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Review Article

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Comparative study of Regulatory requirements of Drug Product in Emerging market

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Abstract

Registration of Pharmaceutical drug product in Emerging Market is most demanding task. Regulatory requirements are harmonized in regulated countries by Common technical document (CTD) filing, while there is diversity of requirements in emerging markets. International conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has brought regulatory authorities and pharmaceutical industries of US, Japan and Europe together for various aspects of drug registration but there are is no such harmonized guideline for emerging market except Association of Southeast Asian Nations (ASEAN) and Gulf Co-operation Council (GCC), ZAZIBONA where harmonization exist in clusters with their mutual concern. The optimization and harmonization requirements has become mandatory and can be examined by the incidence of higher cost involved in availability of drugs, quality requirement of premise and research and development, regional registration requirements. Quality, Safety and Efficacy data has significance importance in dossier registration. Pharmaceutical Industries has to comply with regulatory requirement in Emerging market and for betterment of public Health and safety.

The review explains a brief about Emerging Markets Key Challenges, Regulatory barriers, Global Regulatory Plan, general filing procedure, documents required, and different regulatory requirement for Registration of Pharmaceuticals in Emerging market with tabular comparison.

Keywords: Dossier Registration, Emerging Markets, GCC, ASEAN, Common technical document (CTD), WHO, Harmonization, WAEMU, ZAZIBONA, Drug Product.

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1. Introduction

Drug Regulatory Affairs has evolving and growing and is the one which is least impacted during the Acquisition and Merger, and also during recession. Global harmonization in standards has led to consistent approach in regulatory submissions. The Systematic formulation development acts as a back bone for any dossier preparation in export registration. (1)

The Registration requirement are Varies countries so it is difficult for any company to develop product for each region Therefore; we need to consider majority of requirements during technical data submission which will help in export registration therefore, harmonisation occurs as clusters in Emerging market are necessary for submission of dossier eg. ASEAN Countries such as Thailand, Singapore and Vietnam have harmonisation. (1)

Asia is expected to overtake Europe in pharmaceutical market within the next decade and sales are driven by growth in key emerging markets. More than 85% population lives in the emerging market and so the real economic growth has come from these markets. This promotes many MNC's switched to these emerging countries particularly in China, India, Russia, Korea, Saudi and Mexico. (1)

The growth is increasingly moving beyond the use of CRO's and marketing of well-established products to include early-stage research and technology aimed at specific medical need of patients in these regions. One way to launch new drugs in a timely manner in emerging markets is to include majority of patients from relevant countries in clinical development programs. This practice is routine for most pharmaceutical companies. These development programs attributed to

longer life expectancy and lifestyle changes that are possible through rapid economic growth. (2)

Emerging markets are important and expanding globally and has raised the demand for general and lifesaving medicines. Regional cooperation is required to ensure that the scientific capacity is developed. Apart from this, regional manufacturing capacity is the most expected way to enable economic growth, specified quality standards should meets international export requirements. Legislative and political factors are the most critical one, countries need to have support to develop effective national legislation, as well as cooperating regionally which helps to access to essential medicines. (2)

Pharmaceutical Companies and regulatory agencies are collaborating for improving drug development process and approval ex: ICH guidelines for eCTD submission and QbD which contribute to better first time product quality shortening the review time required by regulatory agency and these guidelines are well accepted by regulated markets and some countries of Emerging market like India and China uses the CTD format. (2)

Pharmaceutical Market is divided into following groups (3)**:**

1. **Regulated Market:** US, EU (Germany, France, Ireland, and Sweden etc.) UK, Japan, Canada, Australia, New Zealand, and South Africa.
2. **Emerging 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): There are nine member states of the Commonwealth of Independent States. These CIS states are Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, and Uzbekistan)

2. Emerging Market overview

Emerging market consists of mainly the countries from Asia pacific, Latin America, Africa and Gulf countries. These countries are differing in their region and also in many other aspects as regulation of Pharmaceuticals, Using different Guidelines for registration, registration fees, Requirements to maintain registration, duration of registration Patent regulation and legislation for the drug. (1)

The optimization in requirements is mandatory and can be judged by the incidence of higher cost involved in availability of drugs, research and development facilities. For better treatment safety and efficacy for the drugs must be justified and rationalize for public security. The quality, safety and efficacy data has its own importance in the registration dossier. The commercial significance of markets is increasing globally. (1)

WHO is continued to play a major role in terms of scientific capacity development, through its prequalification project and other activities. Given that the quality of pharmaceuticals is such a major issue, the WHO and other international organizations, such as developed country drug regulatory authorities, should be encouraged and supported to expand their current programmes which are supporting to developing countries.

GCC:

Ministry of Health of GCC states (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and UAE) are regulatory authorities for the regional pharma sector. They also regulate prices of pharmaceutical products and bring about harmonization of varying prices and the regulatory process, the GCC implemented a centralized system, Gulf Central Committee for Drug Registration (GCC-DR) in May 1999, which currently runs parallel to the regulatory regimes in the region. (1)

Fast-Track Registration and Reliance pathway:

In July 2020, GHC published a circular indicating that a reliance model can be applied for products approved in at least 2 GCC countries. In this case, GHC centrally approves the product within 60 calendar days from submitting the scientific reports issued by the GCC countries.

LATAM:

The regulatory regime in LATAM countries can be divided into three categories i.e. Countries which have established regulations (Brazil, Mexico, and Venezuela) to demonstrate the efficacy, safety through clinical trials or Bioequivalence studies with the innovator's product in the drug approval process. The countries as Argentina, Chile, Columbia, Ecuador, and Paraguay also have the regulations for registration of new or generic drug but are less stringent from first category. The last category of countries (Guatemala, Barbados, Bolivia, Nicaragua and Peru) has imperfectly formed drug regulations for the approval of drugs.

As per our report, the size of the Latin America Generic drugs market has been calculated at USD 37.14 billion in 2022. It is expected to reach USD 50.67 billion by 2027, growing at a CAGR of 6.41% from 2022 to 2027. (4)

The pharmaceutical industry plays a vital role in the growth of generic drugs. The primary drivers of the Latin American generic drugs market are patent expiration it helps initial developer produce lower-cost generic variants and introduce into the market. Generic drugs are of same quality there may some changes in flavor, size, and color but it acts same as the branded

drugs. Dosing, safety, strength, quality, how it operates, how it is taken, and how it should be utilized are all the same as the branded drugs. This market will increase tremendously during the forecast period. Among Latin America (LATAM) countries, some have established regulations (Brazil, Chile, Mexico and Venezuela) to demonstrate efficacy, safety through clinical trials and therapeutic equivalence studies with the proper drug approval systems, while others (Argentina, Columbia, Ecuador, Paraguay) have regulations to register a new drug or generic that are not as stringent as the first category. (4)

Finally, other countries (Guatemala, Barbados, Bolivia, Nicaragua and Peru) have imperfectly formed regulations for drug approval.

ASEAN:

Rest of the region countries insist on following ICH region for some data like stability, clinical trials though it follows majorly its own regulations e.g., the ASEAN countries require data as per ASEAN CTD which is same as ICH CTD for data requirements organized in Parts. The brief contents of CTD and major requirements for various regions are tabulated in Table 1. (1)

Table 1 Structure of Common Technical Document (CTD)

ICH CTD	ASEAN CTD	Description	Remarks
Module 1 Regional and Administrative Information	Part I	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.	Required for generics and New Drug
Module 2 Overall Summary	Part II	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.	Required for generics and New Drug. For generics summary on Quality part & non-clinical and clinical: literature summary and overview is required for some regions
Module 3 Quality		The documents related to Chemistry, manufacturing and Control of both Drug Substance and Drug Product is included in this module.	Required for generics and New Drug
Module 4 Safety	Part III	Non Clinical Study Reports – Data on pharmacologic, pharmacokinetic, and toxicological evaluation of the pharmaceutical product is provided.	Not required for generics
Module 5 Efficacy	Part IV	Clinical Study Reports - A critical assessment of the clinical data and related reports is provided in this module.	Not required for generics except Bioequivalence study

There is a difference in format for documents between ICH CTD and ACTD. As there are 5 modules in ICH CTD named as Module-I to Module-V and the documents in ACTD are named as part-I to part-IV because it does not involve common technical document overview and summaries like in CTD. The rest of the documents are administrative document and product information, quality document, nonclinical documents and clinical documents. (5)

There are some additional documents required at the time of the approval of drug in various countries as samples of drug are not required in Singapore, Malaysia and Indonesia and required in Thailand and Philippines. Another document is the Certificate of Pharmaceutical Product (COPP) and manufacturing license which is required in all countries under the ASEAN region. GMP (Good Manufacturing Practices) is another document, which is PICs in Singapore, Malaysia and Indonesia but not in Thailand and Philippines.

Research and Development focus

With the growing emphasis on the timely introduction of life saving drugs for diseases in Asia, there has also been an increase in discovery research for diseases that are more prevalent in the region than in the United States and in Europe. (2)

Emerging Markets: Key Challenges *(2)*

- Lack of harmonization in regulatory requirements.
- New or changing regulations are not present.
- Lack of quality manufacturing capacity and differences in labeling requirement.
- Changing drug regulatory authority policies, expectations and personnel; Evolving regulations and guidelines
- Health authorities have limited resources in emerging markets.
- Changes in local markets, or expansion or withdrawal from regions.
- Shifting internal company positions and business strategy (due to changing strategic imperatives, or personnel). Effective legislation to allow use of so-called 'TRIPs flexibilities' such as compulsory licensing.

- Emerging market required BE study which is costly and requires volunteers. Availability of volunteers is also a major issue. Due to different RLD, difficult to choose RLD of prime importance satisfying global need while performing study.
- Lack of adequate human resources and funding for drug regulatory activities.
- Lack of adequate regulatory science capacity to assess generic products that potentially meet the need for essential drugs.
- Lack of formal pre-submission meetings or scientific advice.
- Long review timelines for registration hence more uncertainty.
- More detailed documentation, SOPs, validation requests.
- Population and aging.
- New assessments of product benefit-risk or target product labeling (TPL) expectations
- Lack of Harmonization for Electronic submission and validations.
- More technical documents with raw data are needed.
- Validation requirements such as cleaning validation, process validation, equipment validation.
- More requests for inspections (Lack of mutual recognition of ICH countries and amongst countries within region) (6)

Regulatory Barriers

There are key regulatory barriers affecting the drug lag witnessed in the emerging countries. These barriers are Western approval, CPP, GMP, pricing approval, document authentication and harmonization. These barriers need to be overcome in order to reduce drug lag further in the future. (2)

Key Global Regulatory Plan Elements *(2)*

- Proper time management as the registration and company success depends upon the time taken by product to reach the market first Know and be compliant with national requirements.
- Health authority relationships critical, local talent important.
- Planning tool documenting the company's future course of action to optimize program efficiencies and opportunities.
- Tracking tool summarizing relevant regulatory events, agreements, commitments and feedback from drug regulatory authorities, including local insights.
- Risk assessment tool capturing known and potential regulatory and safety risks, and identifying mitigation and contingency plans for each.
- Lifecycle management (LCM) tool outlining product development opportunities. (6)
- Benefit-risk assessment tool outlining current information and evidence supporting the company's
- Core understanding of a product's safety and effectiveness
- Training programme and incentives for Regulatory personnel/Staff by the agency.
- Frequent and early communication with Health Authorities.
- Early integration of emerging market strategy into development plans and integration of regional requirements into a global regulatory plan.
- Rapid responses and rapid publishing support 24/7.
- Be the first with a product for an unmet medical indication and proper invest in the region. (6)

Global Regulatory Plan Components-Sample Table of Contents is:

a) Executive Summary

b) Product Profile, Including Product Description and Proposed Indications

• Product description
• Proposed indications
• Core product benefit-risk assessment (by indication)

c) Risk Mitigation and Contingency Plans

• Regulatory
• Safety
• Technical

d) Regulatory Landscape

• Applicable regional regulatory guidance and policy
• Applicable regional regulatory intelligence and information from competitor products

e) Regulatory Pathways

• Available programs or opportunities for development or review acceleration (i.e., use of real world evidence)
• Available programs or opportunities for expanded access

f) Regulatory Interactions with Drug Regulatory Authorities

• Proposed regulatory interactions with drug regulatory authorities
• Summary of outcomes of regulatory interactions
• Program implications

g) Lifecycle Management (LCM) Planning

• Pharmacovigilance and surveillance plan
• Pediatric development plan (6)
• Device or companion diagnostic development plan
• Lifecycle management opportunities

3. Registration Requirements for Emerging Markets (2)

Administrative Documents

- Certificate of Pharmaceutical Product with Export/Marketing in country of origin as Yes/Yes
- Product Permission
- Product Site Master file
- Manufacturing License
- cGMP Certificate
- Import /Export Certificate
- Artwork (Carton, Label & Package Leaflet & SmPC in line with innovator or proposed PI)

Chemistry, Manufacturing & control documents

API DMF Open part – Following data should be available in Open Part

Regulatory filing Process:

- Nomenclature.
- General Properties.
- Name of the Manufacturer and Site of manufacture.
- Route of Synthesis, flow diagram in brief.
- Structural Elucidation.
- Impurities.
- Specifications and Method of Analysis
- Container Closure System
- Stability testing Retest period & Storage
- API Specification and Method of Analysis & COA of API by the Applicant.

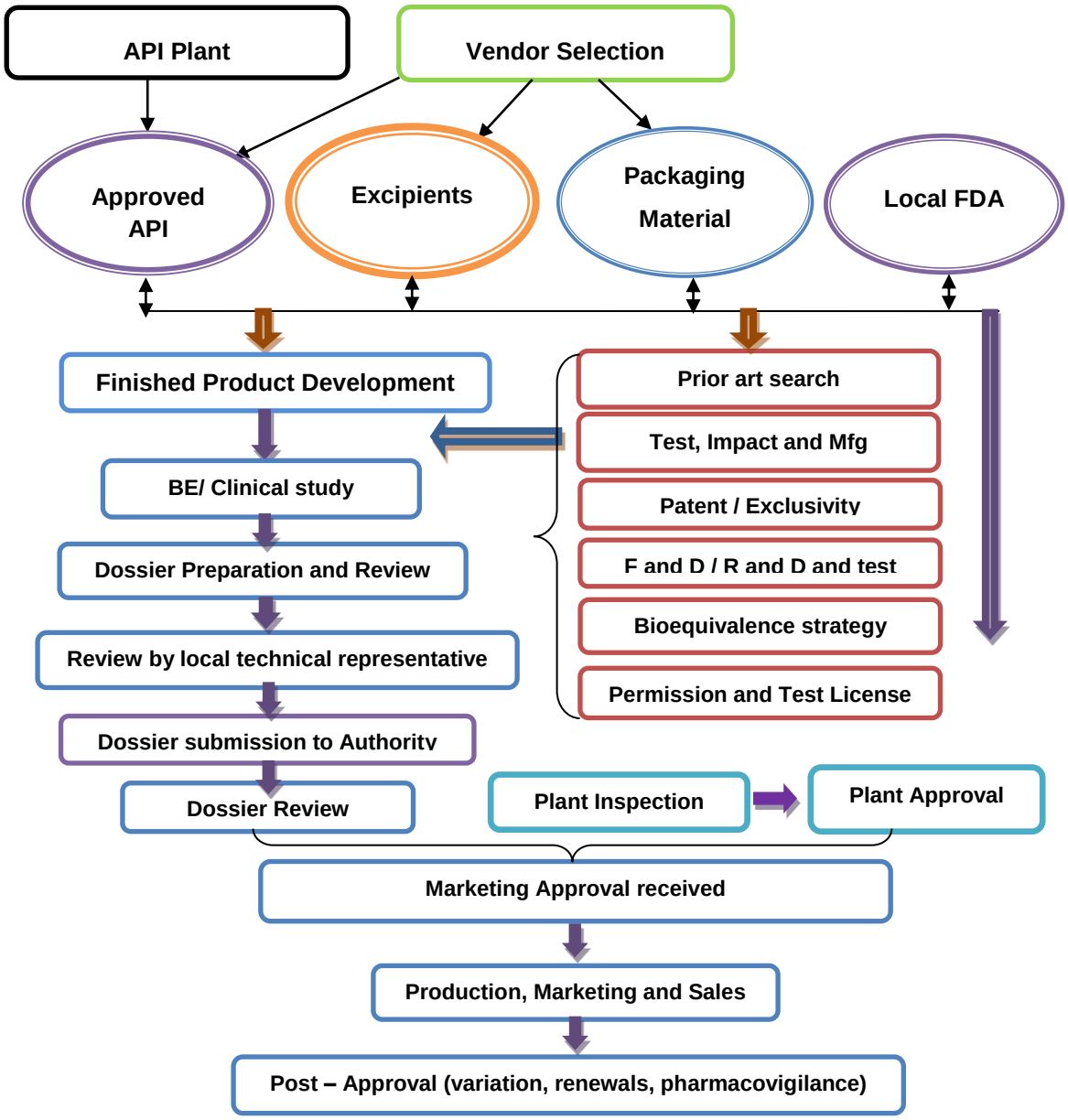

Figure 2. Dossier Application filing for Generic Drug Product in Emerging market (7)

Drug Substance and Drug Product

Structure and property

Nomenclature: IUPAC names, CAS no. are required.

- Nature of drug substance should be discussed.
- Polymorphism and chirality are mentioned adequately.

- The physical constants such as solubility in organic solvent, water, buffers at different pH buffers (pH 1.2, 4.6 & 6.8) and pKa values are described.
- Particle size distribution, Hygroscopicity, granularity, flowability etc. should be described in detail.

Manufacturing Process & Process Controls

- Detail information of manufacturing formula.
- Detail steps of API synthesis and purification are mentioned.
- The specifications of reagents, starting materials, intermediates, catalysts, and solvents used in the reaction.
- Type of equipment, its capacity and scale.
- In process test and control detail
- Master formula and batch manufacturing record are mentioned.
- Process validation protocol (report of 3 batches of same size and similar batch) are submitted.

Control of Critical Steps & Intermediates:

- The Control of Materials should be complemented by the supplier & the In-house Certificate of analysis.
- Flow chart of critical steps and in process control is mentioned.
- Environmental condition such as temperature, humidity and air flow range should be mentioned.

Process Validation and/or Evaluation

- During process validation three consecutive batches must be provided. Three different batches are performed for stability study is performed on Process Validation.
- Process Validation Protocol (PVP) & Report has to be co-related with the Batch manufacturing Records & must be verified for all in-process & critical parameters.
- Sterility Assurance Package for Parentral formulation:
    - Validation protocol & report drug product solution filtration
    - Summary report of Depyrogenation of Product Container
    - Summary report of Steam Sterilizer
    - Summary report of SIP(Sterilization-In-Place) of Vessel
    - Summary report of Terminal Sterilizer(TS Product)
    - Summary report of Media fill validation (for Aseptic Product)

Elucidation of Structure and other Characteristics

- Proper scientific information should be provided for the Polymorphism & Identification of Stereochemistry of the Active Ingredient amongst other spectral studies. (For e.g. IR, UV, NMR, Mass, DSC, XRD etc.) An XRD test report should be included.
- The spectral data such as NMR, X-ray Diffraction, Elemental Analysis and IR as a means for evidence of chemical structure are describe in detail.

Formulation Development

- The final product is manufactured using critical raw materials from two different suppliers. However, no special attention has been given to differences in quality of the end product.
- The development report should be prepared by taking into consideration QbD concept.
- The process control details such as moisture (range), blend uniformity, bulk and tapped densities and particle size distribution should be provided.
- Dissolution methods will have to be developed, the influence of particle size will have to be studied.

Overages

- Formula of API assay potency calculation details provided.

Impurities *(8, 9)*

The following factors to be considered while fixing the specification limits of impurities are;

- API impurity limits data (COA)
- Check ICH requirements.
- Check pharmacopoeia limits, if any.
- API stability data.
- Finished product stability data etc.
- Apart from the normal Process impurities, Residual Solvents & Degradation impurities, impurities due to the Starting material, elemental impurities, Nitrosamine impurities, Azido Impurities etc. should be as per ICH/Pharmacopoeias limit.
- The impurities must be also appropriately captured in the Specification of the Final Product.
- The product from each source impurity profiling should be provided.
- Potential impurities should be described in the impurity profile.
- For the impurities measurement methods should be mentioned.
- In the synthesis hazardous reagents and inorganic toxic substances are used in the reaction their residual limits should be given.
- RLD/RS/Innovator near to expiry testing help to fix the Limit of Specified Impurities in specification of Drug product.

- The unknown impurities present in the API should be not more than ICH limits.

Analytical Procedures *(10)*

- The method reference should be included in the specification page of the DMF.
- The Limit of Quantification (LOQ) and the limit of detection (LOD) should be provided for GC and HPLC methods used to control residual solvents and impurities in the Drug substance.
- Definite validated GLC/HPLC methods for qualify the impurities should be available. TLC report should be provided.
- In MOH laboratory the tests performed for validation are indicated vague.
- The method validated should be the same as that of the final method adopted to test the Drug substance are mentioned.
- Typical chromatograms must be provided for a particular batch of the API.
- In many countries Protocol, Report of validation of analytical method and their chromatograms are mandatory.
- Verification of non-compendia method needs to be validated by agency if required.
- The assay limits at release should be revised and controlled to 95-105%, So that the wider limits for shelf-life could be applied.

Batch Analysis

- Report of 3 initial batches of API production should be provided
- Batch should be selected on the bases of the regulatory requirement of the countries (ICH demand COA report) .The COA's (certificate of analysis) should have the batch size mentioned among other typical details.
- Certificate of Analysis (COA) for working/ secondary standards should be provided.

Excipients *(11)*

- Microbial limits of natural origin excipients should be specified
- TSE/BSE certificates from the manufacture should be incorporated
- Adventitious Agents Information on should be provided, such as Asbestos in Talc
- Permitted & approved Colors and Flavors should be used.
- Non compendia excipients are not recommended. Standard mixtures comprising excipients in Pharmacopoeia are allowed. In such cases table with composition of such mixtures and specifications with test form the supplier should be provided.
- Detail information of excipients, a copy of Monograph along with copies of the methods referred to in monograph but not appearing in monograph should be provided.
- Details of any specifications additional to monograph should be provided.(e.g. particle size, residual solvents)
- Excipients Certificate of Analysis tested against the full set of specifications.
- A quantitative estimation of excipients should prove equivalence b/w the Test & the innovator.

Finished product Specification *(12)*

- It should be prepared as WHO and ICH Q6 method of analysis.

Stability Data and Stability Protocol *(13)*

- Ability of pharmaceutical product to retain its property within specified limits throughout shelf-life.
- The stability program includes sample size, test interval, storage conditions, specific methods and container closure system
- Stability studies should include testing of those attributes of the Finished product that are susceptible to change during storage and are likely to influence quality, safety and efficacy. Stability to be performed on each individual strength & container size of drug product, unless bracketing or matrixing is applied. In conclusion Shelf life should be proposed concluded including the storage condition.
- Testing should cover the physical, chemical, biological and microbiological attributes, preservative content and functionality tests (eg. Nebulizer).
- Microbial limits at release and end of shelf life. Dissolution limit should be same as for release.
- API used shall preferably be of different batches.
- Generally 3 batches (2 pilots, 1 smaller) data is required to be submitted. A pilot scale batch is generally, one tenth of a full production scale or 100,000 units, whichever is larger.
- Recent modification of 30°C/60%RH condition to 30°C/75%RH an attempt at a single long-term global testing condition.
- Testing frequency and storage conditions should as per the ICH guidelines Stability data as per Zone: {Acc.: 0, 3 & 6 months; Long term: 0, 3, 6, 9, 12, 24 & 36 months}.

Packing Material

- Packing material should be suitable for storage, transport and compatible.

- For Primary packing material detailed specifications and method of analysis including Identification for material of construction required.
- For Secondary packing material specifications and method of analysis required
- Printed packing material and PIL specimens and /or colored artworks Certificate of Analysis & Batch Packaging record required.
- IR spectra of the Polybags should be submitted. (Identification for the material of construction)
- For immediate container of the API product polymer is used need to be tested, identified and characterized as per specifications given in Pharmacopeia's General Monographs

Container Closure System

- For the proposed blister pack the moisture permeation data should be provided.
- For final packaging the extractable and leachable study for the plastic containers and stoppers used for the drug product packaging are mentioned.
- Labeling materials (actual/commercial label) it was noted that there's a change in the blister design, as well as, inclusion of ADR Reporting Statement in the Unit Carton Box and Package Insert.
- The primary packaging specifications should have included an identification test for aluminum and an IR test for the PVD coating. Additionally, you were required to provide an IR spectrum for PVC coating.

Bioequivalence *(14)*

- Compares the systemic exposure profile of a test product (Generic) to that of a reference product (Innovator Brand)
- For the test product to be bioequivalent it should exhibit the same rate and extent of absorption as the reference product.
- Required for Tablets, Capsules and Oral Suspensions etc.
- It can be waived for aqueous oral solutions, parenteral solutions or solutions which are locally applied and locally acting, for example eye drops topical products inhalators or nasal spray products.
- If Bioequivalence study is not available then multimedia, multipoint comparative dissolution profile data of the product with innovator product should be submitted. Data should be complied the requirement for F2 factor.
- Generally CDP to be provided with all 3 media with additional media (if there).

Pharmacological, Toxicological data *(15)*

- Published References on Toxicological & Pharmacology studies are attached in the dossier.
- Published data on clinical trials and references are attached in the dossier.
- SmPC and clinical data from RA agency websites should be provided.

Registration fees

- Registration fees should be paid as per the requirements of the Agency of importing country.

Other requirements

- Working Standard and along with certificate of analysis.
- Samples of APIs, Reference/ Working Standards, Columns etc.
- Chromatograms, Spectra of the identification tests wherever applicable.

Samples

- As per the quality, it is mandatory to submit fresh finished product samples along with the dossier. Generally samples should have minimum of 1 year shelf life remaining when they reach to MOH. The quantity of the sample varies as per the registration requirements of the Agency of importing country.

4. Queries raised by various Emerging Markets (16)

- Chromatograms during method validation for assay and impurities. API method transfer documents, Chromatograms for individual time points during stability, etc.
- Complete supporting data for process validation
- Cleaning validation report
- Reconstitution Stability (For oral suspensions)
- Preservative content and microbial limits
- Redispersibility and rheological properties Particle size distribution.
- Computation of batch size.

General Properties

- Nature of drug is not discussed. Drug known to be a polymorphic in nature.
- Polymorphism and chirality is not mentioned adequately.
- Particle size distribution, Hygroscopicity, granularity, flowability etc. not described in detail
- pH buffers (pH 1.2, 4.6 & 6.8) not provided. pKa value not included in section.
- API Overages qty. not mentioned in formula.
- Formula of API assay potency calculation details not provided.
- Functions of material details not provided.

Description of raw material required and Manufacturing Process

- Though Active Pharmaceutical Ingredients (API) is manufactured from two different manufacturers. Name and complete contact details of each API-Vendor are not given.
- case of Advanced Intermediate the Chemistry of the same not included
- In the synthesis of the Drug substance and product most unsafe chemicals Cyanide is used. On the other hand route of synthesis may be changed but the same requires substitution with another secure chemical/reagent.
- The process control information such as, weight variation, average weight hardness, friability, thickness and disintegration time are not provided for tablet dosage form.
- PDR (Pharmaceutical development reports) are not complete.
- Manufacturer complete address for manufacturing plant & Head office with contact of Quality person not mentioned.
- For the sensitive Excipients e.g. Mg-stearate TSE/BSE declaration is not provided.
- TSE/BSE aspects of raw materials are totally ignored and Certificates are not provided as per AR No. used in the batches that are required to be submitted in the marketing application.

Control of Materials

- The residual metals from the reaction procedure are poorly addressed.
- The raw materials, reagents, intermediates and solvents used in the process are not described properly for possible impurities.
- In FP (Finished Product) specification microbial limit is not included.

Control of Critical Steps & Intermediates

- The Control of Materials not complemented by the supplier & the In-house Certificate of analysis.
- Critical parameters defined/captured in Process validation should always be concordant with the Product development.

Process Validation and Evaluation

- Three different batches are performed for stability study not performed on Process Validation.

Elucidation of Structure and other Characteristics

- The spectral data such as NMR, X-ray Diffraction, Elemental Analysis and IR as a means for evidence of chemical structure is missing.
- For Drug substance spectral graphs for UV Spectra, NMR & IR studies performed are unacceptable and interpretation of the studies is inadequate.

Impurities

- Toluene is used as solvent in the synthesis but not tested the same for presence of residual it and benzene class I solvent used in the synthesis of the drug substance and products. The residual limits for class I solvent are not described tested at any point.
- Potential impurities are not described in the impurity profile
- In the synthesis raw materials and intermediates are used. Their specifications of are not described. Although hazardous reagents and inorganic toxic substances are used in the reaction but the same residual limits are not given.
- In the reaction process Excipients used which may carry reactive impurities such as Hydrogen peroxide (other oxidized species), formaldehyde and Formic Acid. Justification for the use of this Excipient is not provided as per Impurities in residual solvents (ICH Q3C).
- Absence of Genotoxicity study, testing and data designed to detect compounds that cause genetic damage. Nitrosamine and Azido impurities information.

Control of Drug Substance

- The quality of the APIs meet only the requirements of specific monographs but does not meet to specifications described in the general monographs of a pharmacopoeia.
- Catalyst if any used in the synthesis of the API may be controlled (not necessary if absence in 3 batches shown)

Analytical Procedures

- Assay & Related substances will have to have a Stability indicating method (although the compendia method may be titration/TLC etc.)
- The Limit of Quantification (LOQ) and the limit of detection (LOD) are not provided for GC and HPLC methods used to control residual solvents and impurities in the Drug substance.
- The method used for the study of Drug substance is not specific. For the Analysis of impurities specific method is used which are not provided.
- Carcinogenic solvents like Methanol Acetone and IPA have been used in synthesis. However, these solvents are not analyzed for chance contamination of Class I solvents from which they are prepared.
- A check on the presence of Genotoxic impurities needs to be studied which may present in the Drug product.
- Certificate of Analysis (COA) and other Quality Control (QC) documents are not signed dated and certified by Quality Assurance (QA) department.

Batch Analyses

- Significant differences between the API manufacturers and FPP manufacturer's batch

study/analysis were noted for acetone, isopropyl alcohol and methanol

- The batch formula not mentioned for the exhibit as well as the proposed commercial batch eg. In drug formulation titanium dioxide is used as Opacifier but mentioned in batch formula. Also the complete composition of the coating materials is not provided.
- The information on some hazardous materials like reagent and solvent is hidden.

Stability Data

- Do not consider zone-conditions for Real-time stability studies.
- In stability report the packaging details are missing.
- The actual studies for stability are not provided. Data is provided from literature of forced degradation study.
- Microbial Attributes test not provided and/or not provided at Initial and final stage in stability data.
- For Powder for solution or suspension In-use shelf life not performed.

Container Closure System

- Primary packaging material Certificate of Analysis (COA) & Standard Test Procedure (STP) are not given.
- Pack style and pack size discussion is not provided.
- For final packaging the extractable and leachable study for the plastic containers and stoppers used for the drug product packaging is not provided.

Microbiological Attributes

- Microbial Contamination results are missing. Pathogen Count and Total Count not provided.

5. Harmonization

- According to WHO, the main cause behind the harmonization is to improve the availability of pharmaceutical and respond to international trade pressure by providing sufficient comprehensive and standardization technical rules on safety quality and efficiency of drug. (17, 18)

Initiation of harmonization in ASEAN

- The first harmonization was initiated by the Association of South East Asian Nations (ASEAN) in 1967. (19) The harmonization was occurs in clusters e.g. ASEAN and Gulf Countries but this should be reformed after translation. Format for marketing application resembles with the EU submission format. Few countries as India, Ukraine, Russia, South Africa and some newly harmonized countries uses the format almost same as EU-CTD format. Thus they are harmonized in regards of formats. Harmonization with GMP has help to improve pharmaceutical trade between ASEAN member countries by removing impeding barriers. (3)
- The countries from Asia pacific and Gulf have almost harmonized their regulatory environment through the Association of Southeast Asian Nations (ASEAN) and Gulf Co-operation Council (GCC) organizations, rest of the regions are yet to come up with the harmonized regulations in their respective regions. (3)

Association of ASEAN Pharmaceutical Product Working Group (ASEAN PPWG)

ASEAN's PPWG was established in 1999 to develop "harmonization schemes of pharmaceutical regulations of the ASEAN member countries to complement and facilitate the objectives of AFTA (ASEAN Free Trade Area), particularly, the elimination of technical barriers to trade posed by regulations, without compromising on drug quality, efficacy, and safety." PPWG works on harmonization efforts for New Chemical Entities (NCEs), biotechnological products, major and minor variation products and generic pharmaceutical products.

Initiation of harmonization in East African Community- Medicines Regulatory Harmonization

The EAC-MRH programme has developed guidelines for medicines registration, GMP inspections, pharmacovigilance, post marketing surveillance, medical devices, clinical trial control and policy frameworks.

East African Community (EAC) is a regional intergovernmental organisation of 6 Partner States: the Republics of Burundi, Kenya, Rwanda, South Sudan, the United Republic of Tanzania, and the Republic of Uganda, with its headquarters in Arusha, Tanzania.

Achievements of EAC – MRH Programme

- Development of Standard Operating Procedures (SOPs) for Medicine Registration, GMP inspections and Quality Management Systems.
- Common Technical Documents (CTDs) were approved, assimilated and rolled out in all countries.
- Conduct joint assessment activities
- Performed joint GMP inspections

Initiation of harmonization in ZAZIBONA

- The ZAZIBONA process is collaboration between national medicines regulatory authorities (NMRAs) in Botswana, Namibia, Zambia, and Zimbabwe. These are four neighboring countries in Southern Africa which have a combined population of around 34 million. This process may be extended to include participation by other interested SADC Member States.

The vision of the ZAZIBONA process is:

- A region in which good-quality medicines are available to all those who need them;
- significantly reduce time taken to grant marketing authorisation in the individual countries; and
- Efficient utilization of resources within regional national regulatory through work sharing.

- The ZAZIBONA collaboration does not represent the replacement of the need to submit applications for registration in participating countries in line with national requirements. However, as described in this document, in order to facilitate cooperation among ZAZIBONA authorities, certain modifications are expected. Although there is close collaboration on assessments and inspections, final national registration decisions are the responsibility of individual participating authorities.

African Medicines Regulatory Harmonization (AMRH)

Many African countries have insufficient legal foundations and/or lack the technical expertise to support adequate or efficient regulatory reviews. AMRH was created "to establish and improve standards and requirements related to the regulation of and access to safe, high-quality medicines for the African population." AMRH, which has been led by African health ministers since 2014, aims to achieve its objective by overseeing "the registration of a selected list of medicines and coordinate regional harmonisation systems on the continent."

World Health Organization (WHO)

Established in 1948, WHO is an agency of the United Nations (UN), whose mission is to provide global leadership in the area of public health. WHO has staff in more than 150 country offices with regional offices covering the WHO African Region, WHO Region of the Americas, WHO South-East Asia Region, WHO European Region, WHO Eastern Mediterranean Region and WHO Western Pacific Region.48 WHO employees work in the areas of:

- health systems
- noncommunicable diseases
- promoting health through the lifecycle
- communicable diseases
- preparedness, surveillance and response
- corporate services

WHO is involved with a number of harmonization initiatives including, but not limited to ICH, IMDRF, AHWP

Initiation of harmonization in GCC countries *(20, 21)*

- The seven Gulf Cooperation Council (GCC) States (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen) also took the initiative after the EU centralized procedure to improve patients' access to safe and effective medicines in the GCC Region by The GCC Central Drug Registration (GCC-DR) Committee is composed of two members from each of the seven countries.

- The procedure is carried out by selecting two authorities alphabetically to review a registration dossier. However, all the GCC authorities are equally responsible for evaluating the quality, safety and efficacy of medicines and therefore all the seven states are provided with copies of the product registration dossier for their individual assessments.

Summary

The urgent requirement to rationalize & harmonize regulation was impelled by instance of rising cost of Health care, R & D & need to meet the public requirement to approach for the safe & efficacious treatments to patient in need. ICH committee has given priority to harmonize the format of reporting data for qualities. Advancement in terms of quality of Pharmaceutical products can be achieved through Quality management system that confirms to international quality standards like FDA, MHRA, WHO GMP & in terms of technology can be achieved improving local R & D capabilities & ICH Q 11- QbD (Quality by design).

The international protection of IPR assumes far greater importance today because of the huge amount of cross-border business. As such, the role of organizations, such as the World Intellectual Property Organization, becomes very important in order to seek harmony amongst national laws. The international treaties have formulated rules in relation to areas such as international filing, disclosure, and compulsory licensing. These treaties and conventions contribute to the process of harmonization of patent laws.

Due to the advancement in Information technology, regulatory authorities from regulated countries throughout the globe started to accept data in electronic format either in eCTD/ NeeS.

Regulatory requirements have evolved over time to protect the public from unsafe products. Regulations vary worldwide based on a number of factors, including product type, risk profile and maturity of the regulatory system. The requirements' number and variations globally can create challenges in navigating the regulatory environment. However, several groups comprising representatives from government, industry and academia have been established for the purpose of initiating harmonization objectives.

Hence, experts from all regions should go with harmonization of regulatory requirements throughout the globe & produce a single harmonized marketing application for registration of drug product/API that will used by all health authorities worldwide.

Table 2 Comparative study of registration requirements for ASEAN countries

Country	Philippines	Vietnam	Malaysia	Thailand	Myanmar
Regulatory Authority	Philippines – Food and Drug Administration	Vietnam – Ministry of Health	National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia.	Thailand – Food and Drug Administration	Myanmar– Food and Drug Administration
Regulatory authority Flag					
Authority Website	https://www.fda.gov.ph/	https://moh.gov.vn/web/ministry-of-health	https://npra.gov.my/index.php/en/	https://www.fda.moph.go.th/sites/fda_en/Pages/Main.aspx	https://www.fda.gov.mm/
Dossier Format	ACTD	ACTD	Country specific-Quest system	ACTD	ACTD
Dossier language	English and/ or official native language	English and/ or official native language	English and/ or official native language	English and/ or official native language	English and/ or official native language
COPP	Notary-Hard copy	Legalized-Hard copy	Only original	Legalized-Hard copy	Notary-Hard copy
Manufacturing license	Required	Legalized-Hard copy	Required	Required	Notary-Hard copy
Registration Validity	5yrs	5yrs	5yrs	5yrs	5yrs
Registration Time	12 to 36 months	12 to 36 months	12 to 36 months	24 to 48 months	24 to 48 months
Registration fees	USD 7000	USD 1500	New Product: 4000 to 5000 RM Generic: 2200 to 3000 RM	New Product: THB 155,000 – 395,000 Generic: THB 39,000 – 59,000	Myanmar- USD 1000
Plant Inspection fees	Desktop Audit-10100 Php Request for Inspection:1010 Php For Inspection: USD 7000	Only Product registration, No plant Inspection	20,000 RM	Modern drug Import and Sale: 11000 THB Modern drug import: THB 38,000-88,000	Only Product registration, No plant Inspection
Inspection/ Audit	Accepts FDA/EU/PICs Approval for FP site.	Accepts FDA/EU/PICs Approval for FP site.	Accepts FDA/EU/PICs Approval for FP site.	Accepts FDA/EU/PICs Approval for FP site.	Accepts FDA/EU/PICs Approval for FP site.
Stability Zone	Zone IV b (30/75)	Zone IV b (30/75)	Zone IV b (30/75)	Zone IV b (30/75)	Zone IV b (30/75)
No. of submission Batches	2 batches-for IR dosage forms 3 Batches-For ER/PR/CR dosage forms	3 Batches compulsory	2 batches-for IR dosage forms 3 Batches-For ER/PR/CR dosage forms	3 Batches compulsory	3 Batches compulsory

Country	Philippines	Vietnam	Malaysia	Thailand	Myanmar
Minimum Stability data	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months
Stability guideline reference	ASEAN	ASEAN	ASEAN	ASEAN	ASEAN
Samples Required	5 packs in a representative pack styles	5 packs in a representative pack styles	Not required	5 packs in a representative pack styles	Myanmar- 500 tablets 50 vials,ampoules,tubes and syrup
Labeling Requirement	Refer GMP Detail description of product. Should be in English and local language. Pack insert req.	Compulsory in Vietnamese language along with English language	Reference product label need to follow for preparation of PI. Some of the requirements must follow in Malaysia language i.e. Storage condition	Compulsory in Thai language along with English language	Regular English artworks are acceptable
BE Study (for Generic)	Against US /EU/Australia reference drug in any Country except Thailand, where BE to be done locally. PE to be done against local reference product in some countries.PE ≠ TE (not necessary)	Any US/EU/Brazil study acceptable	Against US /EU/Australia reference drug in any Country except Thailand, where BE to be done locally. PE to be done against local reference product in some countries.PE ≠ TE (not necessary)	Need to perform locally	Any US/EU/Brazil study acceptable
Number of subjects	12	12	12	12	12
Age	18-55 yrs	18-55 yrs	18-55 yrs	18-55 yrs	18-55 yrs
Gender	Male / female	Male / female	Male / female	Male / female	Male / female
Clinical Study Design	Single dose Two period, two- sequence crossover study	Single dose Two period, two- sequence crossover study	Single dose Two period, two- sequence crossover study	Single dose Two period, two- sequence crossover study	Single dose Two period, two- sequence crossover study
Acceptance criteria C_{max}%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%
Sampling Time interval	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours
Fasting study	Subject should be fast for at least 8 hours or overnight prior to administration of drug.	Subject should be fast for at least 8 hours or overnight prior to administration of drug.	Subject should be fast for at least 8 hours or overnight prior to administration of drug.	Subject should be fast for at least 8 hours or overnight prior to administration of drug.	Subject should be fast for at least 8 hours or overnight prior to administration of drug.
Fed study	Subject should start meal 30 minutes prior to administration. Eat whole meal (Composition under SmPC) within 30 minutes.	Subject should start meal 30 minutes prior to administration. Eat whole meal (Composition under SmPC) within 30 minutes.	Subject should start meal 30 minutes prior to administration. Eat whole meal (Composition under SmPC) within 30 minutes.	Subject should start meal 30 minutes prior to administration. Eat whole meal (Composition under SmPC) within 30 minutes.	Subject should start meal 30 minutes prior to administration. Eat whole meal (Composition under SmPC) within 30 minutes.
Major holdup	Obtaining Certificate of Pharmaceutical product (CPP) may delay the process	Obtaining Certificate of Pharmaceutical product (CPP) may delay the process	Obtaining Certificate of Pharmaceutical product (CPP) may delay the process	Obtaining Certificate of Pharmaceutical product (CPP) may delay the process	Obtaining Certificate of Pharmaceutical product (CPP) may delay the process

Country	Philippines	Vietnam	Malaysia	Thailand	Myanmar
Major holdup	These countries accept branding of the products. Other than CPP, it also takes time to obtain Manufacturing license, GMP and CPP with registered brand name from the COO. Administrative procedures in individual countries, time delay in Approval.	These countries accept branding of the products. Other than CPP, it also takes time to obtain Manufacturing license, GMP and CPP with registered brand name from the COO. Administrative procedures in individual countries, time delay in Approval.	These countries accept branding of the products. Other than CPP, it also takes time to obtain Manufacturing license, GMP and CPP with registered brand name from the COO. Administrative procedures in individual countries, time delay in Approval.	These countries accept branding of the products. Other than CPP, it also takes time to obtain Manufacturing license, GMP and CPP with registered brand name from the COO. Administrative procedures in individual countries, time delay in Approval.	These countries accept branding of the products. Other than CPP, it also takes time to obtain Manufacturing license, GMP and CPP with registered brand name from the COO. Administrative procedures in individual countries, time delay in Approval.
Any other Requirement	CDP requirement compulsory 3+QC media as per WHO Guidance Usually ASEAN countries accept BE studies from US/ EU innovators. However need to provide information on innovator available in ASEAN countries (comparison: wrt brand name, API and excipients, Mfg site/ marketing information) to minimize the cost of MMDP against innovators available in these regions. BCS based biowaivers are acceptable for Class-I and Class-III eligibility molecules as per WHO Guidance	Vietnamese language mode for dossier submission FSC and Not of standard certificate are required in Part-I of the dossier. Usually ASEAN countries accept BE studies from US/ EU innovators. However need to provide information on innovator available in ASEAN countries (comparison: wrt brand name, API and excipients, Mfg site/ marketing information) to minimize the cost of MMDP against innovators available in these regions.	Quest System CDP requirement compulsory 3+QC media as per WHO Guidance Usually ASEAN countries accept BE studies from US/ EU innovators. However need to provide information on innovator available in ASEAN countries (comparison: wrt brand name, API and excipients, Mfg site/ marketing information) to minimize the cost of MMDP against innovators available in these regions. BCS based biowaivers are acceptable for Class-I and Class-III eligibility molecules as per WHO Guidance Samples are not required for dossier submissions Malaysia Application can be used to file for Brunei registration as there are minor changes with respect to registration no and application form only	Not all products require local BE in Thailand. Every time they will release list of products exempted from local BE studies and will accept US/EU studies to speed up the registration and market availability Usually ASEAN countries accept BE studies from US/ EU innovators. However need to provide information on innovator available in ASEAN countries (comparison: wrt brand name, API and excipients, Mfg site/ marketing information) to minimize the cost of MMDP against innovators available in these regions. BCS based biowaivers are acceptable for Class-I and Class-III eligibility molecules as per WHO Guidance and information need to provide in Thai FDA application format.	Dossier need to send in hard copy and all original documents need to send with sign and stamp with blue ink. Samples are required in actual pack at the time of dossier submission. Usually Myanmar relies on Malaysian approval. It's better to submit Myanmar Registration along with Malaysian approval copy. Usually ASEAN countries accept BE studies from US/ EU innovators. However need to provide information on innovator available in ASEAN countries (comparison: wrt brand name, API and excipients, Mfg site/ marketing information) to minimize the cost of MMDP against innovators available in these regions.

Table 3 Comparative study of registration requirements for African countries

Country	Kenya	Uganda	Tanzania	Zimbabwe	Ghana	Botswana	Zambia	Ethiopia
Name of Regulatory Authority	Pharmacy & Poisons Board	National Drug Authority	Tanzania Drug & Medical Device Authority	Medicine Control Authority of Zimbabwe	Food and Drug Authority	Botswana Medicines Regulatory Authority	Zambia Medicines Regulatory Authority	Ethiopian Food and Drug Authority
Abbreviation	PPB	NDA	TMDA	MCAZ	FDA	BOMRA	ZAMRA	EFDA
Regulatory Flag								
Authority Website	https://www.pharmacyboardkenya.org/	https://www.nda.or.ug/	https://www.tmda.go.tz/	https://www.mcaz.co.zw/	http://www.fdaghana.gov.gh/	https://www.bomra.co.bw/	https://www.zamra.co.zm/	http://www.fmhaca.gov.et/
Dossier Format	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD
Dossier Language	English	English	English	English	English	English	English	English
COPP	Required From Country of Origin • As per WHO Format	Required From Country of Origin • As per WHO Format	COPP is not Mandatory	Required From Country of Origin or from any other stringent country where product is registered • As per WHO Format	Required From Country of Origin • As per WHO Format	Required From Country of Origin • As per WHO Format	Required From Country of Origin • As per WHO Format	Required From Country of Origin • As per WHO Format Legalized from Ethiopian Embassy
Manufacturing license	Required	Required	Required	Required	Required	Required	Required	Required, Legalized from Ethiopian Embassy
Registration certificate	Life time validity Annually retention	Life time validity Annually retention	5 years	Life time validity Annually retention	3 years	5 years	Life time validity	4 years
Registration time	12-18 months	12-18 months	12-18 months	12-18 months	12-18 months	12-18 months	12-18 months	12-18 months

Country	Kenya	Uganda	Tanzania	Zimbabwe	Ghana	Botswana	Zambia	Ethiopia
Registration fee	1000 USD	Import: 2000 USD Import drug repacking: 300 USD Retention: 500 usd Variation Major: 700 USD Minor: 400 USD Notification: 100 USD Fast track New approval: 10000 USD Major variation: 2100 USD Minor variation: 1200 USD	Medicine: 2000 USD Biological: 3500 USD Retention: 300 USD Variation: Major: 1000 USD Minor: 300 USD Fast track: Double of above	Generic: 2500 USD Line extension: 1500 USD Re-instatement: 750 USD	240 USD per Annum NCE 360 USD per Annum	Screening fee: 500 BL Re-Screening fee: 500 BL Complementary medicine: 5000 BL Line extension of complementary medicine: 1000 BL Renewal: 4000 BL Annual fee: 400 BL Variation: 500 BL Expedite review: 10000 BL	Generic: 2000 USD NCE: 2800 USD Biological: 2800 USD Abridged Application: 1700 USD Annual Retention: 800 USD Renewal: Generic: 1200 USD NCE: 1200 USD Biological: 1200 USD Variation Major: 500 USD Minor: 100 USD	***Dossier Evolution*** Generic:1500 Birr Generic with BE: 2100 Birr New Medicine: 2100 Birr ***Re-Registration & Major Variation*** Generic:1000 Birr Generic with BE: 10000 Birr New Medicine: 1000 Birr ***Minor Variation*** Generic:750 Birr Generic with BE: 750 Birr New Medicine: 750 Birr
Plant Inspection	Required	Required	Required	Required	Required	Required	Required	Required
Plant inspection fee	4000 USD	Upto 5 product line: within EAC:5000 USD Outside EAC: 6000 USD Outside Africa: 8000 USD Additional product line: Within EAC: 1000 USD per line Outside EAC: 1500 USD per line Outside Africa: 200 USD per line GMP on fast track Within EAC: 300% of inspection fee	East Africa: 4000 USD Rest of Africa: 5000 USD Asia: 6000 USD Europe: 7000 USD America: 8000 USD	Sterile: 3000 USD Premise with more than 3 dosage form (excluding Sterile): 2500 USD Upto 3 dosage form: 2000 USD ***Renewal:*** Sterile: 2000 USD Premise with more than 3 dosage form (excluding Sterile): 1500 USD Upto 3 dosage form: 1200 USD	Africa: 4000 USD Outside Africa: 7500 USD	SADC: 3500 USD Rest of Africa: 5000 USD ASIA: 6500 USD Rest of world: 7000 USD Desk Review: 3500 USD	Southern Africa: 3500 USD Rest of Africa: 5000 USD Far East/Asia: 6500 USD Europe, America & Australia: 7500 USD Addition Production line: 1500 USD Desktop review: 3500 USD	African countries except EAC: 6930 USD Middle east countries: 7750 USD Far east countries: 7400 USD Desktop audit of SRA approved plant: 3500 USD European company not approved by SRA: 7750 USD North American company not approved by SRA: 8950 USD

Country	Kenya	Uganda	Tanzania	Zimbabwe	Ghana	Botswana	Zambia	Ethiopia
Stability zone	Zone IVa	Zone IVa	Zone IVb	Zone IVb	Zone IVb	Zone III	Zone II	Zone Iva
No. of submission Batches	3 consecutive batches for Process validation (PV)in section 3.2.P.3.5 – for all proposed batch size 3 consecutive commercial batch required for all proposed batch size and stability data of 3 PV batches in section 3.2.P.8 – for all proposed batch size	3 consecutive batches for Process validation (PV)in section 3.2.P.3.5 – for all proposed batch size 3 consecutive commercial batch required for all proposed batch size and stability data of 3 PV batches in section 3.2.P.8 – for all proposed batch size	3 consecutive batches for Process validation (PV)in section 3.2.P.3.5 – for all proposed batch size 3 consecutive commercial batch required for all proposed batch size and stability data of 3 PV batches in section 3.2.P.8 – for all proposed batch size	3 consecutive batches for Process validation (PV)in section 3.2.P.3.5 – for all proposed batch size 3 consecutive commercial batch required for all proposed batch size and stability data of 3 PV batches in section 3.2.P.8 – for all proposed batch size	3 consecutive batches for Process validation (PV)in section 3.2.P.3.5 – for all proposed batch size 3 consecutive commercial batch required for all proposed batch size and stability data of 3 PV batches in section 3.2.P.8 – for all proposed batch size	3 consecutive batches for Process validation (PV)in section 3.2.P.3.5 – for all proposed batch size 3 consecutive commercial batch required for all proposed batch size and stability data of 3 PV batches in section 3.2.P.8 – for all proposed batch size	3 consecutive batches for Process validation (PV)in section 3.2.P.3.5 – for all proposed batch size 3 consecutive commercial batch required for all proposed batch size and stability data of 3 PV batches in section 3.2.P.8 – for all proposed batch size	3 consecutive batches for Process validation (PV)in section 3.2.P.3.5 – for all proposed batch size 3 consecutive commercial batch required for all proposed batch size and stability data of 3 PV batches in section 3.2.P.8 – for all proposed batch size
Minimum Stability data	Accelerated stability – 6 months Long Term Stability – 12 months	Accelerated stability – 6 months Long Term Stability – 12 months	Accelerated stability – 6 months Long Term Stability – 12 months	Accelerated stability – 6 months Long Term Stability – 12 months	Accelerated stability – 6 months Long Term Stability – 12 months	Accelerated stability – 6 months Long Term Stability – 12 months	Accelerated stability – 6 months Long Term Stability – 12 months	Accelerated stability – 6 months Long Term Stability – 12 months
Stability guideline reference	National & ICH	National & ICH	National & ICH	National & ICH	National & ICH	National & ICH	National & ICH	National & ICH
Samples Required	Yes	Yes	Not Mandatory	Yes	Not Mandatory	Not Mandatory	Not Mandatory	Not Mandatory
Labelling Requirement	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
BE Study (for Generic)	The comparative BE study profile is required against US/ EU innovator is carried out.	The comparative BE study profile is required against US/ EU innovator is carried out.	The comparative BE study profile is required against US/ EU innovator is carried out.	The comparative BE study profile is required against US/ EU innovator is carried out.	The comparative BE study profile is required against US/ EU innovator is carried out.	The comparative BE study profile is required against US/ EU innovator is carried out.	The comparative BE study profile is required against US/ EU innovator is carried out.	The comparative BE study profile is required against US/ EU innovator is carried out.

Table 4 Comparative study of registration requirements for CIS countries

Country	Ukraine	Russia	Uzbekistan	Kazakhstan	Belarus
Name of Regulatory Authority	State service of Ukraine on Medicines and Drug Control	Ministry of health of the Russian Federation.	Ministry of Health of Republic of Uzbekistan	The Ministry of Health of the Republic of Kazakhstan	The Ministry of Health of the Republic of Belarus
Regulatory Flag					
Authority Website	www.dls.giv.ua	https://minzdrav.gov.ru/ Clinical study - www.grls.rosminzdrav.ru Quality– www.regmed.ru	www.minzdrav.uz	https://www.gov.kz/memleket/entities/dsm?lang=en	http://minzdrav.gov.by/
Dossier Format	CTD	CTD	CTD	CTD	CTD
Dossier Language	Authentic Dossier translation in local language needed	Authentic Dossier translation in local language needed	Authentic Dossier translation in local language needed	Authentic Dossier translation in local language needed	Authentic Dossier translation in local language needed
COPP	Required • From Country of Origin • As per WHO Format • Notarized	Required • From Country of Origin • As per WHO Format • Notarized	Required • From Country of Origin • As per WHO Format • Notarized	Required • From Country of Origin • As per WHO Format • Notarized	Required • From Country of Origin • As per WHO Format • Notarized
Manufacturing license	Required	Required	Required	Required	Required
Registration certificate validity	First registration is for 5 year Renewal – Life time	First registration is for 5 year Renewal – Life time	First registration is for 5 year Renewal – Life time	5 Years	First registration is for 5 year Renewal – Life time
Registration time	12 months	12 months	8 – 12 months	8 – 12 months	12 months
Registration fee	8,000 USD	For Clinical - 75,000 Rubles For Quality – 225,000 Rubles	9,500 USD	5,000 USD	7,000 USD
Plant Inspection	Required First product included in Ukrainian GMP then product dossier needs to file in authority.	Required First product included in Ukrainian GMP then product dossier needs to file in authority.	Not Required	Not Required	Required First product included in Ukrainian GMP then product dossier needs to file in authority.
Plant inspection fee	15,000 USD	30,000 USD	Not applicable	Not applicable	10,000 USD
Stability	Zone II; 25˚C/60% RH	Zone II; 25˚C/60% RH	Zone II; 25˚C/60% RH	Zone II; 25˚C/60% RH	Zone II; 25˚C/60% RH
No. of submission Batches	-3 consecutive batches for Process validation in section 3.2.P.3.5 – for all proposed batch size; Latest 3 consecutive commercial batch required in 3.2.P.5.4 – for all proposed batch size; stability data of PV batches in section 3.2.P.8 – for all proposed batch size	-3 consecutive batches for Process validation in section 3.2.P.3.5 – for all proposed batch size -Latest 3 consecutive commercial batch required in 3.2.P.5.4 – for all proposed batch size stability data of PV batches in section 3.2.P.8 – for all proposed batch size	-3 consecutive batches for Process validation in section 3.2.P.3.5 – for all proposed batch size -Latest 3 consecutive commercial batch required in 3.2.P.5.4 – for all proposed batch size stability data of PV batches in section 3.2.P.8 – for all proposed batch size	-3 consecutive batches for Process validation in section 3.2.P.3.5 – for all proposed batch size -Latest 3 consecutive commercial batch required in 3.2.P.5.4 – for all proposed batch size stability data of PV batches in section 3.2.P.8 – for all proposed batch size	-3 consecutive batches for Process validation in section 3.2.P.3.5 – for all proposed batch size ;-Latest 3 consecutive commercial batch required in 3.2.P.5.4 – for all proposed batch size stability data of PV batches in section 3.2.P.8 – for all proposed batch size

Country	Ukraine	Russia	Uzbekistan	Kazakhstan	Belarus
Minimum Stability data	Accelerated stability – 6 months Long Term Stability – 12 months	Accelerated stability – 6 months Long Term Stability – 12 months	Accelerated stability – 6 months Long Term Stability – 12 months	Accelerated stability – 6 months Long Term Stability – 12 months	Accelerated stability – 6 months Long Term Stability – 12 months
Stability guideline reference	National & ICH	National & ICH	National & ICH	National & ICH	National & ICH
Samples Required	Yes	Required for clinical study on Russia population and for toxicity study	Yes	Yes	Yes
Labeling Requirement	Yes, Label must be approved from MOH prior to commercialization Local language Artwork is required.	Yes, Label must be approved from MOH prior to commercialization Local language Artwork is required.	Yes, Label must be approved from MOH prior to commercialization. Local language Artwork is required.	Yes, Label must be approved from MOH prior to commercialization. Local language Artwork is required.	Yes, Label must be approved from MOH prior to commercialization. Local language Artwork is required.
BE Study (for Generic)	The comparative BE study profile is required against US/ EU innovator is carried out.	BE need on Russia population **Pharmaceutical Equivalence:** 1) Comparative release profile similarity in multimedia. 2) Bioequivalence study against any innovator under fasting and fed condition unless waiver is justified. **Waivers:** BE waiver for products on market for more than 20 years	The comparative BE study profile is required against US/ EU innovator is carried out.	The comparative BE study profile is required against US/ EU innovator is carried out.	The comparative BE study profile is required against US/ EU innovator is carried out.
Other requirement	1. Normative Documents (ND) is very critical documents in CIS countries 2. Normative Documents (ND) includes composition of finished product (FP), Specification of release and shelf life of FP, Analytical procedure of FP, Information on storage condition, information of manufacturer etc. 3. Risk Management Plan need for submission 4. PSUR report needed for renewal 5. Pharmacovigilance System Master File (PSMF) needed for application 6. Qualified Person responsible for Pharmacovigilance (QPPV) needed for applicable in CIS countries 7. Expert declaration & CV needed (Quality, Clinical and Non-Clinical expert) 8. Plant inspection includes review of registration product includes variation and proposed product. 9. EAEU (Eurasian Economic Union) includes Russia, Belarus, Kazakhstan, Armenia and Kyrgyzstan. 10. EAEU is the centralized system for registration of drug in Russia, Belarus, Kazakhstan, Armenia and Kyrgyzstan. 11. Manufacturing plant must have GMP certificate from EAEU member then manufacturer can file registration dossier.				

Table 5. Comparative study of registration requirements for LATAM

Country	Brazil	Mexico	Chile	Peru	Colombia
Regulatory Authority	Brazil - ANVISA (Agência National de Vigilância Sanitária)	COFEPRIS (Comision Federal Para la Proteccion Contra Riesgos Sanitarios)	ISP (Instituto de Salud Pública)	DIGEMID (Dirección General de Medicamentos, Insumos y Drogas)	INVIMA (Instituto Nacional de Vigilancia de Medicamentos y Alimentos)
Regulatory authority Flag					
Authority Website	http://antigo.anvisa.gov.br/en/english	https://www.gob.mx/cofepris	https://www.ispch.cl/	https://www.digemid.minsa.gob.pe/	https://www.invima.gov.co/
Dossier Format	Regional	Regional	Regional	Regional	Regional
Dossier language	Portugese	Spanish	Spanish	Spanish	Spanish
GMP, COPP	Legalized/ Apostille	Legalized/ Apostille	Legalized/ Apostille	Legalized/ Apostille	Legalized/ Apostille
Manufacturing license	Required	Required	Required	Required	Required
Registration Validity	5yrs	5yrs	5yrs	5 years	5 years
Registration Time	24 months	Mexico- 24 months	12 -18 months SRA products: 6-8months	Peru-12 months	Colombia:12 -18 months
Registration fees	USD 2700	USD 4100	USD 1000 to 1600, depending on the type of product and procedure	USD 400 to USD 1,200	USD 5200 (with BE) USD 3200 (without BE)
Inspection/ Audit	Required. Can be waived if site approved by FDA (US), EU health authorities, Health Canada, Pharmaceutical and Medical Devices Agency (Japan), TGA (Australia).	Required. Can be waived if site approved by FDA (US), EU health authorities, Health Canada, Pharmaceutical and Medical Devices Agency (Japan), TGA (Australia) & ANVISA (Brazil).	Not required	Not required	Required. GMP certificate issued by USA, Canada, Germany, Switzerland, France, U.K., Denmark, Netherlands, Sweden, Japan, and Norway, or issued by the F.D.A., WHO / PAHO, and EMA are also recognized.
Stability Zone	Brazil – Zone IVb	Mexico- Zone II	Chile - II	Peru – Zone IVb	Colombia – Zone IVb
No. of submission Batches	3 pilot scale	3 pilot scale	3 pilot scale	3 pilot scale	3 pilot scale
Minimum Stability data	LT-6-12 months ACC- 6 months	LT-6-12 months ACC- 6 months	LT-6-12 months ACC- 6 months	LT-6-12 months ACC- 6 months	LT-6-12 months ACC- 6 months

Country	Brazil	Mexico	Chile	Peru	Colombia
Stability guideline reference	ANVISA and ICH	COFEPRIS and ICH	ICH	ICH	ICH
Samples Required	No	No	No	No	No
Labelling Requirement	As per local regulation. Mock ups required for submission. Local registration number	As per local regulation. Mock ups required for submission. Local registration number	As per local regulation. Mock ups required for submission. Local registration number	As per local regulation. Mock ups required for submission. Local registration number	As per local regulation. Mock ups required for submission. Local registration number
BE Study (for Generic)	Brazil: Against Brazil reference drug in any CRO approved by ANVISA. PE to be done in Brazil **Pharmaceutical Equivalence:** 1) Comparative release profile Similarity in multimedia. 2) Bioequivalence study against Brazilian reference product under fasting condition unless waiver is Justified.	Mexico: Against Mexican reference product, in Mexico Only.	Chile: BE for US/ EU/ Brazil /Mexico is normally accepted. CRO should be approved by INVIMA or SRA country/ies.	Not required	Generally not required. List of products require BE: Study for US/ EU/ Brazil /Mexico can be extended and generally accepted. CRO should be approved by INVIMA or SRA country/ies.
Number of subjects	24	Not specified. To be assessed based on incident of disease.	24	24	24
Age	18-55 yrs	18-55 yrs	18-55 yrs	18-55 yrs	18-55 yrs
Gender	Subjects of one sex are include	Subjects of one sex are include	Subjects of one sex are include	Subjects of one sex are include	Subjects of one sex are include
Clinical Study Design	Two-period, two- sequence crossover or four way crossover	Two-period, two- sequence crossover or four way crossover	Two-period, two- sequence crossover or four way crossover	Two-period, two- sequence crossover or four way crossover	Two-period, two- sequence crossover or four way crossover
Acceptance criteria C_{max}%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%
Major holdup	BE studies need to perform with Brazil Innovator product.	BE to be done in Mexico against Mexico innovator product	Legalizations, Translations	Legalizations, Translations	Legalizations, Translations
Any other Requirement	- Method validations for API and FP need to meet ANVISA requirements. - API stability need to be in Zone IVb - Chromatograms for all the time points during stability **BE Waivers:** Brazilian Health Surveillance Agency. 2011. Resolution n°37, 03 August 2011. Provides information about biowaiver and relative bioavailability/bioequivalence study substitution	- API site/s must have GMP certificate. -When clinical studies are multicentric, Mexican population must be included. - If Mexican patients are not included in the clinical trials: New Molecule Committee will request pharmacokinetic studies to prove safety and efficacy in Mexican population.	--	--	--

Table 6. Comparative study of registration requirements for GCC

Country	Saudi Arabia	Qatar	Oman	Bahrain	UAE
Regulatory Authority & Flag	Saudi Arabia Drug Authority-SFDA	Ministry of Public Health Organisation, Qatar	Ministry of Health-Muscat ,Oman	National Health Regulatory Authority-Bahrain	United Arab Emirates, Ministry of Health & prevention, Dubai
Authority Website	https://www.sfda.gov.sa/en	https://www.moph.gov.qa/english/Pages/default.aspx	https://www.moh.gov.om/en/home	https://www.nhra.bh/	https://mohap.gov.ae/en/home
Dossier Format	eCTD	eCTD	eCTD	eCTD	eCTD
Dossier language	English (PIL-Arabic)	English (PIL-Arabic)	English (PIL-Arabic)	English (PIL-Arabic)	English (PIL-Arabic)
COPP	Legalized	Legalized	Legalized	Legalized	legalized
Manufacturing license	Required	Required	Required	Required	Required
Registration Validity	Five years	Five years	Five years	Five years	Five years
Registration Time	24-36 months	24-36 months	24-36 months	24-36 months	24-36 months
Registration fees#	Saudi Arabia: -USD 10,666	Qatar–USD 250	Oman –USD 160	Bahrain -160 USD	UAE- AED 7100
Plant Inspection fees	80,000 SAR	No fees are required for this service	Yes	RM 20,000.00	AED 50000
Inspection/ Audit	Audit by GCC member countries of FP site	Audit by GCC member countries of FP site	Audit by Oman FDA	Audit by GCC member countries of FP site	Audit by GCC member countries of FP site
Stability Zone	Zone IV a	Zone IV a	Zone IV a	Zone IV a	Zone IV a
No. of submission Batches	3 pilot scale /Commercial	3 pilot scale /Commercial	3 pilot scale /Commercial	3 pilot scale /Commercial	3 pilot scale /Commercial
Minimum Stability data	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months
Stability guideline reference	ICH / WHO-GMP /GCC	ICH / WHO-GMP /GCC	ICH / WHO-GMP /GCC	ICH / WHO-GMP /GCC	ICH / WHO-GMP /GCC
Samples Required	17 Sample Pack of finish product Lab analysis—5 Pack + 2 vial working standard	7 Sample Pack of finish product Lab analysis—5 Pack + 2 vial working standard	5 Sample Pack of finish product Lab analysis—5 Pack + 2 vial working standard	5 Sample Pack of finish product Lab analysis—5 Pack + 2 vial working standard	7 Sample Pack of finish product Lab analysis—5 Pack + 2 vial working standard

Country	Saudi Arabia	Qatar	Oman	Bahrain	UAE
Labeling Requirement * @	Arabic Translation artwork and Detail description of product is required according to stability studies.	Arabic Translation artwork and Detail description of product is required according to stability studies	Arabic Translation artwork and Detail description of product is required according to stability studies	Arabic Translation artwork and detail description of product is required according to stability studies GS1 2D Data Matrix barcode along with Human Readable Interpretation (HRI) of the encoded barcode must be printed on secondary packaging. Artwork Must be register at Brand sync software @ Bahrain	Arabic Translation artwork and Detail description of product is required according to stability studies
	* Information presented on the labeling must be designed to maximize the safe and effective use of the medicine. Labelling covers both outer packaging and inner packaging.				
	@ Generic products are required to follow innovator leaflet and summary of product characteristic.				
BE Study (for Generic)	Bioavailability/Bioequivalence study site should either be approved with Gulf Health Council (GHC) or from approved from any of the two competent authorities: WHO, USFDA, Health Canada, TGA, MHRA & EMA.				
Number of subjects	12-24	12-24	12-24	12-24	12-24
Age	18-50 yrs.	18-50 yrs.	18-50 yrs.	18-50 yrs.	18-50 yrs.
Gender	If females are include effect of gender different and menstrual cycle are examined	If females are include effect of gender different and menstrual cycle are examined	If females are include effect of gender different and menstrual cycle are examined	If females are include effect of gender different and menstrual cycle are examined	If females are include effect of gender different and menstrual cycle are examined
Clinical Study Design	Single dose Two period, two- sequence crossover study	Single dose Two period, two- sequence crossover study	Single dose Two period, two- sequence crossover study	Single dose 2-period, 2-treatment, 2-sequence, crossover study	Single dose, Two period two-sequence crossover study
Acceptance criteria C_{max}%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%
Sampling Time interval	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours
Fasting study	Subject should be fast for at least 10 hours which is continue for at least 4 hour post dose	-do-	-do-	-do-	-do-
Fed study	Drugs are having effect with food. Fed studies are carried in such case.	-do-	-do-	-do-	-do-
Major holdup	+ Delay in registrations. Administrative issues with local regulatory and country laws. + ECTD Submission confirmation from FDA is taking time				
	+ Saudi Arabia – bioequivalence and stability studies are not as per GCC guideline. + Delay in Pharmacovigilance study and clearance	+ Qatar – working standard must be required with samples	+ Oman – working standard must be required at the time of lab analysis	+ Bahrain – working standard must be required with samples	+ UAE– bioequivalence and stability studies are not as per GCC guideline.
Any other Requirement	+ The data requirement for each application will differ, depending on the drug submission type. However, all required data should be in accordance with GHC & ICH Common Technical Document (CTD) in eCTD format.; + Declaration for Excipients, diluent, pork free, Alcohol free, Country of origin must be required for all GCC countries. # Registration fees to be applicable to country specific rules and Laws. It may be varying to country wise and time to time up gradation.				

Table 7 Comparative study of registration requirements for different **Asia countries**

Country	India	Nepal	Bhutan	Sri Lanka	Hong Kong
Regulatory Authority	India-Central Drugs Standard Control Organization (CDSCO)	Nepal-Department of Drug Administration(DDA)	Bhutan: Drug Regulatory Authority(DRA)	Sri-Lanka: National Medicines Regulatory Authority (NMRA)	Pharmacy and Poisons Board of Hong Kong
Regulatory authority Flag					
Authority Website	cdsco.gov.in	http://www.dda.gov.np/	https://dra.gov.bt/	https://nmra.gov.lk/index.php?lang=en	https://www.ppbhk.org.hk
Dossier Format	Country specific	Country specific	Country specific	CTD	Country specific
Dossier language	English	English	English	English	English
COPP	Legalized	Notarized	Notarized	Original	Notarized
Manufacturing license	Required	Notarized	Notarized	Required	Notarized
Registration Validity	3 Years	Nepal-2yrs	Bhutan-3yrs	Srilanka-5yrs	Honkong-5 yrs
Registration Time	6-12 months	3-18 months	3-12 months	12-24 months	6-12 months
Registration fees	5000 USD per product+10000 USD for Site registration	INR200	INR1650 (150 at the time of Application+1500 at the time of registration)	USD 2000 + USD 2000 for site registration	USD 2470
Plant Inspection fees	5000 USD if require	Nepal-N/A	Bhutan-N/A	Sri-Lanka-N/A	Hong Kong-NA
Inspection/ Audit	Accept FDA/EU/PICs approval for FP site.	Accept FDA/EU/PICs approval for FP site.	Accept FDA/EU/PICs approval for FP site.	Accept FDA/EU/PICs approval for FP site.	Accept FDA/EU/PICs approval for FP site.
Stability Zone	Zone IVa and Zone IVb	Zone IVb and IVa	Zone IVa and Zone IVb	Zone IVa	Zone IVa
No. of submission Batches	3 primary batches, out of which min 2 are Pilot scale	3 primary batches, out of which min 2 are Pilot scale	3 primary batches, out of which min 2 are Pilot scale	3 primary batches, Pilot scale	3 primary batches, out of which min 2 are Pilot scale
Minimum Stability data	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months	LT-complete shelf life ACC- 6 months	LT-12 months ACC- 6 months
Stability guideline reference	ICH/WHO	ICH/WHO	ICH/WHO	ICH/WHO	ICH/WHO
Samples Required	50 units minimum or equivalent units for single time analysis	100 Tab/Cap, 15-Dry Syrup/Liquid/Tube, 25-Powder (Oral and External), Injection/Solution/Suspension(40-up to or less then 10ml, 20- 10 to 100 ml, 16- more than 100 ml)	Tab/Cap-50, Oral liquids -6 (15-30ml)/4(more than 30ml), Injection -25, Cream/ointment-10	3 samples of finished product in original container .Tab:50 Ointment, tubes, powders: 5 no.	NA.

Country	India	Nepal	Bhutan	Sri Lanka	Hong Kong
Labeling Requirement	Packaging and product details with package insert. If without carton internal product should contain all the information. Text matter as per D&C act	Packaging and product details with package insert. If without carton internal product should contain all the information. Text matter as per D&C act(India)	Packaging and product details with package insert. If without carton internal product should contain all the information.	Packaging and product details with package insert. If without carton internal product should contain all the information.	Packaging and product details with package insert. If without carton internal product should contain all the information.
BE Study (for Generic)	Reference drug in any Country where BE to be done locally. Ethic committee permission required, BE done on local patients	Reference drug in any Country where BE to be done locally. Ethic committee permission required, BE done on local patients	Reference drug in any Country where BE to be done locally. Ethic committee permission required, BE done on local patients	Reference drug in any Country where BE to be done locally. Ethic committee permission required, BE done on local patients	Reference drug in any Country where BE to be done locally. Ethic committee permission required, BE done on local patients
Number of subjects	16	12	12	12	12
Age	18-44 yrs	18-40 yrs	18-40 yrs	18-40 yrs	18-40 yrs
Gender	Both female and male	Both female and male	Both female and male	Both female and male	Both female and male
Clinical Study Design	Local study with pivotal design. Could be qualified for Waiver in case of unmet medical need.	Studies conducted in China and India can be accepted. Study with pivotal design. Could be qualified for Waiver in case of unmet medical need. Phase I and Phase III (at least 100 patients each arm is Part of global trial). Major impact on dev/registration time	Studies conducted in China and India can be accepted. Study with pivotal design. Could be qualified for Waiver in case of unmet medical need. Phase I and Phase III (at least 100 patients each arm is Part of global trial). Major impact on dev/registration time	Studies conducted in China and India can be accepted. Study with pivotal design. Could be qualified for Waiver in case of unmet medical need. Phase I and Phase III (at least 100 patients each arm is Part of global trial). Major impact on dev/registration time	Studies conducted in China and India can be accepted. Study with pivotal design. Could be qualified for Waiver in case of unmet medical need. Phase I and Phase III (at least 100 patients each arm is Part of global trial). Major impact on dev/ registration time
Acceptance criteria C_{max}%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%
Sampling Time interval	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours
Fasting study	Subject should be fast where SmPC studies at least 10 hour before administration of drug.	Subject should be fast where SmPC studies at least 10 hour before administration of drug.	Subject should be fast where SmPC studies at least 10 hour before administration of drug.	Subject should be fast where SmPC studies at least 10 hour before administration of drug.	Subject should be fast where SmPC studies at least 10 hour before administration of drug.
Fed study	Subject should start meal 30 minutes prior to administration. Eat whole meal (Composition under SmPC) within 30 minutes. (29)	Subject should start meal 30 minutes prior to administration. Eat whole meal (Composition under SmPC) within 30 minutes. (29)	Subject should start meal 30 minutes prior to administration. Eat whole meal (Composition under SmPC) within 30 minutes. (29)	Subject should start meal 30 minutes prior to administration. Eat whole meal (Composition under SmPC) within 30 minutes. (29)	Subject should start meal 30 minutes prior to administration. Eat whole meal (Composition under SmPC) within 30 minutes. (29)
Major holdup	Regulatory delays, Require strong IP laws, Better training is needed	Regulatory delays, Require strong IP laws, Better training is needed	Regulatory delays, Require strong IP laws, Better training is needed	Regulatory delays, Require strong IP laws, Better training is needed	Regulatory delays, Require strong IP laws, Better training is needed

6. Summary and Discussion

Table 3 Comparative study of registration requirements for different Emerging market

Countries group	ASEAN	GCC (22)	LATAM (2)	CIS	Asia Pacific (except ASEAN)	African Countries
Regulatory Authority	Philippines – FDA Thailand – FDA Vietnam – MOH Malaysia: NPRA Myanmar -FDA Board of Authority (23, 24)	Saudi Arabia –SFDA Qatar - MPHO Bahrain - NHRA Oman – MOH UAE –DHA	Brazil – ANVISA Mexico – COFEPRIS Chile – ISP Peru – DIGEMID Colombia - INVIMA	Ukraine- MDC Russia-MOH Uzbekistan- MOH Kazakhstan- MOH Belarus- MOH	India- CDSCO Nepal- DDA Bhutan- DRA Sri Lanka- NMRA Hong Kong- PPB	Kenya-PPB Uganda – NDA Tanzania-TMDA Zimbabwe- MCAZ Ghana – FDA Botswana-BOMRA Zambia-ZAMRA Ethiopia-EFDA
Regulatory authority Flag	Country group is harmonized	Country group is harmonized	Country group is not harmonized	Country group is harmonized	Country group is not harmonized	Country group is harmonized to some extent: African Medicines Regulatory Harmonization (AMRH)
Dossier Format	ACTD	CTD/eCTD	Regional	CTD	Country specific LK–SPC -CTD	CTD
Dossier language	English and/ or official native language	English (PIL-Arabic)	BR-Portugal MX/CL/PE/CO – Spanish	Authentic Dossier translation in local language needed	English	English
COPP	Notary &/Legalized	Legalized	Legalized/ Apostille	Required -From Country of Origin -As per WHO Format -Notarized	Notarized &Legalized & Original	Required From Country of Origin As per WHO Format
Manufacturing license	Required	Required	Required	Required	Notarized & Required	Required
Registration Validity	5yrs	5yrs	5yrs	5yrs Renewal – Life time	LK–SPC/HK -5yrs BT/IN - 3yrs NP -2yrs	Life time validity Annually retention TZ/BW- 5 yrs ET- 5 yrs GH-3 yrs
Registration Time	PH, VT, MY: 12-36 months TH & MM: 24 to 48 months	24-36 months	BR/MX - 24 months CL/CO - 12 -18 months CL - SRA products: 6-8months PE - 12 months	UA/RU/BL-12 months UZ/KZ-8 – 12 months	IN/HK- 6-12 months NP- 3-18 months BT- 3-12 months LK–SPC - 12-24 months	12-18 months

Countries group	ASEAN	GCC (22)	LATAM (2)	CIS	Asia Pacific (except ASEAN)	African Countries
Registration fees	Philippines –15,150 Php Renewal 10,100 Php	Saudi Arabia:-USD 10,666	BR-USD 2700	UA-8,000 USD	IN- 5000 USD per product+10000 USD for Site registration	Kenya-1000 USD UG- Import: 2000 USD New approval: 10000 USD
	Vietnam-USD 1500	Qatar–USD 250	MX-USD 4100	RU- For Clinical - 75,000 Rubles For Quality – 225,000 Rubles	NP- INR200	TZ- Medicine: 2000 USD ZW- Generic: 2500 USD Re-instatement: 750 USD
	Malaysia-	Oman –USD 160	CL- USD 1000 to 1600, depending on the type of product and procedure	UZ-9,500 USD	BT- INR1650 (150 at the time of Application+1500 at the time of registration)	GH- 240 USD per Annum BW- Screening fee: 500 BL Complementary medicine: 5000 BL
	Thailand-	Bahrain -160 USD	PE-USD 400 to USD 1,200	KZ-5,000 USD	LK–SPC- USD 2000 + USD 2000 for site registration	ZM- Generic: 2000 USD NCE: 2800 USD Abridged Application: 1700 USD
	Myanmar- USD1000	UAE- AED 7100	CO-USD 5200 (with BE) USD 3200 (without BE	BL-7,000 USD	HK- USD 2470	ET- ***Dossier Evolution*** Generic:1500 Birr Generic with BE: 2100 Birr
Plant Inspection fees	PH- Desktop Audit-15000 Php TH: Modern drug Import and Sale: 11000 THB Modern drug import: THB 38,000-88,000 MY:20,000 RM MM & VT: Only Product registration, No plant Inspection	SFDA: 80,000 SAR NPRA: RM 20,000.00 UAE: AED 50000	Can be waived if site approved by FDA (US), EU health authorities, Health Canada, Pharmaceutical and Medical Devices Agency (Japan), TGA (Australia) & ANVISA (Brazil).	UA-15,000 USD RU-30,000 USD BL-10,000 USD	IN- 5000 USD if require	IN- 4000 USD ET- African countries except EAC: 6930 USD Middle east countries: 7750 USD Far east countries: 7400 USD Desktop audit of SRA approved plant: 3500 USD
Inspection/ Audit	Accepts FDA/EU/PICs Approval for FP site.	Audit by GCC member countries of FP site	Major countries do audit.(Brazil, Mexico, Colombia)	Required First product included in Ukrainian GMP then product dossier needs to file in authority	Accept FDA/EU/PICs approval for FP site.	Required

Countries group	**ASEAN**	**GCC (22)**	**LATAM (2)**	**CIS**	**Asia Pacific (except ASEAN)**	**African Countries**
Stability Zone	Zone IV b (30/75)	Zone IV a	BR/PE/CO– Zone IVb Mexico- Zone II Chile - II	Uzbekistan- Zone II Russia- Zone II Ukraine- Zone II Kazakhstan- Zone II Belarus- Zone II	India, Bhutan,Nepal: Zone IVa and Zone IVb SL & Hong Kong: Zone IVa	Zone IVa and Zone IVb
No. of submission Batches	3 Batches-For ER/PR/CR dosage forms	3 Batches-For SA/QA/OM/BH/UAE dosage forms	3 Batches-For BR/MX/CL/PE/CO dosage forms	3 consecutive batches for Process validation (PV)in section 3.2.P.3.5 – for all proposed batch size 3 consecutive commercial batch required for all proposed batch size and stability data of 3 PV batches in section 3.2.P.8 – for all proposed batch size	3 primary batches, out of which min 2 are Pilot scale	3 consecutive batches for Process validation (PV)in section 3.2.P.3.5 – for all proposed batch size 3 consecutive commercial batch required for all proposed batch size and stability data of 3 PV batches in section 3.2.P.8 – for all proposed batch size
Minimum Stability data	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months	LT-6-12 months ACC- 6 months	LT-6-12 months ACC- 6 months	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months
Stability guideline reference	ASEAN	ICH / WHO-GMP /GCC	ICH	National & ICH	ICH/WHO	National & ICH
Samples Required	5 unit pack for all countries, Myanmar- 500 tablets 50vials,ampoules,tubes and syrup	Lab analysis—5 Pack + 2 vial working standard. SA-17 Sample Pack of finish product QA/UAE-7 Sample Pack of finish product OM/BH- 5 Sample Pack of finish product	No	RU-Required for clinical study on Russia population and for toxicity study Other countries - YES	IN-50 units minimum or equivalent units for single time analysis. NP-100 Tab/Cap, 15-Dry Syrup/Liquid/Tube, 25-Powder (Oral and External); Injection/ Solution/ Suspension(40-up to or less then 10ml, 20- 10 to 100 ml, 16- more than 100 ml) BT- Tab/Cap-50, Oral liquids:4 to 6; Injection - 25, Cream/ointment-10 LK–SPC- 3 samples ;Tab:50; Ointment, tubes, powders: 5 no.	Not Mandatory & required

Countries group	ASEAN	GCC (22)	LATAM (2)	CIS	Asia Pacific (except ASEAN)	African Countries
Labeling Requirement	Refer GMP Detail description of product. Should be in English and local language. Pack insert req.	Arabic Translation artwork and Detail description of product is required according to stability studies	As per local regulation. Mock ups required for submission. Local registration number	Yes, Label must be approved from MOH prior to commercialization. Local language Artwork is required.	Packaging and product details with package insert. If without carton internal product should contain all the information.	Yes
BE Study (for Generic)	Against US /EU/Australia reference drug in any Country except Thailand, where BE to be done locally. PE to be done against local reference product in some countries.PE ≠ TE (not necessary)	Bioavailability/Bioequivalence study site should either be approved with Gulf Health Council (GHC) or from approved from any of the two competent authorities: WHO, USFDA, Health Canada, TGA, MHRA & EMA.	Brazil: Against Brazil reference drug in any CRO approved by ANVISA. PE to be done in Brazil Mexico: Against Mexican reference. CL/CO- The BE for Brazil /Mexico is normally accepted. CRO should be approved by INVIMA or SRA country/ies.	The comparative BE study profile is required against US/ EU innovator is carried out.	Reference drug in any Country where BE to be done locally. Ethic committee permission required, BE done on local patients	The comparative BE study profile is required against US/ EU innovator is carried out.
Number of subjects	12	12-24	24	12-24	12	12
Age	18-55 yrs	18-50 yrs	18-55 yrs	18-55yrs	18-40 yrs	18-55 yrs
Gender	Male / female	If females are include effect of gender different and menstrual cycle are examined	Subjects of one sex are include	Male/female	Both female and male	Male / female
Clinical Study Design	Single dose Two period, two- sequence crossover study	Single dose Two period, two- sequence crossover study	Two-period, two-sequence crossover or four way crossover	Russian patients in phase III or local trial. Local BE study For generics is required.	India- Local study with pivotal design. Could be qualified for Waiver in case of unmet medical need. Other countries- Studies conducted in China and India can be accepted. Study with pivotal design. Could be qualified for Waiver in case of unmet medical need.	Two-period, two-sequence crossover or four way crossover. (26)

Countries group	ASEAN	GCC (22)	LATAM (2)	CIS	Asia Pacific (except ASEAN)	African Countries
Clinical Study Design					Phase I and Phase III (at least 100 patients each arm is Part of global trial). Major impact on dev/registration time	
Acceptance criteria C_{max}%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%	Should be 80%- 125%	Should be 75%-113%
Sampling Time interval	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours	3-4 sample to achieve C_{max} (0 to infinite) within 72 hours
Fasting study	Subject should be fast for at least 8 hours or overnight prior to administration of drug.	Subject should be fast for at least 10 hours which is continue for at least 4 hour post dose	Subject should be fast for at least 10 hours which is continue for at least 2 hour post dose	Subject should be fast for at least 8 hours or overnight prior to administration of drug.	Subject should be fast where SmPC studies at least 10 hour before administration of drug.	Prior to drug administration and should be standardized and supervised.
Fed study	Subject should start meal 30 minutes prior to administration. Eat whole meal (Composition under SmPC) within 30 minutes.	Drugs are having effect with food. Fed studies are carried in such case.	Drugs having prolonged effect only required fed study (27)	Drug having immediate release effect does not required fed study while other depend on type of drug high fat or high calories meal are given to the subjects. (28)	Subject should start meal 30 minutes prior to administration. Eat whole meal (Composition under SmPC) within 30 minutes. (29)	Meals taken are as per specification (composition) and time administration depends on type of study.
Major holdup	Obtaining Certificate of Pharmaceutical product (CPP) may delay the process, These countries accept branding of the products. Other than CPP, it also takes time to obtain Manufacturing license, GMP and CPP with registered brand name from the COO. Administrative procedures in individual countries, time delay in Approval.	Delay in registrations. Administrative issues with local regulatory and country laws. ECTD Submission confirmation from FDA is taking time SA/UAE– bioequivalence and stability studies are not as per GCC guideline. Delay in Pharmacovigilance study. QA//BH-working standard must be required with samples. OM- working standard must be required at the time of lab analysis	Legalizations, Translations, BR/MX- BE to be done in MX against MX innovator product & BR innovator product	Legalizations, Translations, Fund, Registration cost, Document and time delay	Regulatory delays, Require strong IP laws, Better training is needed	Lack of resources and qualified staff. (30)

7. Conclusion

A comparison against the registration requirements for different group of emerging countries has been done to understand the difference in regulatory requirements of different countries. Since the globally market has different drug approval procedures, it is important for the manufacturers, especially the generic companies, to carefully assess the market interest, cost of development, target regions, regulatory requirements before the development of drugs.

It was evaluated that due to lack of harmonization in emerging markets countries which lead to unnecessary duplication of work and waste of valuable resources and eventually increase drug lag. By having a view at the different regulatory environment, it is impossible to get global market harmonization and approval at same time and launch in all the regions at once. Hence, it is necessary to understand and define the clear regulatory strategy by looking at the target regions, different patent terms and its extension, various application possibilities, data requirements, deadlines for launching products to be marketed in different regions. This eliminates unnecessary studies, minimizes the delay in drug approvals and subsequent launch, and reduces overall cost of research and development.

Export market demands good quality dossier which can be generated through systematic Formulation Development and having the knowledge of guidelines of respective country. The proper planning and execution of Formulation development will help in quality dossier & in answering queries from Regulatory authorities.

Since the world is divided in Regulated and Emerging market the drug approval procedures with the technical data became difficult to register in those countries thus, it is important especially for the generic manufacturers, to carefully judge the market need different patent terms and its extension, various application possibilities, data requirements, potential timeline for marketing launch in different regions Development Cost, target regions, & regulatory requirements before the development of drugs. Hence it is critical to plan and co-ordinate all the activities for successful launch of product in the market on time.

Although the requirements are harmonized in regulated countries by CTD (Common technical document) filing, yet others have enormous diversity in requirements. ICH brought regulatory authorities and pharmaceutical industries of Europe, Japan and US together for various aspects of drug registration should bring some requirement to be harmonized there in emerging market, so that the drug approval process becomes easy and duplication of work and waste of valuable resources avoided. By examining these markets individually, it would be easier to target the areas where they can specifically improve their regulatory barriers, thus leading the way for the emerging markets.

Finally, there needs to be a reassertion that the purpose of drug registration is to protect the public health, not to facilitate profit of pharmaceutical manufacturers. Registration should be seen as a critical step in ensuring access to safe and effective medicinal product.

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Conflict of Interest

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