Review Article

Comparison Study of Marketing Authorization and Regulatory Requirements of Generic Drugs in Brunei Darussalam and Indonesia

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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 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. 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. ASEAN is playing a major role in 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 barriers to trade, 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 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 various differences in the ASEAN countries and India.

INTRODUCTION

An introduction to the ASEAN[1]

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 the 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."

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. The ACTD is a common format and content acceptable for an application in the ASEAN member countries. The ACTR are a set of written requirements or guidelines intended to provide guidance to applicants in order to be able to prepare application dossiers in a way that is consistent with the expectations of all ASEAN DRAs.

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 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 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 becomes 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 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 do not 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).

Dossier Format –ASEAN CTD[2]

As mentioned before, the ASEAN countries established the ACTD as their format for submissions. It is a standard derived from the ICH CTD. The ASEAN CTD is a guideline of the agreed upon common format for the preparation of a well-structured ACTD application that will be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals for human use.

The ACTD is similar to the ICH CTD. The ICH CTD is divided into 5 modules whereas the ACTD contains of 4 parts. The reason for doing this is the fact that the ASEAN countries normally receive a reference application, which is a dossier which was already approved in other countries in the world (mostly EU and USA) and make the evaluation of the parts mainly based on the overviews and summaries. Based on this, the need for detailed documentation is in most of the ASEAN countries less compared to the ICH countries, e.g. most study reports are not required to be submitted. The Module 1 of the CTD containing the regional registration and administrative information is still presented as Part 1 of the ACTD.

Based on this, the need for detailed documentation is in most of the ASEAN countries less compared to the ICH countries, e.g. most study reports are not required to be submitted. The Module 1 of the CTD containing the regional registration and administrative information is still presented as Part 1 of the ACTD. The Module 2 of the CTD does not exist itself for the ACTD. The Quality Overall Summary (QOS) and the overview and summaries of the nonclinical and clinical documentation (similar like the documents in ICH Module 2) are included at the beginning of these Parts. Part II of the ACTD contains the pharmaceutical-chemical-biological documentation (the quality information), which corresponds to the ICH Module 3. The nonclinical information is presented as Part III of the ACTD (equivalent to ICH Module 4) and the clinical documentation is contained in Part IV of the ACTD (to be consistent with ICH Module 5). The differences between ICH-CTD[1] and ACTD[2] are presented in the attached comparison period:

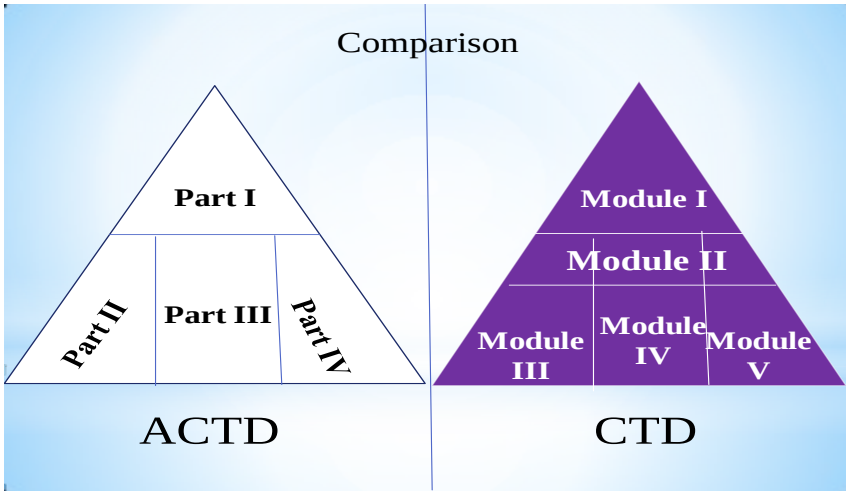


Fig. 1: ACTD & ICH Pyramid

As demonstrated above the ACTD is organized in four parts
• Part I: TOC, Administrative Data and Product Information
• Part II: Quality Document
• Part III: Nonclinical Document
• Part IV: Clinical Document

OBJECTIVES

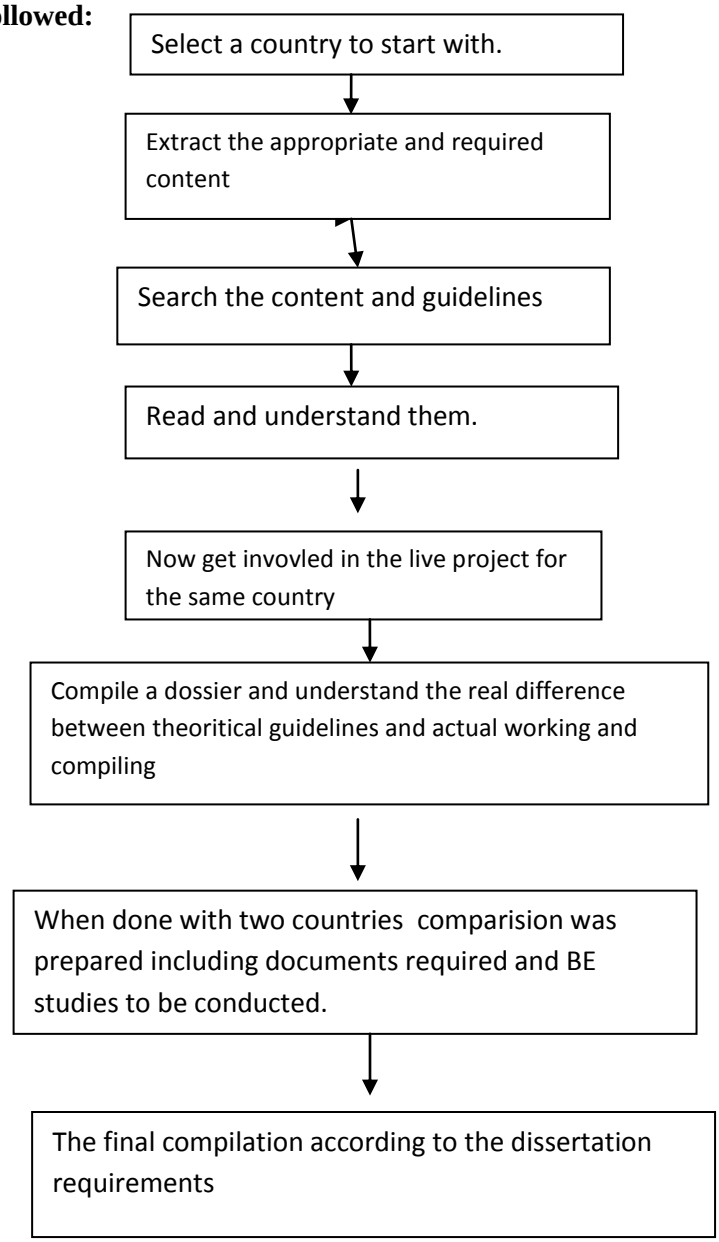
The objectives of this study are to give an overall idea about:

- The requirements for registration of ***Generics*** in the following 10 "**ASEAN**" (association of southeast Asian nation) countries and **INDIA**.
- Marketing authorization procedure for the approval of generic drug in these countries.
- Mark out the differences in the requirements to register generic drug product in these countries.

METHODOLOGY

The dissertation was aimed to place a milestone to project a practical approach in facilitating a pharmaceutical company's entry into the lucrative ASEAN market.
The Research Methodology for this study was done in a process listed below:

➢ **Process followed:**



In order to provide a practical approach to this dissertation all the exploratory research was carried out through reliable sources (communication by e-mail/telephonic & brochures with regulatory distributors, clients in the ASEAN countries) and by using secondary data sources (websites, journals, magazines, review articles etc.).
These 11 countries presented a varied approach with many common features that provided a practical dimension to this dissertation.

Data Collection

- Communication in person / telephonic and or by email with key pharmaceutical clients, companies, distributors in the ASEAN region
- 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 (Express Pharma, Chronicle Pharmabiz, Med Ad News, Google Scholar, Biospectrum Asia etc., to name a few).

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:

- Regional harmonization and regulatory environment in ASEAN.
- Review the approval process as specified by the drug authorities of specific countries.
- Country's specific registration requirements and Format followed.
- Differences in labeling requirements.

DISCUSSION

BRUNEI DARUSSALAM

❖ **Legal Framework and Regulations**[7]

- Food Safety & Quality Control Division under Department of Health Services (MOH) is responsible for enforcement, monitoring and surveillance of food supply in ensuring its safety and quality
- There is collaboration with other ministries in sharing the responsibility in order to improve food safety monitoring and surveillance and strengthen cooperation among agencies concerned.

❖ **Format followed**

ACTD format is followed.

❖ **Application Procedures For Medicinal Product Registration**[8]

➢ The responsibility of applying for product registration rests with the firm responsible for the introduction of the product into the Brunei Darussalam market, i.e.:

- In the case of an imported product, the manufacturer's local representative or it's appointed sole agent.
- In the case of a locally manufactured product, the manufacturer of the product or the local product owner.

➢ Applications for provisional product registration are to be made by submission of the letter of intent and by using the prescribed forms issued by the DPS. Application forms are charged at B$2.00 per set and can be obtained from:

Drug Registration Unit
Drug Administration Section
Department of Pharmaceutical Services
Block 2G:8:03, 8th Floor, Ong Sum Ping Condominium
Bandar Seri Begawan, BA1111
Brunei Darussalam
Tel/Fax: +673 2230001 / +673 2230041

RECOMMENDED MODEL OF LETTER OF INTENT

COMPANY LETTERHEAD

APPLICANT'S COMPANY NAME
AND
ADDRESS

DATE

Drug Registration Unit
Drug Administration Section
Department of Pharmaceutical Services
Block 2G:8:03, 8th Floor
Ong Sum Ping Condominium
Bandar Seri Begawan BA1111
Brunei Darussalam

Dear Sir / Madam

Re: Application for Provisional Product Registration

We would like to apply for a provisional registration of the following product

PRODUCT NAME
DOSAGE FORM AND STRENGTH

with the Drug Regulatory Authority in Brunei Darussalam. We enclose herewith the following documents as required, for your perusal:

Part I

Section I : Application Form (Form No: DPS/DRS/01)
Section II : Letter of Authorisation
Section III : *(Please list the names of certificates enclosed as appropriate)*
Section IV : Samples / Proposed Drafts of Product Labelling for unit carton, inner label & blister strips.
Section V : Samples / Proposed Drafts of Product Information for use in the package Insert / summary of product characteristics / patient information leaflet.

Part II

Section I : Application Form for Quality requirements of the Drug Substance (Form No: DPS/DRS/02/A)

Section II : Application Form for Quality requirements of the Drug Product (Form No: DPS/DRS/02/B)

With regards,

Applicant's signature

Applicant's Name & Designation

- The submitted application will be screened and validated for completeness within 14days.
- Applications are to be submitted by the person responsible for the company to:

  Drug Registration Unit
  Drug Administration Section
  Department of Pharmaceutical Services
  Block 2G:8:03, 8thFloor,Ong Sum Ping Condominium
  Bandar Seri Begawan,BA1111
  Brunei Darussalam
  Tel/Fax: +673 2230001 / +673 2230041
- Submission of the applications must be made by appointment with the concerned officer at the above address.
- The processing fee of B$100.00per product is payable at the point of submission of the application. Payment shall be made in the form of cash and it is non-refundable.
- Upon acceptance of an application, an acknowledgement for the receipt of the application will be issued and a reference number will be generated. The reference number shown in this acknowledgement should be used in all subsequent correspondences relating to the application.

❖ **Documents Required For Application For Registration of Generic Medicinal Products**[8]

All applications for provisional product registration are to be made by submission of the required documents which are in line with the ASEAN Common Technical Dossier (ACTD) for the registration of pharmaceuticals for human use. The application dossier required will consist of 4 parts which are as follows:

PART I: ADMINISTRATIVE DATA AND PRODUCT INFORMATION

Section 1: Application Form(Form No:DPS/DRS/01)
Section 2: Letter of Authorization
Section 3: Certifications
Section 4: Labeling
Section 5: Product Information

PART II: QUALITY

Section 1: Application Form for Quality Requirements of the Drug Substance (Form No:DPS/DRS/02/A)

Section 2: Application Form for Quality Requirements of the Drug Product (Form No:DPS/DRS/02/B)

PART III: NON-CLINICAL (For a submission of New Chemical Entity, Biotechnological Products and some Major Variation Products only)

Nonclinical documents (Part III) are not required for Generic Products, Minor Variation Products and some Major Variation Products.

PART IV: CLINICAL DOCUMENTS (For a submission of New Chemical Entity, Biotechnological Products and some Major Variation Products only)

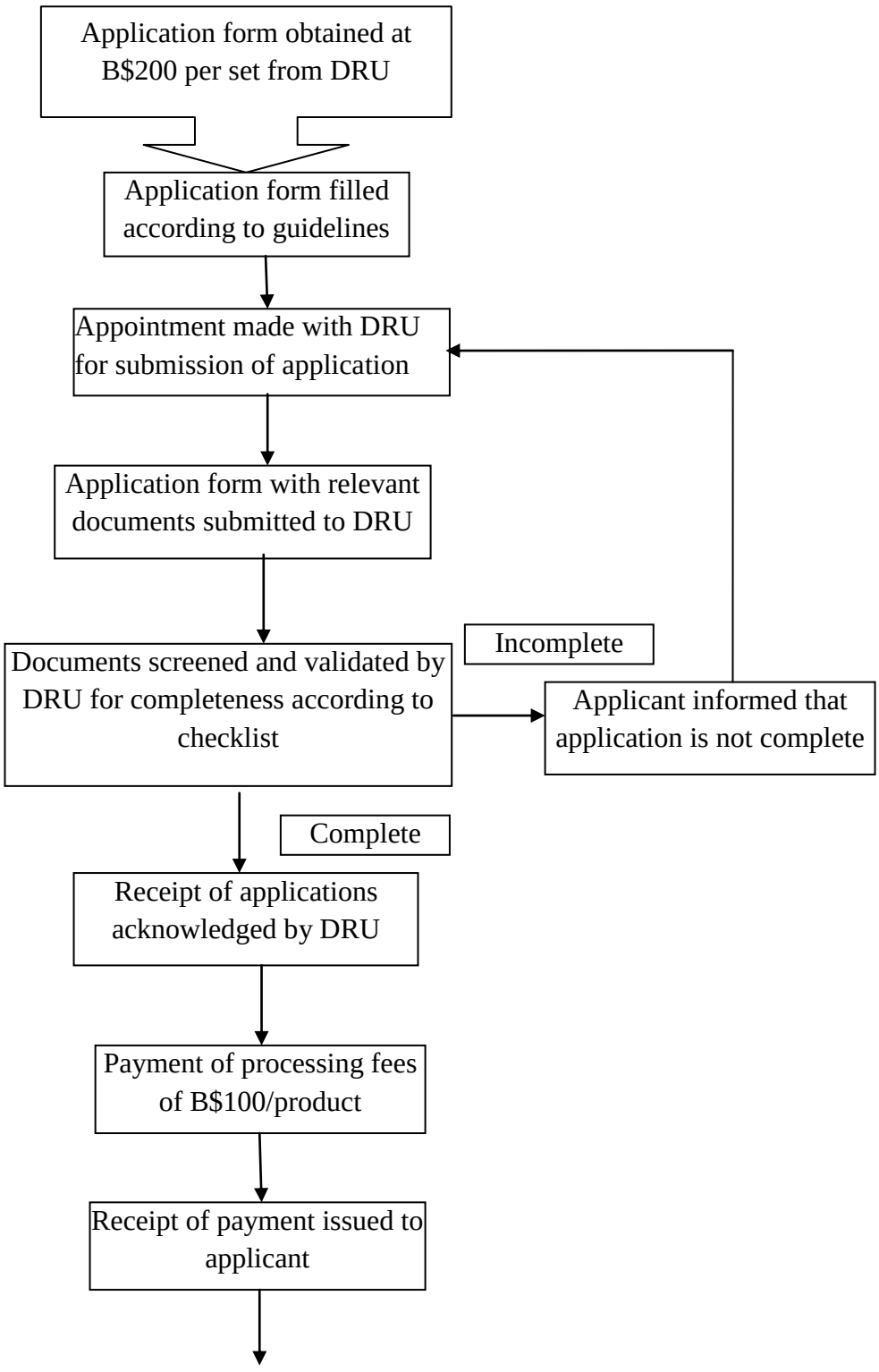
Clinical Summary is not required for Generic Products, Minor Variation Products and some Major Variation Products.

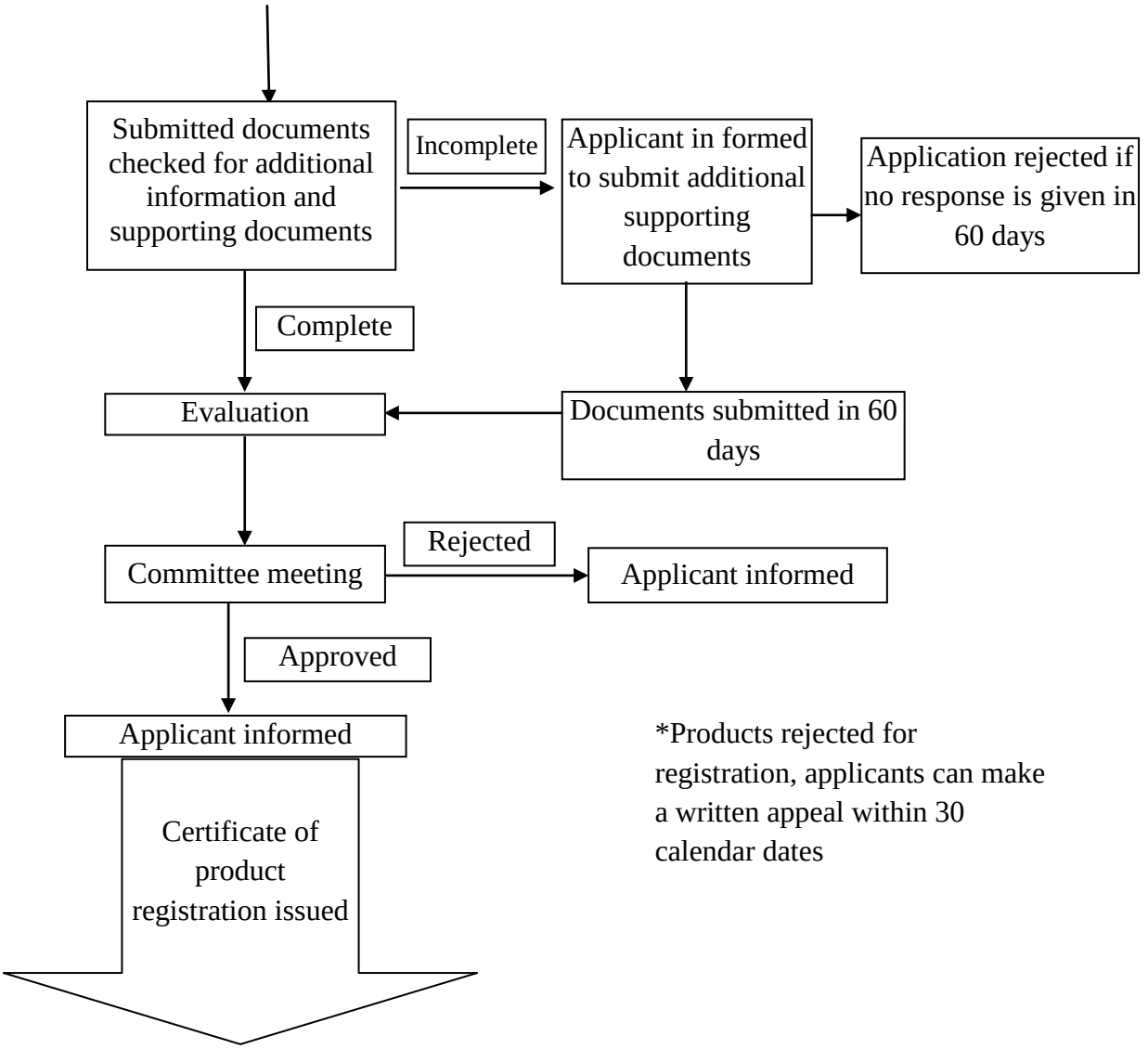
❖ **Processing of Application**[8]

- Review follows the appropriate evaluation queue.
- Priority review may be granted where the product is intended for treatment of a serious or life-threatening disease.
- During product evaluation, the Drug Registration Unit may request for further information and additional supporting documents from the applicant which should be made available within 60 days from the date of the request. The application will be rejected / closed if no response is received from applicant after the 60 days given and anew application will have to be submitted if the applicant wishes to pursue registration of the product.
- The applicant will be informed of the decision of the Drug Registration Committee (Provisional) in writing as to whether the application has been approved or rejected.
- A registration number will be given when a product is registered.

APPEAL AGAINST DRUG REGISTRATION COMMITTEE DECISIONS

For products that have been rejected for provisional registration by the Drug Registration Committee, applicant may make a written appeal to the Chairperson of the Committee by using the prescribed form (Form No: DPS/DRU/Appeal/01) issued by the DPS within THIRTY (30) calendar days from the date of the committee's notification.


Application form obtained at B$200 per set from DRU
Application form filled according to guidelines
Appointment made with DRU for submission of application
Application form with relevant documents submitted to DRU
Documents screened and validated by DRU for completeness according to checklist
Incomplete
Applicant informed that application is not complete
Complete
Receipt of applications acknowledged by DRU
Payment of processing fees of B$100/product
Receipt of payment issued to applicant



❖ **Labeling Requirements (Country Specific)-Brunei Darussalam[11]**

PART 1- Section 4: Product Labeling

- Applicant should provide samples or proposed drafts of product labeling for the application of registration of medicinal products.
- Languages used for labeling shall be English and/ or Malay.
- Samples or proposed drafts of the product labeling are of unit Carton, inner label and **blister/ strip.**

Table: Labeling Requirements-Brunei Darussalam

S. No	Parameters	Unit carton	Inner label	Blister/Strips
1	Product name	√	√	√
2	Dosage form	√	√ *	
3	Name of active ingredient(s)	√	√	√#
4	Strength of active ingredient(s)	√	√	√#
5	Batch number	√	√	√
6	Manufacturing date	√	√*	
7	Expiration dates	√	√	√
8	Route of Administration		√	
9	Storage condition	√	√*	
10	Country Registration number	√	√*	√(optional)
11	Name & address of Marketing Authorization Holder	√		
12	Name & address of manufacturer	√	√*	Name/logo of manufacturer /product owner
13	Special labeling(if applicable) eg if sterile,External use, Cytotoxic, Alcohol content, Animal origin(Bovine,porcine?)	√	√*	
14	Warnings (if applicable)	√	√*	
15	Pack size(unit/ volume)	√	√	
16	Recommended daily allowance (for vitamins and minerals)	√	√*	

Note: # (exempted for multi-ingredients products with more than 3 ingredients. For example multivitamins and multiminerals it is suggested to label as multivitamins and multiminerals)
If there is no outer carton available for the product, all the information required to be stated on the inner label.
With reference to item no 14 on warnings, there are a few standard warnings and cautionary statements that would be required to be stated on the unit carton and inner label such as “POISON” or “MAY CAUSE DROWSINESS” etc. A list on the warning and cautionary statements is available when required.

INDONESIA

❖ **Legal Framework and Regulations**[3,4]

The decree of the head of national agency of drug and food control republic of Indonesia number: HK.00.05.3.1950 on criteria and procedure of drug registration enlists the country specific requirements for Indonesia.
A new regulation issued by the Minister of Health, namely Regulation of the Ministry of Health in Indonesia No. 1010/MENKES/PER/XI/2008 regarding the Registration of Medicines (“**Regulation 1010/2008**”) - enlists that a medicine to be distributed in Indonesia must be first registered before a Distribution License (*Izin Edar*) can be applied for.[3,4]

- **Format followed**
  ACTD format with some country specific requirements.
- **Regulatory system:**

A. Regulatory Structure of Indonesia

a. Drug registration shall be submitted by the applicant to the Head of the National Agency.
b. Drug Registration are categorized into:
   - New Registration
   - Registration of Drug Variations

Category 1 : is new drug registration with new active pharmaceutical ingredient or new derivative or new combination or biological product with new active ingredient or new combination or in a new dosage form

Category 2 : is new drug registration with old composition in a new dosage Form or new strength or similar biological product;

Category 3 : is registration of drug or biological product with old composition with :
3.1. new indications
3.2. new posology

Category 4 : is registration of copy drug :
4.1. copy drug with a trade name
4.2. copy drug with a generic name

Category 5 : is registration of other preparation containing drug

c. The registration of a copy drug (generics) comes under the Category 4.[3]

B. Drug Registration: The Drug Registration Process consists of two stages:

1) Pre- Registration
2) Submission of the Registration Dossier

1) Pre Registration steps:

The pre-registration process is conducted to determine the application review and evaluation pathway. The NA-DFC reviews drug applications via one of three pathways (Path I, II or III).

a) Path I include drug applications for products used to treat serious or life- threatening diseases, or for essential generic drugs for public health programs.
b) New drugs already approved in certain designated countries may qualify for the Path II registration process.
c) Any drug applications for products that do not qualify for Path I or Path II evaluation processes will be reviewed via the Path III process.
Generally, applications are reviewed within the following timeframes:
Path I: 100 working days
Path II: 150 working days
Path III: 300 working days for new drugs; for all other drugs, 80 working days [3,5,6]

2) Registration steps (Submission of registration documents and evaluation process):

The registration forms and accompanying documents can be in Bahasa Indonesian or english. Drugs produced for export-only are not required to have labels in Bahasa Indonesian; only English labels are required[34].

i) For registering a product in Indonesia, complete registration form, floppy disk, receipt of payment of evaluation and registration fee and the result of pre-registration is attached and sent.
ii) For the purpose of evaluation on quality, applicant should submit drug sample for 3 (three) times of analysis and standard raw material conform to the specification and method of analysis of the active ingredient of the objective drug.
iii) Registration dossier of copy drug with an active ingredient that has already been available in the Electronic Information Standard (STINEL =Standar Informasi Elektronik), consist

of floppy disk that has been completed in line with the data in Form A and Form B21-13, and the forms of Forms A, Form B1, Form B214, Form B4, Form C1, and Form D.

iv) Registration dossier of copy drug with an active ingredient that has no STINEL, consist of a floppy disk that has been completed with the data in line with Form A and the forms of Form A, Form B1, Form B2, Form B3, Form C1, and Form D.

a. Forms A- name and address of the applicant and manufacturing industry and information of the drug.
b. Form B1- Administrative Documents
c. Form B2-Product information that covers the aspects of efficacy, safety and quality
d. Form B3- The procedure of Batch numbering system
e. Form B4-Price Information
f. Form C- Contains documents that must be attached to support the information mentioned in Form B2
g. Form C1- Documents on quality and technology
h. Form C2- Preclinical documents
i. Form C3- Clinical Trial Documents
j. Form D- List of submitted drug sample and its reference standard3

Special Requirements:

a) Completion of registration forms should be in Indonesian or in English;
b) Registration documents can be in Indonesian or in English;
c) Labeling of over the counter drug/limited over the counter drug must be in Indonesian;
d) Labeling of drugs for export only should at least be in English[3].

C. Other Country Specific Requirements which may also be included with the ACTD submission:

- Traditional Medicines Name
- Package Size
- Registration Number, name and industry address (at least name of city and
- country)
- Composition (species name of raw ingredient)
- Effects/Usefulness
- Usage
- Warning and contra-indication (if exist)
- Production Code Number
- Expired Date
- Level of Production/Standard Operational Procedure; Utility or machine
- Source of available raw ingredients
- Methods and Test Result of Stability/Durability
- Efficacy and adequate safety proven through pre-clinical and clinical trial
- Proof in accordance to the development of relevant scientific knowledge.
- Production process in accordance with the GMP.
- Specifications and documents of the method of analysis of all materials used in the finished product.
- Letter of Attorney submitted by the applicant of imported drug[10].

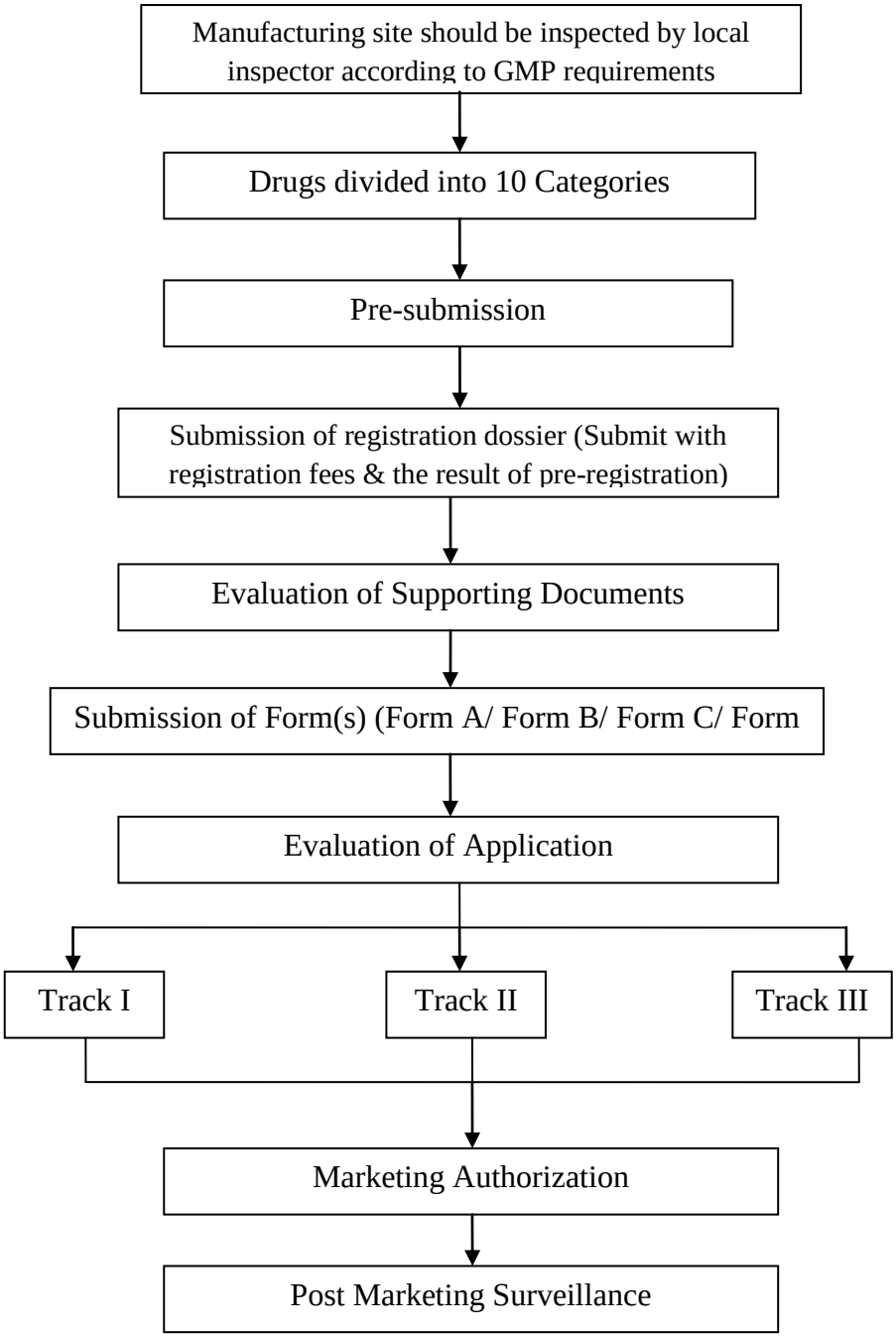


Fig.: The drug registration process in INDONESIA[9]

- **Labeling requirements (country specific) – Indonesia[11]**

Table: Labeling requirements for Indonesia

S. No.	Information to be included	Unit Carton	Inner Labels	Strips / Blisters	Catch Covers / Envelopes	Ampoules / Vials
1	Product Name	√	√	√	√	√
2	Dosage Form	√	√	-	√	√
3	Package Size	√	√	-	√	√
4	a. Name and strength of active ingredient(s)	√	√	√	√	√
	b. Generic name should appear under the brand name, minimal size is 80% of the brand name	√	√	√	√	√
5	*Local production:* - Name of Applicant - Address of Applicant	 √ √	 √ √	 √ -	 √ √	 √ √**
6	*Imported drugs:* - Name of Applicant and Manufacturer of imported drug - Address of Applicant and Manufacturer of imported drug	 √ √	 √ √	 √ -	 √ √	 √ √**
7	*Toll manufacturing:* - Name of Applicant and Manufacturer - Address of Applicant and Manufacturer	 √ √	 √ √	 √ -	 √ √	 √ √**
8	*Local production under License:* - Name of Applicant and Licensee - Address of Applicant	 √ √	 √ √	 √ -	 √ √	 √ √**
9	Registration number	√	√	√	√	√
10	Batch number	√	√	√	√	√
11	Date of production	√	-	-	√	-
12	Expiration date	√	√	√	√	√
13	Indications	√*	*	-	√	-
14	Posology	√*	*	-	√	-
15	Contraindications	*	*	-	√	-
16	Adverse reactions	*	*	-	√	-
17	Drug interactions	*	*	-	√	-
18	Warnings - Precautions	*	*	-	√	-
19	Special warnings (if any)	√	*	-	√	-
20	Storage condition	√	√	-	√	√**
21	Specific information in					

	accordance with valid provisions (if any) e.g. * Source of porcine *Alcohol contents -Specific information on ceiling price	√ √	√ √	- -	√ √	√ √
22	Warning for limited over the counter drug (OTC)	√	√	-	√	-
23	With physician prescription only in Indonesian language (for prescription drug)	√	√	√	√	√
24	Specific round mark of prescription drug / OTC / limited OTC	√	√	-	√	-

Notes:
√ *: Information must be included*
√* *: Information must be included for OTC and limited OTC (Prescription drug could refer to the brochure)*
√** *: Specifically for ampoule or vial more than 2 ml*
* *: Information could refer to the brochure*
- *: Information not necessary to be included*

Point to Remember

Once a drug is registered in Indonesia the company has 2 years to shift its facility to Indonesia or has to get it made locally in Indonesia by contract manufacturing.

CONCLUSION

It is noticeable that harmonisation of standards and regulations, as well as MRAs, 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 Standards Bodies and Regulatory Authorities have been working closely with the private sector 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 and industry to meet frequently and network effectively.

Brunei Darussalam and Indonesia are the only countries in ASEAN who have well-established pharmaceutical regulations and are more strict with regard to quality and safety of drugs. These countries believe in 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 to do with regulatory requirements.

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