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Review Article

Regulatory Requirements for Registration of Generic Products in Singapore & Thailand

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ABSTRACT

The ASEAN pharmaceutical market has experienced strong growth and a rise in the regional standard of living which have made it a region of interest for companies looking to explore new business opportunities. The ASEAN Pharmaceutical market represents huge potential for companies looking to expand operations. Notably, there is strong interest in R&D for generics in this region, which are expected to grow from 8.3% of the total market in 2010 to 12.8% by 2015, when they will be worth USD 12.3bn. Within the next decade, Asia is expected to overtake Europe in pharmaceutical sales, driven by growth in key emerging markets Eightyfive percent of the world's population lives in the emerging markets., and during the past 5 years, all real economic growth has come from these markets. Some observations help to explain why many large pharmaceutical companies have increased their presence in emerging markets in recent years - in particular in ASIA. Notably, this growing presence is increasingly moving beyond the use of contrct resesrch organizations and marketing of established products to include early – stage research aimed at specific medical needs for patients in these regions.

Keywords: ASEAN Common Technical Dossier (ACTD), Regulatory Requirements, Thai FDA (Thailand Food Drug and Administration).

INTRODUCTION

The ASEAN (Association of Southeast Asian Nations,) 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) joined ASEAN.

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 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."

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 systems implemented in the ICH region, development of common technical dossiers with a view of arriving at MRAs (Mutual Recognition Arrangements).

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 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 attached:

- Singapore and Malaysia by December 2005
- Thailand by December 2006
- Indonesia and Vietnam by December 2007
- Philippines, Cambodia, Laos and Brunei by December 2008.

As the full implementation of the ASEAN requirements (like ACTD and ACTR) in the ASEAN countries is not yet finalized, a prolongation/transition period was done. There is an interim period agreed wherein ACTD and national formats allowed in most of the ASEAN countries, whereas in some countries like Singapore ICH CTD is accepted.

The full implementation of ACTD for new products was expected by 31 December 2008 whereas the full implementation for currently registered products is expected to be done until 01 January 2012. 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 became 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 the lack of 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 don't 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- Introduction to Respective Regulatory authorities[1]

1.1 Singapore's Drug Regulatory System

The Center for Drug Administration (CDA) and its drug registration system were established in Singapore in 1987. On 1 April 2001, the Health Sciences Authority (HSA) was established and charged with regulation of health products.3 In January 2004; CDA was placed under the HSA and given responsibility for regulation of new drugs. Pharmaceutical products in Singapore are regulated by many laws and regulations; the main legislative framework includes: • the Medicines Act, 4 enacted in 1987 to ensure that marketed medicinal products in Singapore meet appropriate standards of safety, efficacy and quality the Health Products Act, 5 enacted in 2007 to expand regulatory practice to include all health products, such as medical devices, cosmetics, traditional Chinese medicines and supplements used for health purposes.

1.1.1 Health Sciences Authority (HSA)

HSA is a multi-disciplinary agency. It applies medical, pharmaceutical and scientific expertise to protect and advance public health and safety. The organization serves three key functions: It is the national regulator for health products; it secures the national blood supply through its operation of the national blood bank – Bloodbank@HSA; and it represents the national expertise in forensic medicine, forensic science and analytical chemistry testing capabilities. These support other regulatory and compliance agencies in the administration of justice and in safeguarding public health.

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1.2 Thailand's Food and Drug Administration (FDA)

The Thai FDA regulates the safety, efficacy, and quality of health products. It is split into two divisions, the Support Division and the Health Product Control Division. The Bureau of Drug Control (BDC) and the Bureau of Medical Device Control (BMDC) operate under the latter. These are each responsible for the development and review processes of products within their remit. Regulatory policy and enforcement are handled by six committees under the FDA, including a committee on drugs and a committee on medical devices. These committees serve as law enforcement agencies to ensure compliance with the Drug Act of 1967 and the Medical Devices Act of 1988.

ASEANHARMONISE GUIDELINES FOR GENERIC FILLING[2]

- ✓ ASEAN guidance on ACTD
- ✓ ASEAN guideline for validation of analytical procedures
- ✓ ASEAN guideline on process validation
- ✓ ASEAN guideline for the conduct of Bio availability and Bio equivalence studies
- ✓ ASEAN guideline for drug product stability study

OBJECTIVE

- ➢ To define the pharmaceutical generic product and their regulations in ASEAN countries (Singapore and Thailand)
- ➢ Overview of HSA (Health Science Authority)-Singapore
- ➢ Overview of FDA (Food Drug Administration)- Thailand.
- ➢ Overview of ASEAN (Association Of South East Asean Nations)
- ➢ About ACCSQ pharmaceutical Product Working Group
- ➢ Review of Generic Drugs Organization
- ➢ To understand the evaluation of pharmaceutical generic product
- ➢ To understand the regulatory pathway for pharmaceutical generic product
- ➢ To evaluate stability studies of pharmaceutical generic product
- ➢ To consider the GMP & manufacturing requirements for pharmaceutical generic product
- ➢ To consider the life-cycle management requirements of pharmaceutical generic product
- ➢ To frame the post marketing safety reporting of pharmaceutical generic product

WORK METHODOLOGY

Research was done mainly on collection of data from official websites of HAS and Thai FDA and generic drug regulations and their approvals for market authorization.
The research carried out with the collected data by analyzing the terms of the below parameters:

Types of study

The study was conducted with an objective to chalk out the regulatory framework for generic drug legislations and guidelines.

Source of data

Major part of secondary data collection was done by means of following sources:

Literature review

Typically covered the regulatory guidelines published officially by government authorities, including the academic journals, online journals, market research reports, news paper articles, and other resources. And direct communication with Regulatory authorities.

Internet using the web page content

The literature was collected using numerous search engines and many more. Online books also served as a good source of information.

Criteria for selection of study parameters

The complete life cycle of generic drug consist of three phases. They are:

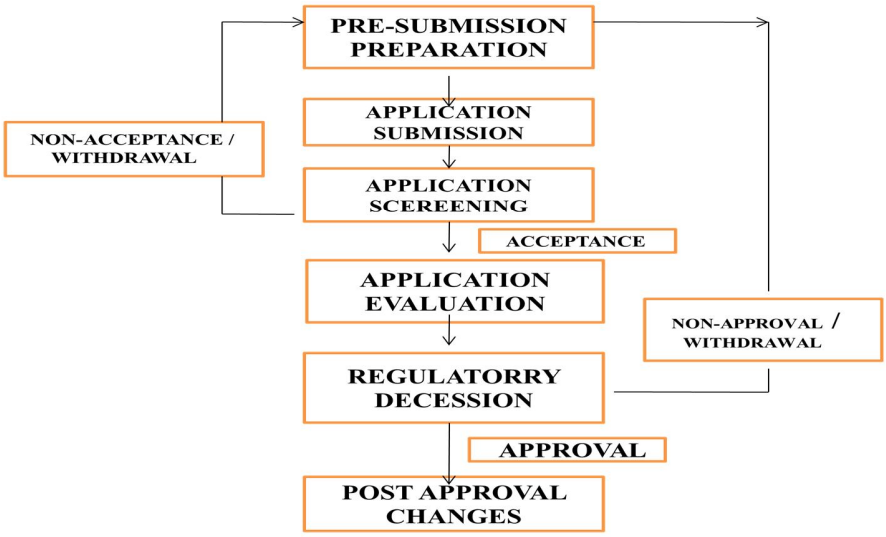
1) Pre approval
2) commercialization
3) Post approval

1) **Pre approval phase**: this is the innovative phase in which the development and regulatory aspects of the generic drug were determined. various steps in this phase are
   I. Determination of primary mode of action of generic drug.
   II. Request for designation.
   III. Determination of marketing application.
2) **Commercialization phase:** this is the main phase in which the innovative combination product will be commercialized in the markets.
   I. Clinical considerations.

II. Manufacturing and stability requirements.
III. Establishment of fees for product approval.

3) **Post approval phase**: in this phase different post markets requirements will be considered.
I. Post market surveillance.
II. Post approval changes.

DISCUSSION: REGISTRATION PROCEDURE FOR SINGAPORE



PRE-SUBMISSION PREPARATION: first step in the registration process is one of the most important because it involves:

1. Knowing which application to apply for;
2. Knowing which evaluation route to choose; and,
3. Arranging for a pre-submission consultation with HSA for advice, if required.

Application types

In applying for a new Product Licence for a medicinal product in Singapore, the categories of application: a generic drug application (GDA)

GDA Generic Drug Application Are Two Types:

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.

Evaluation routes: There are three types of evaluation routes are used

Full dossier

Applies to any product that has not been approved by any drug regulatory agency at the time of submission.

Abridged dossier

Applies to any product that has been evaluated and approved by at least one drug regulatory agency.

Verification dossier

Applies to any product that has been evaluated and approved by HSA‟s reference drug regulatory agencies, which include EMA*, US FDA, Health Canada, TGA and UK MHRA# .

PRE-SUBMISSION CONSULTATION: Applicants are encouraged to contact HSA prior to submission of an application if questions arise or clarification is required. There are two methods to contact HAS

- Pre-submission Inquiry via email
- Pre-submission Meeting

Pre-submission inquiry

The applicant may submit a pre-submission inquiry via e-mail if any clarification on medicinal product registration is needed prior to submission. The e-mail address is: HAS Med Prod Registration@hsa.gov.sg. The subject of the e-mail should state, Pre-submission inquiry", in order for the e-mail to be sent to the relevant officer.

Pre-submission meeting

For complex issues relating to an impending submission, applicants are advised to consult with HSA in a pre-submission meeting. The request for a consultation should be made in writing, with the purpose, agenda and proposed date & time for the meeting, via email to HAS Med Prod Registration@hsa.gov.sg a pre-submission meeting two months prior to the intended submission date of the application dossier.

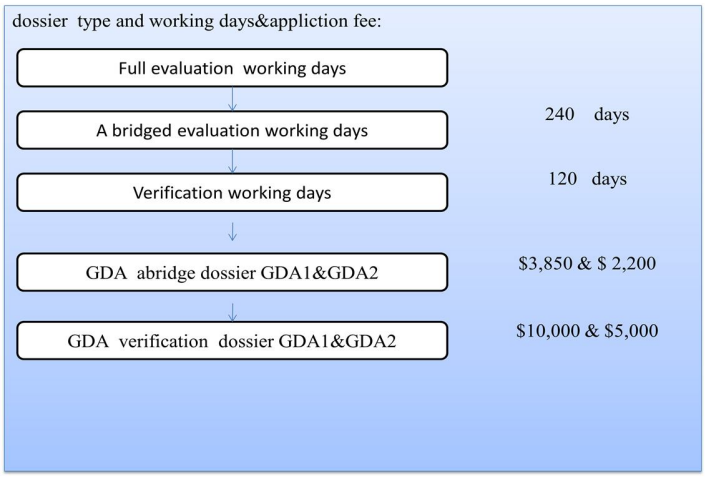
APPLICATION SUBMISSION: Application submission comprises two parts

- Prism application form
- Registration dossier

Dossier requirements

Documents	Location in		Module /part requierd for	
	ICH CTD	ACTD	Abridged GDA	Verification GDA
Administrative Documents and Product Information	Module-1	Part 1	yes	Yes
Commen technical document over view	Module-2	Part 2,3&4	SQOS+QOS	SQOS+QOS
Quality documents	Module-3	Part 2	yes	Yes
Non clinical documents	Module -4	Part 3	No	No
Clinical documents	Module -5	Part 4	BE studies	Yes

APPLICATION SCREENING:



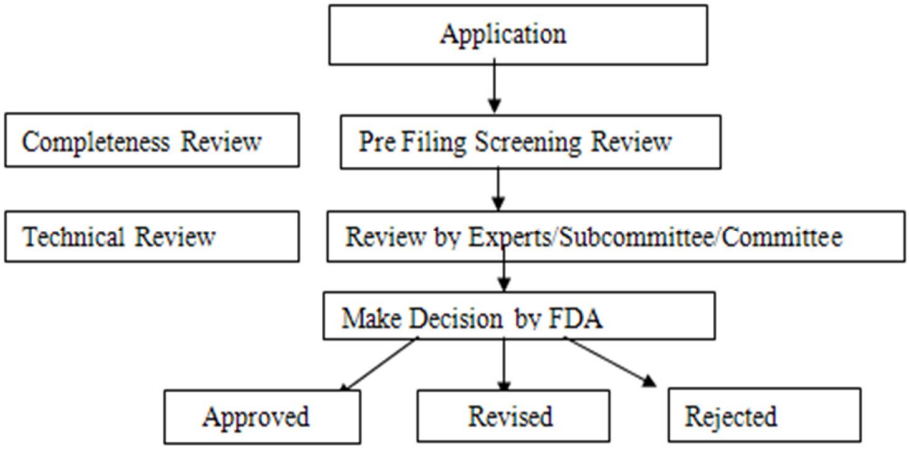
REGULATORRY DECESSION

A regulatory decision is made based on the outcome of HSA"s evaluation of the submitted data package. Applicants will be notified by letter of one of the following outcomes

- Approval – the application has satisfied the registration requirements for quality, safety and efficacy;
- Approvable – when the application has minor deficiencies;
- Non-approvable – when the application has major deficiencies; or

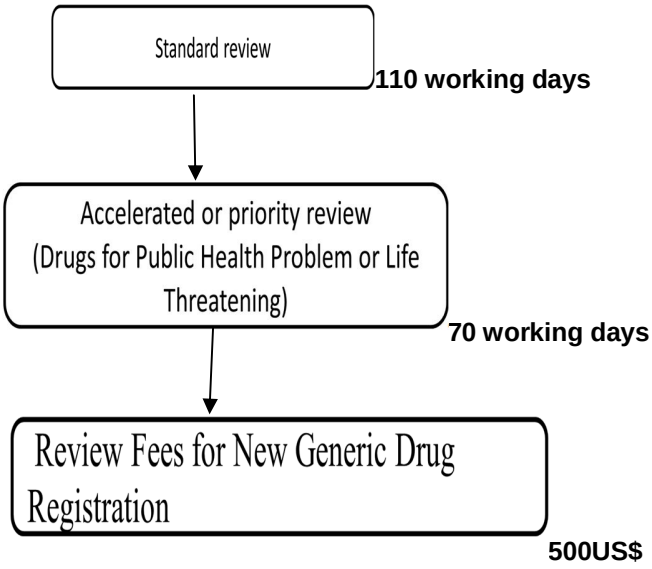
Rejection – when the response provided by the applicant fails to address the major deficiencies highlighted in HSA"s non-approvable decision

Thailand registration procedure



Registration process working days & applications fee:

Review Fees for New Generic Drug Registration



Upto five query no fee above five query per query 50 US $.

Guidance on the Administrative Data and Product Information

- **Application Form**
- **Letter of Authorization**
- **Certification**
- **Libeling**
- **Product Information**
- **Package Insert**
- **Product Data Sheet**
- **Patient Information Leaflet**

Labelling requierments in thailand:

- **Drug name Quantity , Active ingredient(s) ,**
- **Lot/batch number**
- **Manufacturer's name and province ,**
- **Date of production ,**
- **All labeling information must be in Thai or English. Thailand also requires that all other information companies intend to send to doctors, such as reminder advertisements or other promotional material, be included with the registration application. Any changes in labels for products already registered must be approved by the government.**

General Comparison of Singapore & Thailand Validity:

S.No	Country	Validity	Format Followed	Formate Include In Thesis
1	Singapore	5yrs	ACTD	ACTD
2	Thailand	5yrs	ACTD	ACTD

Non Clinical Documents comparision in singapore& thailand

NON CLINICAL DOCUMENTS	SINGAPORE	THAILAND
Non clinical overview	×	yes
Non clinical written & Tabulated summary	×	×
Non clinical study Reports	×	×
Literature references	×	yes

CLINICAL DOCUMENTS COMPARISION IN SINGAPORE& THAILAND

CLINICAL DOCUMENTS	SINGAPORE	THAILAND
Clinical Overview	×	yes
Clinical Summary	×	×
Tabular Listing of All Clinical Studies	×	×
Clinical Study Reports	×	Only BE
List of Key Literature	×	yes

COMPARISION OF ADMINISTRACTIVE DOCUMENTS IN SINGAPORE & THAILAND:

S.NO	ADMINISTRATIVE DOCUMENTS	SINGAPORE	THILAND
1	Application Form	yes	yes
2	Copy of valid certificate of brand Name clearance		
3	Certificate of Pharmaceutical product	yes	yes
4	Free Sale Certificate	×	×
5	Good Manufacture Practice	yes	yes
6	License for pharmaceutical Manufacture	yes	yes
7	Site Master File	×	yes
8	Permission for manufacturing & Marketing in country of origin	×	×
9	Letter of Authorization	yes	yes
10	Labeling Documents	yes	yes
11	Patent Information	yes	yes
12	Summary Product Characteristics	yes	yes
13	Patient Information Leaflet	yes	yes
14	Product Information Already Approved In Any State/country	yes	×

Technical documents comparision of singapore & thailand :

Technical Documents	Singapore	Thiland
Drug Substance	No	×
Quality Overall Summary	No	Yes
General Information	No	Yes
Manufacture Of Drug Substance	No	Yes
Characterization	No	Yes
Quality Control Of Drug Substance		Yes
Reference Standards	No	Yes
Container Closure System	No	Yes
Stability	Yes	Yes
CEP (Certificate Of European Pharmacopeia)	Yes	No
Drug Master File	Yes	No
Drug Product	Yes	Yes
Description & Composition	No	Yes
Pharmaceutical Development	Yes	Yes
Manufacture	Yes	Yes
Quality Control Of Excipients	No	Yes
Quality Control Of Finished Product	Yes	Yes
Reference Standard	Yes	Yes
Container Closure System/ Packing	Yes	Yes
Product Stability	Yes	Yes
Product Interchangeability	Yes	Yes

Conclusion:

The official Health Authority in Singapore is (HSA) which ensure Registered pharmaceutical products are safe, efficacy, effective, and of good quality. Under HSA, CDA was formed which evaluate medicinal product in Singapore. Singapore is an Asian hub for biotechnology and research in Asia, because of its strong infrastructure for research and development and also attracted many global pharmaceuticals companies to operate the multifunction's plants. There are national regulations are Herbal medicines in Singapore but they are no restriction for their sale. But Thailand at very different stages of development. The economic situation & health expenditure vary from singapore country to thailand country. Most of population and low income country Thailand depend on generic drugs. But Singapore country like believe on innovation

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