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COMPREHENSIVE STUDY ON THE REGISTRATION OF GENERIC DRUG PRODUCT IN THE EMERGING MARKET (ASEAN)

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ABSTRACT

Registration method for generics differs reckoning on country. Association of Southeast Asian Nations area unit the market of interest for several pharmaceutical firms attributable to the enlargement of their trade, improvement of their transportation and communications facilities, and enticing the growth of pharmaceutical market. Medications, being a crucial trade goods should be out there to any or all or any. Drug convenience is a crucial issue within the Association of Southeast Asian Nations region because of country-specific restrictive necessities. Therefore, it's quite difficult for the pharmaceutical firms to urge the drug registered in Association of Southeast Asian Nations member states. It is the key responsibility of everybody department to substantiate the standard, safety, and efficaciousness of a drug product in their country, that has the strategy of regulation, monitoring, producing, distributing, and promoting of the generic medicines. The restrictive framework of health authorities shares similar attributes, however the requirements and procedures for registering generic medicine vary by Association of Southeast Asian Nations member state. One in all the primary challenges for pharmaceutical firms is to form certain that the pharmaceutical merchandise area unit developed as per the restrictive necessities of Association of Southeast Asian Nations member states and to optimize this challenge, assessment of essential parameters throughout development should be done. In Association of Southeast Asian Nations region, documentation is filed in the ACTD format. Though ACTD format is necessary, the member countries have their own necessities for registration method like body documents, and labelling. The aim of this text is to provide the elaborate summary on the restrictive necessities (both general and country-

specific) and important problems that occur throughout the registration of drug product in Association of Southeast Asian Nations Member countries.

KEYWORDS: ASEAN, ACTD, Drug registration, Generics.

INTRODUCTION

Emerging marketplace are one of the marketplace who are getting greater engaged with the worldwide markets because it grows, own a few traits of a evolved marketplace (For example- Economic size, wealth, nice of markets, intensity of markets, breadth of markets), however aren't absolutely evolved due to their marketplace volatility, excessive quotes of financial boom and occasional centre earnings according to capita and their transitional character, with transitions going on in financial, political, social and demographic areas. Economy of rising marketplace is transitioning from low earnings, much less evolved, regularly pre-commercial financial system in the direction of a modern, commercial financial system with a better popular of living. One of the Emerging markets consists of the "ASEAN Market" that's a nearby intergovernmental organization.[1] The region is developing fast with an ever-changing regulatory environment that poses both challenges and opportunities to its stakeholders.

On 8th August 1967, ASEAN was founded in Bangkok, Thailand, with the signing of the Bangkok Declaration (also known as ASEAN Declaration) by the pioneers of the ASEAN, specifically Indonesia, Malaysia, Philippines, Singapore and the Thailand. Also, Brunei Darussalam joined ASEAN on 7th January 1984, Viet Nam on 28th July 1995, Lao PDR and Myanmar on 23rd July 1997, and Cambodia on 30th April 1999, making up what's today the ASEAN market (including 10 Member states). The ASEAN Market are of interest for many pharmaceutical companies because of their growing population and attractive pharmaceutical market growth.[2]

Role of ASEAN Consultative Committee on Standards and Quality Pharmaceutical Product working party (ACCSQ PPWG)

Efforts to attain harmonization of ASEAN pharmaceutical guidelines was established in 1992 through the ASEAN Consultative Committee for Standards and Quality. At the thirteenth meeting of ACCSQ held in Manila in March 1999, it was agreed to establish a Pharmaceutical Working Group (PPWG) with Malaysia. Hence the formation of ACCSQ-

PPWG in September 1999 in national capital, Malaysia. The target of the ACCSQ-PPWG is to develop harmonization schemes of pharmaceuticals' regulations of the ASEAN member countries to enrich and facilitate the target of ASEAN trade Area (AFTA), particularly, the elimination of technical barriers to trade posed by these regulations, without compromising on drug quality, safety and efficacy.[3]

DOSSIER SUBMISSION FORMAT

The ASEAN region has developed an ASEAN Common Technical Requirements (ACTRs), that set up an ASEAN Common Technical Document (ACTD) which could be a guideline of the prearranged common format for the preparation of a well-structured Common Technical Dossier (CTD) applications that may be submitted to ASEAN regulatory authorities to get the marketing authorization of pharmaceuticals for human utilization. This time saving format will notably minimizes reduce the resources that are needed to compile applications for registration. Also, ease the preparation of electronic documental submissions.[4,5]

The ACTD is comparable to the ICH CTD. The ICH CTD is split into 5 modules whereas the ACTD contains of 4 parts.

The reason for doing this can be the very fact that the ASEAN countries normally receive a reference application, which could be a dossier which was already approved in other countries within the world (mostly EU and USA) and make the evaluation of the parts mainly supported the overviews and summaries. The necessity for detailed documentation is in most of the ASEAN countries is a smaller amount compared to the ICH countries. The Module 1 of the CTD containing the regional registration and administrative information continues to be presented as Part 1 of the ACTD. The Module 2 of the CTD doesn't exist itself for the ACTD. The standard Overall Summary (QOS) and also the overview and summaries of the non-clinical and clinical documentation (similar just like the documents in ICH Module 2) are included at the start of Part II of ACTD. Part II of the ACTD contains the quality information, which corresponds to the ICH Module 3. The non-clinical information is presented as Part III of the ACTD (similar to ICH Module 4) and therefore the clinical information is contained Part IV of the ACTD (to be according to ICH Module 5).

The differences between ICH-CTD and ACTD are demonstrated from the attached comparison pyramid.

ACTD is organized in four parts: As shown in Figure – 1.

- Part I: Table of contents, Administrative Data and merchandise Information.
- Part II: Quality Document.
- Part III: Non-clinical Document.
- Part IV: Clinical Document.[6]

The subsequent countries are leading ASEAN Common Technical Document (ACTD) and ASEAN Common Technical Requirements

Indonesia, Thailand, Philippines and Malaysia are responsible for Quality part, Efficacy part, Safety part and administrative data, product information and glossary part separately.[7]

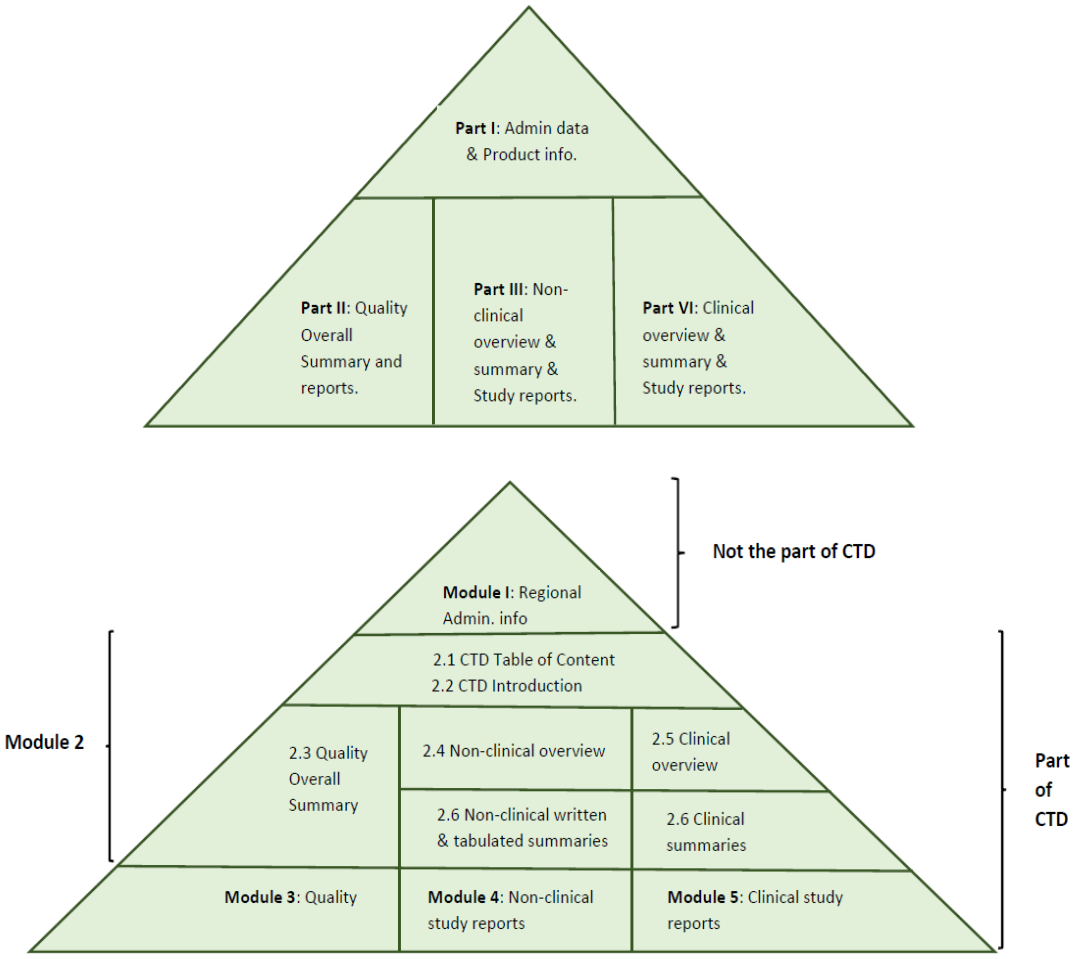


Figure 1: ACTD & ICH-CTD Pyramid.

Registration requirements in ASEAN countries

For the Generic drugs, the pre-requisites for the registration includes only Part I (Administrative documents & product information) and Part II (Quality part) for the review by the drug regulatory authority in the ACTD layout. This article covers the registration

requirements for the following ASEAN countries i.e., Malaysia, Singapore, Thailand, Brunei Darussalam, Indonesia, Lao PDR, Philippines, Myanmar, Vietnam. Also, mark out the variations withinside the requirements to register drug product in the above countries.

1. MALAYSIA

Registration of drug product in Malaysia is regulated by the National Pharmaceutical Regulatory Division (NPRA) by referring to the document i.e., Drug Registration Guidance Document (DRGD), is issued by the Director of Pharmaceutical Services under Regulation 29, Control of Drugs and Cosmetics Regulations 1984.

Format followed for dossier submission: ACTD format.

Generic drugs may be further classified into

a. Scheduled Poison

b. Non-scheduled Poison

Non-Schedule Poison can be categorized into two separate methods of evaluation:

a) Full Evaluation

b) Abridged Evaluation

The registration process involves a series of steps, as shown in Figure-2.

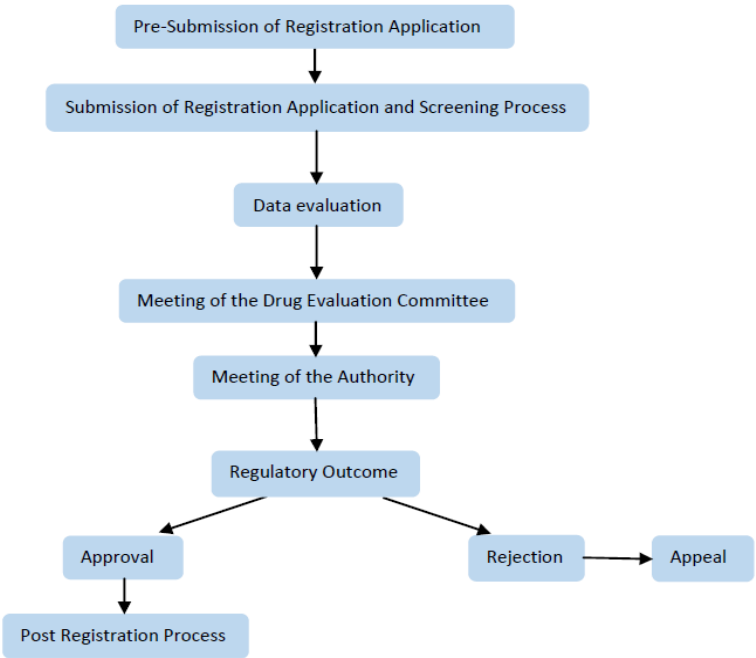


Figure 2: Flowchart showing Generic drug Registration process in MALAYSIA.

Product registration process includes 4 steps

Step 1 – SUBMISSION OF APPLICATION (Application of product registration shall be submitted through the online QUEST system at https://www.npra.gov.my/)

Step 2 – SCREENING OF APPLICATION (if satisfactory proceed to evaluation) OR (If unsatisfied, application is rejected).

Step 3 – EVALUATION OF APPLICATION

Step 4 – REGULATORY OUTCOME (if approved proceeds to Post Registration Process) OR (IF Denied application is appeal).

Before submission of an application for product registration, applicant shall determine/understand the Pre-submission requirements. It includes: The category of the product (different product category requires different data), method of evaluation, general and specific requirements, conditions applied, multiple applications, variants, language.

Documentary requirements

STEP 1: Product Validation

Including Product name (Brand name); Dosage form; API; Excipients; any ingredient from animal source; product details from second source; Details of manufacturers and contract manufacturer (if any); Premix details [including Premix form, Manufacturer name, Manufacturer address; Certificate of Good Manufacturing Practice (GMP), Formulation, Manufacturing Process, Specification of Analysis, Certificate of Analysis (CoA)]; Replacement product; Repackers features; Product for import.

STEP 2: Part I - Administrative Data and Product Information

Section A – Product particulars (including Product Name, Name & Strength of Active Substance and Excipient, Dosage Form, Product Description, Pharmacodynamics, Pharmacokinetics, Indication, Recommended Dose, Route of Administration, Contraindication, Warning and Precautions, Interaction of Other Medicaments, Pregnancy and Lactation, Side Effects, Symptoms and Treatment of Overdose, Storage Condition, Shelf Life, Therapeutic Code/ ATC Code.)

Section B: Product Formula (including Batch Manufacturing Formula, Attachment of Batch Manufacturing Formula Documentation.)

Section C: Particulars of Packing [including Pack Size with fill details by weight, volume, quantity, Immediate Container Type Description, Barcode/ Serial No. (Optional),

Recommended Distributor's Price (RM) (Optional), Recommended Retail's Price (RM) (Optional)].

Section D: Label for Container, Outer Carton, Proposed Package Insert.

Section E: Supplementary Documentation [including Product Owner, Letter of Authorization from Product Owner, Letter of Appointment of Contract Manufacturer from Product Owner, Letter of Acceptance from Contract Manufacturer, Certificate of Pharmaceutical Product (CPP), Certificate of Free Sale (CFS), GMP Certificate, SmPC, Consumer Medication Information Leaflet (RiMUP)/Patient Information Leaflet (PIL), Attachment of Protocol Analysis, Attachment of Analytical Validation, Certificate of Analysis (CoA), Other Supporting Document (if any), Manufacturer (Name and address), Importer (if any)].

PART II: Quality of product

Section P: Drug Product (Finished Product)

Description and Composition, Pharmaceutical Development, Manufacturer, Control of Excipients, Control of Finished Products, Reference Standards or Materials, Container Closure System, Stability, Product Interchangeability/ Equivalent Evidence (Bioavailability/Bioequivalence, BA/BE).

Section S: Drug Substance

General Information (including Nomenclature, Structure and Attachment for Structure of Drug Substance, General Properties); Manufacturer details; Characterisation of drug substance; Control of Drug Substances (including Specifications, Analytical Procedures, Validation of Analytical Procedures, Batch Analysis, Justification of Specifications); Reference Standards or Materials; Container Closure System; Stability. Requirements for abridged evaluation is same as for full evaluation, but it additionally requires Particulars of Product Owner, Manufacturer, Importer and Other Manufacturer(s) Involved and Store address. Also, requires BA/BE Study reports.[8]

SINGAPORE

Health Sciences Authority (HAS) is the regulatory authority for regulating pharmaceutical products in Singapore All pharmaceuticals/drugs require product license to import or sell in Singapore. When applying for a product license, dossiers must be either in the ICH CTD or the ACTD layout. A company seeking to market a therapeutic product in Singapore must obtain marketing approval from HSA through making an application for product registration.

A generic product must have the same qualitative and quantitative composition in active substances and be of the same pharmaceutical form as a currently registered product in Singapore (known as the 'Reference product of Singapore').

Application which is applied for the registration generic drug product is known as "Generic drug application".

2 Types of GDA

GDA-1: For the first strength of a generic chemical product.

GDA-2: The application for the generic chemical product (For subsequent strengths) that has been registered or submitted as GDA-1. The product name and dosage form should be the same as for GDA-1.

Documentary requirements

Part I: Administrative documents

- Cover Letter
- Comprehensive Table of Contents
- Introduction
- Labelling, Package Insert and Patient Information Leaflet
- Approved SPC/PI/PIL
- Assessment Report from Reference Agencies
- Description of Batch Numbering System
- Proof of Approval
- Certificate of Pharmaceutical Product
- Letter of authorization
- GMP Certification/Proof of GMP Compliance
- Patent Declaration
- Declaration on Rejection, Withdrawal and Deferral
- Declaration for GDA Verification and Verification-CECA
- Registration Status in Other Countries
- Confirmation of Reference Agency's Approval of Chemistry & Manufacturing Control (CMC) Aspects.

The registration process involves a series of steps, as shown in Figure-3.

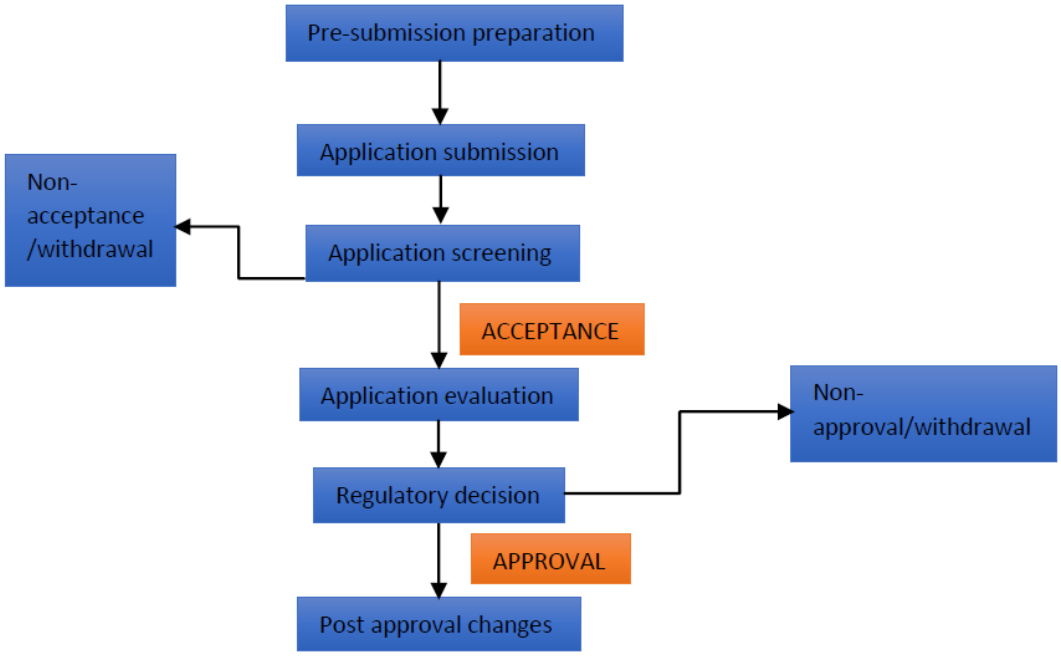


Figure 3: Flowchart showing Generic drug Registration process in SINGAPORE.

Part II: CTD overview and summaries

The ICH or ASEAN Quality Overall Summary is to be inserted into Module 2 of the ICH CTD or into Part II, section B of the ACTD. This document can be submitted either in MS Word format.

3. Quality documents

The quality documents relate to Module 3 of the ICH CTD or Part II of the ACTD.

For drug substance

- All of the drug substance sections of the CTD – i.e., S1 to S7 – must be mentioned in the application. If incomplete, then reference of Drug Master File (DMF) OR Certificate of Suitability of Monographs of the European Pharmacopoeia (CEP) is given.
- Control of Drug Substance.
- Stability Data of Drug Substance.
- For drug product
- Process Validation.
- Control of Excipients.
- Control of Drug Product.
- Container Closure System.

- Stability Data of Drug Product.
- Product Interchangeability – Bioequivalence.
- Product Interchangeability – Comparative Dissolution Profile.
- Submission of Risk Management Plan.[9]

3. BRUNEI DARUSSALAM

The Ministry of Health through the Department of Pharmaceutical Services (DPS) implements the registration system of all medicinal products for human use prior to their use in Brunei Darussalam, to ensure that medicinal product marketed in Brunei Darussalam are safe, efficacious and of good quality. The Brunei Darussalam Medicines Control Authority (BDMCA) was established under the Section 5 of Medicines Order, 2007 has the right to grant, renew, vary, suspend and revoke license for marketing.

A Product License will be issued by the BDMCA for a medicinal product that has been approved for registration in Brunei Darussalam. Medicinal products that are registered in any of the standard regulatory agencies in countries such as Australia, Canada, EU (centralised), Malaysia, Singapore, United Kingdom and United States of America will simplify the registration process for medicinal product.

Documentary requirements

Part I: Administrative Data and Product Information

Section 1: Application Form - Form No: BDMCA/DPS/01

a) Company particulars
b) Applicant particulars
c) Product details including

- Proprietary Name that will be shown on the product labelling i.e., the inner label, outer carton, package insert and Patient Information Leaflet.
- Dosage form
- Product Description
- Product Formula
- Ingredients derived from human blood and animals.
- Pharmacotherapeutic Group - Applicants should indicate the WHO Anatomical Therapeutic Chemical (ATC) code for each distinct therapeutic indication proposed for a product.
- Route of administration.

- Indication.
- Recommended dosage.
- Therapeutic advantage.
- Packaging, Shelf-life and Storage condition
- Forensic Classification in Brunei
- Registration status in other countries.
- Proposed price of products in Brunei Dollars.
- Product owner information

d) Manufacturer's particulars

e) Repackers's particulars

f) Batch release details

g) Declaration

h) Others include: All entries and documents must be made in English. Where applicable, details in other relevant language, i.e., Malay, may also be included in addition to the English version.

Section 2: Letter of Authorisation.

Section 3: Certifications

- Licence of pharmaceutical industries
- GMP certificate of the manufacturer
- Copy of "under-license" agreement
- Contract manufacturing agreement
- Certificate of Pharmaceutical Product issued by the competent authority in the country of origin according to the currently prescribed WHO layout.
- SMF.

The registration process involves a series of steps, as shown in Figure-4.

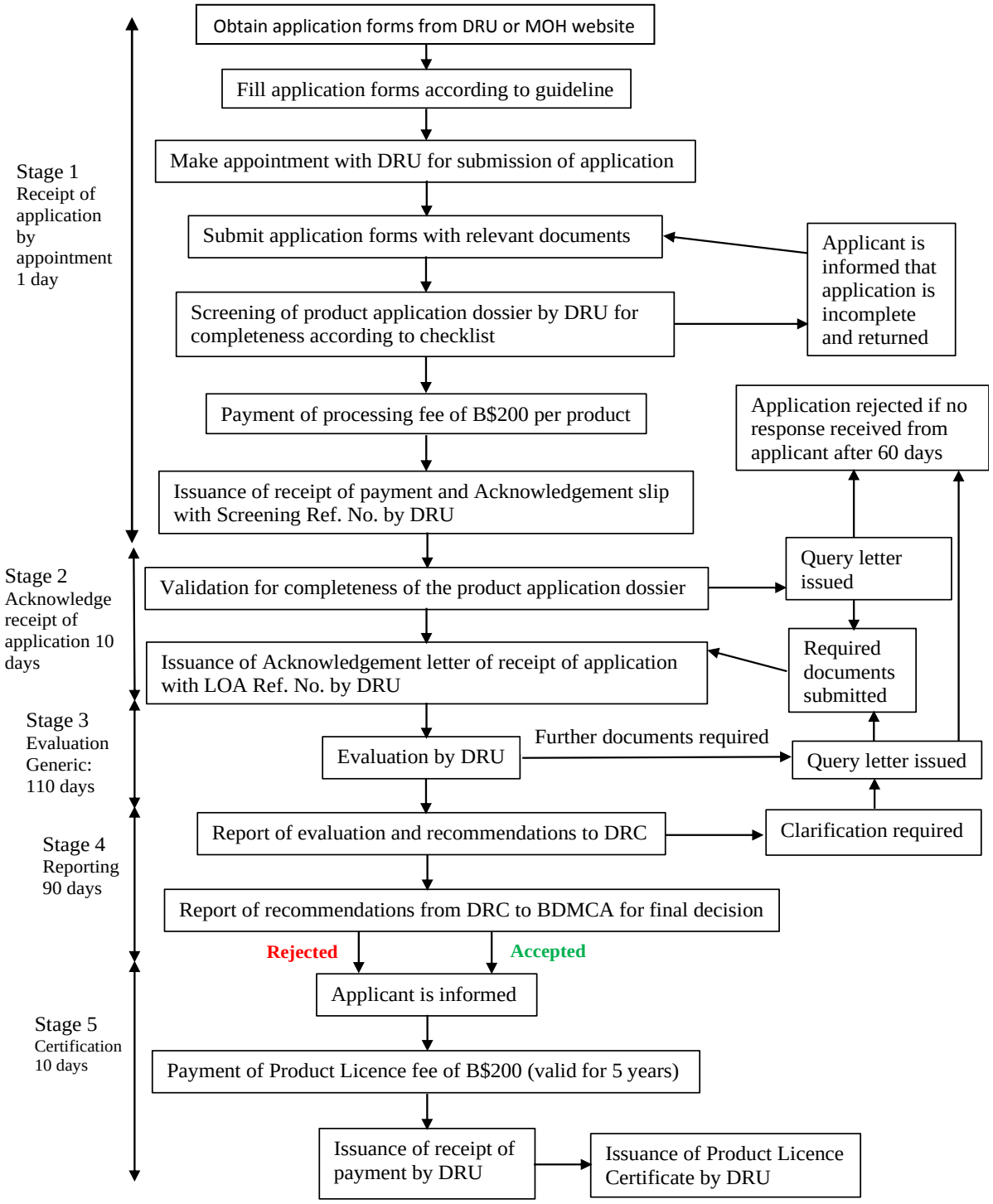


Figure 4: Flowchart of Generic Drug Registration Process in Brunei Darussalam.

Section 4: Labelling (Language used for labelling shall be English and/or Malay.)

Section 5: Product Information

- Summary of Product Characteristics (SmPC) or Package Inserts (for generic products), SmPC (for NCE and Biotechnology products) and Patient Information Leaflets.

Part II: Quality

Section 1: Application Form for Quality attributes of the Drug Substance (Form No. BCMCA/DPS/02/A)

Section 2: Application Form for Quality attributes of the Drug Product (Form No. BCMCA/DPS/02/B)[10]

MYANMAR

The Food and Drug Administration (FDA) in Myanmar, is responsible for the regulatory compliance of food, drugs, medical devices, and cosmetics in the country. FDA is responsible for the pharmaceutical registration dossier evaluation. The Department of Food and Drug Administration (DFDA) under the Ministry of Health and Sports has published the Guideline on Drug Registration Application (Ref: FDA/ (D)2018/149, Dated: 15-2-2018).

Drug Control Division (DCS) is one of the five major divisions of the DFDA. The Drug control division is involved in activities such as registrations, inspection and licensing for manufacturing and import, drug sample collection and analysis, PMS.

Generic products are considered as pharmaceutical equivalents of products already approved for marketing in Myanmar.

The registration application for drug must be submitted to the Department of Food and Drug Administration, Myanmar in the original Form (1), available at 1,000 kyats. As of 26, February 2018, application submission is made by using the online facility at https://user.dcdfdamm.online. In case of online applications, applicant must have a hardcopy of the Form I.

Separate registration has to be applied for pharmaceutical preparations of different strength/dosage form. Form 1 must be filled out in type print (or) (written in upper case) attached with computer print. Documents submitted together with application form shall be marked with proper reference.

Screening is done by FDA for online submissions, if found to be receivable, applicants will be requested to submit a physical dossier consisting of Form (I) accompanied by one set of documentation. One extra copy of the dossier must be kept at the company's premises. Documents have to be submitted in file in an order as listed in the requirements ("Documents Required for Registration of Drugs").

Documents list submitted should be mentioned on the first sheet of the file. Physical dossiers must be submitted within 60 days of being notified by FDA that application is receivable. Failure to meet the 60- day deadline will constitute forgoing of an application by an applicant. If so happens, neither the Registration Assessment Fees remitted nor any documents and drug samples will be returned.

A dossier with incomplete documentation or documentation that does not bear the printed security makings cannot be received. Submission of non-receivable dossiers does not affect the 60-day deadline. As a result, an application will be assumed to be forgone by the applicant if no receivable dossier is submitted within the 60-day deadline. An application must be submitted in person by an authorised representative of product owner. Any application made by mail or any means other than in person, will not be accepted. An authorised representative has to be a resident of Myanmar, the representative shall be a company employee technical competent person authorised to act as a contact person.

Registration assessment fees – 300000 Kyats must have been remitted to MD account of Department of Food & Drug Administration before submission of the application form. The submission must be made within 183 days from the date of payment. A new payment will have to be made in order to submit an application after the payment validity deadline is passed. Applications containing active substances or fixed-dose combinations never marketed in Myanmar can be received only if they have been already authorized for marketing in at least two the following regulatory authorities: TGA, Australia: Health Canada; European Medicines Agency; MHRA, United Kingdom; FDA, United States. Alternatively, they should have been prequalified by WHO or concern indications that are of specific relevance to Myanmar.

For registration applications for medicines manufactured outside Myanmar, the Food and Drug Administration will issue a "drug sample approval" upon receipt of the application. The drug samples specified in the approval are then imported into the country. The content of the owner's consent is not only consistent with the terms set forth in (the product's licensor from the country of origin). As per Ministry of Health Notifications, prior approval shall be obtained from Food and Drug Administration for importation of registration sample drug. FDA will not issue approval certificate for the importation of sample drug without prior approval of the FDA.

Samples for laboratory analysis and retention are normally required. All drug samples must be accompanied with their respective Certificate of Analysis, which must be stated with name and designation of an official. The photocopy of CoA report is not acceptable.

When all the pre-requisites for registration application have been met, only then the evaluation process for registration will get initiate.

- Payment of registration Assessment Fees.
- Complete documents.
- Adequate quantity and good shelf life of drug samples.

The applicant will be notified by FDA (on notice board) to remit 500000 Kyats as Registration Fees, when the drug is approved for registration. Failure to pay registration application fees within 90 days from the date of intimation will represents drop of an application by an applicant. In this case, the registration assessment fee, registration documents and drug samples will not be refunded.

If the applicant is unable to make a follow-up for an application, for more than six months from the date of remittance of assessment fees, will result in decline of an application. When the acknowledgement of receipt of payments issued by FDA is submitted, then the registration certificate (Form II) will be issued. Submitted documents cannot be retrieved if the request is denied.

Documentary requirements for submission

1. Administrative documents

- A certificate of product issued by the regulatory authority of its own country that the product is authorized to be sold in country of origin.
- A copy officially certified with a valid manufacturing license.
- GMP certificate of manufacturing premises.
- A letter of authorization is required for legal representation of owner of product in Myanmar.
- Registration certificate of local representatives (for business).

PART I: ADMINISTRATIVE DATA AND PRODUCT INFORMATION

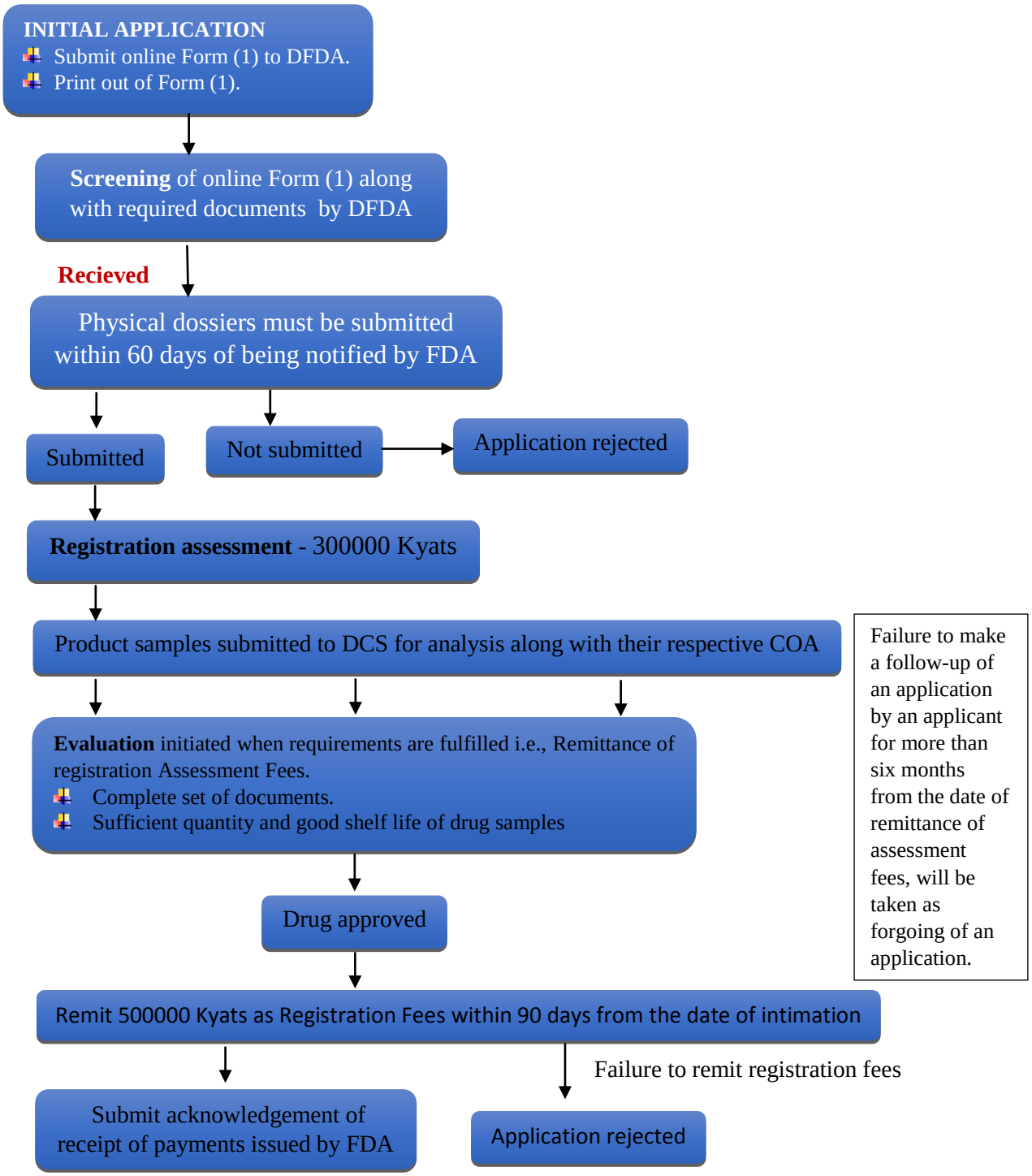
1. Application Form
2. Letter of Authorisation

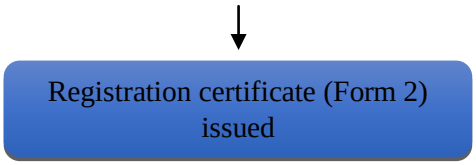
3. Certification

3.1 For contract manufacturing

- License of pharmaceutical industries and contract manufacturer.
- Contract manufacturing agreement.
- Copy of "under-license" agreement.

The registration process involves a series of steps, as shown in Figure-5.





3.2 For imported products

- License of pharmaceutical industries/ importer/ wholesaler (country specific).
- CPP according to the current WHO format, issued by the competent authority in the country of origin.
- Site master file of manufacturer (country specific).

4. Labelling

4.1 United Carton

4.2 Inner Label

4.3 Blister/Strips

5. Product Information

5.1 Package insert (needed for generic products).

5.2 SmPC (required for NCE & Biotechnology products).

5.3 Patient Information Leaflet (required for OTC Products).

Additional requirements

- A certificate of product issued by the regulatory authority of its own country that the product is authorized to be sold in country of origin.
- A duly approved copy of a valid manufacturing license.
- GMP certificate of manufacturing premises.
- A letter of authorization for legal representation of product owner in Myanmar.
- Registration certificate of local representatives (for business). [11]

VIET NAM

The Drug Administration of Viet Nam (DAV) is a sectoral regulatory administration/department under the Ministry of Health, which assists the Minister of Health to undertake the state regulatory functions, to organize the law enforcement and to direct and steer the professional and technical activities in the pharmaceutical and cosmetic fields. Drug Marketing Authorization Advisory Committee is tasked to provide advice to the Ministry of Health in terms of granting drug marketing authorizations in Viet Nam, policies on

harmonization of the drug registration regulation in the region and the world, policies on drug production, import and marketing in Viet Nam, including the use of drugs for the Vietnamese bodies to judge/evaluate the safety and efficacy of drugs when necessary. Drug registration dossier evaluator is tasked to provide the DAV with advice related to evaluation of drug registration dossiers and to propose/recommend the approval, refusal or requirement of document supplement. The Ministry of Health provides Circular on Registration of human-use drugs (No. 22/2009/TT-BYT) for circulation in Vietnam.

Language used

- Registration dossiers of local medicines must be in Vietnamese.
- Registration dossiers of imported medicines must be either in Vietnamese or in English. In case English is used, the information in the package insert, summary of product particulars or patient information leaflet must be in Vietnamese.

Format followed for dossier submission – ACTD format.

Documentary requirements

Part I – Administrative part and product information

I. Cover (Form 1/TT)

Title on the cover: DRUG REGISTRATION DOSSIER

The information on the cover should include:

1. Name and address of the drug Applicant, license for operating in Medicines, Pharmaceutical Starting Materials in Vietnam (in case of foreign pharmaceutical businesses).
2. Name and address of the medicine manufacturer.
3. Name of medicine – strength – content.
4. Dosage form
5. Type of medicine registered
6. Type of registration

II. Table of contents

III. Application (Form 2/TT)

For first time registration of generics, Application (Form 2A/TT) could be used.

IV. Power of Attorney (Form 3/TT)

V. License of the applicant (The applicant is a Vietnamese medicine business)

VI. Certificate of Pharmaceutical Product (CPP) or Free Sale Certificate (FSC) + Good Manufacturing Practice (GMP)

VI. Label (including label and package insert)

VII. Product information (Generics: package inserts)

IX. Medicine post-marketing report (Form 5/TT)

X. Master file: in accordance with Form (4/TT)

XI. Samples of medicines and pharmaceutical starting material

XII. Checklist of documents to be submitted per each type of registration.[12]

The registration process involves a series of steps, as shown in Figure-6.

INDONESIA

The Indonesian Food and Drug Regulatory Authority or Indonesian FDA – The National Agency of Drug and Food Control (NA-DFC), (Indonesian: Badan Pengawas Obat dan Makanan) or Badan POM, is a government agency of Indonesia, BPOM is responsible for drug registration, application review process, and grants drug approvals in the form of a marketing approval license. Regulation No. 24 of 2017 on Criteria and Drug Registration Procedure ("Regulation 24") was enacted by BPOM on 24th November 2017.

Format followed: ACTD Format is followed for the drug product registration.

Category of registration

- **Registration consists of**

a. New Registration.

b. Variation Registration

c. Re-registration.

New Registration, letter a consists of:

- Category 1: Registration of New Medicines and Biological Products, including Biosimilar Products.
- Category 2: Registration of Generic Drugs and Branded Generic Drugs.
- Category 3: Registration of other preparations containing drugs with special technology, can be in the form of transdermal patches, implants, and beads.

Registration of variations, letter b consists of:

- Category 4: Major Variation Registration.

- Category 5: Minor Variations Registration.
- Category 6: Registration of Notification Variations.

Re-registration, letter c consists of: Category 7.

Registration Procedures

1. General

- Registration consists of:
- Pre-registration stage.
- Registration stage.
- Application for pre-registration and registration shall be submitted by Registrant in writing to the Head of Agency by attaching pre-registration documents and registration documents.
- Application shall be submitted by filling out the Form as per instructions specified in the Regulation of the Head of Agency.
- Pre-registration documents and registration documents must use Indonesian or English.
- Applications for pre-registration and registration can be submitted electronically in accordance with the applicable provisions or shall be submitted manually.
- The application for pre-registration and registration:
- Shall be subject to fees as non-tax state revenue in accordance with the provisions of laws and regulations.
- The fee must be paid no later than 10 (ten) days from the date of issuance of the Order for Payment for Public Services (SPB-LP).
- Registrants are required to confirm SPBLP payment and submit pre-registration documents or registration documents no later than 3 (three) days from the date of payment.
- In the event the Registrant does not confirm SPB-LP payment and submits pre-registration documents or registration documents, the application will be announced revoked.

Registration Documents consist of

Part I: Administrative documents, Product Information and Labels.

Administrative document consists of

1. Cover Letter.

2. Registration Form.

3. Registrant's Statement.

4. Certificates and Other Administrative Documents.

4.1. Domestic Medicines.

4.1.1. Pharmaceutical Industry Permit.

4.1.2. CPOB certificates that are still valid for dosage forms that is registered.

4.1.3. CPOB Certificate for Active Substance producer.

4.1.4. Latest CPOB inspection data and most related changes two years old issued by the Drug Supervisory Agency and Food.

4.2. License drug.

The registration process involves a series of steps, as shown in Figure-7.

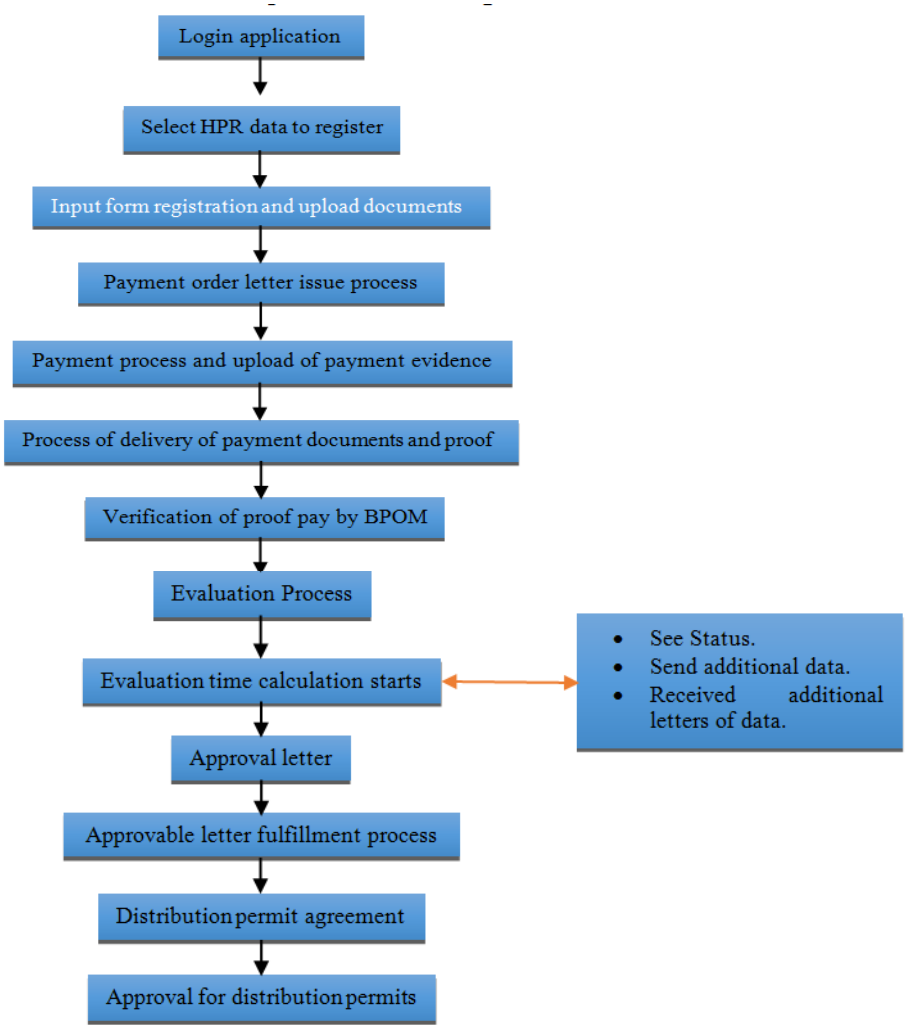


Figure 7: Flowchart of Generic Drug Registration Process in Indonesia.

4.2.1. Pharmaceutical Industry Permit or supporting documents with evidence sufficient for the research agency / institution as the provider licence.

4.2.2. Pharmaceutical Industry Permit as a licensee.

4.2.3. Certificate of CPOB for Pharmaceutical Industry, still licensed recipient applies to the registered dosage form.

4.2.4. CPOB Certificate for Active Substance producer.

4.2.5. License agreement.

4.3. Domestic Production Contract Medicines.

4.3.1. Pharmaceutical Industry Permit of Registrant or Contract Giver.

4.3.2. Pharmaceutical Industry Permit as Contract Recipient.

4.3.3. Pharmaceutical Industry CPOB Certificate of Registrant or Giver The contract is still valid.

4.3.4. Contract Recipient's CPOB Certificate for Pharmaceutical Industry still valid according to the dosage form of the drug contracted out.

4.3.5. CPOB Certificate for Active Substance producer.

4.3.6. Contract agreement.

4.4. Export Special Medicine.

4.4.1. Pharmaceutical Industry Permit.

4.4.2. Registrant's CPOB Certificate.

4.4.3. CPOB certificate or other equivalent document from the producer according to the registered dosage form (for imported drugs export specialty).

4.4.4. CPOB Certificate for Active Substance producer.

4.5. Imported Medicine.

4.5.1. Pharmaceutical Industry Permit for producers and Registrants.

4.5.2. Letter of appointment from the pharmaceutical industry or product owner abroad are exempted for Registrants who are affiliates of the parent company.

4.5.3. Certificate of Pharmaceutical Product (CPP) or other documents the equivalent of the producing country and / or country where issued a batch release certificate (if necessary).

4.5.4. A valid CPOB certificate from the producer for registered dosage forms or other documents equivalent (including CPOB certificate for Active Substance producer Biological Products).

4.5.5. Latest CPOB inspection data and most related changes two years duration issued by the supervisory authority Local drugs and / or drug regulatory authorities in other countries.

4.5.6. CPOB Certificate for Active Substance producer.

4.5.7. Import justification.

4.5.8. Proof of balance of export and import activities (if necessary).

5. Pre-registration results.

6. Receipt / Proof of Payment.[13]

PHILIPPINES

The Food and Drug Administration (FDA) under the Department of Health regulates the pharmaceuticals in the Philippines and ensures the safety, quality, efficacy, purity of products through effective implementation of the national regulatory framework harmonizing with the international guidelines.

Generic products are considered to be bioequivalent or essentially similar to reference drugs. These are drugs that are not covered by patent protection and are pharmaceutically equivalent but may or may not be therapeutically equivalent, and labelled solely by their international non-proprietary name or generic name.

Generic drugs in the Philippines are classified depending on the dispensing category as follows

- Prescription drug products.
- Non-prescription drug products.

Therefore, the requirements differ based on the drug category.

For a company to be able to market a drug product in the Philippines, obtaining a marketing authorization in the form of a Certificate of Product Registration (CPR) is important. A a particular drug product covered under CPR, shall be a principal evidence of the registrant's marketing authority for the said drug product in connection with the activities permitted pursuant to the issuance of an License to operate.

The process begins with the submission of an electronic copy application using the Integrated Application Form at the Public Assistance, Information, and Receiving (PAIR), by appointment schedule of an applicant company (which may be a licensed manufacturer, trader, or supplier). After the submission of dossier by the applicant, CDRR evaluates the same and determines if the product meets the standards of safety, efficacy, and quality. CPR is issued, if the product meets these standard requirements (CPR validity - 5 years).

Deficiencies should be noted, depending on the criticality, a Notice of Deficiency (NOD) or Letter of Disapproval (LOD) may be issued.

Philippines's drug regulatory authority follows the ACTD and common technical requirements for the registration of drug product for human use.

Figure 8: Generally describes the process of registration

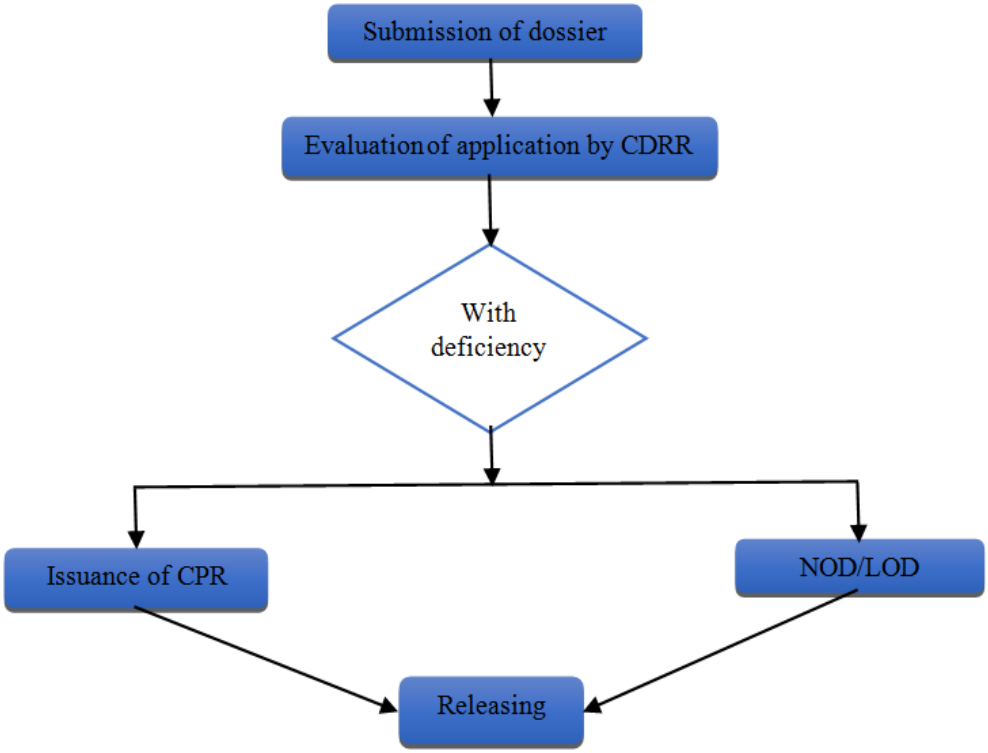


Figure 8: Flowchart of Generic Drug Registration Process of Philippines.

Registration Documents consist of

Part I: Administrative Data and Product Information

Section A: Introduction

This section contains the Administrative Data and Product Information.

Section B: Table of Contents

1. Application Form
2. Letter of Authorisation
3. Certifications
4. Labelling
5. Product Information

Section C: Guidance on the Administrative Data and Product Information

- Duly accomplished and notarized Integrated Application Form (with proof of payment). English and/or official native language (Filipino) shall be used.
- Details of applicant and manufacturer.
- Product details.
- Evidence of patent/trademark, where applicable.
- Reference product, where applicable.
- Applicant declaration (country specific)

2. Letter of Authorisation (where applicable)

3. Certifications

For contract manufacturing

- Licence of pharmaceutical industries and contract manufacturer
- Contract manufacturing agreement
- GMP certificate of contract manufacturer

For manufacturing "under-licence" (country specific)

- Licence of pharmaceutical industries
- GMP certificate of the manufacturer
- Copy of ''under-licence'' agreement.

For locally manufactured products (excluding the above)

- Licence of pharmaceutical industries
- GMP certificate (country specific)

For imported products

- Licence of pharmaceutical industries/importer/wholesaler (country specific)
- Certificate of Pharmaceutical Product issued by the competent authority in the country of origin according to the current WHO format.
- Site master file of manufacturer (country specific).

4. Labelling

English and/or Filipino language shall be used.

5. Product Information

For generic product either SPC or package insert is acceptable. English and/or Filipino language shall be used.

For Part II: Quality, the following may be submitted:

Sec. A: Table of Contents

Sec. B: Quality Overall Summary

Sec. C: Body of Data

Drug substance

S 1 General Information

S 1.1. Nomenclature

S 1.2. Structural Formula

S 1.3. General Properties

S 2 Manufacture

S 2.1. Manufacturer(s)

S 3 Characterization

S 3.1. Structure Elucidation and Characteristics

S 3.2. Impurities

S 4 Control of Drug Substance

S 4.1. Specifications

S 4.2. Analytical Procedures

S 4.3. Validation of Analytical Procedures

S 5 Reference Standards or Materials

S 7 Stability

Drug product

P 1 Description and Composition

P 2 Pharmaceutical Development

P 3 Manufacture

P 4 Control of Excipients

P 5 Control of Finished Product

P 6 Reference Standards or Materials

P 7 Container Closure System

P 8 Product Stability

P 9 Product Interchangeability/Equivalence Evidence (if applicable)

Note: For Part II: Quality - Drug Substance (S), the following may be submitted

Option 1: Full submission (S1-S7)

Option 2: Certificate of Suitability (CEP) –with sections/sub-sections: S1, S2.1, S4.4 and S7 (if retest period is not stated) only. Copy of the latest version of the CEP shall be provided.

Option 3: Active Pharmaceutical Ingredient Master File (APIMF)

- ICH Common Technical Document format is acceptable provided that the products are approved in ICH member countries / regions.[14]

Lao PDR

The drugs which shall be used, trafficked and distributed in the Lao PDR must be first subject to registration with the Department of Food and Drugs under the Ministry of Health. Before permitting the drug registration, the Department of Food and Drug must review and comply with the processes, conditions and requirements of regional and international standards to ensure quality, efficacy and safety.

The imported drugs and medical products for distribution in the Lao PDR, must be subjected to registration with the Department of Food and Drug of the Ministry of Health.[15]

Supporting Document

- For domestic drugs: Those planning to manufacture must submit a sample drug registration application using Form No. 1 (LP1 or ຢ 1).

After approval, manufacturers can apply for Registration Form No. 2 (LP 2 or ຢ 2) within 3-6 months.

- For medicines imported domestically: Those who wish to import medicines must submit import registration documents.1 (IP1 or 1). Once approved to manufacture a sample drug, the manufacturer must submit an application form 2 (LP 2 or ນ ຂ 2) within 3 to 6 months.

Drug registration Principles

1. Application for drug registration will be considered only after the following conditions have been fully complied:

- Registration of drug is in accordance with the National Medicines Policy,
- Person must be legally permitted to manufacture, to import modern and traditional drug for selling in Lao PDR.

- Supporting documents.
- 2. Application for drug registration will not be considered in the following cases:
- Documents are not completed as prescribed in the application form No. LP1, LP2, IPI, IP2.
- Notification has been given for any error correction, but no amendment is made.
- Failure of submission of application form no. LP2 or IP2 within 12 months for drug registration.
- Drug listed under banned drugs in Lao PDR.
- Drug which is withdrawn by the manufacturing company.
- Drug with more than three APIs except for multi-vitamins and basic essential substances for body (including drug for external use, amino acids, minerals).
- Drug with copied trade name and copied package that has already been registered in Lao PDR.

The committee for drug registration appointed by the Minister of Health must be responsible for drug registration. The food and Drug Department has authority to issue the certificate of drug registration for all drugs (essential medicines). The consideration period for the issuance of each certificate of drug registration is around 180 days. After the approval of drug product, the Food and Drug Department will issue a registration number and a certificate of drug registration, thereof the license shall be entitled to manufacture, and import as well.

Receiving the application for drug registration

In the case if drugs are not required to undergo a laboratory test, before issuing the certificate of drug registration, the sample of drugs should be taken for the testing at the time of importation. In the case of unavailability of reference substances for analysis the related drug company should supply the reference substances for analysis along with other related documents. The drug registration application forms must be original, along with the red mark of Food and Drug Department (FDD). Also, other related certificates: if they are the photocopy of the original documents, they must be certified by the company to confirm the authenticity of the original documents.

Code number for drug registration

For drug allotted with registration numbers, the registration number must be printed on the labels, boxes, containers, blisters, vials by the respective product owners. If there is no possibility to print the necessary Lao content on the label for every imported drug, the leaflets

are prepared in Lao version by related importing company before distribution, which must be inserted into all different types of packages.

Table 1: Code number for Drug Registration.

Modern drug imported	XX (Month) ix xx (Number)/year A. D
Traditional Drug imported	XX (Month) ITXX XX (Number)/year A. D

Each certificate of drug registration is valid for three years from the date of signature. The product owner shall submit renewal application, within not less than ninety days before the expired date, to the Food and Drug Department (FDD). Otherwise, the registration must be withdrawn.

Documentary requirements

PART I. Administrative and prescribing information

Section A: FDD Application Form No. 2

Section B: Applicant nomination certified by the manufacturer of the Product

Section C: Supplementary Documentation

- Stage 1 Approval Letter
- Certificate of Pharmaceutical Product (CPP)
- Certificate of Drug Registration (COR)
- Certificate of Good Manufacturing Practice (GMP)
- Certificate of Free sale (CFS)
- Summary of Product Characteristics (SmPC)

PART II. Quality Documents

Section A: Tablet of contents

Section B: Quality of contents

Body of Data

- Drug Substance
- Drug Product
- List of Key Literature Reference [16]

THAILAND

Thailand's national Drug Control System established from its Drug Act BE 2510 (1967) and its four amendments. The Drug Control Division of the FDA under the Ministry of Public

Health (MOPH), is responsible for regulating the system. Interested companies (manufacturing or exporting pharmaceutical products) shall obtain approval in the form of license from the FDA before marketing of drug product in the Thailand. The Drug Control Division is also authorized to approve or withdraw pharmaceutical registration, standard specifications, criteria and guidelines, including suspending or withdrawal of licenses to manufacture, import, distribute or sell.

Submission Format: ACTD format with additional country specific requirements.

Type of Application: Registration requirements differ for general drugs such as generics, new medicines, new generics, and traditional drugs.

Types of drugs in Thailand

- New medicines
- Generics
- New generics

Generics mean pharmaceutical products is same as reference product (in terms of API and the dosage forms), but manufactured by different manufacturers. Following is the flowchart showing registration process in Thailand.

Generic drug registration procedure is classified into 2 main steps

Step 1: Application to permit import or manufacture of drug sample intended to be registered.

Documents required

1) Application form filled by authorized licensee.
2) Drug formula [APIs only]
3) Drug literature
4) Drug labelling and packaging

Step 2: Application for the issuance of granted credential certificate

Documents required

1) Application form filled by authorized licensee.
2) Permit to import or manufacture drug sample.
3) Drug samples as per requirements.
4) Pharmacological and toxicological study.
5) Clinical trials data.

6) Drug formula

7) Drug literature

8) Labelling and packaging should include name of the drug, registration number, amount of drug content per packaging, formula which shows APIs and quantity of strength, lot no. batch control number, name and address of manufacturer, manufacturing date, the words " dangerous drug"/ "specially controlled"/ "for external use"/ "for topical use" written in Thai and in red colour if the drug is considered to be 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.

9) Certificate of Free sale (for imported drug)

10) Method of manufacturing.

11) In-process control with acceptable limits.

12) Raw material specifications of APIs and inert ingredients with the corresponding control methods.

13) Finished drug product specification with the corresponding control methods.

14) Certificate of analysis of APIs [To be required in case of that active substance dose not conform to official pharmacopoeias (USP, NF, BP).

15) Analytical control method for drug

16) Packaging

17) Storage condition

18) Stability study data of finished product

19) Certificate of GMP (for imported drug)

Note: CFS should be issued/legalized by the competent authorized officer and endorsed by Thai Embassy / Thai consular Office residing in correlation to the country where the documents being issued.

Generic Drug registration procedure involves three steps

1. Application for the allowance to manufacture or import of drug samples.
2. Application for an approval of analytical methods and drug quality control.
3. Application for granting of a certificate for the drug registration.

Both Step 1 and 3 are completed at Thai-FDA and Step 2 is completed at Department of Medical Sciences.[17]

Registration process of Thailand as shown in Figure-9.

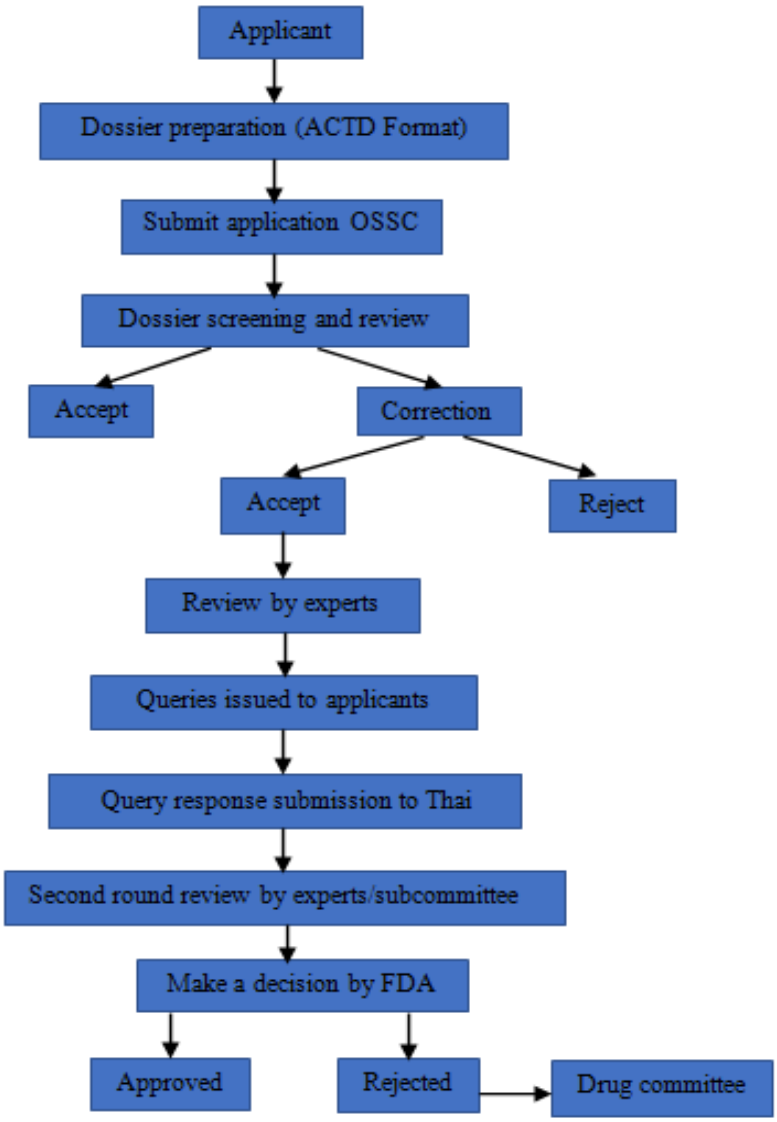


Figure 9: Flowchart of Generic Drug Registration Process in Thailand.

CONCLUSION

The purpose of this work has served to spotlight the regulations and requirements for the registration of generic drug products within the ASEAN member countries. The ASEAN region is emerging within the pharmaceutical marketplace with several countries leading in quality, efficacy, safety, BE/BA, and variations. The regulatory framework of the ASEAN member countries is structured to assure safety of the drug product and thus they require an intensive analysis of all critical steps and aspects prior to the registration of drug. All ASEAN member countries follow ACTD format for the dossier submission. For generic drugs, the registration process is far easier than the registration of an NCE because it involves only Part I (Administrative documents and products information) and Part II documentation (Quality documents for drug substance and drug product). When studied intimately it absolutely was

found that every administrative unit had its own format of canopy letter, application form, and appropriate updates to the regulatory technical dossier submission regulations. There are many challenges in current drug registration process, as a result, regulatory mechanisms are still evolving. Economic diversity, language, uneven distribution of wealth, property, and lack of harmonization of guidelines and their implementation are a number of the challenges currently creating hurdles for pharmaceutical companies looking to penetrate these regions more easily. It is important for the region to own more ASEAN countries accredited to PIC/S for the implementation and maintenance of harmonized cGMP standards and quality system and having a standard filing procedure with full mutual acceptability within the ASEAN region, which is able to ensure rapid patient access to drugs, like seen within the EU with Mutual Recognition Procedure (MRP), Decentralized Procedure (DCP), and Centralized Procedure (CP). From the study it had been found that thanks to variation in regulatory requirement in various countries it's a significant challenge for pharmaceutical companies to register their pharmaceutical products. For pharmaceutical companies so as to develop a drug formulation which might be simultaneously submitted in numerous countries for approval at the identical time is grinding. Therefore, continuous process of harmonization is disbursed everywhere the globe to beat this problem. It gives a quick information about the regulatory requirements for registration of pharmaceutical product. It will be concluded that the industry should target on submission or registration of pharmaceutical product at different countries betting on their stability, regional and other country specific documents.

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