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RESEARCH ARTICLE

Comparative Study of Regulation and Registration Process of Parenteral Product in US and Malaysia

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ABSTRACT

Requirement of drug registration of every country is different so it is difficult to get global marketing approval at same time and launch product at once in all regions. So one has to understand strategy of all regions by looking at target region, patent terms, data requirement timelines for launching product in different regions. Parenteral product provides maximum bioavailability and efficacy than the oral dosage form due to which the demand for parenteral preparation increases day by day. So it has stringent regulation in many countries. Parenteral products if not sterile, non-pyrogenic can cause severe harm to health causing life-threatening risk to patient. So its regulation is necessary. The study of the differences and similarities will help to find methods for global harmonization, which is currently a vital need for Pharmaceutical Regulation. Regulatory point of view this kind of evaluation will help the newly developing industry for better understanding of requirements, process and timeline for registration, so based upon better understanding they can plan good strategy to get best outcomes within short time.

KEYWORDS

Parenterals, Regulation of Parenterals, Administrative and Prescribing Information

INTRODUCTION

Definition

Parenteral preparations are sterile preparations which contain one or more active ingredients intended for administration by injection, infusion or implantation into the body. They are packaged in either single-dose or multidose containers.[1]

Types of Parenteral Preparation [2]

1. Injections
2. Infusion
3. Concentrate for Injection or Infusion
4. Powders for Injection or Infusion
5. Implants

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Parenteral Drug Product Regulation and Registration Requirement in US

The Food and Drug Administration (FDA or USFDA) is an agency of the United States Department of Health and Human Services.

Application Types/Filing to USFDA

1. ***IND (Investigational New Drug Application):*** The IND is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials).

2. ***NDA (New Drug Application):*** When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to FDA a new drug application (NDA).
3. ***ANDA (Abbreviated New Drug Application):*** An ANDA contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product.
4. ***OTC Application (Over-the-counter Drug Application):*** OTC drug products are those drugs that are available to consumers without a prescription. CDER oversees OTC drugs.
5. ***BLA (Biologics License Application):*** A biologics license application is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical affects of the biologic product.[3]

CTD Modules[4]

The Common Technical Document (CTD) is a set of specification for application dossier for the registration of Medicines and designed to be used in Europe, Japan and the United States. It was developed by the European Medicines Agency (EMEA, Europe), the Food and Drug Administration (FDA, U.S.) and the Ministry of Health, Labour and Welfare (Japan). The CTD is maintained by the ICH.

Module 1: Administrative Information and Prescribing Information

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region.

Module 2: Common Technical Documents Summaries

It includes the summary documents and begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use.

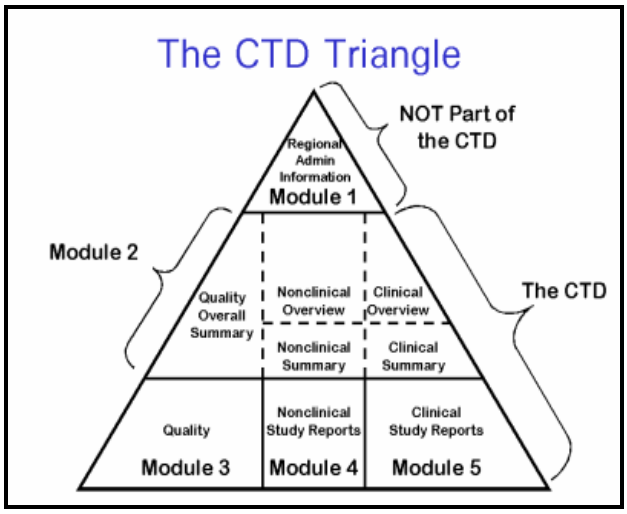

Figure 1: ICH CTD

It contains following information:

- CTD Table of Contents
- CTD Introduction
- Quality Overall Summary
- Nonclinical Overview
- Clinical Overview
- Nonclinical Written and Tabulated Summaries
- Clinical Summary

Module 3: Quality

Information on Quality should be presented.

Module 4: Nonclinical Study Reports

Information on Nonclinical Study Reports should be presented

Module 5: Clinical Study Reports

Information on clinical study reports is presented.

General Requirements for Submission

- The general requirements for submitting ANDAs are provided in the Regulations in 21 CFR 314.94. ANDA is submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs.
- Amendments and Supplements CTD format can be used to supplements to an original application or amendments to either the

original application or subsequent supplements.

- Organizing Documents: All documents should be binded in separate volumes, or documents separated by tab identifiers.
- Number of copies: Requires archival, review, and field copies for ANDAs.
- Paper size: U.S. letter size paper (8.5 x 11 inches) is used for all submissions.
- Paper margins: margin of at least 0.75 inches from the bound edge of the printed page prevents information from being obscured
- Fonts: Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying and narrative text is submitted in Times New Roman 12 point font.
- Binding volumes: The front cover of the binder should be 9 by 11.5 inches, and the back cover should be 9 by 12 inches. Binders are used to to distinguish the different copies of the applications. For ANDAs, archival copy should be blue, the review copy should be red and the field copy should be green.
- Volume size: Volumes should not be more than 2 inches thick.
- Volume numbering of the Volumes is done by module
- Volume identification: All copies of the submission, including the review copies, should use the same volume numbers.
- Pagination: Page numbering should be at the document level and not at the volume or module level.
- Cross referencing documents is done by volume, CTD module, tab identifier, and page number.[4]

Parenteral Drug Product Regulation and Registration Requirement in Malaysia[5,6,7]

- Association of Southeast Asian Nations (ASEAN) was established on 8th Aug 1967 in Bangkok by 5 original members namely Indonesia, Malaysia, Philippines, Singapore and Thailand.
- Brunei Darussalam joined on 8th January 1984
- Vietnam on 28th July 1995
- Lao PDR and Myanmar joined on 23th July 1997
- Cambodia on 30th April 1999[5]

There are many countries in south East Asia but only 10 countries are included in the ASEAN region. The member countries of the ASEAN region are

1. Brunei Darussalam
2. Myanmar
3. Cambodia
4. Philippines
5. Indonesia
6. Singapore
7. Laos
8. Thailand
9. Vietnam
10. Malaysia

Although regulatory environment in all ASEAN countries is similar but still requirements and process of registration varies among the countries of ASEAN region.

The Drug Control Authority of Malaysia is Biro Pengawalan Farmaseutikal Kebangsaan (BPFK) also known as National Pharmaceutical Control Bureau (NPCB), Ministry of Health Malaysia is the executive body which is established under the Control of Drugs and Cosmetics Regulations 1984.

The ACTD gives information on the format and structure of the dossier that shall be commonly used for applications in the ASEAN region. ACTD format is harmonized and mandatory from 2009 for all 10 countries but still every country is varies in some local requirement such as Administrative data and labeling.[5]

Types of Registration Application in Malaysia

i. Application for Product Registration for the Following Categories:

a) New Drug Products

b) Biologic

c) Generic

d) Health supplements

e) Natural Products

ii. Registration of Combination Pack

Refer to products which are packed together in combination for a therapeutic regimen such as for the treatment of (Helicobacter Pylori, Hepatitis C, etc.). Shall be register as a single product.

iii. Registration of Product for Export Only (FEO)

Refers to locally manufactured products for export only which are not marketed locally with a different formulation (e.g. colour or strength of ingredients) or shape compared to a registered product. For products containing ingredients / formulations which are not allowed by Authority for local use.[6]

Organization of ACTD Dossier

This ASEAN Common Technical Dossier (ACTD) is a guideline of common format for the preparation of 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 which will significantly reduce the time and resources needed to compile applications for registration and will ease the preparation of electronic documental submissions. Regulatory reviews and communication with the applicant shall be facilitated by a standard document of common elements.[7]

The overall organization of the Dossier is presented in Parts as:

Part I: Table of Content Administrative Information and Prescribing Information

Section A: Introduction

Section B: Overall ASEAN Common Technical Dossier Table of Contents

Section C: Documents required for registration (for ex, application forms, Labeling,

Product Data Sheet, prescribing information)

Part II: Quality Document

Section A: Table of Contents

Section B: Quality Overall Summary

Section C: Body of Data

Part III: Nonclinical Document

Section A: Table of Contents

Section B: Nonclinical Overview

Section C: Nonclinical Written and Tabulated Summaries

Section D: Nonclinical Study Reports

Part IV: Clinical Document

Section A: Table of Contents

Section B: Clinical Overview

Section C: Clinical Summary

Section D: Tabular Listing of All Clinical Studies

Section E: Clinical Study Reports

Section F: List of Key Literature References

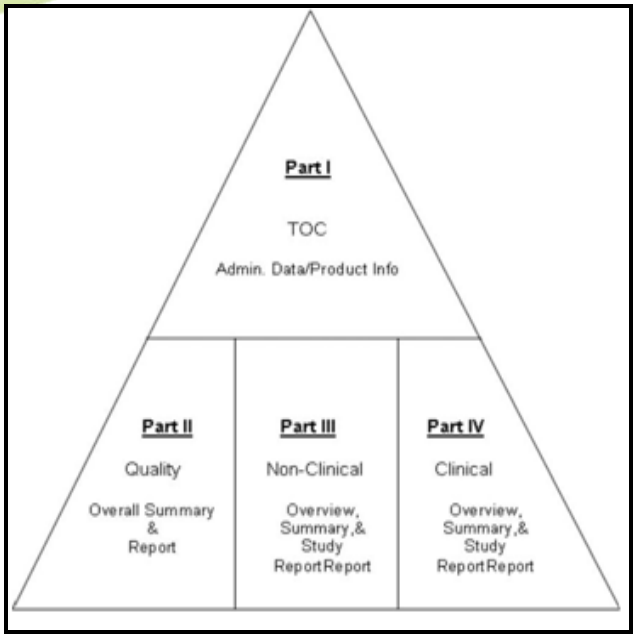

Figure 3: ACTD

General Dossier Submission Requirements

- To register a drug in Malaysia, applicants must submit all data to Malaysia's Drug Control Authority (DCA).
- For registration of products, only web-based online submissions via QUEST at: //www.bpfk.gov.my shall be accepted.
- The display of information should be unambiguous and transparent, to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents.
- Text and tables should be prepared using margins that allow the document to be printed on either A4 or 8.5 x 11 paper.
- The left-hand margin should be sufficiently large that information is not obscured by the method of binding.
- Font and size, (Times New Roman, 12-point font), for text and tables should be of a style and size that are large enough to be easily legible.
- Every page should be numbered, with the first page of each part designated as page 1. For a paper, Common Technical Acronyms and abbreviations should be defined the first time they are used in each part.[7]

Registration Process for generic Parenteral drug in US and MALAYSIA

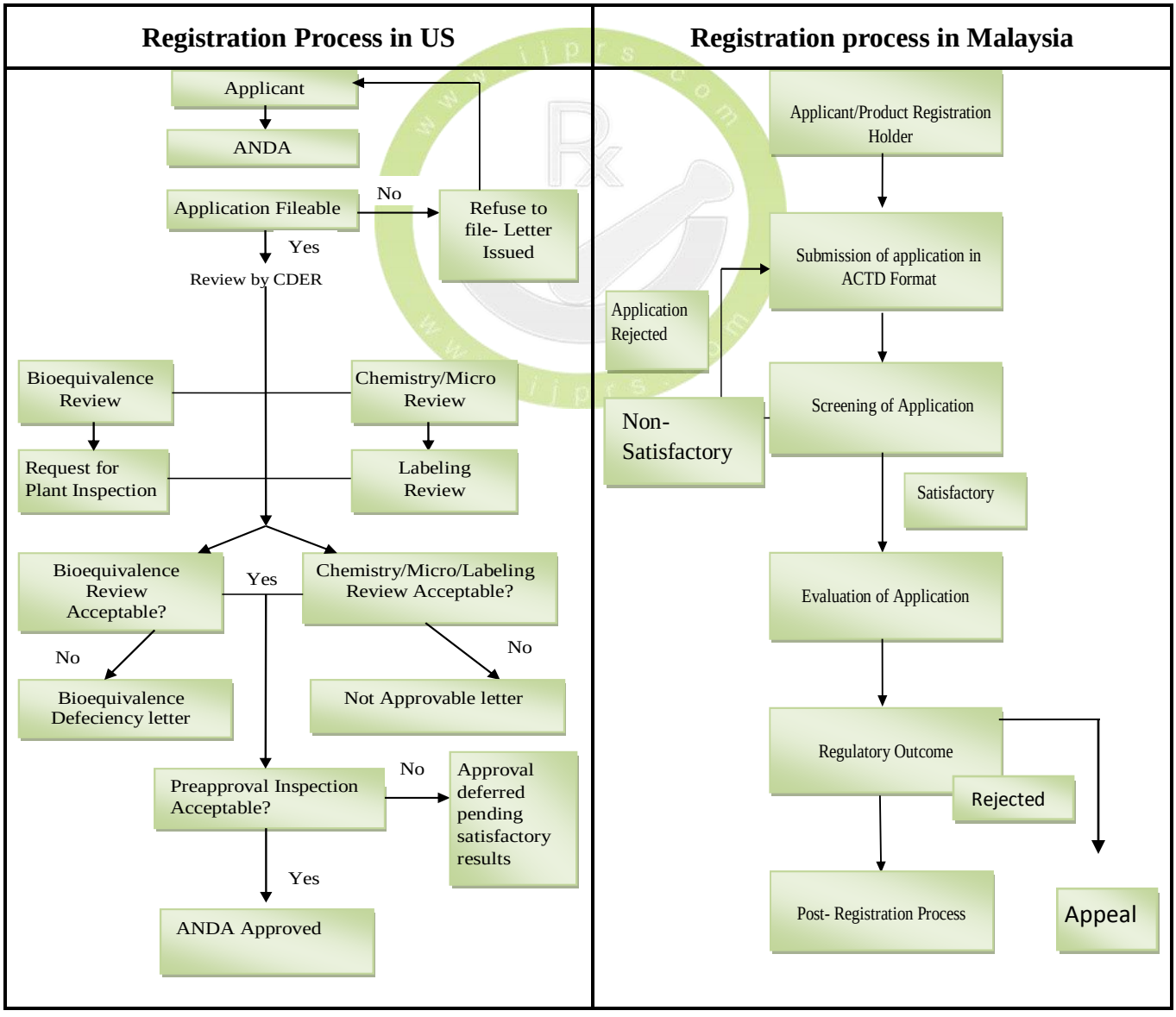

Table 1: Comparison of Regulatory Guideline of Parenteral Product in US and MALAYSIA

Criteria	US	MALAYSIA
Regulatory Authority	Food And Drug Administration (FDA)	Biro Pengawalan Farmaseutikal Kebangsaan (BPFK) also Known As National Pharmaceutical Control Bureau (NPCB), Ministry Of Health Malaysia.
Applicable Regulations	21 CFR 314.50, 314.94, and 601.2 provide general requirements for submitting NDAs, ANDAs, and BLAs respectively.	Drug Registration Guidance Document (DRGD)
Submission Format	ECTD	ACTD
Types Of Submissions	1. NDA 2. ANDA 3. OTC 4. BLA	1. **Application for product registration for:** a) New Drug Products b) Biologic c) Generic d) Health supplements e) Natural Products 2. **Registration of combination pack** 3. **Registration of Product for Export Only (FEO)**
Application Form For Registration	Form 356h	BPFK-413
Approval Timeline	18-20 months approx.	210 Working days
Fees	$58,730	Single active ingredient: RM 2,200.00 Two or more active ingredient: RM 3,000.00
API	Submitted as USDMF	Submitted as one of the 3 ways: 1. DMF 2. CEP 3. Full details of "Part II S ACTD" in the product Dossier
Generic exclusivity	180 day (Those generic companies who are the first to file ANDAs incorporating Paragraph IV Certifications	N/A
Plant GMP Approval	Accepts USFDA approval	Accepts FDA/EU/PICS approval for Finished product site

Table 2: Comparison of Administrative& Prescribing Information in US and MALAYSIA i.e Module 1

Criteria	US	MALAYSIA
Application	ANDA	Generic (Scheduled Poison)
Copies	3(archival, review, field)	1 copy
Letter of Application	Require	Not Require
Cover letter	Require	Not Require
GDUFA user fee cover sheet (FDA Form 3794).	Require	Not Require
Letter of appointment	Require	Not Require
Financial certification	Require	Not Require
Patent information and certification.	Require	Not Require
Debardment certification	Require	Not Require
Application form	Require	Require
Proposed product information	Package insert	Package insert
Agent authorization	Require	Require
Mock-ups and Specimens of Labeling	Require	Outer/carton labels Inner/Blister labels
summary of product characteristic	Not require	Require
Letter of Access to DMF/PMF/CEP	Require	Not Require
Summary of Biopharmaceutics studies	Require	Not Require
COPP	Require	Require
Environmental assessment statement	Require	Not Require
Free sale certificate	Not Require	Require
Sponsor's Declaration	Require	Not Require
GMP Certification	Not Require	Require

CONCLUSION

Parenteral products are nowadays widely used for the emergency situation, as it provides maximum bioavailability. Parenteral product regulation is necessary because if not sterile, non-pyrogenic can cause severe harm to health causing life-threatening risk to patient. From the above study it is concluded that the registration of Parenteral product in Malaysia is easier then US because in Malaysia the regulation are not so stringent and registration timeline is also less. Malaysia is not such big leader as compare to US but it is in now developing phase and moving toward stringent regulation. It does not have bigger market but it will helpful to those who want to opportunity in small market because all companies are not able to go for US due to financial issues. As discussed above comparative study of regulation and registration process for Parenteral dosage form will be useful regulatory point of view as well as business development point. We can conclude that the Industry can harmonies dossier application in better way, which will help in reducing time for products to go in market.

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