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Drug Registration and Marketing Approval Process in Vietnam

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RamaKishore E G [1*], Ravi Shankar N[2], Chagi Venkatesh[3], S B Puranik[4]

[1]Research scholar Sunrise University, Alwar, Rajasthan, India

[2] Asst. Professor VIPS, Bangalore-70, India

[3]Research Guide Sunrise University, Alwar, Rajasthan, India

[4]Director, Drishti Institute of Distance Learning, Bangalore, India

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ABSTRACT

ASEAN is a model of a regional integration initiative undergoing dynamic development and changes. ASEAN's drug regulatory authorities and industry have worked very close regionally but also increasingly with global organizations to develop several 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. 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 the economic community in 2015. ASEAN is playing a major role in the pharmaceutical industry. The challenge of ASEAN was to define regional accepted standards for pharmaceutical harmonization which facilitates intra and inter-ASEAN trade of pharmaceuticals. It is a great challenge to develop standards for the region that are appreciated by trade partners and that encourage foreign direct investment. The ultimate goal is to eliminate technical trade barriers, however ensuring those pharmaceutical products penetrating the ASEAN market are safe, efficacious and of quality. The focus of this study is to examine the stringency in which the regulatory framework of the ASEAN countries work, their country-specific requirements, evaluation process and harmonization between these countries. The Indian Drug Regulatory Requirements for filing of Generics are also covered as a part of the study for an easy compilation of the dossiers for India as a part of ASEAN-FTA. Several comparisons have been made through this project to highlight the differences in the ASEAN countries and India.

INTRODUCTION:

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 – to 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 the ASEAN countries couldn't 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 are 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 becomes mandatory by end of 2008 for MAAs and already registered products have to be transferred to ACTD until 2012.

❖ **About the Country: [1]**

Area:	331,689 km^2
Population:	83 million
Capital City:	Hanoi (population 3.5 million)
Largest City:	Ho Chi Minh City (population 7.8 million)
People:	Kinh Vietnamese 85%, plus 53 other ethnic groups
Languages:	Vietnamese, minority languages
Religion(s):	Mainly Buddhism, also Catholicism, Protestantism, Cao Dai, and Hoa Hao religions
Currency:	Vietnamese Dong (VND)
Government:	Vietnam is a one-party communist state
Official name:	Socialist Republic of Vietnam
GDP Per Capita:	Purchasing power parity $2,600

❖ **The registration process in Vietnam[2]**

a. Marketing approval procedures: Any drug moving in the market should be registered. They shall meet all the registration requirements concerning quality, safety and they must be following the regulation on the registration of drugs in Vietnam. All pharmaceutical products must be permitted by Drug Administration of Vietnam before marketing them in Vietnam. For obtaining the permission of Drug Administration of Vietnam, the manufacturer (applicant) must file an application dossier comprising of full particulars and documents as required in the Regulation on Registration of Drugs.

b. Types of drug registration

Pharmaco-chemical drugs, medical bio-products, vaccines, serum containing antibody, bio-products for diagnosis in vitro, traditional drugs, drugs originated from pharmaceutical materials, medicinal raw materials shall be registered in the following types:

1. First-time registration;

2. Registration of major variations;

3. Registration of minor variations;

4. Registration renewal

c. Required dossiers[3]

1. First-time registration dossier of a new pharmaco-chemical drug, vaccines, serum containing antibody, medical bio-product should include:

a) Part I. Administrative dossier and product information;

b) Part II. Quality dossier;

c) Part III. Pre-clinical dossier;

d) Part IV. Clinical dossier.

2. First-time registration dossier of **generic drugs** (only apply for pharmaco chemical drugs), should include:

a) Part I. Administrative dossier and product information;

b) Part II. Quality dossier.

c) Part III. Pre-clinical dossier;

d) Part IV. Clinical dossier.

3. Registration renewal dossier, including:

a) Part I. Administrative dossier and product information;

b) Part II. Quality dossier;

c) Part III. Post-marketing report (Form 5/TT).

The dossiers should be arranged following ACTD format. In case new pharmaco-chemical drugs, vaccines, serum-containing antibodies, medical bio-products cannot be arranged by ACTD, they may be arranged according to the Common Technical Document of the International Conference on Harmonization for pharmaceuticals (ICH – CTD).

Specific regulations for the administrative dossier and product information[3]

Administrative dossier and product information shall include:

Cover page – Form 1/TT

List of content

Application – Form 2/TT

Letter of Authorization (if any) – Form 3/TT

License for foreign companies conducting operations in medicines and raw medicinal materials in Vietnam if the applicant is a trading company of imported drugs or Certificate for satisfying drug trading company if the applicant is a Vietnam drug trading company.

CPP - Form 1/ACTD for imported drugs.

FSC in case the applicant of imported drug does not have CPP.

GMP certificate for a local manufacturer or GMP certificate for a manufacturer of imported drugs in case the drug applicant submits FSC or CPP in which there is no certification that the manufacturer meets the GMP standard. In case there are many manufacturers involved in the manufacturing process of the drug, the drug applicant must submit a GMP certificate for all these manufacturers who are involved in the manufacturing process of finished products.

1. Drug label.

2. Product information:

a) The package insert for generic drugs

b) Summary of product characteristics for new pharmaco-chemical drugs, vaccines, serum containing antibody and medical bio-products – Form 2/ACTD

c) The patient information leaflet for non-prescription drugs – Form 3/ACTD.

3. Post-marketing report for registration renewal dossiers – Form 5/TT.

4. Under-license agreement or contract regarding drugs manufactured under-license.

5. Certificates, protection license, contract of transferring industrial property rights concerned (if any).

6. Other legal documents (if any).

Specific regulations for quality dossier[3]

The quality dossier should be implemented by the guidance under Part II – ACTD and include the following documents:

1. Table of contents

2. Brief of quality

3. Contents and data

4. References

5. Master file of manufacturer – Form 4/TT. In case a product undergoes many manufacturing stages, the master file should be the general one including all manufacturers involved in the production before marketing the product.

Specific regulations for pre-clinical dossier[3]

A pre-clinical dossier should be implemented by the guidance under Part III – ACTD and include the following documents:

1. Table of contents

2. General information of pre-clinical study

3. Brief of pre-clinical study

4. Report on pre-clinical study

5. References.

Specific regulations for clinical dossier[3]

The clinical dossier should be implemented in accordance with the guidance under Part IV – ACTD and include the following documents:

1. Table of contents

2. General information of clinical study

3. Brief of clinical study

4. List of clinical studies

5. Reports on clinical studies

6. References.

❖ **Country-Specific Requirements for Vietnam**:[4]

Vietnam has its drug registration format and also follows ASEAN CTD. The majority of the product application can be completed in English.

The following documents and information are required with the application package.

a. Free Sale Certificate from the country of origin. The product to be sold in Vietnam must have the same specifications as the product on sale in the country of origin.

b. GMP Certification of the manufacturing facility from the country of origin.

c. Product information includes indication for use, dosage, drug interactions, management of overdose, shelf life and storage conditions.

d. A detailed description of the product manufacturing process and the in-process control procedures.

e. Real time stability data from three batches.

f. Quality specifications and the relevant analytical methods for the finished product, raw materials and excipients.

g. Three samples of the finished product with the Certificates of Analysis for the finished product, active ingredients and excipients.

h. Packaging material for the finished product including a Vietnamese language insert leaflet.

i. Study Report on Toxicology, Experimental Pharmacology, Pharmacokinetics, Bioavailability and Clinical Pharmacology.

j. Quality Specifications and Analytical Methods (fully detailed) and Certificate of Analysis released by the manufacturer.

Some product approval processes only require product sample analysis, though this occurs only in about ten percent of all application processes. In this case, the product application and sample will be forwarded to the Vietnam Institute of Quality Control. The Institute will analyze the sample and compare the results with the Certificate of Analysis included in the registration application. The applicant is responsible for paying the testing fee; the amount depends on the number and complexity of the test(s).

❖ **Labeling requirements (country-specific) – Vietnam[5]**

The labeling requirements of Vietnam are legal ones in compliance with the government decree on goods labeling and circular No. 14/2001/TT-BYT dated 26 June 2001 of the Ministry of Health instructing to label medicines and cosmetics directly affecting human's health.

Labeling requirements for Vietnam

S. No	Parameters	Requirement	Vials, ampoules	Blister/Strips	Package Insert
1	Product name	√	√	√	√
2	Name of active substance(s)	√	√ (1)	√ (1)	√
3	Strength of active substance(s)	√	√	√	√
4	Expiry date	√	√	√	√ (7)
5	Name & address of manufacture	√	Name of manufacturer	Name of manufacturer	√
6	Batch number	√	√	√	√
7	Indications	√	√		√
8	Remarkable note	√ (5)	√ (6)		√ (5)
9	Dosage form	√			√
10	Contraindications	√			√
11	Dosage/route of Administration	√			√
12	Adverse reactions	√			√ (2)
13	Drug interactions	√			√
14	Manufacturing date	√			√
15	Storage condition	√			√
16	Registration number	√			√
17	Name & address of the importer	√			√
18	Pack sizes (unit / volume)	√			√
19	Warnings (if applicable)				√
20	Name & content of excipients				√
21	With physician prescription only (for prescription drug)	√ (3)			√ (4)
22	Quality specification	√			√

√ (1): Applied to drugs with a single content.

√ (2): Must be written: "Inform doctors about unexpected reactions after using drugs".

√ *(3): The drugs that belong to the prescription list must be written: "Drug sold by prescription", and marked Rx on the left top corner; the eye drop must be written: "Eye drop"; the nose drop must be written: "Nose drop".*

√ *(4) Package inserts must be written: "This drug is administered according to doctors' prescription".*

√ *(5) Remarkable note: "Keep out of reach of children"; "Read carefully the package insert before use".*

√ *(6) For injectable drugs, the route of administration must be stated intramuscular injection, subcutaneous injection, or intravenous injection; the orally administered drug bottle must be written "No injection".*

√ *(7) Shelf-life of drugs must be stated.*

- Vials, ampoules, and blister/strips must be contained in the labeled box according to regulations.
- For parameters No. 5, 6, and 7, if the box is too small to mention those parameters, the sentence *"Please read the package insert"* must be written.
- Imported drugs must state the name of the manufacturing country.
- Expiry date must be written by 2 numbers of a month and 2 numbers of a year (for example, 20/03/06).
- Package insert must be written in Vietnamese.

❖ **Validity of drug registration number**

The maximum validity of a registration number is five (05) years from the date of signing Decision on issuing registration number. In special cases, the Ministry of Health shall consider issue-specific stipulations. Within six (06) months before and six (06) months after the expiry date of the registration number for circulation, the relevant applicant may submit a dossier for registration renewal. Exceeding the above duration, the applicant must resubmit dossier as for the first-time drug registration.

- The review and approval process takes twelve to eighteen months.

❖ BIOEQUIVALENCE STUDIES:[6]

Reference product/comparator product:

A 'Reference Product' used must be the same as given and drug regulatory authority of the country.

International BE:

Accepted

Guidelines followed:

"Asian Guidelines For The Conduct Of Bioavailability And Bioequivalence Studies"

BE required only of the following drugs

S.no	API for which BE is to be given	Company name
1	Amlodipin	Pfizer PGM (Phap) Pfizer PGM (France)
2	Azithromycin	Pfizer Italia CY)
3	Carbamazepin	Novatis Pharma S.p.A (Y)
4	Cefixim	Famar Lyon (Phap)
5	Cefuroxime Axetil	Glaxo Operation UK Ltd (Vuong quac Anh)
6	Clarithromycin	Abbott Laboratories Ltd. . (Vuong quac Anh) PT Abbott Indonesia (Indonesia)
7	Glibenclamide	Aventis Pharma (Nhat Ban)
8	Gliclazide	Les Laboratoires Servier Industrie (Phap)
9	Metformin	Merck Sante s.a.s. (Phap)
10	Metoprolol	AstraZeneca (Philipin)
11	Nifedipine	R.P. Scherer GmbH & Co. Germany (Duc) Bayer Health Care (Due)
12	Rifampicin	Novatis (ThVY Sy)

GENERAL INFORMATION

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

*1=5 yrs & may be less in some particular cased if they are not satisfied.

ADMINISTRATIVE DOCUMENTS COMPARISON

S. NO	ADMINISTRATIVE DOCUMENTS	VIETNAM
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	✗
16	Product Information Already Approved In Any State /country	✗

1=provided in 1st dossier then the reference is cited.

TECHNICAL DOCUMENTS COMPARISON

	VIETNAM
DRUG SUBSTANCE	
Quality Overall Summary	✓
General Information	✓
Manufacture Of Drug Substance	✓
Characterization	✓
QC of Drug Substance	✓
Reference Standards	✓
Container Closure System	✓
Stability	✓
CEP	✗
DMF	✗

	VIETNAM
DRUG PRODUCT	
Description &Composition	✓
Pharmaceutical Development	✓
Manufacture	✓
QC of Excipients	✓
QC of Finished Product	✓
Reference Standard	✓
Container Closure System / Packing	✓
Product Stability	✓
Product Interchangeability	✓

REGIONAL FORMAT COMPARISON

NON CLINICAL DOCUMENTS	VIETNAM
Non Clinical Overview	✓
Non Clinical Written & Tabulated Summary	✗
Non Clinical Study Reports	✗
Literature References	✓

CLINICAL DOCUMENTS	VIETNAM
Clinical Overview	✓
Clinical Summary	✗
Tabular Listing of All Clinical Studies	✗
Clinical Study Reports	Only BE
List of Key Literature References	✓

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
17	Unit Dose & Batch Formula
18	Master Formula
19	Manufacturing Process
20	In-Process Specs
21	Process Validation Of FP
22	Monograph- Excipients
23	COA- FPP
24	Specs of FPP
25	Monograph of FPP
SR.NO	**DOCUMENTS**
26	Analytical Method Validation
27	Container Closure System
28	Stability
29	Labels
30	Pharmacology, Toxicology
31	Raw Material Spec
32	Product If Already Approved In Other Country
33	BE Requirements

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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