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Marketing Authorization and Its Requirements in Thailand

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ABSTRACT

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 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."

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INTRODUCTION:

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 region is 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 the future[1-5]. Moreover, the worldwide pharmaceutical market is shifting from mature to pharmerging or tier-2 pharmerging market. The pharmaceutical industries in each of the 10 ASEAN member countries - Brunei, Myanmar, Cambodia, Indonesia, Laos, Malaysia, Philippines, Singapore, Thailand, and Vietnam – are at very different stages of development. The economic situation & health expenditure vary from one country to another country. Most of the population in these low-income countries like Vietnam, the Philippines, Indonesia & Thailand depend on generic drugs. But countries like Singapore and Malaysia believe in innovation. It is noticeable that harmonization of standards and regulations as well as MRA's are a 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 established the so-called ASEAN Common Technical Document (ACTD) and the ASEAN Common Technical Requirements (ACTR)[6-7] 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 is a set of written requirements or guidelines intended to guide applicants to be able to prepare application dossiers in a way that is consistent with the expectations of all ASEAN DRAs.

About the Country:

Area: 513,115 sq km (196,512 sq miles)

Population: 64,076,033 (2011 as per statistics)

Capital city: Bangkok (9.4 million)

People: Thai, Chinese, and Malay

Languages: Thai, Yawi (far South)

Religion(s): Buddhist (94%), Muslim (5%), Other (inc. Christian, and Hindu 1%)

Currency: Baht

Government: Constitutional Monarchy

Legal Framework and Regulations[8]

- Covers the acts under its Legal framework and Regulations
- Drug Act 1987 (5th revision)
- Food Act 1979
- Cosmetic Act 1992
- Narcotic Act 1987 (3rd revision)
- Psychotropic Substances Act 1992(3rd revision)
- Volatile Substances Act 1990
- Medical Devices Act 1988

Medicines are classified into two major groups: **Modern and Traditional drugs**.

Modern Drugs are further divided into four categories, namely:

1. Household remedies whose sales require no license;
2. Ready-packed drugs that can be sold in drugstores by nurses or other medical professionals;
3. Dangerous drugs; and
4. Specially controlled drugs.

Dangerous drugs can be bought without a prescription but must be dispensed by pharmacists. Drugs that may possess a potentially harmful effect on health, if misused, will be listed in the last category whose sales require a prescription.

Traditional drugs are those intended to be used in indigenous or traditional medical care as monographed in the official pharmacopeia of traditional medicines or those declared by the Minister of Public Health as traditional medicines or those permitted to be registered as traditional medicines. The control and registration of drugs in this group are less stringent than those for modern drugs.[9]

❖ **Format followed:**

ACTD format with some country-specific requirements.

❖ **PHARMACEUTICAL REGULATIONS IN THAILAND**

a. Regulatory Procedure

Thailand's national drug control system stems from its Drug Act BE 2510 (1967) and its four amendments. The MOPH, along with the Drug Control Division of the FDA, is responsible for administering the system. Companies interested in manufacturing or exporting pharmaceutical products must obtain prior approval from the FDA. Both manufacturers and importers are required to get a license to produce, sell or import any pharmaceutical products into Thailand.

The pharmaceutical control system is divided into a pre-marketing and post-marketing phases. In the pre-marketing phase, companies must obtain a license to produce, sell or import any

pharmaceuticals into Thailand, as well as register their products in the country. The Bangkok metropolitan area's Drug Control Division and surrounding provincial health offices are in charge of licensing. There are nine categories of licenses, including a license to produce, a license to sell, a license to act as a wholesaler of modern drugs, etc.[10]

b. Registration: Pre-Marketing Phase

The pre-marketing phase also includes the registration of products. FDA's Drug Control Division is in charge of Steps 1 and 3, while the Department of Medical Sciences handles Step 2. Thailand also has a regulatory procedure for new drug registration.

Generally, there are three important steps for drug registration in Thailand:

1. Application for permission to manufacture or import drug samples. (at Food and Drug Administration)

2. Application for approval of drug quality control and analytical methods. (at Department of Medical Science)

3. Application for granting of a drug registration certificate. (at Food and Drug Administration)[10]

Registration: Post-Marketing Phase

In the post-marketing phase, following registration and sale of pharmaceuticals, the quality control system at the government level tends to focus on output, i.e. the last stage of the production process, rather than input/raw materials or in the actual production process itself. In this phase, pharmaceutical quality monitoring is done by regular inspection and pharmaceutical sampling through the National Adverse Drug Reactions Monitoring Center and its 19 regional offices. Academics from outside the FDA are often hired to consider technical papers involved in drug registration. However, follow-up drug reevaluations are not routinely performed.[10]

❖ **Drug Registration**

The registration process is necessary to ensure the quality, safety, and efficacy of the drugs being marketed in the country. Only authorized licensees are qualified to apply for product registration.

Manufacturing plants, in which drug products are manufactured, are subject to inspection for GMP compliance.

According to the new Drug Act (expected to be enacted within 2003), a certificate of product registration is valid for five years from the date of issuance. The process of drug registration will be carried out in 2 channels, which differ in degrees of control and dossier submission:

1. Registration of general medicines
2. Registration of Thai traditional medicines

Because of differences in the requirements for dossiers to be submitted for product approvals, the general medicines will have to be further defined as:

- **Generics** whose registrations require only dossiers on product manufacturing and quality control along with product information.
- **New medicines** whose registrations require a complete set of product dossiers.
- **New generics** whose registrations require dossiers of bioequivalence studies in addition to the required dossiers for generics submission.[10]

Generics means pharmaceutical products with the same active ingredients and the same dosage forms as those of the original products but manufactured by different manufacturers.

New medicines include products of new chemicals, new indications, new combinations or new delivery systems, and new dosage forms.

New generics are medicines with the same active ingredients, doses, and dosage forms as those of the new compounds registered after 1992. [10]

➢ **The process of drug registration of generic medicines is divided into 5 procedures**:

- Generic drug registration
- Traditional drug registration
- New drug registration

– Original New Drug

– New Generic Drug

- Biological product registration
- Herbal medicine registration

Generic Drug registration involves *three* steps:

1. Application for permission to manufacture or import drug samples. (at Food and Drug Administration)

2. Application for approval of drug quality control and analytical methods. (at Department of Medical Science)

3. Application for granting of a drug registration certificate. (at Food and Drug Administration)

The New Generic Drug registration procedure has the following steps:

- A protocol on Bioequivalence study must be submitted for 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.

The details of drug registration are listed on the official site ***www.fda.moph.go.th*** of the Thai FDA.

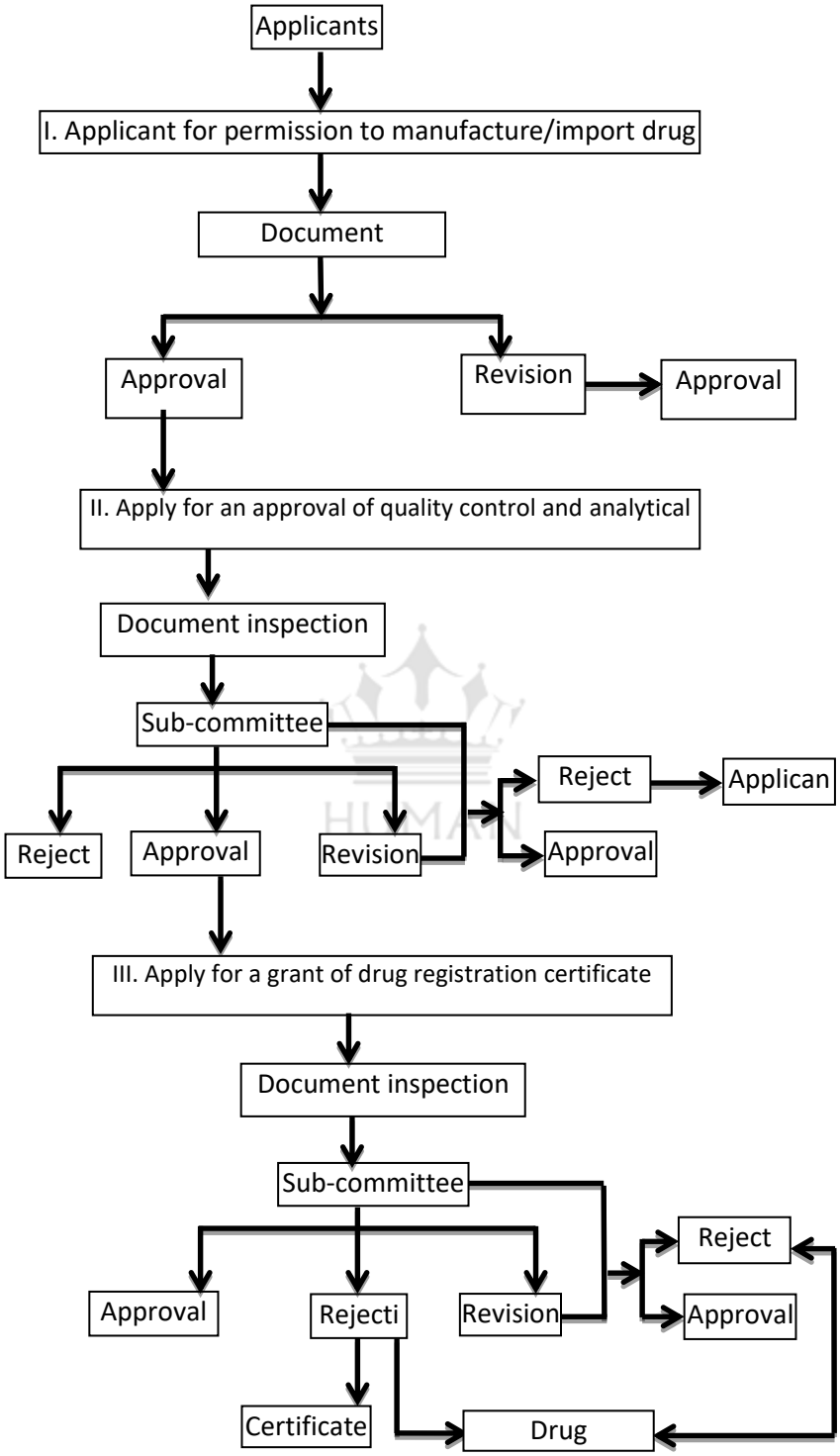

Figure 1. A: Registration Of Generic Drugs[11]

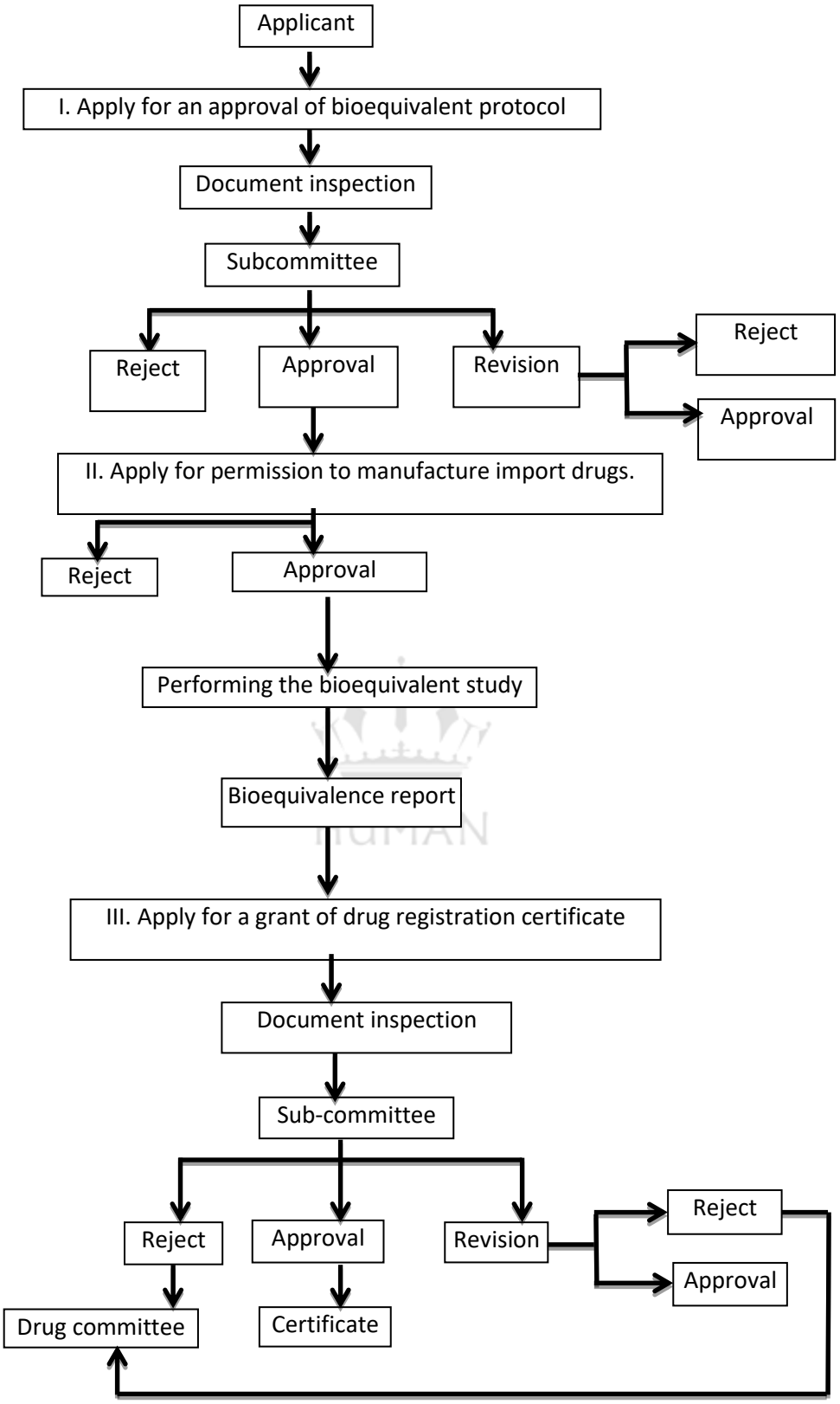

Figure 1. B: Registration Of New Generic Drugs[11]

❖ **Documents Required for Generic Drug Registration[11]**

The procedure of generic drugs registration is divided into 2 main steps:

Step 1: Application for permission to import or manufacture drug samples intended to be registered.

The following documents are required:

a. Application form to be filled by authorized licensee

b. Drug formula [active ingredients(s) only]

c. Drug literature

d. Drug labeling and packaging

Step 2: Application for the approval of the ***granted credential certificate.***

The following documents are required:

Application form to be filled by an authorized licensee

a. Permit to manufacture or import drug sample

b. Drug sample

c. Pharmacological and toxicological study (if any)

d. Clinical trials, safety, and efficacy study (if any)

e. Complete drug formula

f. Drug literature

g. Labeling and packaging should consist of the name of the drug, registration number, the quantity of drug per packaging, formula which shows active ingredient (s) and quantity of strength, lot no. batch control number, name of manufacturer and address, manufacturing date, the words "dangerous drug"/"specially controlled"/ "for external use"/ "for topical use" written in Thai and red color if the drug is considered to be one of them, the word "household

remedy drug" written in Thai if the drug is considered to be, the word "for veterinary use" written in Thai if the drug is considered to be, and the expiry date.

h. Certificate of Free sale (in case of imported drug)

i. Manufacturing method

j. In-process control with the relevant acceptable limits

k. Raw material specifications of active(s) and inert ingredients with the corresponding control methods in details

l. Finished product specification with the corresponding control methods in detail

m. Certificate of analysis of active ingredient (s) (raw material) [To be required in case of that active substance does not conform to official pharmacopeias (USP, NF, BP,……etc.)

n. Drug analytical control method

o. Packaging

p. Storage condition

q. Stability studies of the finished product

r. Certificate of GMP (in case of imported drug)

Note: Certificate of Free Sale should be issued/legalized by the competent authorized officer and endorsed by the Thai Embassy / Thai Office residing in correlation to the country where the documents are being issued.[10]

❖ **FEES FOR APPROVAL**

Registration fees = 12,0000 Thai Bhat (approx. 4000 US$)

❖ **Labeling requirements (country-specific) – Thailand [12]**

According to the various Drug Acts, the following words have to **be written in Thai;**

Dangerous drug, especially controlled drug, For external use, Common household remedy, Topical use, Expiry date.

According to Ministerial notification there are **standard warning and precaution for specific drugs such as** Antibiotics, Antihistamines, Aspirin, Dipyrone, Phenylbutazone and Indometacin for internal use, Tranquilizer for internal use, Sedatives and Hypnotics, Anorexigenics, Antiepileptics, Imipramine, Mianserin, Contraceptive drugs, Diethyl Stilbestrol, Dienestrol, Hexestrol, Benzestrol, Corticosteroids for internal use, Corticosteroids for eye treatment, Antidiabetic drugs, Antineoplastics drugs, Arsenic compound, Atropine, Hyoscine, Hyoscyamine, Stramonium, Injection with Benzyl alcohol, Boric acid, Camphorated Opium Tincture, Cinchophen, Neocinchophen, Diamthazole for external use, Ephedrine, Hexylresorcinol, tetrachlorethylene, Iodine, Iodide for internal use, Laxative, Loperamide, Hair growth stimulant including Minoxidil, Theophylline and derivative, Combination of anabolic steroid and vitamins or anabolic steroid and cyproheptadine or anabolib steroid, vitamins and cyproheptadine, Combination with fat soluble vitamins, Glafenine, Floctafenine, Paracetamol, Angiotensin, Converting Enzyme Inhibitors, Solution with Ethyl alcohol, Retinoid and derivative for external use, Retinoid and derivative for internal use, Cisapride, Flutamide, Sildenafil, Ethambutol, Anti HIV drugs (non-nucleoside reverse transcriptase inhibitor), Famotidine, HMG-CoA reductase inhibitor and Anti-tuberculosis Drugs.

According to Ministerial Notification, some drugs are under limited distribution; these include:

- **To be used only in hospital**; Anticancer drugs, HIV treatment drugs, Anti-acne of Retinoid group, Cisapride, Misoprostol, Dinoprostone, Sulprostone, Combination of L- tryptophan for medicated supplement and Chloramphenicol for human use.

- **To be used in clinic and hospital**; New drug approval with the condition, Sildenafil, Caverject, and Muse.

❖ **Thailand BE studies:** [13]

Reference product/comparator product:

A 'Reference Product' must be an 'innovator' product. If the innovator product is not available in the country, an alternative comparator product approved by the drug regulatory authority of the country can be used.

Population:

The studies are accepted only if done on the Thai population.

International BE:

Not accepted

Guidelines followed:

Thai guidelines for the conduct of bioavailability and bioequivalence studies adopted From "ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies"

Table 1. A: General comparison

SR NO	COUNTRY	VALIDITY	FORMAT FOLLOWED	FORMAT INCLUDED IN THESIS
1	THAILAND	5 yrs	ACTD	ACTD

ONLY ACTD FORMAT

ADMINISTRATIVE DOCUMENTS COMPARISON

S. NO	ADMINISTRATIVE DOCUMENTS	THAILAND
1	Application Form	✓
2	Copy of Valid Certificate of Brand Name Clearance	✓
3	COPP	✓
4	FSC	✗
5	GMP	✓
6	License For Pharmaceutical Manuf.	✓
7	SMF	✓*1
8	Permission For Manufacturing & Marketing In Country of Origin	✓
9	LOA	✓
10	Labeling Documents	✓
11	Patent Information	✓
12	SPC	✓
13	PIL	✓
14	Mock Up And Specimen	✓
15	Environmental Risk Assessment	DEPENDS
16	Product Information Already Approved In Any State /country	✗

1=provided in 1st dossier then reference is sited.

TECHNICAL DOCUMENTS REQUIRED

	THAILAND
DRUG SUBSTANCE	
Quality Overall Summary	✓
General Information	✓
Manufacture Of Drug Substance	✓
Characterization	✓
QC of Drug Substance	✓
Reference Standards	✓
Container Closure System	✓
Stability	✓
CEP	✗
DMF	✗
	THAILAND
DRUG PRODUCT	
Description &Composition	✓
Pharmaceutical Development	✓
Manufacture	✓
QC of Excipients	✓
QC of Finished Product	✓
Reference Standard	✓
Container Closure System / Packing	✓
Product Stability	✓
Product Interchangeability	✓

NON CLINICAL DOCUMENTS	THAILAND
Non Clinical Overview	✓
Non-Clinical Written & Tabulated Summary	✗
Non-Clinical Study Reports	✗
Literature References	✓
CLINICAL DOCUMENTS	
Clinical Overview	
Clinical Summary	
Tabular Listing of All Clinical Studies	
Clinical Study Reports	
List of Key Literature References	

REGIONAL FORMAT

SR.NO	DOCUMENTS
1	Application Form
2	Certificate Of Pharmaceutical Product
3	Site Master File
4	Summary of Product Characteristics/PI
5	GMP Certificate of API Mfr.
6	Manufacturing License of FPP Mfr.
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 Specs
13	API COA
14	Monograph
15	Stability Testing
16	Analytical Method Validation

BIOEQUIVALENCE STUDY

	COUNTRIES	BIOEQUIVALENCE STUDY ACCEPTABLE	Other Countries Bioequivalence Study Acceptable
1	**VIETNAM**	• "ASEAN Guidelines for the Conduct Of Bioavailability and Bioequivalence Studies"	ACCEPTED

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