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COMPARATIVE STUDY OF KEY REGULATORY REQUIREMENTS FOR THE SUBMISSION OF DOSSIERS TO USFDA, WHO, SINGAPORE (ASEAN) WITH EMPHASIS ON APPROVAL OF GENERIC DRUGS

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ABSTRACT

The regulatory requirements of various countries of the world vary from each other. Therefore, it is challenging for the companies to develop a single drug which can be simultaneously submitted in all the countries for approval. The role of the regulatory authorities is to ensure the quality, safety, and efficacy of all medicines in circulation in their country. **Background:** The purpose of the present study was to compare dossier requirements of different countries like USFDA (United States Food and Drug Administration), WHO (World Health Organization) and ASEAN. **Methods:** Collection of the following dossier format of USFDA (United States Food and Drug Administration), WHO (World Health Organization) and ASEAN (Association of South East Asian Nation) Identifying the critical and major differences among those three dossiers related to technical document. Comparison of common technical document for those critical and major differences among three countries (USFDA, WHO & ASEAN) **Results:** After pooling all the information and data that was collected in due course of time of the research, was made into comparative chart format where it is shown that among group of countries (like WHO, ASEAN) and also these guidelines were compared with regulated market USFDA. It was found that, there was less harmonization and various differences in dossier requirements. **Discussion:** Regulations may create costs as well as benefits and may produce unintended reactivity effects, such as defensive practice. Efficient regulations can be defined as those where total benefits exceed total costs. Regulatory

reviews and communication with the applicants will be facilitated by a standard document of common elements. In addition, exchange of regulatory information between Regulatory Authorities will be simplified. **Conclusion:** Regulation creates, limits, or constrains a right, creates or limits a duty, or allocates a responsibility. Regulation can take many forms: legal restrictions promulgated by a government authority, contractual obligations that bind many parties, self-regulation by an industry such as through a trade association, social regulation, and co-regulation, third-party regulation, and certification, accreditation or market regulation.

KEYWORDS: Regulatory requirements, USFDA, WHO, ASEAN, HSA.

INTRODUCTION

Regulatory Network: Drug Regulatory Affairs regulate pharmaceutical business through designing appropriate laws (rules) and enforcing the same so that the drugs meeting the highest standards of Quality are brought into the Global Trade. Rules and regulations are being prepared considering Global, Regional and National pharmaceutical trade as well as necessity of the drugs based on patient population.[1] Most of the national guidelines for drug development and marketing authorization application are defined based on Global and Regional Harmonized guidelines.

To understand it better, let's see

-Global Regulatory Network

-Regional Regulatory Network

-National Regulatory Network.

Figure1. Worldwide regulatory network

METHODOLOGY

USFDA: USA is the major market for the pharmaceutical industry. Drug registration in USA is majorly categorized by two types of applications: New Drug Application (NDA) and

Abbreviated New Drug Application (ANDA). ANDA is filled for generic drug products; those require marketing authorization and are of exact or close copies of already approved drugs. The evolution of the current drug regulatory system in USA is recognized globally as the gold standard for drug safety and efficacy.[2]

WHO: The World Health Organization (WHO) provides United Nations agencies with advice on the acceptability, in principle, of pharmaceutical products for procurement by such agencies. This activity of WHO aims to facilitate access to priority essential medicines that meet WHO-recommended norms and standards of acceptable quality.[3] WHO undertakes a comprehensive evaluation of the quality of pharmaceutical products, based on information submitted by the manufacturers of such products or other applicants, and on an inspection of the corresponding manufacturing facilities and clinical sites this is done through a standardized procedure which is based on WHO-recommended quality standards.

SINGAPORE (ASEAN): The ASEAN was established on 8 August 1967 in Bangkok by the five original member countries (Indonesia, Malaysia, Philippines, Singapore and Thailand). Meanwhile five additional countries (Brunei, Darussalam, Vietnam, Laos, Myanmar and Cambodia) were joined ASEAN in the later stage.

Among the member countries, only Singapore-this has the most Advanced R&D and regulatory capability in the group-adopts a Registration system that relies on product assessment and approval of other competent DRAs. All ASEAN countries are net importers of pharmaceuticals.[4]

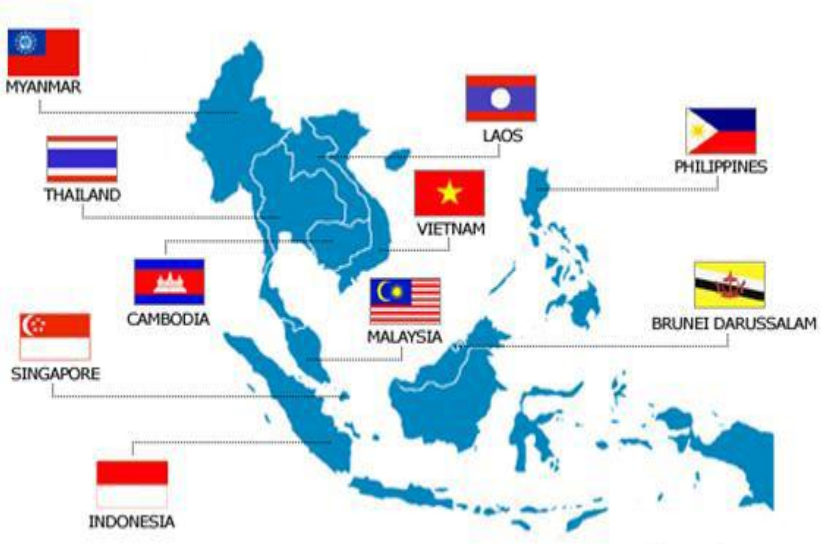

Figure.2 Map of ASEAN Countries

COMMON TECHNICAL DOCUMENT (CTD)

A CTD is Common Technical Document that gives the common format for the preparation of a well-structured technical document for applications that will be submitted to regulatory authorities. A common format for the technical documentation will significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and will ease the preparation of electronic submissions. Regulatory reviews and communication with the applicants will be facilitated by a standard document of common elements. In addition, exchange of regulatory information between regulatory authorities will be simplified.[5]

An eCTD is the Electronic Common Technical Document that allows for the electronic submission of the CTD from applicant to regulator. While the table of contents is consistent with the harmonized CTD, the eCTD also provides a harmonized technical solution to implementing the CTD electronically.

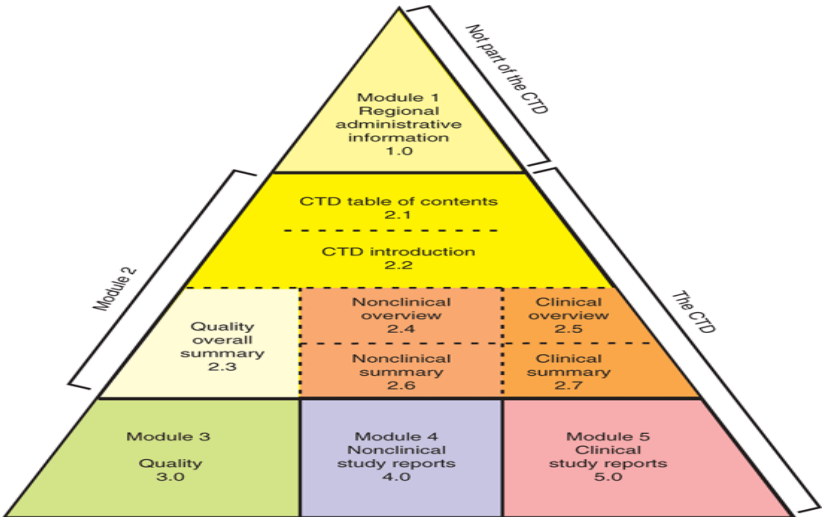

Figure 3 Diagrammatic representation of organization structure of ICH-CTD

CTD FORMAT FOR EACH SUBMISSION

According to the CTD format, each submission of a marketing application is a collection of documents, grouped into 5 modules.

Documents in each Module: Module Information

1. Administrative and prescribing information (region specific)
2. Summaries and overview
3. Information on product quality

4. Nonclinical study reports

5. Clinical study reports

KEY ASPECTS OF USFDA (CTD), WHO (CTD), ACTD

The brief contents of CTD and major requirements for various regions are tabulated

Table no 1. Difference of CTD structure between USFDA, WHO & ASEAN

USFDA CTD	WHO CTD	ASEAN CTD	Description	Remarks
Module 1- Administrative Info	Module 1- Administrative Info & Prescribing Info	Part I ToC, Administrative Data and Product Information	Contains documents that are specific to each region. This module is not part of CTD. Basically consists of administrative documents like Application form, legal documents (GMP, Licenses etc.), labeling etc.	Required for generics and New Drug
Module 2- CTD Summaries	Module 2- CTD Summaries	Part II Quality Document	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	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-Non clinical study reports	Module 4-Non clinical study reports	Part III Nonclinical Document	Non Clinical Study Reports – Data on pharmacologic, pharmacokinetic, and toxicological evaluation of the pharmaceutical product is provided.	Not required for generics
Module 5- Clinical study reports	Module 5- Clinical study reports	Part IV Clinical Document	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

COMPARISON OF USFDA, WHO & SINGAPORE (ASEAN)

Table no.2 Comparison of USFDA, WHO & SINGAPORE (ASEAN)

KEY REGISTRATION REQUIREMENTS	USFDA	WHO	SINGAPORE (ASEAN)	REMARKS
Application Form	ANDA (form FDA 356h)	No specific name ,but details as per country requirement should be filled	Prism application form	USFDA has specific name for form ANDA
Site registration	yes	yes	yes	Required for drug approval process
Plant GMP approval	Accepts USFDA approval	Issued by competent authority in terms of WHO Certification scheme	Accepts FDA/EU/PICs approval for site	Required for drug approval process
Copies	eCTD	1 Paper copies + CDs/DVDs	1 original hard copy and 1 electronic copy (in PDF on CD-ROM)	CTD submitted as per the regulatory requirement
Debartment Certification	Required	Not required	Not required	Required for US
Pharmacovigilance	Not required	Not required	Not required	Nil
Agent authorization	Required	Not Required	Required	For WHO Agent Authorization is not required
MANUFACTURING AND CONTROL				
No. of Batches	One pilot scale or minimum 100,000 units whichever is higher	Two pilot scale batches At least one batch with pilot scale 100,000 tabs/caps Second batch which may be smaller 50,000 tabs/caps	3 pilot scale (2 pilot +1 production)	Difference in batch's to be submitted to regulatory authority
Packaging	Minimum 1 lakh unit	20 packs (sample of commercial batch with COA)	20 packs (sample of commercial batch with COA)	WHO & ASEAN have same packaging packs but US is different
Process Validation	Required at the time of submission	Should be provided in product dossier	Required at the time of submission	Nil
STABILITY REQUIREMENT				
No. of Batches	3 pilot scale or minimum 100,000 units whichever is higher	3 pilot scale batches. At least one batch with pilot scale 100,000 tabs/caps Second batch which may be smaller 50,000 tabs/caps	Min.2 for conventional dosage form and stable drug substances Min.3 for critical dosage form or unstable drug substances.	Difference is shown among USFDA, WHO and ASEAN

Data and time of Submission	6 months	6 months	12 months	Date of submission depends on significant changes
Climatic Zones	Zone II	Zone IVb is real time condition for pre qualification project. Zones II only if justified	Zone II & IVb	Different climatic zone
Stability conditions	25˚C±2˚C 60%±5%RH	30˚C±2˚C 75%±5%RH	30˚C±2˚C 75%±5%RH	Different stability conditions
BIO EQUIVALANCE REQUIREMENT				
BE Study (for generic)	Against US reference listed drug (RLD) in any country. To refer "BE recommendation" in FDA site for guidance. CRO should be approved by USFDA	Medicinal product must be listed in Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification of Medicines Programme. WHO Model List of Essential Medicines [6].	Against US/EU/Australia reference drug in any country except Thailand, where BE to be done locally. BE to be done against local reference product in some countries	References for generic drugs are different

DISCUSSION

Some national authorities consider that listing of a product as WHO-prequalified confers added value on that product. And some research-based international companies recognize that WHO-prequalification of a product is beneficial when seeking national registration and/or participating in procurement tenders. In some countries, review by the national medicines regulatory authority of a WHO-prequalified product will take precedence over review of a US FDA- or EMA-approved product. In other countries, the reverse is true[7]. Thus manufacturers may need to adapt their strategies for seeking regulatory approval depending upon the country in which they plan to operate.

CONCLUSION

The purpose of the present study was to compare dossier requirements of different countries like USFDA (United States Food and Drug Administration),WHO (World Health Organisation),Singapore ASEAN (Association of South East Asian Nation).It was found that, there was less harmonization and various differences in dossier requirements.

As norms for Dossier are constantly changing, it is the responsibility of the Pharmaceutical Companies on regular basis to update their knowledge, which helps the Pharmaceutical Companies to file dossiers in respective countries. It can be concluded that by practicing the

particular dossier norms, the pharmaceutical companies not only comply regulatory requirement but also satisfaction of providing quality medicine with the needy and sufferers. With ICH formation, the dossier format prepared by ICH has been followed by many countries. But still country to country varies in dossier filling, therefore worldwide there should be a harmonization in dossier format, so that quality drug product will be sold in each part of the world.

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