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Comparative study of regulatory requirements for the approval of generic drugs for Association of South East Asian Nation (ASEAN), Gulf Co-Operative Council (GCC) & United States Food And Drug Administration (USFDA)

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ABSTRACT

Background: The purpose of the present study was to compare dossier requirements of different countries like ASEAN (Association of South East Asian Nation), GCC (Gulf Cooperation Council) and USFDA (United States Food and Drug Administration). **Methods:** Collection of the following dossier format like ASEAN (Association of South East Asian Nation), GCC (Gulf Cooperation Council) and USFDA (United States Food and Drug Administration). Identifying the critical and major differences among those three dossiers (ASEAN, GCC& US-FDA) related to technical document. Comparison of common technical document for those critical and major differences among three countries (ASEAN, GCC & USFDA) **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 ASEAN, GCC) and also these guidelines were compared with regulated market USFDA. It was found that, there was less harmonisation and various differences in dossier requirements. **Discussion:** In its legal sense regulation can and should be distinguished from primary legislation on the one hand and judge-made law on the other. 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, co-regulation, third-party regulation, and certification, accreditation or market regulation.

Keywords: Regulatory Authorities, regulatory information, efficient regulations

INTRODUCTION

Regulatory Affairs is a comparatively new profession which has developed from the desire of governments to protect public health by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines. The companies responsible for the discovery, testing, manufacture and marketing of these products also want to ensure that they supply products that are safe and make a worthwhile contribution to public health and welfare[1]. Most companies, whether they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of Regulatory Affairs professionals – and those who don't rely on the expert advice of independent regulatory consultants to meet their obligations.

The Association of South East Asian Countries (ASEAN) and Gulf cooperation council (GCC) region is considered as "Emerging market" for pharmaceutical export and bilateral trade. The understanding of the regulatory requirements of this region can be beneficial for pharmaceutical export. Some incidents of the year 2008-09, like recession or economic slowdown in highly well off and regulated market of the EU and US, raised the demand for alternate destinations for business. The regulations of ASEAN and Gulf countries are encouraging the import of quality generic products, which can be good news to the drug manufacturers.

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ASEAN (Association of South East Asian Nations)

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. ASEAN member countries share a number of common characteristics with regards to their pharmaceutical sector and regulation. Some of these characteristics can be said to reflect what found in developing countries in general. Key relevant characteristics are: Drug regulatory frameworks in ASEAN member countries do not appear to discourage research and development of drugs and vaccines. Drug regulatory capacities in the majority of ASEAN members are constrained by limited human and financial resources[2]. Gaps exist between written regulation and actual enforcement in a number of ASEAN member countries. 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. All except Singapore do not have capability for new drug development[3].

Gulf Cooperation Council

Established in 1976 by Saudi Arabia, Kuwait, Oman, United Arab Emirates, Bahrain Qatar and Yemen, The GCC is a co-operation organ in different domains including health. The various councils of ministers of the participating countries meet twice a year to discuss existing and new co-operation issues. Coordinating and ensuring communication with and between the Ministers of Health of member countries, Organizing conferences, seminars, and training courses[4]. Conducting field surveys and researches for common interest of Gulf States, Procurement of safe and efficient pharmaceutical products, hospital sundries and equipment's of high quality. Although there is a centralized and quite harmonized process for drug registration in GCC countries, the regulatory requirements of a few big countries like Saudi Arabia and UAE are separate. These countries have their well-established regulatory system and its enforcement[5].

US-FDA ECONOMICS OF GENERICS

Generic drugs are usually sold for significantly lower prices than their branded equivalent. One reason for the relatively low price of generic medicines is that competition increases among producers when drugs no longer are protected by patents. Companies incur fewer costs in creating generic drugs (only the cost to manufacture, rather than the entire cost of development and testing) and are therefore able to maintain profitability at a lower price. The prices are low enough for users in many less-prosperous countries to afford them. For example, Thailand has imported millions of doses of a generic version of the blood-thinning drug[6].

Generic drug companies may also receive the benefit of the previous marketing efforts of the brand-name drug company, including media advertising, presentations by drug representatives, and distribution of free samples. Many drugs introduced by generic manufacturers have already been on the market for a decade or more, and may already be well known to patients and providers (although often under their branded name). Competition is also seen between generic and branded drugs with similar therapeutic uses when physicians or health planners adopt policies of preferentially prescribing generic drugs as in step therapy. With multiple firms producing the generic version of a drug the profit-maximizing price generally falls to the on-going cost of producing the drug, which is usually much lower than the monopoly price[7].

KEY ASPECTS OF ACTD, GCC (CTD) and US-FDA (CTD)

Dossier Format- ASEAN CTD

ASEAN countries established the ACTD as their format for submissions. It is a standard derived from the ICH CTD. The ASEAN CTD is a guideline of the agreed upon common format for the preparation of a well-structured ACTD application that will be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals for human use[8].The ICH CTD is divided into 5 modules whereas the ACTD contains of 4 parts, ie., contents wise ACTD is similar to the ICH CTD. But Module wise it is different. The reason for doing this is the fact that the ASEAN countries normally receive a reference application, which is a dossier which was already approved in other countries in the world (mostly EU and USA) and make the evaluation of the parts mainly based on the overviews and summaries. Based on this, the need for detailed documentation is in most of the ASEAN countries less compared to the ICH countries, e.g. most study reports are not required to be submitted[9]. The Module 1 of the CTD containing the regional registration and administrative information is still presented as Part 1 of the ACTD. The Module 2 of the CTD does not exist itself for the ACTD. The Quality Overall Summary (QOS) and the overview and summaries of the nonclinical and clinical documentation (similar like the documents in ICH Module 2) are included at the beginning of these Parts. Part II of the ACTD contains the pharmaceutical-chemical-biological documentation (the quality information), which corresponds to the ICH Module 3. The nonclinical information is presented as Part III of the ACTD (equivalent to ICH Module 4) and the clinical documentation is contained in Part IV of the ACTD (to be consistent with ICH Module 5)[10].

The differences between ICH-CTD and ACTD are presented in the attached comparison pyramid:

Fig.1 Modular Structure of Common Technical Document

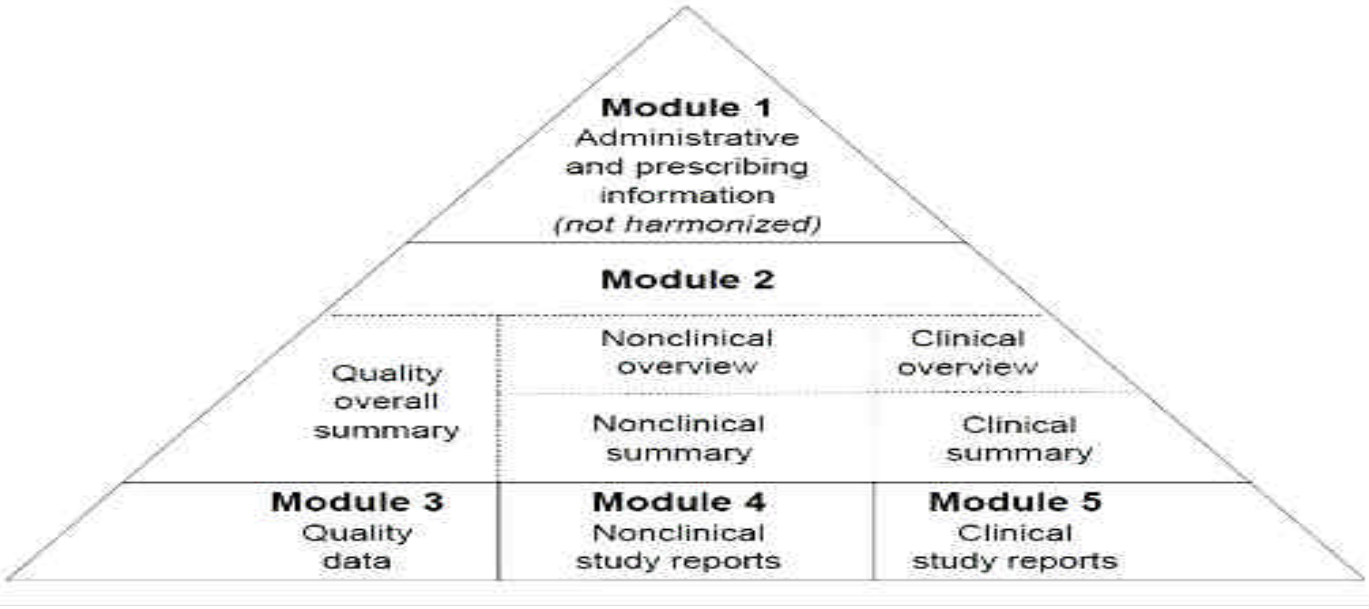
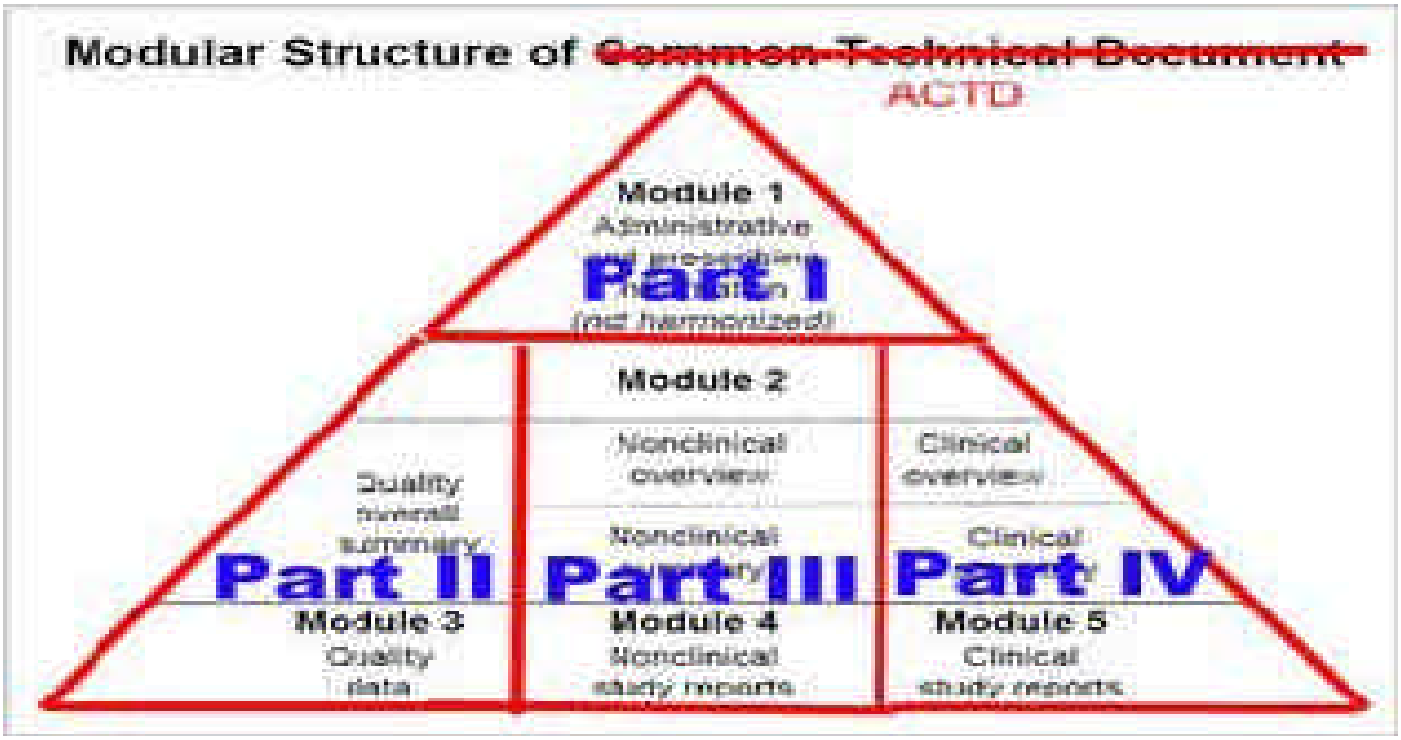


Fig.2



As demonstrated above the ACTD is organized in four parts

1. Part I: ToC, Administrative Data and Product Information
2. Part II: Quality Document
3. Part III: Nonclinical Document
4. Part IV: Clinical Document

Dossier Format - USFDA 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[11]. In addition, exchange of regulatory information between Regulatory Authorities will be simplified. An eCTD is the Electronic Common Technical Document that allows for the electronic submis-

sion 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. The Ectd specification is based on XML technology. No time frame has yet been introduced for mandatory electronic CTD submissions but, it is becoming widely known that eCTD is the future[12].

Through the ICH process, considerable harmonization has been achieved among the three regions, in the organization of a submission for the registration of pharmaceuticals for human use. The CTD format and organization are presented in a series of four documents, known as the CTD guidance's[13].

M4: Organization of the CTD, M4E: The CTD – Efficacy, M4Q: The CTD – Quality, and
M4S: The CTD – Safety

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 as listed[14, 15].

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

RESULTS AND DISCUSSION

COMPARISON OF ASEAN, GCC AND US-FDA

REQUIREMENT ADMINSTRATIVE	USFDA ANDA	ASEAN	GCC	Remarks
Application Form	(Form FDA 356h)	No specific name, but details as per country requirement should be filled	No specific name, but details as per country requirement should be filled	USFDA has specific name for form ANDA
Approval Time line	18 Month	24 - 36 months	24 - 36 months	ASEAN and GCC takes more time for approval
Copies	3 (archival, review, field)	1 original hard copy and 1 electronic copy(in PDF on CD-ROM)	For all doses one dossier to be prepared.1 CD (Numbered Electronic copy)	US needs 3 copies whereas ASEAN and GCC needs 2copies
Debarment Certification	Required	Not Required	Not Required	Nil
Pharmacovigilance	Not Required	Not Required	Not Required	Nil
Agent Authorization	Required	Required	Required	Nil
MANUFACTURING AND CONTROL				
No. of Batch's	One pilot scale or minimum 100,000 units whichever is higher	3 pilot scale (2 pilot + 1 production)	3 pilot scale	Difference in batch's to be submitted to regulatory authority
Packaging	Minimum 1 Lakh Unit	20 packs(samples of commercial batch with COA)	20 packs(samples of commercial batch with COA)	ASEAN and GCC have same packaging packs but US is different
Process Validation	Required at the time of submission	Required at the time of submission	Required at the time of submission	Nil
FINSH PRODUCT CONTROL				
Assay	90-100%	95.0 – 105.0%	95.0 – 105.0%	ASEAN and GCC is same
Identification Test	Single test	Required	Required	Nil
Colour identification	Not Required	Not Required	Not Required	Nil
Water Content	Required	Required	Required	Nil
Disintegration Test	Not Required	Not Required	Not Required	Nil
STABILITY REQUIREMENT				
No. of Batch's	One pilot scale or minimum 100,000 units whichever is higher	Min. 2 for conventional Dosage form and Stable drug substances Min. 3 for critical dosage Form or unstable drug substances	Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.	Difference is shown among USFDA,ASEAN and GCC
Date and Time of Submission	3 months	12 months	12 months	ASEAN and GCC are similar
Climatic Zone	Zone I & II	Zone II, IVa & IVb	Zone III & IVa	Different climatic zone
Stability requirements	25 ° ± 2 ° C 60% ± 5% RH	30 ° ± 2 ° C 65% ± 5% RH	30 ° ± 2 ° C 65% ± 5% RH	Similar stability requirement for ASEAN and GCC
BIOEQUIVALENCE 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	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	Against US/EU/Australia Reference drug in any country.	ASEAN and GCC follows reference drug from regulated countries

CONCLUSION

The purpose of the present study was to compare dossier requirements of different countries like ASEAN (Association of South East Asian Nation), GCC (Gulf Cooperation Council) and USFDA (United States Food and Drug Administration). As norms for Dossier are constantly changing, it is the responsibility of the Pharmaceutical Companies to impart training to their entire employee 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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