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Review Article

Study of Regulatory Requirements for Registration of Pharmaceutical Products in Africa Market

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ABSTRACT

In 2014 Africa imported US$ 15.1 billion. With Algeria with a share of 16.7 percent. Like this South Africa 13.7 per cent, Egypt 12.5 per cent, Morocco 3.9 percent, Tunisia3.8 per cent and Kenya 65 per cent. India is the second largest source Africa gets its pharmaceutical products. It comes under semi regulatory Market. Where countries like Algeria, Zambia, Ethiopia, Ghana, Kenya, Malawi, Mozambique, Namibia, Nigeria, Sierra Leone, Tanzania, Zimbabwe are following CTD format.

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1. INTRODUCTION

In 1820 establishment of US Pharmacopeia occur. With it the new era of drug regulation was started. In 1906, USA Congress passed the original Food and Drugs Act according to which drugs must meet official standards[1]. After that in 1937 due to sulphanilamide tragedy a new provision that drug must be shown safe before marketing was enacted.[2] Which started influencing other regions also. Within this Regulatory Affairs came to existences. Drug Regulatory Affairs is constantly evolving field. Only systematic formulation can act as a back bone for Regulatory department. There are different requirements in different countries for Drug product registration.[3] It is really very difficult task for any company to develop product for each specific region.

Pharmaceutical Market is divided into following groups[4]:

Markets	Countries
1. Regulated Market:	US, EU, Japan, Canada, Australia, New Zealand.
2. Semi regulated Market	(a) **Asia:** (Sri-Lanka, India, Bangladesh, China, Pakistan, Bhutan, Nepal). (b) **ASEAN**: 10 Countries group - Philippines, Vietnam Singapore, Malaysia, Thailand, Indonesia, Laos, Cambodia, Brunei Darussalam, and Myanmar. (c) **African countries:** (Algeria, Zambia, Ethiopia, Ghana, Kenya, Malawi, Mozambique, Namibia, Nigeria, Sierra Leone, Tanzania, Zimbabwe etc.) (d) **Middle East countries:** (Gulf Co-operation Council countries i.e. Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE) (e) **Latin America** (Mexico, Brazil, Panama, Peru, Guatemala, Argentina, Chile, Dominican Republic) (f) **CIS:** (common wealth of independent states): Russia, Ukraine, Post Soviet States (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kirghizstan, Moldova, Tajikistan, Turkmenistan, and Uzbekistan etc.)

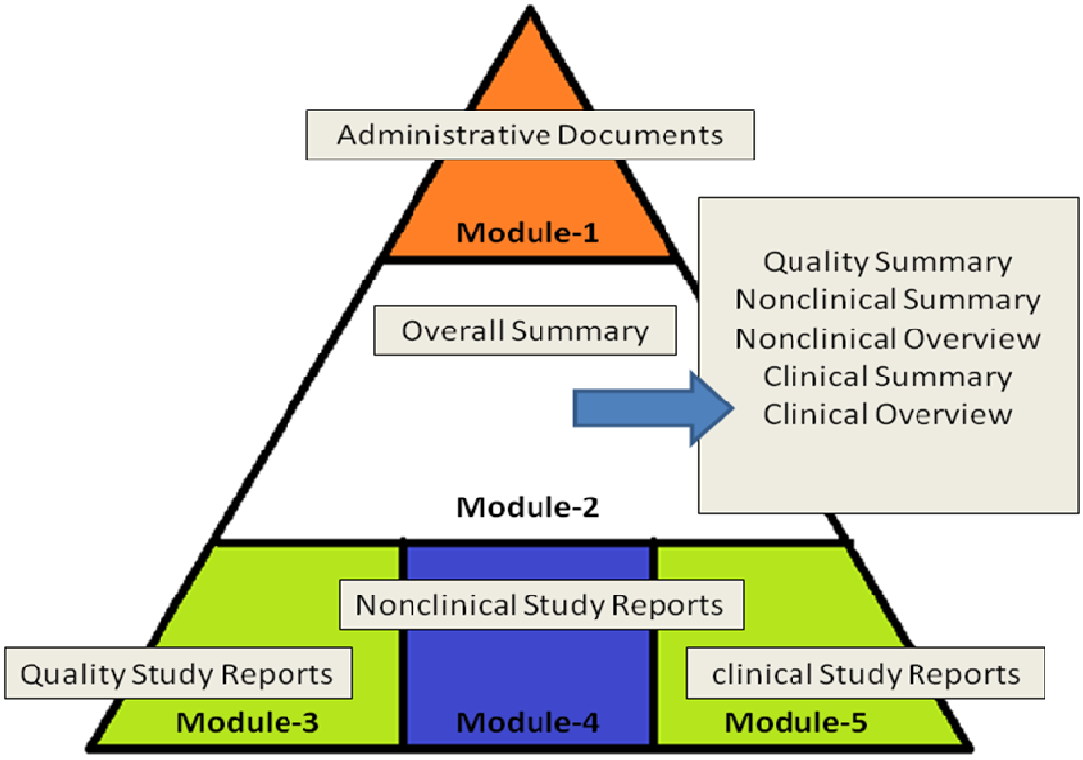

Figure 1 - Organization of CTD

Table 1 - Modules of CTD[9]

CTD	Description
Module 1 (Administrative Information)	Contains documents that are specific to each region. This module is not part of CTD. Basically consists of administrative documents like Application form, legal documents (GMP, Licenses etc.), labeling etc.
Module 2 (Overall Summary)	This module summarizes the Module 3, 4 and 5. It includes Quality Overall summary, Non-Clinical Overview and Summary and Clinical Overview and Summary. The summary provides reviewer the abstract of documents provided in the whole application
Module 3 (Quality)	The documents related to Chemistry, manufacturing and Control of both Drug Substance and Drug Product is included in this module.
Module 4 (Non-Clinical)	Non Clinical Study Reports – Data on pharmacologic, pharmacokinetic, and toxicological evaluation of the pharmaceutical product is provided
Module 5 (Clinical)	Clinical Study Reports - A critical assessment of the clinical data and related reports is provided in this module.

MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

Module 1: should contain all administrative documents. For example, application forms and certification, labelling, general correspondence and annexes environmental assessments, and oversees valuation reports, as needed. Documents should be organized in the under listed below.

The annexes to the module should be submitted in separate volumes Official language is English and/or Swahili copies shall be presented together with certified Kiswahili or English translations.[10]

1.1 Comprehensive table of contents for all modules

Table of contents for all module 1 should be given.

1.2 Cover letter

Applicants shall include a cover letter for each submission. The cover letter shall be signed by the applicant and stamped.[11]

1.3 Comprehensive table of content

The Comprehensive table of contents should include a complete list of all documents provided in all modules.

1.4 Application form

The submission must be accompanied by a completed, signed, dated and stamped application form.[12]

1.5 Product Information

This include summary of product characteristics, labeling, patient information leaflet, artwork and samples.

1.5.1Summary of product characteristics

All prescription medicines should be accompanied by SMPC.

1.5.2Labelling

Product should be labelled as prescribed in the Guidelines on Formal and Content Labelsfor Pharmaceutical Products.[13]

1.5.3 Patient information leaflet

Languages used for PL and labelling should be clearly expressed in English.

1.5.4Artwork

If the product applicant has a specimen or mockup of the samples presentation of the medicine available at the time of initial application, it should be included in Module1.[14]

1.6 Information on the experts

It is important to emphasize that well prepared expert reports greatly facilitate the evaluation of dossier and contribute towards the speedy processing of applications. Authors of export reports must be chosen in the basis of their relevant qualifications.[16]

1.7 Environmental Risk Assessment

The applicant must include an evaluation for any potential risks of the product to the environment. This should include risks to the environment arising from use, storage and disposal of products and not for risks

arising from the synthesis or manufacture of products.[17]

1.8 Pharmacovigilance

a. Pharmacovigilance System

It shall contain a detailed description of the pharmacovigilance system including the proof that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction.[18]

b. Risk Management Plan

A detailed description of the risk management system which the applicant will introduce should be provided, when appropriate.

1.9 Certificates and documents

a. Good Manufacturing Practice (GMP) certificate

The Applicant must submit a valid GMP Certificate bound by competent Authority in the country of origin of the product.[19]

b.CPP or free sale

The CPP must be in accordance with WHO guidelines.

c. Certificates of analysis

For active ingredient and finished product should be submitted.

d. Certificate of analysis

Specifications sheet from either supplier or finished product manufacturer should be submitted. In case of having pharmacopoeia excipient, the specifications sheet must cover all thepharmacopoeia parameter.[20]

e. Bovine Spongiform Encephalopathy (BSE) certificate.

BSE certificate must be submitted for materials originating from animals.

f. Certificate of suitability of monographs of the European pharmacopoeia (CEP)

If available, applicant should present copy of CEP.

g. Certificate of suitability for Transmissible Spongiform Encephalopathy

A valid TSE certificate issued by the competent authority must be submitted

h. Diluents and colouring agents is the product formula

A declaration letter in an official company letter head stating the diluents and colouring agents used in the product formula must be submitted.[21]

i. Patent information

A declaration letter in an official company letterhead stating the patient status of the product must be submitted.[22]

j. letter of access or acknowledgment of DMF

If applicable, a letter written by DMF owner to permit the Authority to make reference to information in the DMF on behalf of applicant must be submitted.[23]

k. Good Clinical Practice (GCP) or Good Laboratory Practice (GLP)

If available provide evidence such as accredited certificate for GCP or GLP for sites participating in the clinical and nonclinical studies.

i. List of countries in which a similar product is registered.[24]

The applicant should provide a list of countries in which similar product has registered.

MODULE 2: OVERVIEW AND SUMMARIES

2.1 Table of Contents of Module 2-5

There should be table of content that list all documents included in modules 2 to 5.

2.2 Introduction

A description of the product and its composition should be provided.

2.3 Quality Overall Summary (QOS)

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of data in Module 3.[21]

2.3.S Quality Overall Summary of Substance/Preparation

2.3.P Quality Overall Summary of finished Product

2.3.P Quality Overall Summary of Appendixes

2.3.R Quality Overall Summary of Regional Information

2.4 Non - Clinical overview

A bibliographic review of the safety data and (upon additional request by the Authority) data necessary for assessing the safety of the product should be provided.[25]

2.5 Clinical overview

The clinical overview should generally be a relatively short document (about 3 pages). The length, however, will depend on the complexity of the application.

ICH Guidance on the Common Technical Document for the registration of for human use Efficacy (M4E) for guidance on the format and the content of this part.[22]

2.6 Non clinical summary

The length of the non-clinical summaries will vary substantially according to the information to be conveyed, but it is recommended that the total lengths of the Non Clinical Summaries in general not exceed 100-150 pages.[26]

2.7 Clinical summary

The Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the CTD. The lengths of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that the Clinical Summary will usually be in the range of 50 to 400 pages.[27]

MODULE 3: QUALITY

3.1 Table of contents of Module 3

The table of content should list all documents included in Module 3.

3.2 Body of data

3.2.S Active Pharmaceutical Ingredient (API)

The information on API can be submitted in one of the following options

a) Certificate of suitability (CEP).

b) Drug Master File (DMI), or

c) Complete information on the 3.2.S active ingredient sections

3.2. S.1 General information

The qualitative and quantitative composition of all the constituents of the product should be described.[28]

3.2.S.1.1 Nomenclature

For Active herbal Ingredient which is used in the finished herbal product in the form of herbal material (s), the following information should be provided.

3.2.S.1.2 Structure

The following information where applicable, should the provided.

a) Physical form

b) Description of the constituents with knows therapeutic activity or markers

c) Other constituent(s)

d) If relevant, toxic constituents

3.2.S.1.3 General properties

A list should be provided of physicochemical and other relevant properties of API. This includes the physical descriptions such as appearance and colour, density, particle size. flowability, solubility in common solvents, pH values UV absorption refractive includes (for liquids), hygroscopicity, partition coefficient etc.[30]

3.2.S.2.1 Manufacturers

The name, address, and responsibility of each manufacturer/supplier, including contractors and each proposed production site or facility involved in production/collection and testing of the active herbal ingredient(s) should be provided.[31]

3.2.S.2.2

Description of manufacturing process and process controls information should be provided to adequately describe the production.[32]

3.2.S.2.3 Control of materials

This is only applicable herbal preparations. Materials used in the manufacture of the active ingredients (eg raw materials, starting material solvents, reagents, catalysts) should be Listed identifying where each material is used in the process.

3.2.S.2.4

Controls of critical steps and intermediates

Critical Steps Tests and acceptance criteria performed at the critical steps identified in the manufacturing process to ensure that the process should be provided.[33]

3.2.S.2.5 Process validation and/or evaluation

Process validation and/or evaluation studies should be provided, especially if it is a non-standard process.

3.2.S.2.6 Manufacturing Process Development

A brief summary describing the development of the preparation, when applicable should be provided.

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of structure and other characteristics

Information on the botanical, macroscopical, microscopical, phytochemical characterization and biological activity, if necessary, should be provided.

3.2.S.3.2 Impurities

Potential contaminants originating from the substance production and post-harvesting treatments such as pesticides and fumigants residues, toxic metals mycotoxins microbial contamination and radioactive contamination as well as potential adulterants should be discussed.

3.2.5.4 Control of active ingredients

3.2.S.4.1 Specification

A specification is a list of tests, references to analytical procedures, appropriate acceptance criteria and reference of each tested parameter. Copies of the All specifications, dated and signed by the concerned individuals should be provided.

3.2.S.4.2 Analytical procedures

All analytical procedures used for testing of API should be provided.

3.2.S.4.3 Validation of analytical procedures

Copies of the validation reports for the analytical procedures used to generate testing results should be provided in the dossier.

3.2.S.4.4 Batch analyses

Description of batches and results of batch analyses should be provided.

3.2.S.4.5 Justification of specification

Justification for the proposed specifications should be provided unless it is based on a recognized pharmacopoeia monograph.

3.2.S.5 Reference standards or materials

If applicable Information on the reference standards or reference materials used for testing the API error should be provided.

3.2.5.6 Container closer system

A description of the container closure systems should be provided.

3.2.S.7 Stability

Materials or preparations shall comply with specifications before use.

3.2.S.7.1 Stability summary and conclusions

The ICH guidelines for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products (FPP) should be consulted for recommendations on the stability data.

3.2.S.7.2 Post approval Stability Protocol and Commitment

The post-approval stability protocol and stability commitment should be provided.

3.2.S.7.3 Stability Data

Results of the stability studies should be presented in an appropriate format such as tabular.

3.2.P Finished product

3.2.P.1 Description and composition of the finished product

A description of the medicinal product and composition should be provided.

3.2.P.2 Pharmaceutical development

3.2.P.2.1. Components of the finished product

3.2.P.2.1. Active ingredient(s)

Key physicochemical characteristics (e.g., water content, Solubility, particle size distribution, ash value of the API s) that can influence the performance of the medicinal product should be discussed.

3.2.P.2.1.2 Excipients

Relevant, compatibility study results should be included to justify the choice of excipients.

3.2.P.2.2 Finished product

3.2.P.2.2.1 Formulation development

A brief summary describing the development of the medicinal product taking into consideration.

3.2.P.2.2.2 Overages

In general, use of an overage of All to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged.

3.2.P.2.3 Physicochemical and biological properties

If possible, parameters relevant to the performance of the herbal medicinal product such as pH, ionic strength, dissolution, re-dispersion, re-constitution, particle size distribution aggregation. polymorphism, rheological properties, potency, biological and/or immunological activity should be discussed.

3.2.S.2.3 Manufacturing process development

The scientific rationale for the choice of the manufacturing, filling, and packaging processes that can influence finished product quality and performance should be discussed.

3.2.P.2.4 Container Closer system

The suitability of the container closure system used for the storage transportation (shipping) and use of the medicinal product should be discussed.

3.2.P.2.5 Microbiological attributes

Where appropriate the microbiological attributes of the dosage form should be discussed with limits.

3.2. P.2.6 Compatibility

Relevant information on compatibility of the medicinal product with reconstitution Limits Should be provided.

32.P.3 Manufacture

3.2.P.3.1 Manufacturers

The name, address and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and

testing of finished product should be provided.

3.2.P.3.2

Batch formula

A batch formula for the intended batch size should be provided that includes a list of all components of the dosage form to be used in the manufacturing process.

3.2.P.3.3 Description of manufacturing process and process controls

A flow diagram should be presented giving the steps of the process and showing where materials enter the process.

3.2.P.3.4 Controls of critical steps and intermediates

Information on the quality and control of intermediates isolated during the process should be provided.

3.2.P3.5 Process validation and/or evaluation

Copy of proms validation protocol and port for at least three consecutive commercial batches

should be provided for verification.

3.2.P.4 Control of excipients

Specifications

3.2P.4.1 Specifications

The specifications should be presided for all excipients, including those that may not be added to every batch.

3.2.P.4.2 Analytical procedures

The analytical procedures used for testing the excipients should be provided, where appropriate. Copies of the in-house analytical procedures used to generate testing results should be provided.[27]

3.2.P.4.3Analytical procedures

The analytical procedures used for testing the excipients should be provided.

3.2.P.4.3 Validation of analytical procedures

If possible analytical validation information for in house methods should be provided.

2.3.2.P.4.4 Justification of Specifications

Justification for the proposed excipient specifications should be provided

3.2.P.4.5 Excipients of human or animal origin

The excipients of human or animal origin (eg magnesium stearate, lactose, gelatin...) information should be provided.

3.2.P.4.6 Novel excipient

For excipients used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterization and controls, with crisis references to supporting safety data should be provided.[28]

3.2.P.5 Control of finished product

3.2.P.5.1 Specification(s)

The specifications for the medicinal product should be provided. A copy of the finished product specifications release and shelf-life specifications, dated and signed by authorized personnel should be provided.[25]

3.2.P.5.2 Analytical procedures

The analytical procedures used for testing the herbal medicinal product should be provided Copies of the non-compendia analytical procedures used during pharmaceutical development as well as those proposed for routine testing should be provided.

3.2.P.5.3 Validation of analytical procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the herbal medicinal product, should be provided in accordance with ICH and Q6B.[27]

3.2.P.5.4 Batch analyses

A description of batches (strength, batch number, hatch size, hatch type, date and site of

production date of analysts) and salts of at least three batches' analysis should be provided.

3.2.P.5.5 Characterization of impurities

Information on the characterization of impurities should be provided, if not previously provided

3.2.P.5.6 Justification of Specification

Justification for the proposed herbal medicinal product specifications should be provided. The discussion should be provided on the omission or inclusion of certain tests, evolution of tests.[30]

3.2.P.6 Reference standards or materials

Information on the reference standards or reference materials used for testing of the medical product should be provided, if not previously provided.[31]

3.2.P.7 Container Closer system

A description of the container closure systems should be provided including unit count or fill

size, container size or volume, the identity of materials of construction of each primary

packaging component.

3.2.P.8 Stability

3.2.P.8.1 Stability summary and conclusions

The guidelines on "Stability Testing Requirements for Act Pharmaceutical Ingredients (API) and Finished Pharmaceutical Products (FPP) should be followed for recommendations on the stability data required for the finished Product.[28]

3.2.P.8.2 Post- approval stability protocol and stability commitment

Post-approval stability protocol and if applicable, stability commitment should be provided.

3.2.P.8.3 Stability Data

Results of the stability studies should be presented in a Tubular format. The results of all testing parameters related to each batch for the entire testing period should be presented in one table.

3.2.P.8.4 Literature References

A list and copies of all bibliographical references cited in support of this application should be provided.

MODULE 4 NON CLINICAL

4.1 Table of Contents of Module 4

A table of contents should be provided that lists all of the non-clinical study reports and indicate the location of each study report in the dossier.[21]

4.2 Study Reports

A bibliographic review of the safety data and data necessary for assessing the safety of the product should be provided.

1. Route of administration
2. Dose levels
3. Number of animals or subjects per dose level
4. Animals or subject origin, gender, weight range and age
5. Frequency at which observations were made
6. Duration of each study
7. The relationship between the time of administration and the onset of the effects
8. All measurements made[30]

4.3 Pharmacology

Primary Pharmacodynamics Studies on primary pharmacodynamics should be provided and evaluated

4.4 Pharmacokinetics

Refer ICH guideline on pharmacokinetics guidance for repeated dose tissue distribution studies for guidance on circumstances when repeated dose tissue distribution studies should be considered.

4.5 Toxicology

Reference from ICH Note for guidance on toxico kinetics should be considered.

4.5.1 Single-Dose Toxicity (in order by species by route)

Reports of acute oral toxicity studies on at least one mammalian species should be provided.

4.5.2 Repeat-Dose Toxicity

Repeat-dose studies (short-term, sub-chrome and chronic toxicity) allow proper, long-term assessment of the substance of its metabolites, which may accumulate in the body. The length of the repeat-dose study should be related to the duration of the proposed therapeutic use of the substance.[31]

4.5.3Genotoxicity

Mutagenicity studies are aiming to determine the potential for a substance to contribute to genetic damage in humans. If positive correlation is observed and in vivo or invitro test shall be studied.

4.5.4 Carcinogenicity

Where the conditions suggest the need for carcinogenicity study, data should be submitted.

4.5.5 Reproductive and Developmental Toxicity

ICH Guidance on Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility (S5) for

guidance on tests for reproductive toxicity.[32]

4.5.6 Local Tolerance

Iocal tolerance testing of medicinal products for recommendations on the evaluation of local tolerance to be performed.

4.5.7 Other Toxicity studies

Other toxicity studies, Photo safety evaluation should be submitted.

4.6 Literature References

A list of cited references should be provided.

MODULE 5: CLINICAL STUDY REPORTS

This module provides guidance on the organization of clinical study reports, other clinical data.

The table of content should list all documents included in Module 5.

5.2 Tabular Listing of All Clinical Studies

if data is available on have been requested it should be presented in a tabular format.

5.3 Clinical Study Reports

Efficacy of the product as well as information on the safety of use should be addressed.[38]

5.4 Literature References

A list of cited references should be provided.

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