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Regulatory Requirement for the Approval of generic Drug in Thailand as per ASEAN Common Technical Dossier (ACTD) – A Review

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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 Eighty-five 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 contract research organizations and marketing of established products to include early-stage research aimed at specific medical needs of patients in these regions.

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

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INTRODUCTION:

Generic Drug Product[1]

Generic medicines are those where the original patent has expired and which may now be produced by manufacturers other than the original innovator (patent-holding) company. The term “generic drug” or “generic medicine” can have varying definitions in different markets, however the term is commonly understood, as defined by the World Health Organization (WHO), to mean a pharmaceutical product which:

1. Is usually intended to be interchangeable with an innovator product,

2. Is manufactured without a license from the innovator company, and

3. Is marketed after the expiry date of the patent or other exclusive rights

There are differing legal requirements in different jurisdictions that define the specifics of what a generic medicine is. However, one of the main principles underpinning the safe and effective use of generic medicines is the concept of bioequivalence.

Bioequivalence has been defined as follows: two pharmaceutical products are

bioequivalent if they are pharmaceutically equivalent and their bioavailability (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards.

Criteria for the approval of marketing of Generic drug

Contain the same active ingredient as the originator medicine (inactive ingredients may vary)
Be identical in strength, dosage form, and route of administration
Have the same use indications
Be bioequivalent
Meet the same batch requirements for identity, strength, purity, and quality
Be manufactured under the same strict standards of good manufacturing practice regulations
Required for originator products.

Brief Insight on ASEAN (Association of South –East Asian Nation) Regulatory agencies

1) Brunei Darussalam[2]

Department of pharmaceutical service which is responsible for pharmaceutical matters under the Ministry of the Health. Brunei participates in work of ASEAN consultative committee on standard and quality (ACCSQ) .

2) Cambodia[2]

The system of drug registration started in 1994.The Department of Drug and Food(DDF) is the regulatory agency under the Ministry of Health. Responsible for ensuring safety, efficacy, quality of drug, device and safety, efficacy of food and cosmetics.

3) Indonesia[3]

Indonesia is largest country in the ASEAN in terms of Population. Indonesian pharmaceutical industry produces drugs under the license more commonly the generic drugs The Indonesian Drug and Food Control Agency(BPOM) is the regulatory body of the Indonesia .

4)Lao People's Democratic Republic[4]

Prior to 1990, The Ministry of health was directly in charge of matters of pharmaceuticals through Department of Pharmacy.

5) Malaysia[5]

Regulation of pharmaceutical comes under the Drug Control Authority (DCA) and National Pharmaceutical Control Bureau (NPCB) as its secretariats.

6) Myanmar[6]

In 1992 The National Drug law was enacted regulation for the enforcement by Ministry of Health comes in 1993. The Food and Drug Administration (FDA) established since 1995, takes care of the safety and quality of Food, Drugs, Medical Devices and Cosmetics the center body is the Myanmar Food and Drug Board Authority (MFDBA).

7) Philippines[7]

The Food, Drug and Cosmetic Act provide the legal framework to the Pharmaceutical regulation. The Bureau of Food and Drugs (BFAD) within the Philippines Department of Health, is the responsible to carry out activities stipulated in the act.

8) Singapore[8]

Health Science Authority (HAS) been formed on 1 April 2001 with the integration of five specialized agencies under the Ministry of Health: the Centre for Drug Evaluation; Institute of Science and Forensic Medicine; National Pharmaceutical Administration; Product Regulation Department; and Singapore Blood Transfusion Service. Today, the agency's professional knowledge, skills and competencies are

9) Vietnam[9]

The Ministry of Health is responsible for the regulation. The Drug Law regulates the manufactured, distribution, selling of the medicinal product. Three departments, the Drug Administration, the Pharmaceutical Inspection Department and the National Institute of Drug Quality Control are charged with the drug regulation.

10) Thailand[10,11]

Food, Drug and Administration of Thailand (FDA-Thailand)

Consumer protection activities on food and drugs have begun in Thailand since 1909

Established in 1922 as a Narcotic division

In 1937, the agency renamed to Food and Drug division

In 1953, the agency renamed to Division of Food and Drug Control.

In 1974, Division of Food and Drug Control was promoted to be the Office of Food and Drug Administration, having the status as department of Ministry of Public Health.

Roles and Responsibility

Major is to ensure that health products (i.e. food, drug etc.) available to consumers are of standard quality, efficacy, and safety.

Main tasks are to control and monitor both pre- and post-marketing phases of manufacture, import, transport, storage and sale

Thailand has its own drug registration format and also follows ASEAN CTD.

ASEAN Pharmaceutical Harmonization[12]

History

Association of Southeast Asian Nations (ASEAN) established on 8th Aug 1967 in Bangkok by 5 original members namely Indonesia, Malaysia, Philippines, Singapore and Thailand
Brunei Darussalam joined on 8th Jan 1984
Vietnam on 28th July 1995
Lao PDR and Myanmar on 23th July 1997
Cambodia on 30th April 1999

Strategies of harmonization

Comparison of existing product registration requirements for pharmaceuticals
Development of common technical requirements (CTR) for pharmaceutical product registration
Development of common technical dossier(CTD) towards MRA
Implementation of harmonized ASEAN Pharmaceutical Product Dossier

ASEAN Harmonized Products

ASEAN Common Technical Requirements and Dossier (ACTR/ACTD) on Quality, Safety and Efficacy plus Administrative Data and Glossary
Guidelines on Analytical and Process Validation
Guidelines on Stability Studies
Guidelines for Bioavailability/Bioequivalence

ASEAN Common Technical Dossier (ACTD) [13]

Association of South – East Asian Nations (ASEAN) follows ASEAN – CTD. ASEAN is a geo-political and economic organization of ten countries located in Southeast Asia as shown in Figure 1, which was formed on August 8, 1967 by Indonesia, Malaysia, Singapore and Thailand. Since then the membership has extended to Brunei, Myanmar, Philippines, Cambodia, Laos PDR and Vietnam. Even though some of the individual ASEAN countries have their own drug registration formats, all ASEAN countries accept the ACTD.

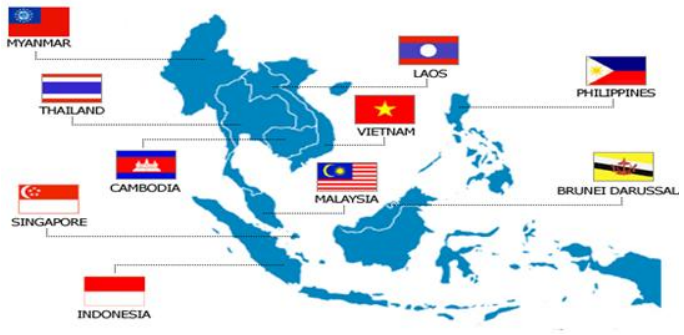

Figure 1: Map of ASEAN countries

Advantages of ACTD (ASEAN Common Technical Dossier)[14]

One dossier can be used for the application of registration of pharmaceutical for human use for whole region, rather than filling individual application for different countries.
Significantly reduce the time and resources used for compiling an application.
Transparency in the regulatory authorities of member countries.
Transparency in the structure of regulatory framework to be follows for single filling.
Faster review and approval process those are more transparent.
Reduced costs for industry, as the format is less expensive for dossier preparation.
Improved access to medicines in all countries.
Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements.
Single filling, single monitoring, improved public trust in the Approved medicines.

Drug Registration Procedure and Approval System of Thailand[15]

Thai Regulatory System

The Drug Act provides that decisions of the Secretary-General, FDA, be made with advice of a Drug Board made up of principal relevant Departmental Directors General in the MoPH (Ministry of Public Health) as well as representatives from related organizations, plus five to nine drug experts.

The Drug Board meets monthly and may give recommendations or opinions on licensing and registration decisions such as approved, withdraw or suspend the licenses.

Licensing Regulation in Thailand

The drug Act requires that persons who wish to sell, produce, or import drugs into Thailand have to obtain a license from the FDA.

Drug Registration Process

Applicants: Only authorized licensees are qualified to apply for product registration.

Manufacturing plants: GMP compliance

Flow Chart of Drug Review Process(as shown in figure 2)

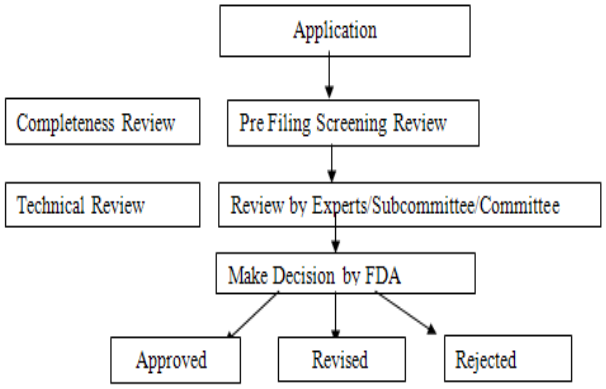

Figure 2: Flow chart of drug review process in Thailand

Review Period of New Generic Drug Registration

Track 1: Standard Review

110 Working Days

Track 2: Accelerated or Priority Review

(Drugs for Public Health Problem or Life Threatening)

70 Working Days

Review Fees for New Generic Drug Registration

Fees of New Generic Drug Registration500 US $.

Up to five query no fees.

Above five query per query 50 US $.

The ASEAN Common Technical Dossier (ACTD) For the Registration of Pharmaceuticals for Human Use Guideline[16]

This ASEAN Common Technical Dossier (ACTD) is a guideline of the agreed upon **common format** for the preparation of a well-structured Common Technical Dossier (CTD) applications that will be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals for human use. **This guideline describes a CTD format that will significantly reduce the time and resources needed to compile applications for registration** and in the future, will ease the preparation of electronic documental submissions.

Throughout the ACTD, the display of information should be **unambiguous and transparent**, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on either **A4 or 8.5 x 11 papers.** The lefth and margin should be sufficiently large that information is not obscured by the method of binding. Font and size,(**Times New Roman, 12-point font**), for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Every page should be **numbered**, with the first page of each part designated as page 1. For a paper, Common Technical Acronyms and abbreviations should be defined the first time they are used in each part.

The ASEAN Common Technical Document is organized into four parts.

Part I. Table of Contents, Administrative Data and Product Information

Part II. Quality Document

Part III. Nonclinical Document

Part IV Clinical Document

Part I: Table of Contents, Administrative Data and Product Information

Section A:

Introduction

This section contains the Administrative Data and Product Information which is the Part I of the ASEAN Common Technical Document (ACTD) for application to the Drug Regulatory Authority

Section B:

Table of Contents

1. Application Form

2. Letter of Authorization **(where applicable)**

3. Certifications

4. Labeling

5. Product Information

Section C:

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

Labeling Requirement in Thailand:

The Drug Act of 1967, as amended in 1988, contains labeling requirements. Printed packaging material, including package inserts, must be submitted for approval. The following information must appear on the package label.

Some of the labeling requirements for drugs include:

Drug name

Quantity

Active ingredient(s)

Lot/batch number

Manufacturer's name and province

Date of production

Drugs classified as Specially-controlled drugs, dangerous drugs or common household drugs should be labeled as such Expiration date Where applicable and on a red label: "Ya Antarai" (Dangerous Drug) in Thai, "Special Control" in Thai, "External or Topical Use" in Thai.

Package inserts also are required and are expected to contain the product name; active ingredients; indications; instructions for use, including warnings, precautions, adverse drug reactions, and contraindications; dosage, and storage

for use, including warnings, precautions, adverse drug reactions, and contraindications; dosage, and storage information .

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.

PART II- QUALITY DOCUMENT

ASEAN Specific Quality Guidelines

ASEAN Guideline for Validation of Analytical Procedures

This guideline is mainly adopted from two ICH guidelines ICHQ2A and ICHQ2B.This guideline givesknowledge about Analytical method validation, as an important part of dossier submission for Drug registrationin ASEAN. This guideline was developed with Thailand as lead country in year 2003.

ASEAN Guideline on Process Validation

Process Validation is a means of ensuring that manufacturing processes are capable of consistently producing a finished product of the required quality. It involves providing documentary evidence that key steps in the manufacturing process are consistent and reproducible. This guideline was developed with Singapore as lead country in year 2003.

ASEAN Guideline for conduct on BA/BE Studies

Bioequivalence studies are the preliminary requirement for generic products to enter in the market. The manufacturer (generic) must be in limit with that of innovator (branded) formulation within the limits approved by respective governing bodies. The ASEAN Guideline for the conduct of Bioavailability and Bioequivalence studies was developed with Malaysia as lead country and adopted in 2004.

ASEAN Guideline for Stability Studies

ASEAN guideline for Stability Studies is based on ICH Guidelines ICH Q1A (R2), Q1 B, Q1C Q1D, Q1EQ1F), EMEA Guideline, Who Guideline, ASEAN GMP guideline, Expert Consultation Meeting. This guideline was developed with Malaysia as lead country and adopted in 2004 (shown in table 1).

Table 1: ASEAN Storage Condition

PARAMETER	STORAGE CONDITION
Products in containers permeable to water vapors	30°C ±2°C/75%RH±5% RH
Products in containers impermeable to water vapors	30°C ±2°C/RH not specified
Accelerated studies	40°C ±2°C/75%RH±5% RH
Stress studies for analytical process validation	40°C ±2°C/75%RH±5% RH

Section A: Table of Content

Section B: Quality Overall Summary

Section C: Quality Data

Quality Regulatory Requirements for the Generic Drug(shown in table 2)

Table 2: Quality Regulatory Requirements for the Generic Drug

NO.	PARAMETERS	COMPONENTS
S	**Drug Substance**	
S 1	**General Information**	
	1.1. Nomenclature	Information from the S1
	1.2. Structure	Structural information
	1.3. General Properties	Physico- chemical characteristic
S 2	**Manufacture**	
	2.1. Manufacturers	Name and Address of manufacturers
	2.2. Description of Manufacturing Process and Process Controls	Information on the manufacturing process, which purification and modification reaction, filling, storage and shipping conditions.
	2.3. Control of Material	Starting materials, solvents, reagents, catalysts, and any other materials used in
	2.4. Controls of Critical Steps and Intermediates	− Critical steps : Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.
		− ensure that the process is controlled. − Intermediates : Specifications and Analytical procedure, if any, for intermediates isolated during the process.
	2.5. Process Validation and/or Evaluation	Process validation and/or evaluation studies for aseptic processing and sterilization.
	2.6. Manufacturing Process Development	Description and discussion of significant changes made to the manufacturing process
S3	**Characterization**	
	3.1. Elucidation of Structure and other characteristics	− Compendial requirements or appropriate information from the manufacturer
	3.2. Impurities	− Summary of impurities monitored or tested for during and after manufacture of drug substance − Compendial requirements or appropriate information from the manufacturer
S4	**Control of Drug Substance**	
	4.1. Specification	− Detailed specification, tests and acceptance criteria. − Compendial specification or appropriate information from the manufacturer
	4.2 Analytical Procedures	− The analytical procedures used for testing of drug substance. − Compendial methods or appropriate information from the manufacturer
	4.3. Validation of Analytical Procedures	− Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance − Non-compendial methods
	4.4. Batch Analysis	Description of batches and results of the analysis to establish the specification
	4.5. Justification of Specification	Justification for drug substance specification
S5	**Reference Standard and material**	
		− Compendial reference standard.
S6	**Container Closure system**	
		Descriptions of the container closure systems.

S7	**Stability**	
		Stability Report Literature Data
P	**Drug Product**	
P1	**Description and Composition**	
		Description − Dosage form and characteristics. − Accompany in reconstitution diluents (s) if any. − Type of container and closure Composition used for the dosage form and reconstitution diluents (s), if applicable. Name, quantity stated in metric weight or measures, function and quality standard
P2	**Pharmaceutical Development**	
	2.1. Information on Development Studies	Data on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes and usage instruction are appropriate for the purpose specified in the application.
	2.2.Components of the Drug Product	− Active ingredient − Excipients Justification of the choice of excipients
	2.3. Finished Product	− Formulation Development A brief summary − Overages Justification of any overage in the formulation(s) − Physicochemical and Biological Properties
	2.4. Manufacturing Process Development	− Selection and optimization of the manufacturing process − Differences between the manufacturing process (es) used to produce pivotal clinical batches
	2.5. Container Closure System	Suitability of the container closure system used for the storage, transportation (shipping) and use of the finished product.
	2.6. Microbiological Attributes	Microbiological attributes of the dosage form, where appropriate
	2.7. Compatibility	Compatibility of the finished product with reconstitution diluents (s) or dosage devices.

P3	**Manufacture**	
	3.1. Batch Formula	Name and quantities of all ingredients
	3.2. Manufacturing Process and Process Control	Description of manufacturing process and process control
	3.3. Control of Critical steps and Intermediate	Tests and acceptance criteria
	3.4. Process Validation and/or Evaluation	Description, documentation, and results of the validation and/or evaluation studies for critical steps or critical assays used in the manufacturing process.
P4	**Control of Excipients**	
	4.1. Specifications	Compendial requirements or appropriate information from the manufacturer
	4.2. Analytical Procedures	Compendial requirements or appropriate information from the manufacturer
	4.3. Excipient of Human or Animal Origin	Information regarding sources and or adventitious agents.
	4.4. Novel Excipients	For excipient(s) used for the first time in a finished product or by a new route of administration, full details of manufacture, characterization and controls, with cross reference to supporting safety data (non clinicalor clinical)
P5	**Control of Finished Product**	
	5.1. Specification	The specification(s) for the finished product
	5.2. Analytical Procedures	Analytical procedures used for testing the finished product
	5.3. Validation of Analytical Procedures	Information including experimental data, for the analytical procedure used for testing the finished product Non-compendial method
	5.4. Batch Analyses	Description and test results of all relevant batches
	5.5. CharacterizationofImpurities	Compendial requirements or appropriate information from the manufacturer
	5.6. Justification of Specification	Justification of the proposed finished product specification(s). Compendial requirements or appropriate information from the manufacturer

		specification(s). Compendial requirements or appropriate information from the manufacturer
P 6	**Reference Standards and Materials**	
		Information on the reference standards or reference materials used for testing of the Finished product. Compendial requirements or appropriate information from the manufacturer
P 7	**Container Closure system**	
		Specification and control of primary and secondary packaging material, type of packaging and the package size, details of packaging inclusion (e.g. desiccant, etc)
P 8	**Stability**	
		Stability report : data demonstrating that product is stable through its proposed shelf life. Commitment on post approval stability monitoring
P 9	**Product Interchangeability Equivalence evidence**	
		− In Vitro Comparative dissolution study as required − In Vivo Bioequivalence study as required

Part III: Non-Clinical Data

Not Applicable for Generic Drug.

Part –IV: Clinical Data

In the ASEAN region for filing of Generic Drug their main emphasis on quality document. They permit the official research article related to drug product in clinical Data.

Conclusion:

ASEAN's drug regulatory authorities and industry have worked very close regionally but also increasingly with global organizations to develop a number of harmonized documents. These are the common submission dossier known as the ASEAN Common Technical Dossier and the ASEAN Common Technical Requirements, which are steadily evolving.

Even though ACTD format is mandatory from 2009 the member countries have their ownrequirements for registration process like administrative documents, labeling. Regional harmonization can only be achieved by bridging the gaps between ASEAN member countries in the establishment of regulatory systems and implementation ofcommon requirements.

Global co-operation provides opportunities for development and improvements, paving the way for international recognition. Establishing MRA is crucial to ensure effective harmonization.

Largely they have been realized already, the next step will be to focus on mutual recognition of pharmaceutical registrations and implementing a harmonized placement system. There is still much work to be carried out in the implementation.

The future will show if this can be achieved by the versioned end goal of economic community in 2015.

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