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COMPARISION OF GENERIC DRUG REGISTRATION REQUIREMENTS IN ASEAN COUNTRIES & IN INDIA

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ABSTRACT

To demonstrate how the requirements and guidelines can be applied are used as references to file investigational new drug application. To develop and design the regulatory filing strategies for US investigational new drug and European investigational medicinal product dossier. To understand General investigational plans how to approach the regulatory agencies. To reduce the regulatory burden on industries while filing for new drug application. To understand the comparative regulatory strategies for US regulatory body and Europe regulatory agency. To support by filing to get approval of the sponsor's wishing to conduct clinicalstudies with an investigational drug. To understand the safety studies to clear overall risk and benefit assessment.

KEYWORDS: US IND, EU IMPD, Guidelines, Regulatory Requirements.

1. INTRODUCTION[1-4]

Southeast Asia, with its fast-growing, young population and uninsured majority represent a great opportunity for generics in the pharmaceutical industry. Although the generic market is currently quite small, improved access to medicines in the region means that it is growing rapidly and is expected to reach US$5.9 billion by 2025. This fact is expected to both intensify competition and attract multinational pharma companies to the area. Bigger markets in the region with low access to medicines, such as Indonesia, will drive the need for operational efficiency due to the increasing number of players, which is expected to drive down prices. In fact, Indonesia already introduced compulsory prescribing of generics in 2025 and plans to implement universal healthcare coverage by 2025.

The expanding middle class is also expected to drive demand for medicines, and especially generics, in the region. The development of better infrastructure will facilitate multinational companies being able to set up facilities in Southeast Asia. The growth in generics, coupled with the fact that many governments in the region support local business, puts local generics manufacturers in a strong position. This means that most foreign companies will need to set up local partnerships, giving a welcome boost to local generics companies.

Generic Drug Development: Pharmaceutical drug discovery and development has seen tremendous changes over the recent decades. For the innovator and the generic drug manufacturer, the regulatory perspective to reach various populations has been but a tough route. Country specific regulations have become stringent over the years keeping in mind the needs of its people and their health. Majority of the countries in the world have government programs to obtain generic versions of drugs for its people. This has often led to collaborations between various government departments and pharmaceutical companies.

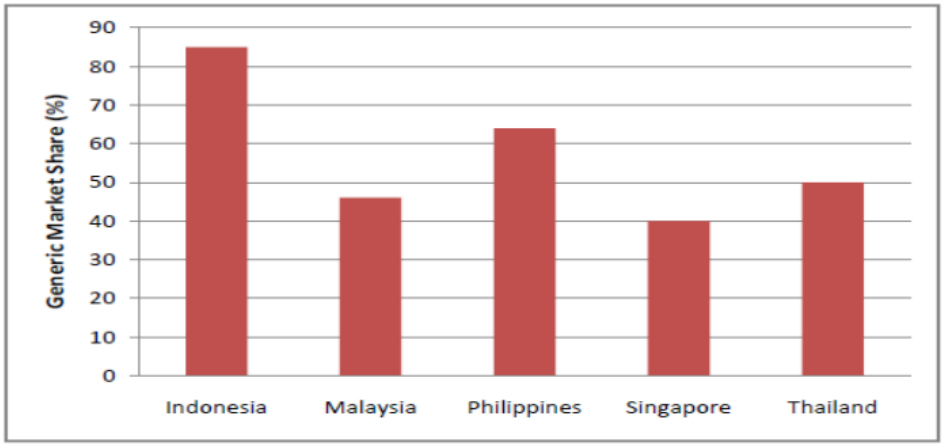

Fig-1: Generics Market Share in Selected Southeast Asian Countries (2025).

The ASEAN (Association of Southeast Asian Nations) group of nations, namely Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia is recently the eye catcher for most pharmaceutical companies due to the growing population and attractive pharmaceutical market growth. A recent development includes the Harmonization of regulations favoring the market entry to these nations.

Introduction to ASEAN: ASEAN was established on 8 August 1967 in Bangkok by the five original member countries Indonesia, Malaysia, Philippines, Singapore and Thailand. On 8 January 1984 Brunei Darussalam joined ASEAN, Vietnam on 28 July 1995, Laos and

Myanmar on 23 July 1997, and Cambodia on 30 April 1999. In 1999 a harmonization initiative was started among the 10 ASEAN countries One aim of this harmonization should be to harmonize quality guidelines that are valid for all countries involved.

Another focus lies in the technical co-operation. Therefore the ASEAN Consultative Committee on Standards and Quality Pharmaceutical Product Working Group (ACCSQ PPWG) was established. The objective of the ACCSQ PPWG is the development of "harmonization schemes of pharmaceuticals' regulations of the ASEAN member countries to complement and facilitate the objective of ASEAN Free Trade Area (AFTA), particularly, the elimination of technical barriers to trade posed by these regulations, without compromising on drug quality, safety and efficacy." ASEAN established the so called ASEAN Common Technical Document (ACTD) and the ASEAN Common Technical Requirements (ACTR) to create harmonized requirements and a common format for all submissions of dossiers in the ASEAN countries.

The ACTD is a common format and content acceptable for an application in the ASEAN member countries. The ACTR are a set of written requirements or guidelines intended to provide guidance to applicants in order to be able to prepare application dossiers in a way that is consistent with the expectations of all ASEAN DRAs. The strategy of the ACCSQ PPWG is the "exchange of information on the existing pharmaceutical requirements and regulation implemented by each ASEAN member countries, to study the harmonized procedures and regulatory system implemented in the ICH region, development of common technical dossiers with a view of arriving at MRAs (Mutual Recognition Arrangements)."

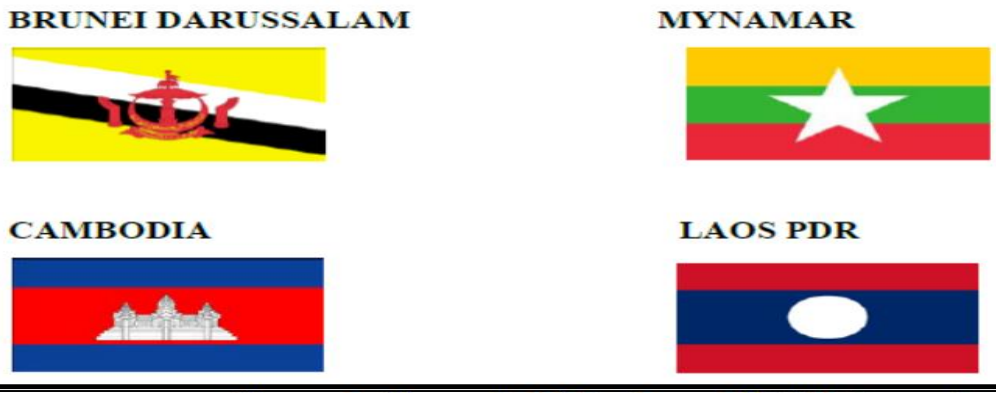

Figure 2: Flags of all Members ASEAN Countries

From August 2003 – December 2004 each ASEAN country should implement a trial implementation period for the ASEAN requirements (like ATCD and ACTR). The full implementation of the ASEAN requirements was originally planned for January 1st, 2005. The transition period for the ASEAN requirements was extended to December 31st, 2008 as it was not possible for the ASEAN countries to implement the ACTD until January 1st, 2005. The full implementation of ACTD for new products was planned to be done in the ASEAN countries at different points in time between 2005 and 2008, which are summarized below: · Singapore and Malaysia by December 2005

· Thailand by December 2006

· Indonesia and Vietnam by December 2007

· Philippines, Cambodia, Laos and Brunei by December 2008

Figure 3: Symbol of ASEAN

According to information received from the ASEAN countries (January 2009) some of the ASEAN countries still accept the CTD-format for MAAs of NCEs and NBEs whereas for RENs and VARs only the ACTD-format is accepted by ASEAN countries. According to the

information of the "forum institute seminar on October 21st and 22nd in Cologne" the full implementation of ACTD becomes mandatory by end of 2008 for MAAs and already registered products have to be transferred to ACTD until 2012. All regulatory agencies in these 10 countries have a relatively weak infrastructure and limited resources. The agencies are structured differently and standards of scientific guidelines are not well established. A big problem of the agencies is the lack of consistency and transparency especially regarding the evaluation of dossier. To solve these problems they are constantly improving with more dialogues with the industry. In all ASEAN countries a Certificate of a Pharmaceutical Product (CPP) from the reference country is required and builds the basis of the drug approval as the DRAs do not have the possibilities, capacities and scientific know-how to make a full evaluation of the submitted dossier (especially with regard to preclinical and clinical data).

ASEAN Common Technical Documents The 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. The ACTD is similar to the ICH CTD. The ICH CTD is divided into 5 modules whereas the ACTD contains of 4 parts. 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.

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 are contained in Part IV of the ACTD (to be consistent with ICH Module 5).

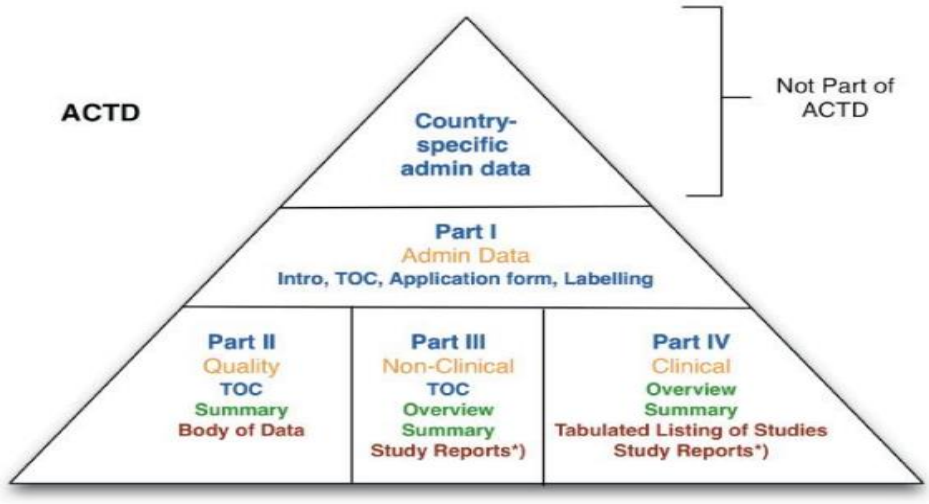

Figure 4: Organization of ACTD

As demonstrated above the ACTD is organized in four parts

Part I: Administrative Data and Product Information

Part II: Quality Document

Part III: Nonclinical Document

Part IV: Clinical Document

2. METHODOLOGY[5-10]

The dissertation work was done in order to project industrial approach in facilitating a pharmaceutical company's entry into the market of South East Asian Countries.

Criteria for selection of study parameters.

Part-I

Requirement for filing application: Application for generic drug registration should be in local language of country or English language (if required) in which we need registration of generic drug.

Part-II

Documents and study information required for submission: To collect the information about the extent of information and data is one of the most important parts of any kind of regulatory submission.

a) Legal documents: GMP certificate, Letter of Authorization, Certificate of Pharmaceutical product (COPP), Free Sale Certificate (FSC) should be notarized.

b) Pharmaceutical information: Normative documentation contains main pharmaceutical information in ASEAN countries dossier, which needs to be filed in local language only.

c) Bioequivalence study information: Literature search have to be included.

Part-III

Product registration and Dossier submission: During product registration, application & dossier submission, screening, evaluation, regulatory decision, fee, etc., depends on the country guidelines & certain parts needs to be filed in local languages or translated to the local language from original documents as per country regulatory requirements. After translation the documents should be notarized.

Part-IV

- Comparison Study: This includes comparison of Administrative Documents, Manufacturing & Control, Drug Registration Form, Specific Labelling Requirements, Storage Requirements Package Inserts, Patent Information and Certifications. In order to provide a practical approach to this dissertation all the exploratory research work was carried out by using reliable sources (Like websites of various regulatory authorities and industry clients) and by using secondary data sources (other websites, journals, magazines, review articles etc).
- **Data Collection was done by**

❖ Regulatory guidelines published officially by government authorities Research articles in various national as well international journals and on websites.

❖ Working papers from certain related government funded institutions.

❖ Articles available on the web in various pharma news letters.

- **The study was designed to learn about the regulatory requirements**
- The acquired details would provide an overview of regulatory environment in the ASEAN region.
- **In this part of study, efforts were made to find out the following.**

• Review the approval process as specified by the drug authorities of specific countries.

• Country's specific registration requirements and Format followed

3. RESULTS[10-18]

Table 2: General Comparison of ASEAN Countries.

S NO	COUNTRY	VALIDITY	FORMAT FOLLOWED	FORMAT INCLUDED IN THESIS
1	Singapore	5 yrs	ACTD	ACTD
2	Malaysia	5 yrs	ACTD	ACTD
3	Thailand	5 yrs	ACTD	ACTD
4	Philippines	5 yrs * 1	Country specific &ACTD	Countryspecific
5	Indonesia	5 yrs	ACTD	ACTD
6	Vietnam	5 yrs	ACTD	ACTD
7	Brunei Darussalam	5 yrs	ACTD	ACTD
8	Myanmar	5 yrs	Country specific &ACTD	Countryspecific
9	Cambodia	5 yrs	ACTD	ACTD
10	Laos	5 yrs	Country specific &ACTD	Countryspecific

Table 3: Administrative Documents Comparison of ASEAN Countries.

S NO	ADMINISTRAT IVE DOCUMENTS	SINGA PORE	MALA YSIA	THAI LAND	INDON ESIA	VIET NAM	BRU N EI	CAMB ODIA
1	Application Form	✓	✓	✓	✓	✓	✓	✓
2	Copy of valid certificate ofbrandNameclearance	✓	✓	✓	✓	✓	✓	✓
3	Certificate of Pharmaceuticalproduct	✓	✓	✓	✓	✓	✓	✓
4	Free SaleCertificate	✗	✓	✗	✗	✗	✗	✓
5	Good Manufacture Practice	✓	✓	✓	✓	✓	✓	✓
6	License for pharmaceutical Manufacture	✓	✗	✓	✓	✓	✓	✓
7	Site MasterFile	✗	✗	✓	✓	✓	✓	✓
8	Permission for manufacturing	✗	✗	✗	✗	✗	✗	✗
9	Letter of Authorization	✓	✓	✓	✓	✓	✓	✓
10	Labeling Documents	✓	✓	✓	✓	✓	✓	✓
11	Patent Information	✓	✓	✓	✓	✗	✓	✓
12	Summary Product characteristics	✓	✓	✓	✓	✓	✓	✓
13	Patient Information Leaflet	✓	✓	✓	✗	✗	✗	✗
14	Product Information Already Approved In Any State/country	✓	✓	✗	✗	✗	✓	✗

Table 4: Technical Documents Comparison of ASEAN Countries.

	SINGAPORE	MALAYSIA	THAILAND	INDONESIA	VIETNAM	BRUNEI	CAMBODIA
DRUG SUBSTANCE	✗	✓	✓	✓	✓	✓	✓
Quality overall Summary	✗	✓	✓	✓	✓	✓	✓
General information	✗	✓	✓	✓	✓	✓	✓
Manufacture ofDrug substance	✗	✓	✓	✓	✓	✓	✓
Characterization	✓	✓	✓	✓	✓	✓	✓
Quality control of drug substance	✗	✓	✓	✓	✓	✓	✓
Referencestandards	✗	✓	✓	✓	✓	✓	✓
Container Closure System	✗	✓	✓	✓	✓	✓	✓
Stability	✓	✓	✓	✓	✓	✓	✓
CEP	✓	✓	✗	✗	✗	✗	✗
Drug Master File	✓	✗	✗	✗	✗	✗	✗
	Singapo re	**Malaysia**	**Thailand**	**Indonesia**	**Vietnam**	**Brunei**	**Cambodia**
DRUG PRODUCT	✗	✓	✓	✓	✓	✓	✓
Description & Composition	✓	✓	✓	✓	✓	✓	✓
Pharmaceutical Development	✗	✓	✓	✓	✓	✓	✓
Manufacture	✓	✓	✓	✓	✓	✓	✓
Quality Control of Excipients	✓	✓	✓	✓	✓	✓	✓
Quality Control of Finished Product	✓	✓	✓	✓	✓	✓	✓
Reference Standard	✓	✓	✓	✓	✓	✓	✓
Container Closure System/ Packing	✓	✓	✓	✓	✓	✓	✓
Product Stability	✓	✓	✓	✓	✓	✓	✓
Inter changeability	✓	✓	✓	✓	✓	✓	✓

Table 5: Non-Clinical Documents Comparison of ASEAN Countries.

NON CLINICAL DOCUMENTS	SINGAPORE	MALAYSIA	THAILAND	INDONE SIA	VIETNAM	BRUNEI	CAMBODIA
Non Clinical Overview	✗	✗	✓	✓	✓	✓	✓
Non Clinical Written & TabulatedSummary	✗	✗	✗	✗	✗	✗	✗
Non ClinicalStudy Reports	✗	✗	✗	✗	✗	✗	✗
LiteratureReferences	✗	✗	✓	✓	✓	✓	✓

Table 6: Clinical Documents Comparison of ASEAN Countries.

CLINICAL DOCUMEN TS	SINGA PORE	MALA YSIA	THAIL AND	INDON E SIA	VIETN AM	BRUN EI	CAMB ODIA
Clinical Overview	✗	✗	✓	✓	✓	✓	✓
Clinical Summary	✗	✗	✗	✗	✗	✗	✗
Tabular Listing of All ClinicalStudies	✗	✗	✗	✗	✗	✗	✗
ClinicalStudy Reports	✗	✗	Only BE	Only BE	Only BE	OnlyBE	Only BE
List of KeyLiterature	✗	✗	✓	✓	✓	✓	✓

Table 7: Regional Format Comparison of ASEAN Countries.

S NO	DOCUMENTS	PHILIPPINES	MYANMAR	LAOS
1	Application Form	✓	✓	✓
2	Certificate Of Pharmaceutical Product	✓	✓	✓
3	Site Master File	✗	✗	✗
4	Summary of Product Characteristics/PI	SPC depends	PI	PI
5	GMP Certificate of API Mfr.	✓	✗	✗
6	Manufacturing License of FPPMfr	✗	✓	✓
7	Marketing Authorization In The Country of Origin/ FSC	✗	✓	✓
8	WHO-GMP Certificate	✓	✓	✓
9	Properties of API	✗	✓	✗
10	Route of Synthesis of API	✗	✓	✓
11	Process Validation of API	✗	✗	✓
12	API Specification	✗	✓	✓
13	API Certificate of Analysis	✓	✓	✓
14	Stability Testing	✓	✗	✗
15	AnalyticalMethodValidation	✗	✗	✓
16	Unit Dose & Batch Formula	✓	✗	✗
17	Master Formula	✓	✓	✓
18	Manufacturing Process	✓	✗	✓
19	In-Process Specifications	✓	✓	✗
20	Process Validation Of FP	✗	✗	✗
21	Monograph- Excipients	✓	✓	✓
22	COA-Finished Pharmaceutical Product	✓	✓	✓
23	Specifications of Finished Pharmaceutical Product	✓	✓	✓
24	Monograph of Finished Pharmaceutical Product	✓	✓	✓
25	Analytical Method Validation	✓	✗	✗
26	Container Closure System	✓	✓	✓
27	Stability	✓	✓	✓

28	Labels	✓	✓	✓
29	Pharmacology, Toxicology	✗	✓	✗
30	Raw Material Specifications	✓		✓
31	Product If Already Approved In Other Country	✗	✓	✓
32	BE Requirements	✗	✗	✓

4. SUMMRY

The Southeast Asian pharmaceutical industry is at a crossroads: The transition from underdeveloped nations to developing and now emerging markets has brought with it many conundrums and many opportunities. The shape of the sector across the regions expected to drastically change, and today's picture is evolving quickly. The ASEAN pharmaceutical market is relatively small but the region remains attractive due to the predicted double digit growth potential in future. Moreover the worldwide pharmaceutical market is shifting from mature to pharmerging or tier to pharmerging market. The pharmaceutical industries in each of the 10 ASEAN member countries - Brunei, Myanmar, Cambodia, Indonesia, Laos, Malaysia, Philippines, Singapore, Thailandand Vietnam – are at very different stages of development.

The economic situation & health expenditure vary from one country to another country. Most of population in these low income countries like Vietnam, Philippines, Indonesia & Thailand depend on generic drugs. But countries like Singapore and Malaysia believe on innovation. It is noticeable that harmonization of standards and regulations as well as MRA's area major contribution to the integration of the ASEAN market. Even if tariffs are done away with and even with the most efficient transportation, true market integration will be out of ASEAN's reach if the flow of products is hampered and slowed down by inconsistent regulations and varying standards. ASEAN Standards Bodies and Regulatory Authorities have been working closely with private sectors to address these technical barriers. None of the above achievements can happen without regional cooperation and strong collaboration of stakeholders. Moreover, regional cooperation on standards and standards officers, regulators as well as industry to meet frequently and network effectively.

The focus on countries like Indonesia and Thailand is because of high population rate, maximum share of ASEAN pharmaceutical market, low income. But these countries are ranked after Vietnam and Philippines because of some restriction by countries government for foreign players. Singapore and Malaysia are the only countries in ASEAN, who have well

established pharmaceutical regulations and more strict to quality & safety of drugs. These countries believe on innovation and give full protection to them. Hence there may not be many opportunities for small and medium scale generic companies in these countries unless their manufacturing procedures are well to do with regulatory requirements.

This thesis gives a simplified overview of the Drug Regulatory Authority of 10countries (ASEAN) taken in project and in detail registration & regulatory requirements for filing a dossier for a generic drug product in the markets selected.

5. CONCLUSION

ASEAN-CTD	ICH-CTD
Part I: Table of Contents, Administrative Data and Prescribing Information Section A: Introduction Section B: ACTD Table of Contents Section C: Administrative Documents (Application Form, Letters of Authorization, Certification Documents, Labeling, Product Data Sheet, Prescribing Information, etc.)	Module 1: Administrative & Prescribing Information 1.1 Overall Table of Contents 1.2 Region-Specific Documents, Administrative Data & Prescribing Information
	Module 2: CTD Summaries 1.1 CTD Table of Contents (Modules 2-5) 1.2 CTD Introduction 1.3 Quality Overview 1.4 Nonclinical Overview 1.5 Clinical Overview 1.6 Nonclinical Written and Tabulated Summaries 1.7 Clinical Summary
Part II: Quality Document Section A: Table of Contents Section B: Quality Overall Summary Section C: Body of Data (Reports)	Module 3: Quality 1.1 Module 3 Table of Contents 1.2 Body of Data 1.3 Published References
Part III: Non-Clinical Document Section A: Table of Contents Section B: Nonclinical Overview Section C: Nonclinical Written and Tabulated Summaries Section D: Study Reports (upon request only)	Module 4: Nonclinical Reports 4.1 Module 4 Table of Contents 4.2 Nonclinical Study Reports (Body of Data) 4.3 Published References
Part IV: Clinical Document Section A: Table of Contents Section B: Clinical Overview Section C: Clinical Summaries Section D: Tabular Listing of Clinical Studies Section E: Clinical Study Reports (upon request only) Section F: List of Key Literature References.	Module 5: Clinical Reports 5.1 Module 5 Table of Contents 5.2 Tabular Listing of all Clinical Studies 5.3 Body of Data (Final Reports) 5.4 Published References

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