Review Article

New Drug Approval Process In Singapore – A Detailed Dissertation For Registration of Multi - Source Drug Products

P. Nagaraju[1*], B. Manoj Kumar[2], N. Flary[2],

D. Nagarjunareddy[2] and MV. Nagabhushanam[2]

[1]Department of Pharmaceutical Analysis, Hindu College of Pharmacy, Guntur, Andhra Pradesh-522 002, India.
[2]Department of Pharmaceutical Management & Regulatory Affairs, Hindu College of Pharmacy, Guntur, Andhra Pradesh-522 002, India.

ABSTRACT

Association of south East Asian nations (ASEAN) imitative to harmonize the requirements for drug registration is in progress and there will be single ASEAN market by 2015.ASEAN pharmaceutical market mostly depends on imports to meet the demand of health facilities and through development of ACTD they have provided a single window for drug approval in all 10 countries .therefore this review will try to focus on some main issues of the drug regulations throughout a very practical approach..A regulatory process, by which a person/organization /sponsor /innovator gets authorization to launch a drug in the market ,is known as drug approval process .every country has its own regulatory authority ,which is responsible to enforce the rules and regulations and disuse the guidelines to regulate the marketing of the drugs. 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 the human use.

Keywords: ASEAN common technical document (ACTD) ,Health science authority (HAS).

INTRODUCTION

The ASEAN was established on 8 August 1967 in Bangkok by the five original member countries (Indonesia, Malaysia, Philippines, Singapore and Thailand). Meanwhile five additional countries (Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia) joined ASEAN.

In 1999 a harmonization initiative was started among the 10 ASEAN countries. One aim of this harmonization should be to harmonize quality guidelines that are valid for all countries involved. Another focus lies in the technical co-operation. Therefore the ACCSQ PPWG was established. The objective of the ACCSQ PPWG isthe development of “harmonization 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."

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 summarized attached:

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

As the full implementation of the ASEAN requirements (like ACTD and ACTR) in the ASEAN countries is not yet finalized, a prolongation/transition period was done. There is an interim period agreed wherein ACTD and national formats allowed in most of the ASEAN countries, whereas in some countries like Singapore ICH CTD
is accepted.

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 DRAs don’t 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).

DISCUSSION

Health Sciences Authority (HSA)

The Health Sciences Authority (HSA) was established in April 2001 to ensure the quality, safety and efficacy of drugs, medical devices, cosmetics, and other health related products in Singapore.

In January 2004, the Center for Drug Administration (CDA) was established under the HSA.The CDA was formed by merging two previously-existing agencies: The Center for Pharmaceutical Administration (CPA) and the Center for Drug Evaluation (CDE), which was both responsible for the regulation and evaluation of medical products in Singapore. The CDA's mission for Singapore pharmaceutical regulations is to simplify and streamline the evaluation and registration processes.

The Center for Drug Administration (CDA) leads Singapore pharmaceutical regulations and separates them under the following five regulatory guidelines: Medicines Act, Poisons Act, Sale of Drugs Act, Medicines (Advertisement and Sale) Act and the Misuse of Drug Regulations.The CDA's responsibilities include, but are not limited to, inspection and licensing of pharmaceutical manufacturers/ wholesalers, ensuring Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) standards, and post-marketing surveillance.

Health Products Regulation Group (HPRG)

The Health Products Regulation Group (HPRG) safeguards public health by ensuring that medicinal and health-related products in Singapore meet appropriate standards of safety, quality and efficacy. HPRG carries out pre-marketing evaluation of medicinal products before they are allowed to be marketed in Singapore. Products currently regulated include western medicinal products, Chinese proprietary medicines and cosmetic products. The regulatory framework for health supplements is being developed.

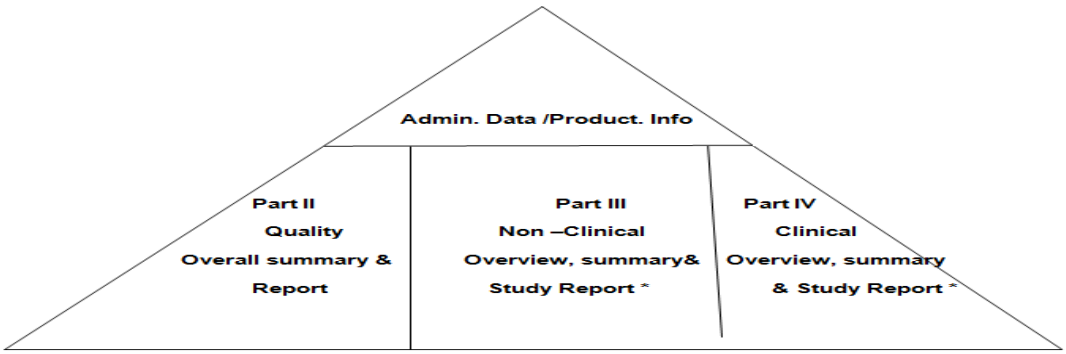
The Innovative Therapeutics Group (ITG)

The ITG was formerly known as the Centre for Drug Evaluation (CDE). The CDE was set up under the Ministry of Health in December 1998 as a joint collaboration between the Ministry of Health and the National Science and Technology Board now known as the Agency for Science, Technology and Research. CDA's ITG will facilitate the timely introduction and availability of new and innovative quality medicines in Singapore and the region, including medicines targeted for diseases prevalent in the region.

The ASEAN Common Technical Dossier (ACTD) for the Registration of Pharmaceuticals for Human Use Organization of the 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.

Part I : Toc



The Common Technical Document is organized into four parts as follows

Part 3.1.1 Table of Contents, Administrative Data and Product Information

Part I contains initially the overall Table of Contents of the whole ACTD to provide basically the information that could be looked through respectively. Secondly, the next content is the Administrative Data where required specific documentation in details is put together such as application forms, label, and package insert etc. The last section of this part is Product Information where necessary information includes prescribed information, mode of action, side effects etc.

A general introduction to the pharmaceutical, including its pharmacologic class and mode of action should be included.

Part 3.1.2 Quality Document

Part II should provide the Overall Summary followed by the Study Reports. The quality control document should be described in details as much as possible.

Part 3.1.3 Nonclinical 1 Document

Part III should provide the **Nonclinical** Overview, followed by the Nonclinical Written Summaries and the Nonclinical Tabulated Summaries. The document of this part is not required for Generic Products, Minor Variation Products and some Major Variation Products. For ASEAN member countries, the Study Reports of this part clinical" may not be required for NCE, Biotechnological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. Therefore, the authority who requires specific Study Reports should ask for the necessary documents.

Part 3.1.4 Clinical Document

Part IV should provide the Clinical Overview and the Clinical Summary. The document of this part is not required for Generic Products, Minor Variation Products and some Major Variation Products. For ASEAN member countries, the Study Reports of this part may not be required for NCE, Biotechnological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. Therefore, the authority who requires specific Study Reports should ask for the necessary documents.

The overall organization of the Common Technical Dossier is presented on the following in Parts:

Part 3.1.1 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 example, application forms,
Labelling, Product Data Sheet, prescribing information)

Part 3.1.2 Quality Document

Section A: Table of Contents
Section B: Quality Overall Summary
Section C: Body of Data

Part 3.1.3 Nonclinical Document

Section A: Table of Contents
Section B: Nonclinical Overview
Section C: Nonclinical Written and Tabulated Summaries

1. Table of Contents
2. Pharmacology
3. Pharmacokinetics
4. Toxicology

Section D: Nonclinical Study Reports

1. Table of Contents
2. Pharmacology
3. Pharmacokinetics
4. Toxicology

Part 3.1.4 Clinical Document

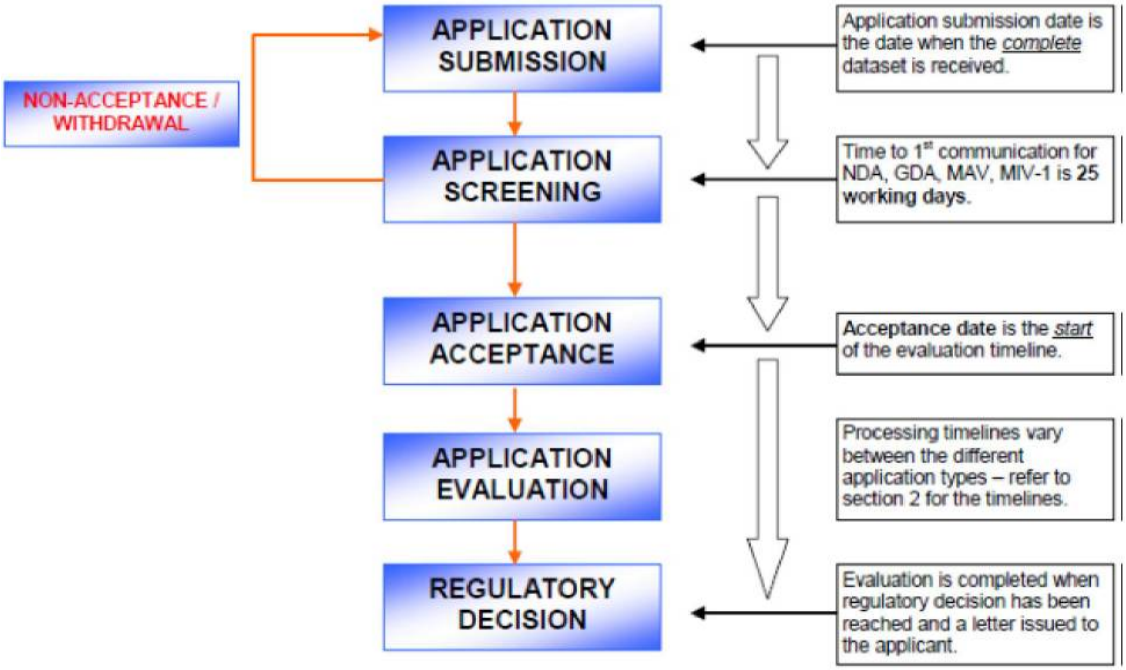
Section A: Table of Contents
Section B: Clinical Overview
Section C: Clinical Summary

1. Summary of Bio-pharmaceutics and Associated Analytical Methods
2. Summary of Clinical Pharmacology Studies
3. Summary of Clinical Efficacy
4. Summary of Clinical Safety
5. Synopses of Individual Studies

Section D: Tabular Listing of All Clinical Studies
Section E: Clinical Study Reports
Section F: List of Key Literature References

Registration Process in Singapore

One part of a product's life cycle is the pre-marketing activities, namely registration of a product prior to market entry. The registration process involves a series of steps as seen in Figure-below:



A schematic diagram to illustrate the various types of applications.

Pre-Submission Preparation

- The first step in the registration process is one of the most important because it involves
- I. Knowing which application to apply for;
- II. Knowing which evaluation route to choose; and,
- III. Arranging for a pre-submission consultation with HSA for advice, if required.

Application Types

In applying for a new Product License for a medicinal product in Singapore, there are two categories of applications: a new drug application (NDA) and a generic drug application (GDA):

NDA (New Drug Application)

NDA-1

For the first strength of a product containing a new* chemical or biological entity.

NDA-2

i) For the first strength of a new drug product.

- containing a new* combination of registered chemical or biological entities;
- containing registered chemical or biological entity(ies) in a new dosage form;
- Containing registered chemical or biological entity (ies) for use by a new route of administration; or, new indication(s), dosage recommendation(s) and/or patient population(s).

ii) For new drug products that do not fall under the requirements for NDA-1, NDA-3 or GDA.

NDA-3

- For subsequent strength(s) of a new drug product that has been registered or has been submitted as an NDA-1 or NDA-2.
- The product name, pharmaceutical dosage form, indication, dosing regimen and patient population shall be the same as that for the NDA-1 or NDA-2.

GDA (Generic Drug Application)

GDA-1

For the first strength of a generic chemical product.

GDA-2

- For subsequent strength(s) of the generic chemical product that has been registered or has been submitted as a GDA-1.
- The product name and pharmaceutical dosage form shall be the same as that for the GDA-1.

- A generic product is essentially similar to a currently registered product in Singapore (known as the „Singapore reference product but excludes biologics.

Multiple Evaluation Routes

For NDA in Singapore, there are three evaluation routes in which companies may undertake in order to have the new medicine registered; the routes are full, abridged and verification evaluation. The routes are varied by the eligibility criteria and the levels of technical data required are different. The level of submission depends on whether the drug is approved by a competent regulatory agency. (e.g. Australia Therapeutic Goods Administration (TGA);USFDA; the European Medicines Agency (EMEA), as defined by the WHO).The routes are identified by whether the same chemical entity has been reviewed and approved by another regulatory agency. Regulatory decision from verification evaluation route can be as short as 60 days and a new medicine can be approved by HSA within five months.

Full Evaluation Route

This applies to product containing a new chemical entity that has *not been approved by any* competent drug regulatory agency at the time of submission in Singapore. Among all the routes available, HSA has spent the most resources on the full evaluation route to ensure drugs could be approved with the highest standard and in a timely manner. This route was developed to promote the access of life-saving drugs for patients carrying rare/ Asia specific diseases and unmet medical needs. A full set of manufacturer's profile, pharmacological, clinical documentation and chemical/ biological data are required for evaluation.As no country has approved the same drug before, therefore, full evaluation route takes the longest review timeline.

Abridged Evaluation Route

This route could be executed when a product has been approved by *at least one competent* drug regulatory agency. Prior review could be requested at the time of submission if the product is intended to the treat serious life-threatening condition or disease conditions that are of local public concerns (e.g. cancer and infectious disease).

Verification Evaluation Route

Medicinal products which have been evaluated and approved by *at least two of the HSA's* reference drug regulatory agencies can submit their application via the verification evaluation route. The approval from the WHO referenced countries, HSA will recategorise the application but it does not obligate HSA to approve the product immediately.

Pre-Submission Meeting

For complex issues relating to an impending submission, applicants are advised to consult with HSA in a pre-submission meeting. The request for a consultation should be made in writing, with the purpose, agenda and proposed date & time for the meeting, via email to HSA_MedProd_Registration@hsa.gov.sg.For a submission under the full evaluation route, the applicant is required to notify HSA via a pre-submission meeting two months prior to the intended submission date of the application dossier.

Application Submission

Application submission comprises of two parts: the PRISM application form and the registration dossier.

Prism Application Form

All applications must be made on-line via PRISM. Refer to Chapter J of guidance on medicinal product registration in Singapore for guidance notes for submitting a PRISM application.

Registration Dossier

The registration dossier contains the documents to support the evaluation of the submitted application. 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 HSA receives the complete dataset for the application.

Comparison between ICH CTD - ACTD

The main differences between these two formats are the numbering and naming of the sections.

Documents	Location In	
	ICH CTD	ACTD
Administrative documents & Product information	Module 1	Part I
Common technical document overview & summaries	Module 2	Incorporated Parts II, III, and IV
Quality documents	Module3	Part II
Non-clinical documents	Module4	Part III
Clinical documents	Module5	Part IV

CONCLUSION

- The purpose of the study is to know about new drug Approval process in Singapore – A detailed dissertation of multi- source drug products.
- Among 'ASEAN' numbers Singapore is selected for new drug approval products because of its largest capabilities and resources for research and development in new medicines.
- The official Health Authority In Singapore is (HSA) which ensure Registered pharmaceutical products are safe, efficacy, effective, and of good quality. Under HSA, CDA was formed which evaluate medicinal product in Singapore.
- Singapore is an Asian hub for biotechnology and research in Asia, because of its strong infrastructure for research and development and also attracted many global pharmaceuticals companies to operate the multi-functions plants.
- There are national regulations are Herbal medicines in Singapore but they are no restriction for their sale.
- A memorandum of interest for exchange of medicinal products is signed with china and Australia.

REFERENCES

1. ASEAN common technical dossier for pharmaceutical registration actd clinical checklist for product clarification.
2. The asean common technical dossier (actd) for pharmaceutical registration for human use, organization of the dossier.
3. The asean common technical dossier (actd) for pharmaceutical registration for human use, part iii: non clinical document.
4. The asean common technical document (actd) for the registration of pharmaceuticals for human use – organization of the dossier http://www.hsa.gov.sg/publish/etc/medialib/hsa_library/health_products_regulation/western_medicines/files_guidelines.par.22449.file.dat/actd_organizationofdossier.pdf
5. The asean common technical dossier (actd) for pharmaceutical registration for human use, part: quality.
6. The asean common technical dossier (actd) for pharmaceutical registration for human use, part IV clinical document.
7. Has, guideline for renewal of product licence, 31 October 2008
8. Egulatory agencies, patel henal, sudeendra bhat r., balamuralidhara v* and pramod kumar t.m.
9. Pharmaceutical quality assurance group, dept. Of pharmaceutics, jss college of pharmcomparison of stability testing requirements of ich with other international racy, JSS university, Mysore.
10. The basic regulatory considerations and prospects for conducting bioavailability/ bioequivalence (ba/be) studies – an overview. Shaik mastan, thirunagari bhavya latha, sathe ajay. This article publish in the following dove press journal: comparative effectiveness research,21 march 2011.
11. A comparison of the drug review process at five international regulatory agencies. Mayu hirako, bsc, PhD. Neil mcauslane, bsc, msc, PhD. Sam salek, bsc, rph, PhD, mfpm. Carly Anderson, bsc, PhD. Stuart walker, bsc, phd, mfpm, frsc, fibiol, finstd, frcpath.
12. Ranjith Y, Janodia, Manthan D, Jagadish PC, Bhat KM and Karande swati and Udupa N. Scenario of generic drug regulations for asean countries. scenario of generic drug regulations for asean countries. Inventi rapid: pharmacy practice, 2012;(3):1-8. Issn 0976-3848.