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Review Article

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) 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 also explains a brief about different regulatory requirement for Registration of drug product in Emerging market and comparative data for registration of dossier application in Emerging market.

Keywords: Dossier Registration, Emerging Markets, GCC, ASEAN, Common technical document (CTD), WHO, Harmonization, WAEMU, 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 different for different 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 markets 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. e.g., China is deemed to be the largest pharmaceutical market after the United States by 2020.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 semi regulated market like India and China uses the CTD format. (2)

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

1. **Regulated Market:** US, EU (UK, Germany, France, Ireland, and Sweden etc.), Japan, Canada, Australia, New Zealand, and South Africa.
2. **Semi regulated Market:**

(a) **Asia:** (Sri-Lanka, India, Bangladesh, China, Pakistan, Bhutan, Nepal).

(b) **ASEAN**: 10 Countries group - Philippines, Vietnam Singapore, Malaysia, Thailand, Indonesia, Laos, Cambodia, Brunei Darussalam, and Myanmar.

(c) **African countries:** (Algeria, Zambia, Ethiopia, Ghana, Kenya, Malawi, Mozambique, Namibia, Nigeria, Sierra Leone, Tanzania, Zimbabwe etc.)

(d) **Middle East countries:** (Gulf Co-operation Council countries i.e. Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE)

(e) **Latin America** (Mexico, Brazil, Panama, Peru, Guatemala, Argentina, Chile, Dominican Republic)

(f) **CIS:** (common wealth of independent states): Russia, Ukraine, Post Soviet States (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kirghizstan, Moldova, Tajikistan, Turkmenistan, and Uzbekistan etc.)

Table1 Emerging Market global share (4)

Tier	Markets	Global share %
1	China, Japan	24
2	Brazil, Russia, India	8
3	Algeria, Egypt, Nigeria, Saudi Arabia, South Africa, Indonesia, Pakistan, Thailand, Vietnam, Poland, Romania, Turkey, Ukraine, Argentina, Colombia, Mexico, Venezuela	10

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 Asia Pacific market is expected to grow from USD 187 billion in 2009 to nearly USD 275 billion in 2013 and has developed to a great extend till date, at a CAGR of more than 13%. The main reason behind this is, due to low cost availability of generic medicines, rising income, growth of business and health insurance schemes. (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. 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. The Latin American markets are forecast to grow at a robust 10% CAGR from USD 37.6 billion in 2009 to USD 62

billion in 2012, due to changes in regulatory policies and increased manufacturing base for generic drugs by the US drug makers. Strong economic growth in these countries will drive lucrative growth in these markets. (1)

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. 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 2. (1)

Table 2 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 only required
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

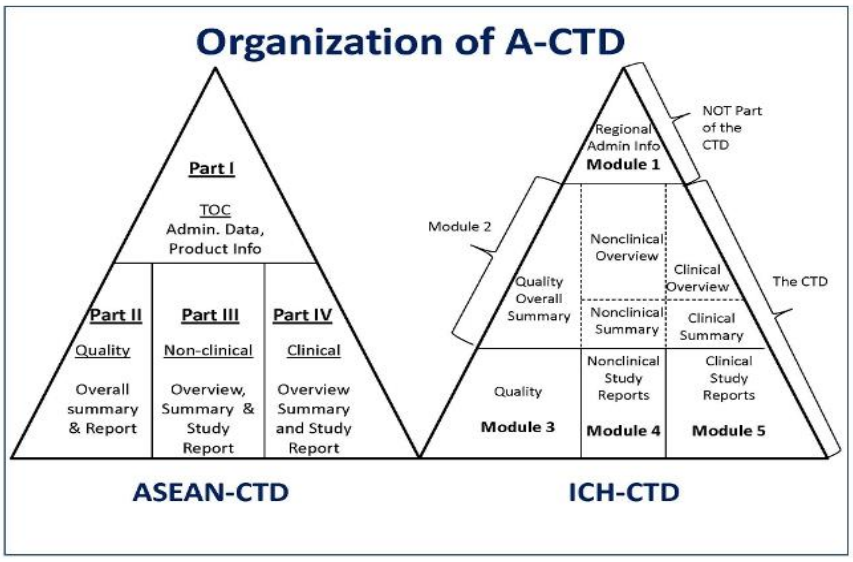

Figure 1. Organization of A-CTD and CTD

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. (6)

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.
- Health authorities have limited resources in emerging markets.
- Lack of effective legislation to allow use of so-called 'TRIPs flexibilities' such as compulsory licensing.
- They require local patients in clinical trials B.E study to participate. Patient may/may not participate in Phase I
- 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.
- Lack of Electronic submission and validation.
- 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)

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)

Strategy for Success *(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.
- Training programme and incentives for agency staff.
- 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.

3. Registration Requirements for Emerging Markets (2)

Administrative Documents

- Certificate of Pharmaceutical Product

Product Permission

- Manufacturing License
- cGMP Certificate
- Import /Export Certificate
- Artwork (Carton, Label & Package Leaflet)

Chemistry, Manufacturing & control documents

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

- 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.

Regulatory Filing Process

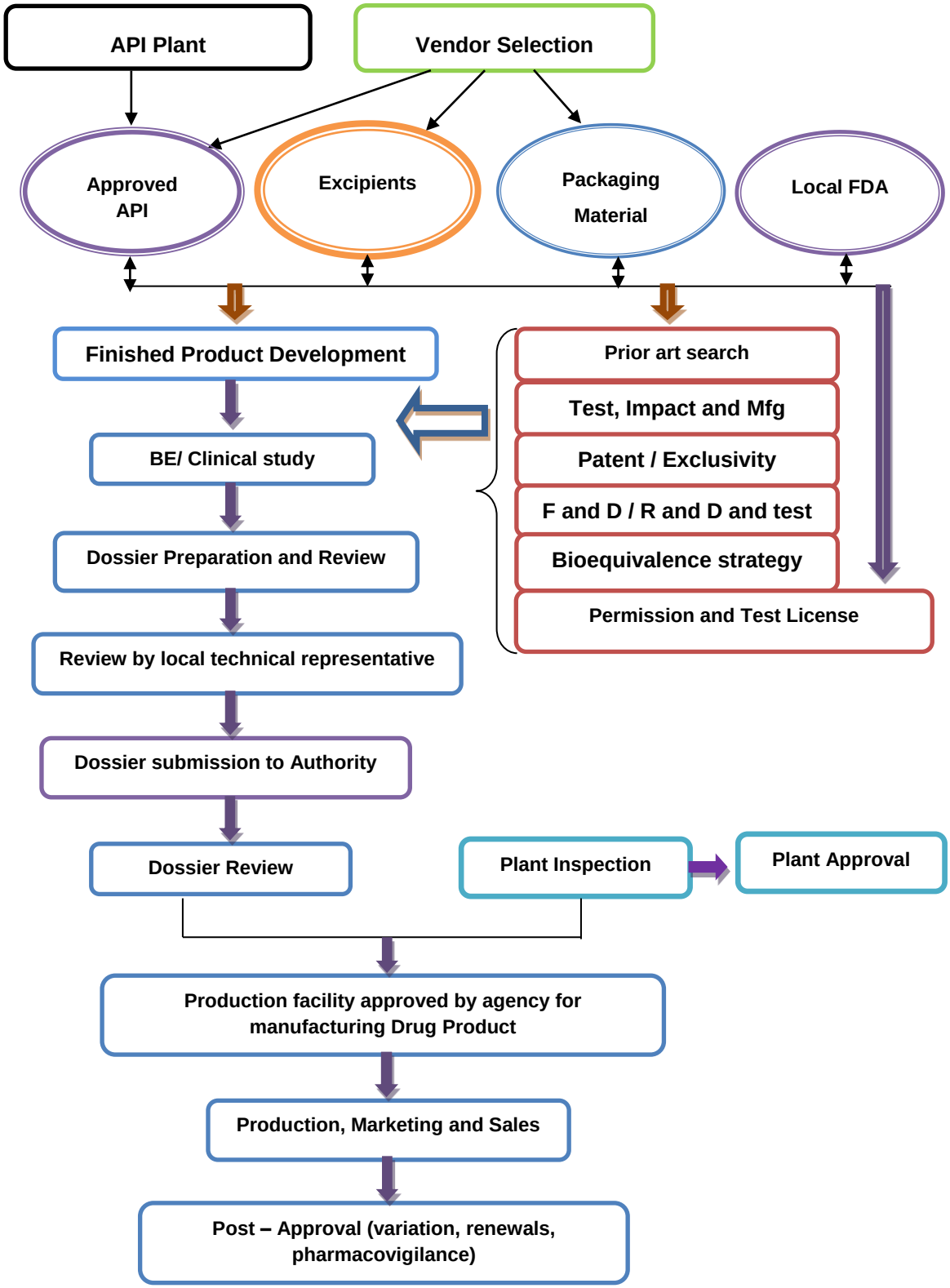

Figure 2. Dossier Application filing for Generic Drug Product in Emerging market

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.

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 should be as per 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.
- 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 report of validation of analytical method are not mandatory.
- Verification of non-compendia method needs to be validated by agency if required.
- The assay limits at release should have been revised to 95-105% 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.
- 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.
- 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.
- 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, 1, 2, 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, but no application for change of product labeling (MiV-PA2). Company has to provide the requirements as per ASEAN Variation Guideline for Pharmaceutical Products and pay the corresponding fee.
- 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 API and Excipients.
- 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 read 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.
- 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.

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.

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

- 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. The first harmonization was initiated by the Association of South East Asian Nations (ASEAN) in 1967. 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)

Effect of ASEAN harmonization of guidelines on pharmaceutical market

Harmonization of regulatory guidelines by ASEAN countries has a huge impact on drug approval as well as pharmaceutical market. Harmonization procedure for drug approval and registration has a positive effect on pharmaceutical market in this group of countries. The total trade of countries has been increase by implementing CTD format for registration of drug and has strong position in global level. (19)

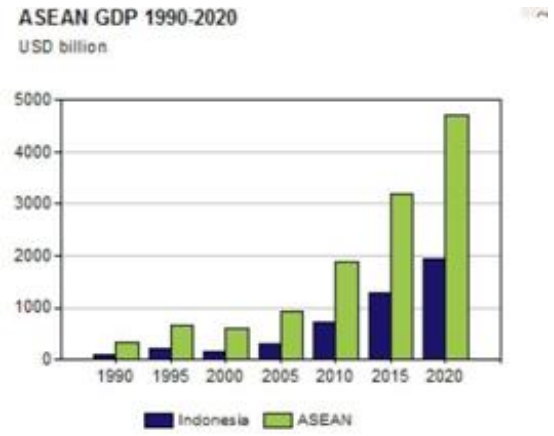

Figure 3. ASEAN GDP from 1990-2020

Initiation of harmonization in African countries *(17)*

- The Harmonization of Drug Endorsement in Africa (HHMA) initiative, led by the African Union (AU), made it possible to formulate proposals for the harmonization of pharmaceutical regulations within the different economic community's sub-regional level.
- In western African countries the process of harmonization has been carried out by western African economic monetary union (WAEMU) which constitutes the legal basis for the process of harmonization of pharmaceutical regulations in this union.
- In Central Africa, the process of harmonization is essentially carried out by the Economic Community of Central African States (CEMAC), which after a situational analysis in prompted the adoption
- It must therefore be concluded that, in both regions, the process of harmonizing pharmaceutical regulations is dynamic and not yet completed. The different African sub-regions need to draw inspiration from each other's specific experiences to optimize the process of harmonizing pharmaceutical regulations in Africa.

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.
- The pharmaceutical market in GCC countries exceeds 6 billion USD. This market is growing rapidly and is expected to reach around 10 billion USD by 2020. The aforesaid meeting, the first ever of its kind in that sector, is aimed at achieving several objectives including to create a forum for the exchange of ideas and dialogue among pharmaceutical companies in GCC, propose a multi-client study that will address the needs of the pharmaceutical industry in the region, and identify the need for establishing a pharmaceutical trade association for GCC producers.
- 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 (Electronic common technical document)/ NeeS (Non eCTD electronic submission).
- 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.
- 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).
- 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.

6. Summary and Discussion

Table 3 Comparative study of registration requirements for different emerging markets

Countries group	ASEAN	GCC (22)	LATAM (2)	CIS	Asia Pacific (except ASEAN)	African Countries
Regulatory Authority	Philippines – FDA Vietnam - MOH Myanmar -FDA Board of Authority (23, 24)	Saudi Arabia -SFDA Oman – MOH UAE –DHA	Brazil - ANVISA Agência National de Vigilância Sanitária	Russia- Federal Service on Supervision in the Sphere of Public Health Services and Social Development (Roszdravnadzor).	India- CDSCO Central Drug Standard Control Organization China – CFDA Nepal-Department of Drug Administration	Kenya-Pharmacy and poisons board Ghana – FDA Uganda- National Drug Authority African medicines regulatory authority.(MRAs)
Regulatory authority Flag			Country group is not harmonized		Country group is not harmonized	Country group is not harmonized
Dossier Format	ACTD	CTD/eCTD	Country specific (CTD and eCTD in Chile Other: Country specific)	Country specific (Resemble CTD Other: Country specific)	Country specific (India: Resemble CTD Other: Country specific)	Country specific (Resemble CTD Other: Country specific)
Dossier language	English and/ or official native language	Arabic language and English	Brazil-Portugal Chile and Peru –Spanish	English	English	English
COPP	Legalized	Legalized	Country Specific Legalized	Legalized	Legalized	Legalized
Manufacturing license	Required	Required	Required	Required	Required	Required
Registration Validity	Philippines – 3yrs	Saudi Arabia -5yrs	Brazil-5yrs	Russia-5yrs	Srilanka-5yrs	Kenya-5yrs
	Vietnam-5yrs	Oman –5yrs	Peru-5yrs	Ukraine-5yrs	Bhutan-3yrs	Ghana –3yrs
	Myanmar-5yrs	UAE -5 yrs	Chile-5yrs	Kazakistan-5yrs	Nepal-2yrs	Uganda-5yrs
Registration Time	12 months	24-36 months	Peru-7 days Brazil- 24 months Chile-6 -18 months.	Russia-6-24 months Belarus-180 days	8-24 months	15-18 months
Registration fees	Philippines –USD 7000	Saudi Arabia:-USD 10,666	Brazil-USD2700	Russia-30000 rubles	Sri-Lanka-USD110	Kenya-USD 1000
	Vietnam-USD 1500	Oman –USD160	Peru-USD2500		Bhutan-INR1650	Ghana –USD3600
	Myanmar- USD1000	UAE –USD 2500	Chile-USD 2,231	Kazakhstan-2000USD	Nepal-INR1875	Uganda-USD1250
Plant Inspection fees	Philippines – N/A	Saudi Arabia –YES	Brazil-N/A	Russia-70,000-1,00,000USD	Sri-Lanka-N/A	Kenya-USD5000
	Vietnam-N/A	Oman –YES	Peru-N/A	Ukraine-N/A	Bhutan-N/A	Ghana –N/A
	Myanmar-N/A	UAE –YES	Chile-N/A	Kazakhstan-20,000USD	Nepal-N/A	Uganda-N/A

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)	Audit by CIS member countries of FP site	Accept FDA/EU/PICs approval for FP site.	Accept FDA/EU/PICs approval for FP site.
Stability Zone	Zone IV b	Zone IV a	Zone IVa and IVb Brazil – Zone IVb Mexico- Zone II Chile - ZoneIVa	Uzbekistan- Zone II Russia- Zone II Ukraine- Zone II Tajikistan- Zone II	Zone IVa and Zone IVb India and Nepal –Zone IVb Sri-Lanka and Bhutan– Zone IVa	Kenya and Uganda – Zone IVa Ghana – Zone IVb
No. of submission Batches	3 pilot scale	3 pilot scale	3 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, out of which min 2 are Pilot scale
Minimum Stability data	LT-12 months ACC- 6 months	LT-12 months ACC- 6 months	LT-6-12 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	GCC	ANVISA and ICH	ICH	ICH/WHO	WHO/OMS
Samples Required	Myanmar- 500 tablets 50vials,ampoules,tubes and syrup	17 samples of finish product are submitted.	2 samples of finished product in original container	3 samples required	3 samples of finished product in original container .Tab:50 Ointment, tubes, powders: 5 no.	Kenya- 8 packs Uganda – 5packs
Labeling Requirement	Refer GMP Detail description of product. Should be in English and local language. Pack insert req.	Detail description of product is required according to stability studies.	As per local regulation. Mock ups required for submission. Local registration number and pharmacist detail (25)	Braille code is required on labeling with detail information of drug formulation.	Packaging and product details with package insert. If without carton internal product should contain all the information.	Uganda-Detail description of the product should be mentioned in both English and local language. Should be approved by NDA
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)	Against US /EU/Australia reference drug in any Country.	Brazil: Against Brazil reference drug in any CRO approved by ANVISA. PE to be done in Brazil Mexico: Against Mexican reference, in Mexico Only. Others: The BE for Brazil /Mexico is normally accepted.	Reference drug in any Country where BE to be done locally. PE to be done against local reference product in some countries.	Reference drug in any Country where BE to be done locally. PE to be done against local reference product in some countries. Published Literature data eg. Sri Lanka, Nepal, Bangladesh	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	Subjects of one sex are	Male/female	Both female and male	Male / female

		of gender different and menstrual cycle are examined	include			
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. China- Phase I and Phase III (at least 100 patients each arm is Part of global trial). Major impact on dev/registration time	Two-period, two-sequence crossover or four way crossover. (26)
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, Administrative procedures in individual countries, time delay in Approval.	Delay in registrations. Administrative issues with local regulatory and country laws. Saudi Arabia – bioequivalence and stability studies are not as per GCC guideline. Delay in Pharmacovigilance study.	Legalizations, Translations, GMP audits, local requirements, time delay	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 judge the difference in regulatory requirements of different countries. Since the world is divided in the 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.

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 semi regulated markets 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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