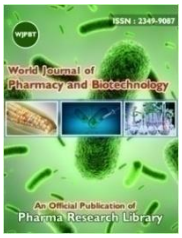

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Comparison of CTD Modules with Southeast Asian Countries

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A b s t r a c t
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$3.9 billion by 2016. 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 2010 and plans to implement universal healthcare coverage by 2014.The transition from under developed nations to developing and now emerging markets has brought with it many conundrums and many opportunities. The ASEAN pharmaceutical market is relatively small but the region remains attractive due to the predicted double digit growth potential in future. The economic situation & health expenditure vary from one country to another country. Most of population in these low income countries like Philippines, Indonesia & Thailand depend on generic drugs. 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 conformance compels standards officers, regulators as well as industry to meet frequently and network effectively. The focus is 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.

Keywords: Centre for drug Administration, Centre for drug Evaluation, Bioequvalence, Bioavailability, Certificate of Analysis.

A r t i c l e I n f o

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C o n t e n t s

1. Introduction

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. 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 favouring 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. 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), 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. 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

2. Methodology

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:

As the generic drug registration in ASEAN countries is a sequential process, four parameters are selected for the understanding and studying the regulatory Registration& requirements.

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:

- Communication in person / telephonic and or by email with key pharmaceutical clients, companies, distributors of various countries.
- 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 newsletters

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.

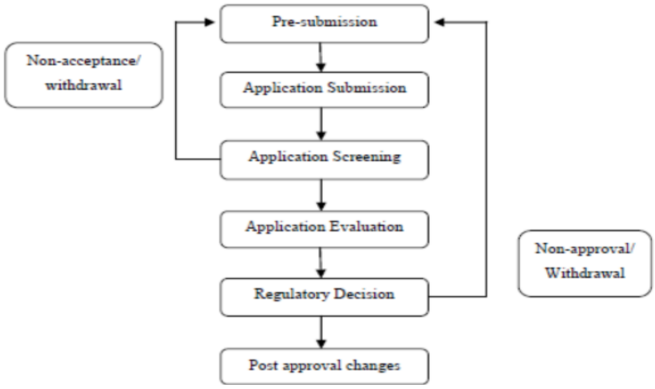
3. Results and Discussion

Generic Drug Registration and Requirements in Singapore

Legal Frame & Regulations: The Health Sciences Authority (HSA) was established in April 2001. In January 2004, the Centre for Drug Administration (CDA) was established under the HSA. The CDA was formed by merging two previously-existing agencies: The Centre for Pharmaceutical Administration (CPA) and the Centre for Drug Evaluation (CDE), which was both responsible for the regulation and evaluation of medical products in Singapore. The Centre for Drug Administration (CDA) leads Singapore pharmaceutical regulations and separates them

under the following five regulatory guidelines: Medicines Act, Poisons Act, Sale of Drugs Act, Medicines (Advertisement and Sale) Act and the Misuse of Drug Regulations.

General Overview of Registration Requirements in Singapore:



The registration process involves a series of steps

NDA (New Drug Application)

NDA-1: For the first strength of a product containing a new chemical or biological entity

NDA-2: 1) For the first strength of a new drug product

- containing a new combination of registered chemical or biological entities;
- containing registered chemical or biological entity (i.e.) in a new dosage forms;

NDA-3: For subsequent strength(s) of a new drug product that has been registered or has been submitted as an NDA-1 or NDA-2.

GDA (Generic Drug Application)

GDA-1: For the first strength of a generic chemical product.

GDA-2: For subsequent strength(s) of the generic chemical product that has been registered or has been submitted as a GDA-1. The product name and pharmaceutical dosage form shall be the same as that for the GDA-1.A generic product is essentially similar to a currently registered product in Singapore (known as the Singapore reference product) but excludes biologics.

Generic Drug Registration and Requirements in Malaysia

Generics: *1. Scheduled Poison* (Known as Controlled Medicine/ Controlled Poison)

Products containing poisons as listed in the First Schedule under Poisons Act 1952.

2. Non-scheduled Poison (Known as Non-Poison or "Over-the-Counter", OTC)**.** Products containing active ingredients which are not listed in the First Schedule under Poisons Act 1952; and is excluding active ingredient which is categorized under health supplements or natural products or cosmetics.

Requirements for Product Registration

i. General requirements (either for full or abridged evaluation
ii. Full Evaluation; (In accordance to ASEAN ACTD/ ACTR or ICH guidelines)

- Part I - Administrative data and product information;
- Part II - Data to support product quality (Quality Document);
- Part III- Data to support product safety (Nonclinical Document); and
- Part IV- Data to support product safety and efficacy (Clinical Document

Generic Drug Registration and Requirements in Thailand

Legal Framework & Regulation:

The Food and Drug Administration (FDA), under the Ministry of Public Health (MOPH), is the main agency in charge of drug approval and registration. Its main sections relating to pharmaceutical registration are:

- Drug Products, under the Drug Control Division;
- Import Licenses, under the Division of Manufacturing and Import Facilities Control;
- Product Registration, under the Food Control Division, and
- Label Registration, which is also under the Food Control Division.[9]

Generic Drug registration involves three steps:

- Application for permission to manufacture or import of drug samples. (at Food and Drug Administration)
- Application for an approval of drug quality control and analytical methods. (at Department of Medical Science)
- Application for granting of a drug registration certificate. (at Food and Drug Administration)[22]

New Generic Drug registration procedure has following steps:

- A protocol on Bioequivalence study must be submitted for an approval at the Drug Control Division.
- Application to seek permission for import or manufacture the drug samples.
- Performing the Bioequivalence study according to the approved protocol in a specified government institute.
- Submitting an application for registration along with the bioequivalence report and other useful documents.

Generic Drug Registration and Requirements in Philippines

Legal Framework & Regulations:

- Marketing authorization/registration
- Inspection
- Import control
- Licensing
- Market control
- Quality control
- Medicines advertising & promotion
- Clinical trial control
- Pharmacovigilance

Registration of Pharmaceutical Products in Philippines

Drug Registration:

All products which fall under the definition of drugs are required to be registered following the procedure. If all the criteria and requirements for registration have been\met, all

applications undergoing final evaluation are issued an approval of registration whose validity period is as follows:

- Initial registration of drugs for general use shall be issued for either 2 years or 5 years validity based on the application of the company.
- Drugs which fall under the new drug monitored release category shall be given 3 years registration validity.
- Renewal registrations are valid for 5 years.

Table 1: Percentage of Evaluation Fee Payable at Each Stage & Application Status

Application Type	Evaluation Route	Evaluation Status			
		Accepted for Evaluation	Active Evaluation	Midway in Evaluation	Evaluation Completed
GDA-1 GDA-2	Abridged or Verification	30%	40%	40%	40%
		Application is accepted for evaluation. is marks the start of the evaluation timeline	When active evaluatio-n isinprogress for the application	Application is approximately midway through the evaluation.	Evaluation is completed for the application. Application is now undergoing the regulatory decision phase, after which a regulatory decision letter*would be Issued.

Table 2: Method of Evaluation According to Product Categories in Malaysia

S No	Product Category	Method of Evaluation	
		Full Evaluation	Abridged Evaluation
1	Generics(Scheduled Poison)	√	Not Applicable
2	Generics(Non-Scheduled Poison)	All products from this category,unless stated in Abridged Evaluation	Includes, but not limited to the following: Antiseptics/ skin disinfectants; Locally actinglozenges /pastilles;Topical nasal decongestants; Emollient/ demulcent/ skinprotestants; Keratolytics;

4. Conclusion

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 stake holders. Moreover, regional cooperation on standards and conformance compels standards officers, regulators as well as industry to meet frequently and network effectively. The focus is 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.

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