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REGULATORY REQUIREMENTS FOR THE APPROVAL OF ANTI-CANCER DRUGS IN PHILIPPINES AS PER ACTD

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ABSTRACT

South East Asian pharmaceutical market is rising quickly. In Asian country, the regulatory environment is parallel among all countries. But still requirements and procedure of registration is changing among countries of Asian region. Although ACTD is harmonized for all ten countries but still every country varies in some of the local requirements such as administrative, technical, clinical and non-clinical documents. Among this country Philippines systematically control the manufacture, import, export, storage, distribution and sale of drugs. Aim of the current study is to discuss developing challenges and requirements posed by compulsory licensing for drugs in diseases such as cancer. In this article we have observed documents requires for registration fitting to anti-cancer category in Philippines. Documents like batch manufacturing record, process validation records, stability study which include long term and enhanced stability studies as per zone specification of Philippines, packing requirements for anti-cancer drug and certificate for product authorization required for registration, which has enclosed all features from manufacturing to its packing and registration. This article will give the easy understanding on the drug registration necessities for anti-cancer drug in Philippines.

KEYWORDS: ASEAN, ACTD, Philippines, Anti-Cancer, Registration.

INTRODUCTION

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 decrease the time and resources required 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.

The Association of Southeast Asian Nations (ASEAN) contains the following 10 countries like Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia were established in 1967 to endorse pharmaceutical market in ASEAN countries ASEAN region is considered as "Emerging market for pharmaceutical export and bilateral trade. The understanding of the registrations & regulatory requirements of this region can be beneficial for pharmaceutical export. The regulations of ASEAN countries are encouraging the import of quality Anti-cancer products.

Dossier requirements

This ASEAN Common Technical Dossier (ACTD) is a guideline of the approved upon common format for the preparation of a well-structured Common Technical Dossier (CTD) application that will be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals and biologics for human use. Even though the current ASEAN Common.

Technical Requirements (ACTR) has not included specific requirements for biosimilar products, the ACTD format is also applicable for biosimilar products. This guideline describes a CTD format that will significantly reduce the time and resources needed to compile applications for registration and in the upcoming days, will comfort the preparation of electronic documental submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements.

This guideline merely demonstrates an appropriate write-up format for acquired data.

However, applicants can modify, if needed, to provide the best possible presentation of the technical information, in order to facilitate the understanding and

evaluation of the results upon pharmaceutical registration.

DISCUSSION

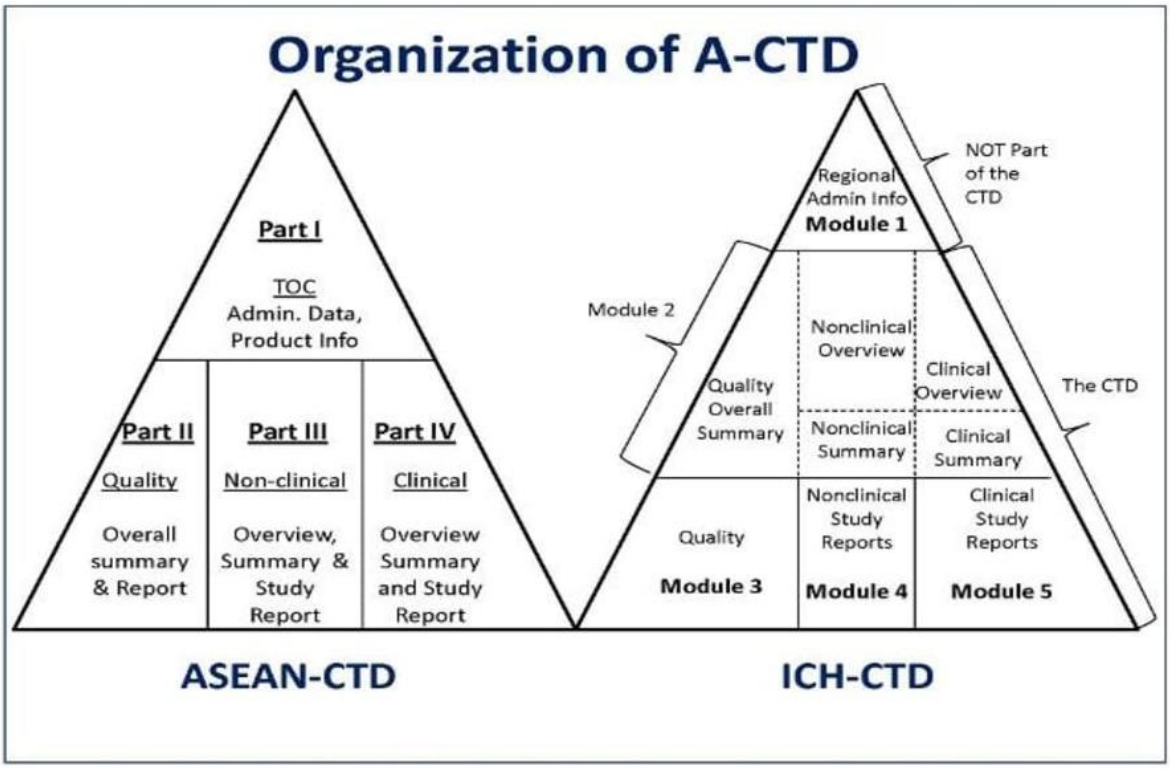

Figure 1: Organization of ACTD.

Table 1: Difference of ACTD & ICD CTD.

Documents	Location in	
	ICH CTD	ACTD
Administrative Documents and Product Information	Module 1	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.

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	5 yrs	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

DISCUSSION

Pharmaceuticals in Philippines

The Philippines has a vigorous-growing pharmaceutical market, with total sales of about 236 billion Philippine pesos in 2022. About 90 percent of sales are supplied through retail outlets, particularly drugstores, while the residual share comes from hospitals. Meanwhile, ethical products or prescribed medicines account for about 70 percent of the market, followed by over-the-counter (OTC) drugs. Pharmaceutical products are supplied by multinational companies (MNCs) and local companies. MNCs are marketing and distributing finished medicine

products and raw and intermediate materials. Among the leading MNCs in the country were Pfizer, GlaxoSmithKline, BOE Ingelheim, and AstraZeneca. Meanwhile, local pharmaceutical companies have more miscellaneous roles in the supply chain. Among the leading ones were Unilab and Pascual Laboratories which manufacture their medicines. Other local companies manufacture for MNCs or are limited to packaging, distribution, and retail. There were 398 registered drug manufacturers in the Philippines, with drugstores accounting for most of the country's licensed drug establishments. The domestic market is segmented into three license categories and is dominated by generic drugs.

Technical Documents required

1. Administrative documents
2. Comprehensive Table of Contents
3. Introduction
4. Application
5. Labelling, Package Insert and Patient Information Leaflet
6. Approved Summary Product Characteristics (SPC) /Patient Information Leaflet (PIL)
7. Assessment Report from Reference Agencies
8. Description of Batch Numbering System
9. Proof of Approval
10. Authorization Letters
11. GMP Certification/Proof of GMP Compliance
12. Patent declaration
13. Declaration on rejection, withdrawal and deferral
14. Declaration for GDA verification
15. Registration status in other countries

Quality documents

Body of Data

Drug substance

1. Drug Master File (DMF)
2. Certificates of Suitability (CEP)
3. Control of Drug Substance
4. Stability Data of Drug Substance

Drug Product

1. Pharmaceutical Development
2. Process Validation
3. Control of Excipients
4. Control of Drug Product
5. Container Closure System
6. Stability Data of Drug Product
7. Product Interchangeability
8. Blank Production Batch Records

Drug Registration procedure and approval system of Philippines

The process starts with the submission of an electronic copy application by the applicant using. A hard copy of the integrated application form is required. Once an applicant submits the application dossier, the FDA through the Centre for Drug Regulation and Research (CDRR), evaluates the documents and determines if the product meets the requirements of safety, efficacy, and quality. If the product meets these standards, a Certificate of Product Registration (CPR) is issued. Depending on the conditions of deficiencies, a Notice of Deficiency (NOD) or Letter of Disapproval (LOD) may be issued.

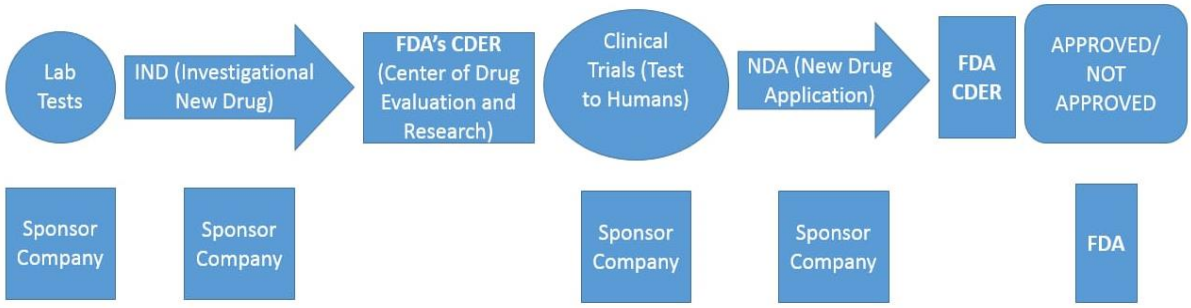

Figure 2: Flow chart of Drug approval process.

Comparison of ASEAN Countries for the documentation requirements

Table 3: Comparison of Administrative documents in ASEAN countries.

Sr no	*Administrative Documents*	*Singapore*	*Malaysia*	*Thailand*	*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	Labelling 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.

Sr no	*Technical Documents*	*Singapore*	*Malaysia*	*Thailand*	*Indonesia*	*Vietnam*	*Brunei*	*Cambodia*
1	Drug substance	×	×	×	×	×	×	×
2	Quality Overall Summary	×	√	√	√	√	√	√
3	General Information	×	√	√	√	√	√	√
4	Manufacturing 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 Finished Products	√	√	√	√	√	√	√
17	Reference Standard	√	√	√	√	√	√	√
18	Container Closure System/ Packing	√	√	√	√	√	√	√
19	Product Stability	√	√	√	√	√	√	√
20	Product Interchangeability	√	√	√	√	√	√	√

Table 5: Non-clinical documents comparison of ASEAN countries.

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 report	×	×	×	×	×	×	×
4	Literature references	×	×	√	√	√	√	√

Table 6: Clinical documents comparison in ASEAN countries.

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 report	×	×	Only BE	Only BE	Only BE	Only BE	Only BE
5	List of Key literature	×	×	√	√	√	√	√

Table 7: Documentation requirements for Philippines.

Sr no	*Document*	*Philippines*
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 another Country	×
32	BE Requirements	√

CONCLUSION

The ASEAN region is evolving in the pharmaceutical marketplace with several countries leading in quality, efficacy, safety, BE/BA, and variations. It is significant for the region to have more ASEAN countries accredited to PIC/S for the execution and maintenance of harmonized cGMP standards and quality systems. In the author's knowledge, it would be good to have common

filing procedures with full mutual acceptability in the ASEAN region. This will ensure rapid patient access to drugs, such as seen in the EU with Mutual Recognition Procedure (MRP), Decentralized Procedure (DCP) and Centralized Procedure (CP). Economic diversity, language, uneven distribution of wealth, intellectual property, and lack of harmonization of guidelines and their implementation, are some of the challenges presently creating hurdles for pharmaceutical companies looking to penetrate these regions more effectively.

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

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 Philippines.

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