



Review Article



Regulatory requirements for the approval of Anti-Cancer drug (Mercaptopurine) in Myanmar as per ACTD

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ABSTRACT

South East Asian pharmaceutical market is growing rapidly. In Asian country, the regulatory environment is similar among all countries. But still requirements and process of registration is varying among countries of Asian region. Although ACTD is harmonized for all ten countries but still every country differ in some of the local requirements such as administrative, technical, clinical and non clinical documents. Among this country Myanmar systematically regulate the manufacture, import, export, storage, distribution and sale of drugs. Aim of the present study is To discuss emerging challenges and requirements posed by compulsory licensing for drugs in diseases such as cancer. In this article we have observed documents requires for registration of Mercaptopurine drug belonging to anti – cancer category in Myanmar. Documents like batch manufacturing record, process validation records, stability study which include long term and accelerated stability studies as per zone specification of Myanmar, packing requirements for anti – cancer drug and certificate for product permission required for registration, which has covered all aspects from manufacturing to its packing and registration. This article will give the easy understanding on the drug registration requirements for anti – cancer drug such as Mercaptopurine in Myanmar.

Keywords: ASEAN, ACTD, Myanmar, Mercaptopurine, Anti– Cancer, Registration.

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1. Introduction

1.1. Introduction to ASEAN Common Technical Dossier

This ASEAN Common Technical Dossier (ACTD) is a guideline of the agreed upon common format for the preparation of a well-structured Common Technical Dossier (CTD) applications that will be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals for human use. This guideline describes a CTD format that will significantly reduce the time and resources needed to compile applications for registration and in the future, will ease the preparation of electronic documental submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements (1).

The ASEAN (Association of Southeast Asian Nations) group of nations, [namely Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia] is an eye

catcher for most pharmaceutical companies due to the growing population and attractive pharmaceutical market growth. ASEAN established the CTD so it is called as 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 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 Drug Regulatory Authorities (DRAs) (2).

1.2. 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 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 in most of the ASEAN countries is 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 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) (2).

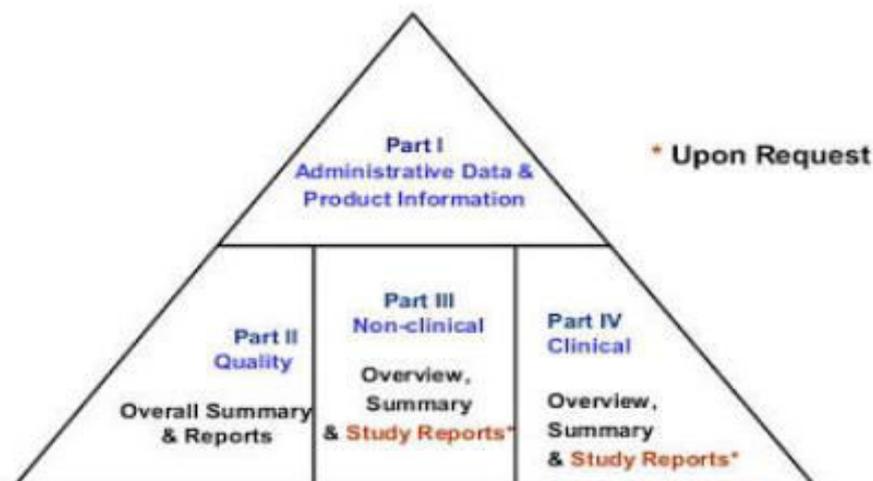


Figure 1. Organization of ACTD (3)

Table 1: Difference of ACTD & ICH CTD (3)

Documents	Location in	
Administrative Documents and Product Information	ICH CTD Module 1	ACTD Part I
Common Technical Document Overview and Summaries	Module 2	Incorporated in Parts II, III & IV
Quality documents	Module 3	Part II
Non-clinical documents	Module 4	Part III
Clinical documents	Module 5	Part IV

Table 2 General Comparison of ASEAN Countries (3)

Sr no	Validity format	Country	Followed format	Included in thesis
1	5 yrs	Singapore	ACTD	ACTD
2	5 yrs	Malaysia	ACTD	ACTD
3	5 yrs	Thailand	ACTD	ACTD
4		Philippines	Country specific & ACTD	Country specific
5	5 yrs	Indonesia	ACTD	ACTD
6	5 yrs	Vietnam	ACTD	ACTD
7	5 yrs	Brunei Darussalam	ACTD	ACTD
8	5 yrs	Myanmar	Country specific & ACTD	Country specific
9	5 yrs	Cambodia	ACTD	ACTD
10	5 yrs	Laos	Country specific & ACTD	Country specific

2. Discussion

2.1 Pharmaceuticals in Myanmar

The National Drug Law, 1992, of Myanmar or Burma. This legislation, which is the main law governing pharmaceuticals in Myanmar, systematically regulates the manufacture, import, export, storage, distribution and sale of drugs in the country. The authors take the reader through the intricacies of the Act and the institutions and regulatory regimes it creates, describing their operations and problems (4).

The Myanmar (Burma) government enacted the National Drug Law ('the ND Law') in 1992. The basic purpose of the ND Law is to control and systematically regulate the manufacture, import, export, storage, distribution and sale of drugs (4).

Technical Documents required

Administrative documents

- Comprehensive Table of Contents
- Introduction
- Application
- Labeling, Package Insert and Patient Information Leaflet
- Approved Summary Product Characteristics (SPC) /Patient Information Leaflet (PIL)
- Assessment Report from Reference Agencies
- Description of Batch Numbering System
- Proof of Approval
- Authorization Letters
- GMP Certification/Proof of GMP Compliance
- Patent declaration
- Declaration on rejection, withdrawal and deferral
- Declaration for GDA verification
- Registration status in other countries (5)

Quality documents

Body of Data

Drug Substance

- Drug Master File (DMF)

- Certificates of Suitability (CEP)
- Control of Drug Substance (3.2.S.4)
- Stability Data of Drug Substance (3.2.S.7) (5)

Drug Product

- Pharmaceutical Development (3.2.P.2)
- Process Validation (3.2.P.3.5)
- Control of Excipients (3.2.P.4)
- Control of Drug Product (3.2.P.5)
- Container Closure System (3.2.P.7)
- Stability Data of Drug Product (3.2.P.8)
- Product Interchangeability (3.2.P.9)
- Blank Production Batch Records (5)

Registration dossier

The complete dossier should be submitted within 2 working days after the PRISM application submission to prevent delays in processing of the application. The date of submission will be defined as the date when HAS receives the complete data set for the application (5)

2.2 Drug Registration procedure and approval system of Myanmar

An application for registration of drug must be submitted to the **GOVERNMENT OF THE REPUBLIC OF THE UNION OF MYANMAR**, Ministry of Health, in the original prescribed form (Form 1 Registration). Form (1) is available at one thousand Kyat each at office of the Department of Food and Drug Administration, Department of Food and Drug Administration Naypyitaw and Yangon (6).

Separate registration has to be applied for pharmaceutical preparations of different strength or different dosage form. Documents have to be submitted in file in an order as listed in "Documents Required for Registration of Drugs". A list of documents submitted should be shown on the first sheet of the file. All drug samples must be accompanied with their respective analytical report (the certificate of analysis) (6).

A sample (20gm) has to be submitted together with the application. The sample must be packed & labeled properly (6).

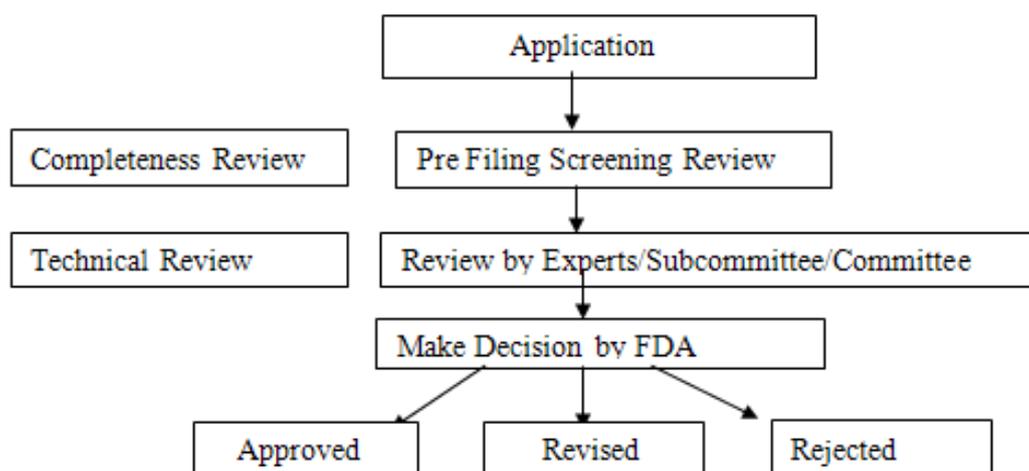


Figure 2. Flow Chart of Drug Review Process (7)

2.3 Comparison of ASEAN Countries for the documentation requirements

Table 3 Comparison of Administrative documents in ASEAN countries (3)

Sr no	Administrative Documents	Singapore	Malaysia	Thiland	Indonesia	Vietnam	Brunei	Cambodia
1	Application Form	√	√	√	√	√	√	√
2	Copy of valid certificate of brand Name clearance	√	√	√	√	√	√	√
3	Certificate of Pharmaceutical Product	√	√	√	√	√	√	√
4	Free Sale Certificate	×	×	×	×	×	×	×
5	Good Manufacture Practice	√	√	√	√	√	√	√
6	License for pharmaceutical Manufacture	√	×	√	√	√	√	√
7	Site Master File	×	×	√	√	√	√	√
8	Permission for manufacturing & Marketing in country of origin	×	×	×	×	×	×	×
9	Letter of Authorization	√	√	√	√	√	√	√
10	Labeling Documents	√	√	√	√	√	√	√
11	Patent Information	√	×	√	√	×	√	√
12	Summary Product Characteristics	√	√	√	√	√	√	√
13	Patient Information Leaflet	√	√	√	×	×	×	×
14	Product Information already approved In any State/country	√	√	×	×	×	√	×

Table 4 Technical documents comparison of ASEAN countries (3)

Sr no	Technical Documents	Singapore	Malaysia	Thiland	Indonesia	Vietnam	Brunei	Cambodia
1	Drug Substance	×	×	×	×	×	×	×
2	Quality Overall Summary	×	√	√	√	√	√	√
3	General Information	×	√	√	√	√	√	√
4	Manufacture of Drug Substance	×	√	√	√	√	√	√
5	Characterization	×	√	√	√	√	√	√
6	Quality Control of Drug Substance	√	√	√	√	√	√	√
7	Reference Standards	×	√	√	√	√	√	√
8	Container Closure System	×	√	√	√	√	√	√
9	Stability	√	√	√	√	√	√	√
10	CEP (Certificate of European Pharmacopeia)	√	×	×	×	×	×	×
11	Drug Master File	√	×	×	×	×	×	×
12	Drug Product	√	√	√	√	√	√	√
13	Description & Composition Pharmaceutical Development	√	√	√	√	√	√	√
14	Manufacture	√	√	√	√	√	√	√
15	Quality Control of Excipients		√	√	√	√	√	√
16	Quality Control of	√	√	√	√	√	√	√

17	Finished Product Reference Standard	√	√	√	√	√	√	√
18	Container Closure System/ Packing	√	√	√	√	√	√	√
19	Product Stability	√	√	√	√	√	√	√
20	Product Interchangeability	√	√	√	√	√	√	√

Table 5 Non-clinical documents comparison of ASEAN countries (3)

Sr no.	Non-clinical Documents	Singapore	Malaysia	Thailand	Indonesia	Vietnam	Brunei	Cambodia
1	Non-clinical overview	×	√	√	√	√	√	√
2	Nonclinical written & Tabulated summary	×	×	×	×	×	×	×
3	Non clinical study Reports	×	×	×	×	×	×	×
4	Literature references	×	×	√	√	√	√	√

Table 6 Clinical documents comparison in ASEAN countries (3)

Sr no.	Clinical Documents	Singapore	Malaysia	Thailand	Indonesia	Vietnam	Brunei	Cambodia
1	Clinical overview	×	×	√	√	√	√	√
2	Clinical Summary	×	×	×	×	×	×	×
3	Tabular Listing of All Clinical Studies	×	×	×	×	×	×	×
4	Clinical Study Reports	×	×	Only BE	Only BE	Only BE	Only BE	Only BE
5	List of Key Literature	×	×	√	√	√	√	√

Table 7 Documentation requirements for Myanmar (3)

Sr no	Documents	Myanmar
1	Application Form	√
2	Certificate Of Pharmaceutical Product	√
3	Site Master File	×
4	Summary of Product Characteristics/PI	×
5	GMP Certificate of API Mfr	×
6	Manufacturing License of FPP Mfr	√
7	Marketing Authorization In The Country of Origin/ FSC	×
8	WHO-GMP Certificate	√
9	Properties of API (Active pharmaceutical Ingredient)	√
10	Route of Synthesis of API	×
11	Process Validation of API	×
12	API Specification	√
13	API Certificate of Analysis	√
14	Stability Testing	×
15	Analytical Method Validation	×
16	Unit Dose & Batch Formula	×
17	Master Formula	√
18	Manufacturing Process	×
19	In-Process Specifications	√
20	Process Validation of FP	×
21	Monograph- Excipients	√
22	COA- Finished Pharmaceutical Product(Certificate of Analysis)	√
23	Specifications of Finished Pharmaceutical Product	√
24	Monograph of Finished Pharmaceutical Product	√
25	Analytical Method Validation	×
26	Container Closure System	√
27	Stability	√
28	Labels	√

29	Pharmacology, Toxicology	√
30	Raw Material Specifications	×
31	Product if already approved in other Country	√
32	BE Requirements	√

3. Conclusion

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 ASEAN Common Technical Requirements, which are steadily evolving. Even though ACTD format is mandatory from 2009 the member countries have their own requirements for registration process like administrative documents, labeling. This article simplifies & secures document management. It includes all benefits & ability to manage even more complex documents.

This article helps, to create, assemble, update & publish a composite document(s) from various individual document sources & formats. All documents are managed as a single, consistent structured & unified document.

Documents required are BMR, Process validation record, stability study which include long term & accelerated stability study as per zone specification of Myanmar, packing requirements for anti- cancer drugs & certificate for product permission, which has covered all aspects from manufacturing to its packing & registration.

It provides scientifically sound means of establishing the quality, safety, and efficacy of therapeutic products. It will help in understanding documentation requirements for registration of products in Myanmar.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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