

Comparison of Marketing Authorisation and its Requirements for Brunei Darussalam and Indonesia



Abstract:

The availability of generic medication is an important issue in the ASEAN region. The regulatory requirements of various countries of the world vary from each other. Therefore, it is challenging for companies to develop a single drug which can be simultaneously submitted in all countries for approval. The regulatory strategy for product development is essentially to be established before commencement of developmental work in order to avoid major surprises after submission of the application. The role of the regulatory authorities is to ensure the quality, safety, and efficacy of all medicines in circulation in their country. It not only includes the process of regulating and monitoring the drugs but also the process of manufacturing, distribution, and promotion. One of the primary challenges for regulatory authority is to ensure that the pharmaceutical products are developed as per the regulatory requirements of that country. This process involves the assessment of critical parameters during product development. Regulatory requirements and generic drug registration for ASEAN regions is made at the end of the section. In the ASEAN region, documentation can be filed in the ACTD format.

Keywords: ASEAN, ACTD, Documentation, Regulatory Authority.

Introduction

The ASEAN (Association of Southeast Asian Nations) group of nations, namely Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia, has recently been the eye-catcher for most pharmaceutical companies due to the growing population and attractive pharmaceutical market growth. A recent development includes the harmonisation of regulations favouring the market entry to these nations².

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, followed by Vietnam on 28 July 1995, Laos and Myanmar on 23 July 1997, and Cambodia on 30 April 1999. In 1999 a harmonisation initiative was started among the 10 ASEAN countries. One aim of this harmonisation should be to harmonise 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 “harmonisation 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 harmonised 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 (Mutual Recognition Arrangements) MRAs.”

From August 2003 – December 2004 ASEAN countries implemented 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 summarised here:

- Singapore and Malaysia by December 2005
- Thailand by December 2006
- Indonesia and Vietnam by December 2007
- Philippines, Cambodia, Laos and Brunei by December 2008

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 Drug Regulatory Authorities (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

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 five modules whereas the ACTD contains of four 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. Module 1 of the CTD, containing the regional registration and administrative information, is still presented as Part 1 of the ACTD. Module 2 of the CTD does not exist itself for the ACTD. The Quality Overall Summary (QOS) and the overview and summaries of the non-clinical and clinical documentation (similar to 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 ICH Module 3.

The non-clinical 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 and ACTD are presented in the comparison pyramid (Figure 1).

As demonstrated in figure 1 the ACTD is organised in four parts

- Part I: TOC, Administrative Data and Product Information
- Part II: Quality Document
- Part III: Non-Clinical Document
- Part IV: Clinical Document

Dossier Requirements

The requirements for the dossier for the ASEAN countries are in principle very similar to the requirements for the ICH countries.

The non-clinical overview and summary, as well as the clinical overview and summary, is put at the beginning of part 3 and 4, followed then by the study reports and literature. For some ASEAN countries these non-clinical and clinical overviews and summaries are sufficient and no additional study reports need to be submitted. In most of the cases, it is sufficient to submit some publications from the mentioned studies in addition to the non-clinical and clinical overviews and summaries.

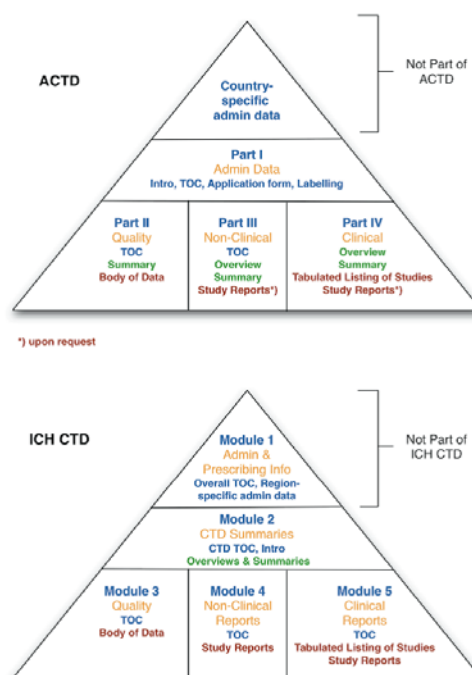


Figure 1: ACTD & ICH Pyramid

Brunei Darussalam

Legal Framework and Regulations²

- The Food Safety & Quality Control Division under the 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 Registration³

1. 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 its appointed sole agent.
 - In the case of a locally manufactured product, the manufacturer of the product or the local product owner.
2. Applications for provisional product registration are to be made by submission of the
3. letter of intent and by using the prescribed forms issued by the DPS. Application forms are charged at B\$2.00.
4. The submitted application will be screened and validated for completeness within 14 days.
5. Submission of the applications must be made by appointment with the concerned officer at the above address.

6. The processing fee of B\$100.00 per 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.
7. 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 correspondence relating to the application.

Documents Required for Application for Registration of Generic Medicinal Products³

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 four parts, 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: Labelling
- 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)

Non-clinical 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 Application³

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 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 the applicant after the 60 days given, and a new 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, an 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.

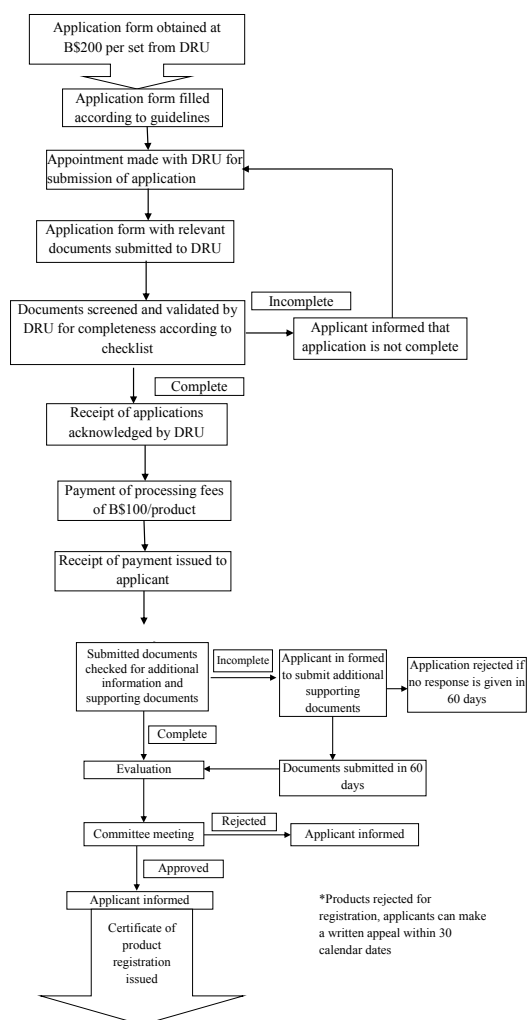


Figure 2: Flowchart on the Procedure of Application for Provisional Registration of Medicinal Products⁴

Indonesia

Legal Framework and Regulations^{5,6}

The decree of the head of the 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 the Regulation of the Ministry of Health in Indonesia No. 1010/MENKES/PER/XI/2008 regarding the Registration of Medicines (“**Regulation 1010/2008**”) - states that a medicine to be distributed in Indonesia must be first registered before a Distribution License (Izin Edar) can be applied for.

Format followed

ACTD format with some country-specific requirements.

Regulatory system:

Regulatory Structure of Indonesia

1. Drug registration shall be submitted by the applicant to the Head of the National Agency.
2. Drug registrations are categorised into:
 - New registration
 - Registration of drug variations

Category 1 : is a new drug registration with new active pharmaceutical ingredient, 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 another preparation containing the drug

c. The registration of a copy drug (generic) comes under Category 4.⁵

Regulatory Requirements:

- a. Completion of registration forms should be in Indonesian or in English;
- b. Registration documents can be in Indonesian or in English;
- c. Labelling of over-the-counter drug/limited over-the-counter drug must be in Indonesian;
- d. Labelling of drugs for export only should at least be in English.⁵

C. Country-specific Requirements which may also be Included with the ACTD Submission:

- Traditional medicine 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 they 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 with 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 drug⁹

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 includes drug applications for products used to treat serious or life-threatening diseases, or for essential generic drugs for public health programmes.
- 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.^{5, 7, 8}

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.⁸

- 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 analysis 3 (three) times, and standard raw material should 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), should consist of a floppy disk that has been completed in line with the data in Form A and Form B21-13, and Forms A, B1, B214, B4, C1, and D.
- iv. Registration dossier of copy drug with an active ingredient that has no STINEL should consist of a floppy disk that has been completed with the data in line with Form A and Forms A, B1, B2, B3, C1, and D.
 - a. Form 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 standard 31.

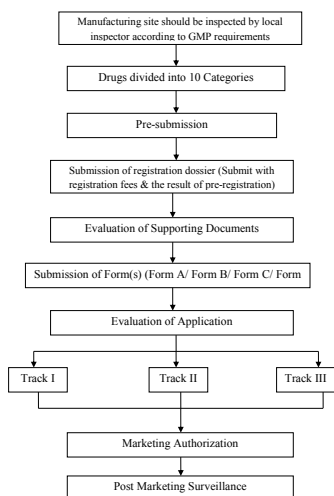


Figure 3: The drug registration process in Indonesia

S. NO	ADMINISTRATIVE DOCUMENTS	INDONESIA	BRUNEI
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	✓	✓
8	Permission For Manufacturing & Marketing In Country of Origin	✗	✗
9	LOA	✓	✓
10	Labeling Documents		
11	Patent Information	✓	✓
12	SPC	✓/PI	✓/PI
13	PIL	✗	✗
14	Mock Up And Specimen		
15	Environmental Risk Assessment	✗	✗
16	Product Information Already Approved In Any State /country	✗	✓

*I=provided in 1st dossier then reference is cited.

Table 1: Administrative Documents Comparison

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

Table 2: Technical Documents Comparison

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

Table 3: Technical Documents Comparison

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

Table 4: Non Clinical Documents Comparison

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

Table 5: Clinical Documents Comparison

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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