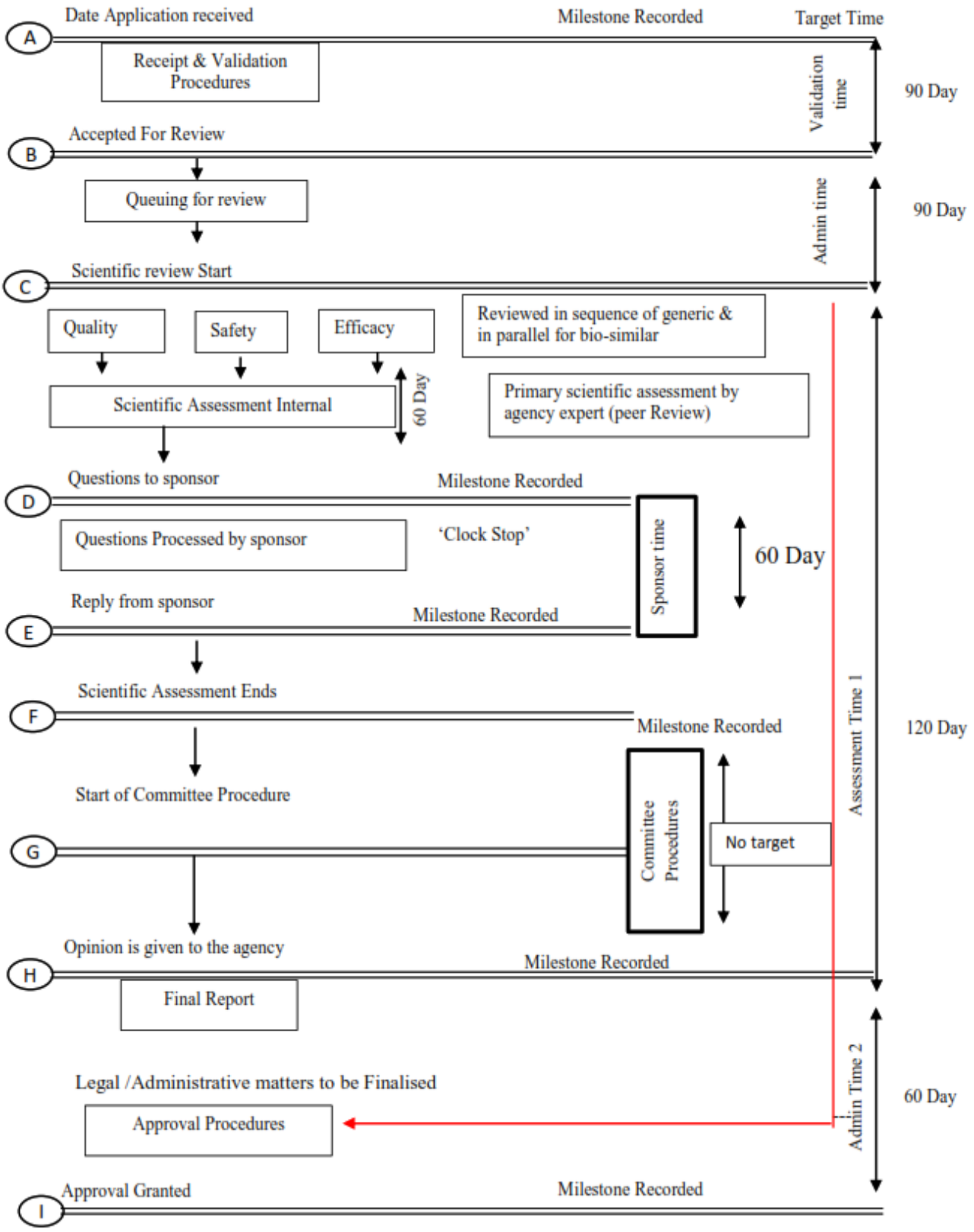

Figure 1. Zimbabwe Regulatory drug registration and Review Process

4.3 Registration Process and Review Process Myanmar

The Government of the Republic of The Union Of Myanmar, Ministry of Health, shall receive applications for drug registration in the original specified form (Form 1 Registration). Department of Food and Drug Administration offices in Naypyitaw and Yangon, as well as form (1), are all accessible. (13)

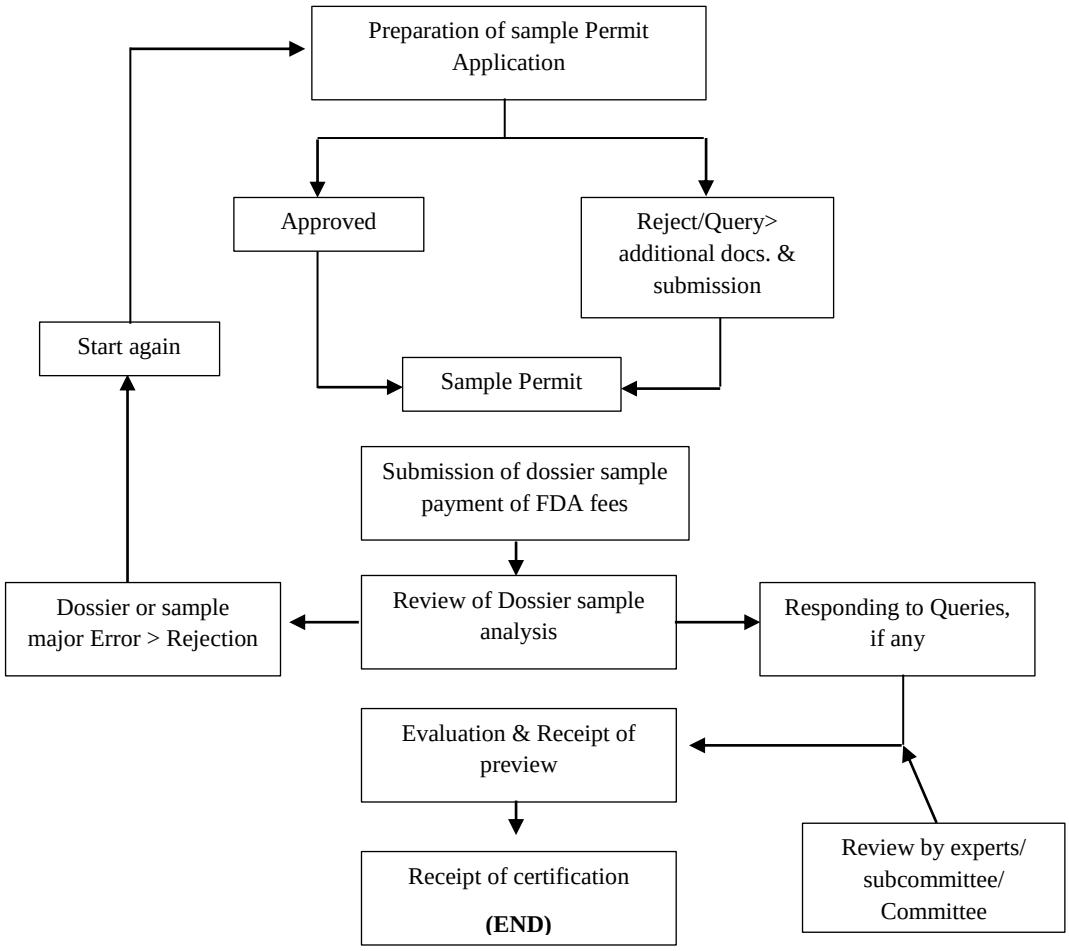

Figure 2. Myanmar Drug registration and Review Process

5. Comparison between regulatory requirements for preparation of dossier for MCAZ and FDA.

Table 2. Comparison for MCAZ and FDA

Parameters	**Zimbabwe**	**Myanmar**
Regulatory Authority	Medicines Control Authority of Zimbabwe (MCAZ)	Food and Drug Administration, Myanmar (FDA)
Regulatory authority Flag		
Dossier Format	CTD(Common Technical Document) • The Common Technical Document is divided into five modules.	ACTD (Asian Common Technical Document) • Asian Common Technical Document divided into Four Parts
Dossier language	English	English and/ or official native language
Types of application	1.New chemical entity application (biological and biosimilar medicines are included under this group) 2.Generic drug application 3.Line extension application	New Chemical Entity Generic drug Application
Registration Validity	5 year	5 year
Registration Time	12- 18 months	12-18 Months
Registration fees	$ 3000 for NCE Registration $ 2500 For generic $ 1500 for line Extensions	Registration Assessment 300000 kyats + fee for lab analysis. Registration fee 500000 kyats Variation of registration 100000 kyats of each variation

Plant Inspection fees	50000 USD	Not Required
Inspection/ Audit	Accepts FDA/EU/PICs Approval for FP site.	Not Required

Table 3. Country Specific Comparison

Sr. No	MCAZ	FDA, Myanmar
1.	A4 (8.27×11.69 inches) paper size is used for the dossier preparation with font size 12 in Times New Roman	A4 (8.27×11.69 inches) paper size is used for the dossier preparation with font size 12 in Times New Roman
2.	Completed, signed and dated MC8 form	Country Specific Application Form
3.	Biowaiver request is applicable BCS classification of drug for (BSC class I) and (BSC class II) and When drug substance test and reference product is identical	Biowaiver request is applicable BCS classification of drug for (BSC class I) and (BSC class II) and When drug substance test and reference product is identical
4.	Bioequivalence application form (BAF)	Not Required
5.	Quality Information Summary	Not Required
6.	Artwork (Labels, carton, Leaflet)	Artwork (Labels, carton, Leaflet) If our product is licenced for loan. Mansion is the manufacturer's licence number, according to the artwork.
7.	Certificates:- 1. COPP 2 GMP	Certificates:- COPP GMP Product Permission Site Master File
8.	Not Required	Additional Documents Proforma Statement- Part 1 in 6.1 Summary Drug Information Sheet Part 1 in 6.2 Drug Sample Statement Part 1 in 6.3 Its standard Draft Provided in Myanmar country specification guideline of Annex V, Annex VI Annex VII
9.	Sample requirement :-	Sample requirement :- Nearly 500 samples are needed for each category of dosage form in Myanmar, according to sample requirements.

Nature of product	Pack Size	Number of Containers
Tablets Capsules	24	4
	30	3
	60	2
	90	1
	100	1
	120	1

Table 4. Technical Comparative Study

Parameters	Zimbabwe	Myanmar
Quality Overall Summary	Module 2	Part 2 is a quality document, but in ACTD format, Part 2 provides the quality overall summary As well as Quality document.
Finished product control requirements		
1.Color identification	Needed	Required
2. Disintegration	Required	Required
3. Water content	Required	Required
4. Supporting documents	WHO TRS 95,2009	Government Of The Republic Of The Union Of Myanmar-2014
Product Part	According to ICH, eight subtypes	According to A-CTD, nine subtypes P 9. Product Interchangeability
Stability Zone	Zone II	Zone IV b
No. of submission Batches	2 Commercial batch and 1 Pilot Scale batch OR 1Commercial batch and 2 Pilot Scale batches	Complete stability study of all 2 Commercial batch and 1 Pilot scale batch OR 1 Commercial Batch and 2 Pilot scale batches.
Minimum Stability data	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months

Storage conditions long-term intermediate accelerated	40°C±2°C/75% RH±5% RH 6 months 30°C±2°C/75% RH±5% RH 12 months	40°C±2°C/75% RH±5% RH 6 months 30°C±2°C/75% RH±5% RH 12 months LT Complete stability study.
Stability guideline reference	WHO/OMS	ASEAN-CTD
Bioequivalence Study (for Generic)	The comparative BE study profile is required against US/ EU innovator is carried out.	In all countries except than Thailand, where BE must be carried out domestically, against US/EU/Australia reference drugs. In certain nations, PE will be conducted using national standards.(Not required) PE ≠TE
Number of subjects	Base on the therapeutic category of the drug	Base on the therapeutic category of the drug
Age	18-55 yrs.	18-55 yrs.
Clinical Study Design	Two-period, two sequence crossover or four way crossovers.	Single dose Two period, two- sequence crossover study
C_{max}	80–125% C_{max} In Some special Cases of drug with narrow therapeutic range the BE acceptance criteria 73- 133% C_{max}	80–125% C_{max}

6. Conclusion

In this article the comparison between general registration procedure and requirements of Zimbabwe and Myanmar have been discussed. In Zimbabwe CTD format of dossier is used while in case of Myanmar ACTD format for drug registration is used. This article differentiates the basic differences between CTD and ACTD format for dossier filing. Medicines Control Authority of Zimbabwe (MCAZ) is the regulatory authority of Zimbabwe whereas Food and Drug Administration, Myanmar (FDA) is the regulatory authority of Myanmar.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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