

A Study of procedures for Dossier Preparation and their marketing authorisation in different countries of selected drug(s)

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ABSTRACT

Dossier is a collection of documents on the particular subjects. Any preparation of pharmaceutical product for human use go through the process of reviewing and assessing the dossier of pharmaceutical product which contains details information about administrative, quality, non-clinical and clinical data. This process is governed and permitted by Drug Regulatory Authority of a particular country and process is called as NDA in USA, MAA in EU and other countries as simply Registration Dossier. There are basically two formats for dossier preparation i.e. ICH-CTD and ACTD. ICH-CTD followed by ICH countries as well as low economical or developing countries where as ACTD is followed by ASEAN countries. ACTD act as bridge between regulatory requirements of developed and developing countries. Also if both guidelines of CTD and ACTD can be harmonized then differences and variation between both guidelines can be minimized.

Keywords: Dossier Preparation, ASEAN countries, ACTD, ICH guidelines

INTRODUCTION

Dossier ^[1-4]: The word 'Dossier' has the English meaning as a collection or file of documents on the particular subject, especially a file containing detailed information about a person or a topic. Any formulation is prepared for human use i.e. designated to modify or explore physiological systems or pathological states for the benefit of the recipient is called as "Pharmaceutical product for human use". Process of critiquing and assessing the dossier of pharmaceutical product containing its detailed about administrative, chemistry, preclinical & clinical information and the permission granted by the regulatory agencies of a country with a view to support its marketing or approval in a country is called as "Marketing approval or Registration", "Marketing Authorization or " Product Licensing". "Registration Dossier" of the pharmaceutical product is a document that contains all technical data (administrative, quality, nonclinical, and clinical) of a pharmaceutical product to be approved / registered / marketed in a country. It is more commonly called as New Drug Application (NDA) in the USA or Marketing Authorization Application (MAA) in

European Union (EU) and other countries as simply Registration Dossier.

The International Conference on Harmonization (ICH) process has considerably harmonized on the organization of the registration of documents with the issuance of the Common Technical Document (CTD) guideline. This recommended format in the CTD guideline for registration applications has become widely accepted by regulatory authorities both within and beyond the ICH Regions.

Thus dossier is a file document that has to be submitted based on the requirement of the drug approval/ market authorization process. It is a comprehensive scientific document used to obtain worldwide licensing approval/ market authorization of a drug by diverse health authorities. Its creations, processing, compilation & dispatch to the field by a regulatory affairs department, is dependent upon many interrelated activities, the filling and authorization process in the emerging markets will be depends upon the region.

Globalization of the pharmaceutical industry has created the need to harmonize the recommendations for the development of new pharmaceuticals, as well as the regulatory

requirements of various countries. Thus, a common format of submission will help in overcoming these hurdles. Through ICH process, the CTD's guidance have been developed for Japan, European Union, and United States. Almost Most of the countries have adopted the CTD format.

COMMON TECHNICAL DOCUMENT (CTD) ^[5]

CTD is a set of specification for application dossier for the registration of Medicines and designed to be used across Europe, Japan and the United States. It was developed by the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, U.S.) and the Ministry of Health, Labor and Welfare (Japan). The CTD is maintained by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The agreement to assemble all the quality, safety and efficacy information in a common format has revolutionized the regulatory review processes.

General Consideration

- CTD is –
 - * Only a harmonized format for submission of information to relevant regulatory authorities.
 - * Template for presenting data in the dossier.
 - * A guideline that merely indicates an appropriate format for the data that have been acquired.
- CTD is not –
 - * A statement of data for application of data.
 - * A guideline that intends to indicate what studies are required.
 - * Define the content.

- CTD should be –

- * Have clear and unequivocal information.
- * Have style & font size that is large enough to be easily readable.
- * Follow the ICH guidelines for:
 - Document pagination and segregation.
 - Submission requirements/ methodology for CTD.
- * Contained all abbreviation that are used & be listed at the end of the dossier.
- * Give proper information of source of bulk drug(s) for manufacturing finished formulation.

Regulation & regulatory bodies of CTD ^[5]

- * The regulation under Drugs and Cosmetics Act & Rules 122A, 122B and 122D and further Appendix I, IA and VI of Schedule Y, describe the information required for approval of an application to import or manufacture of new drug for marketing.
- * Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue guidelines for drug development, licensing, registration, manufacturing, marketing and labeling of pharmaceutical products.
- * Almost all the independent countries of the world have their own regulatory authorities.

Evolution of CTD ^[6]

Effort over the past 15- 20 years by ICH of technical requirements for "registration of pharmaceutical for human use" have resulted in a uni-field dossier for drug applications. CTD was officially signed off in November 2000, at 10th anniversary of ICH; San Diego, California.

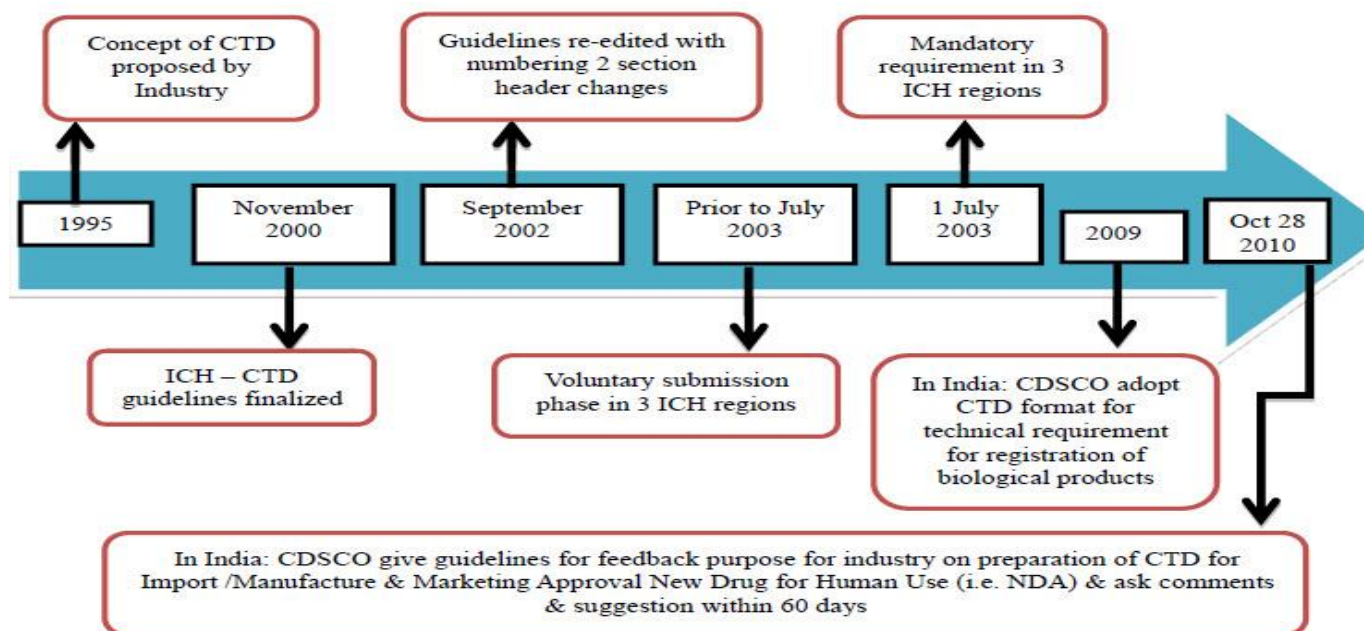


Fig 1 : Evolution of CTD

The following are the examples of a few of them (Regulatory Authority):

Table 1 : List of countries and their Regulatory Authority (ICH-CTD)^[4]

Country	Regulatory Authority
Australia	Therapeutic Goods Administration (TGA)
Argentina	National administration of Drugs, Food & Medical Technology (ANMAT)
Armenia	Drug & medical Technology Centre, Ministry of Health
Austria	Federal ministry for Health
Brazil	National Agency for Sanitary Vigilancia (ANVISA)
Belgium	Federal public services(FPS) Health
Bolivia	Ministry of Health and Sports
Bulgaria	Bulgarian Drug Agency (BDA)
Canada	Health Canada
China	State Food and Drug Administration (SFDA)
Colombia	National Institute of Food and Drug monitoring(INVIMA)
Croatia	Ministry of Health and Social Welfare
Denmark	Danish Medicines Agency
Ecuador	Ministry of Public Health
Egypt	Ministry of Health & population
Estonia	State Agency of Medicines
Europe	European Medicines Agency (EMA)
Fiji	Ministry of Health
Finland	Finnish Medicines Agency
France	French Agency for Sanitary Safety of Health Products, ministry of Health
Germany	Federal Institute for Drugs and Medical Devices
Georgia	Ministry of Labor, Health and Social Affairs of Georgia
Greece	National Organization for Medicines (EOF)
Guam	Department of Public Health and Social Services
Hong Kong	Department of Health: Pharmaceutical Services
Hungary	National Institute for Pharmacy
Iceland	Icelandic Medicines Agency
India	Central Drug Standard Control Organization (CDSCO)
Ireland	Irish Medicines Board
Italy	Italian Pharmaceutical Agency
Jamaica	Ministry of Health
Japan	Ministry of Health, Labour & Welfare(MHLW)
Jordan	Ministry of Health
Kenya	Ministry of Health
Latvia	State agency of medicines
Lithuania	State Medicines Control Agency
Maldives	Ministry of Health and Family
Malaysia	National Pharmaceutical Control Bureau, Ministry of Health
Mauritius	Ministry of Health and Quality of Life
Namibia	Ministry of Health and Social Services
Nepal	Ministry of Health and Population
New Zealand	Medicines and Medical Devices Safety Authority (MEDSAFE)
Nigeria	National Agency for Food and Drug Administration and Control (NAFDAC)
Norway	Norwegian Medicines agency
Panama	Ministry of Health

Paraguay	Department of Health: Pharmaceutical Services
Poland	Ministry of Health & Social Welfare
Portugal	The National Institute of Pharmacy and Medicines
Romania	National Medicines Agency (ANM)
Russia	Ministry of Health and Social Development
Senegal	Ministry of Health & Prevention
Serbia	Medicines and Medical devices Agency (ALIMS)
Singapore	Center for Pharmaceutical Administration Health Sciences Authority
South Korea	Food and Drug Administration
South Africa	Medicines Control Council (MCC)
Spain	Medicines and Health Product Agency (AEMPS)
Switzerland	Swiss Agency for Therapeutic Products (SWISSMEDIC)
Taiwan	Department of Health
Tanzania	Ministry of Health and Social Welfare
Thailand	Ministry of Public Health
UK	Medicines and Healthcare Products Regulatory Agency (MHRA)
USA	Food and Drug Administration (FDA)
Uruguay	Ministry of Public Health
Venezuela	Ministry of Public Health
Vietnam	Ministry of Health
Yemen	Ministry of Public Health and Population
Zimbabwe	Medicine Control Authority of Zimbabwe (MCAZ)

INTERNATIONAL ORGANIZATIONS ^[7-10]

Some of the international regulatory agencies and organizations which also play essential role in all aspects of pharmaceutical regulation related to drug product registration, manufacturing, distribution, price control, marketing, research and development and intellectual property protection.

World Health Organization (WHO) ^[7]

When diplomats met to form the United Nations in 1945, one of the things they discussed was setting up a global health organization.

Constitution of the World Health Organization : The Constitution was adopted by the International Health Conference held in New York from 19 June to 22 July 1946, signed on 22 July 1946 by the representatives of 61 States and entered into force on 7 April 1948 - a date we now celebrate every year as World Health Day.

Pan American Health Organization (PAHO) ^[8]

The Pan American Health Organization (PAHO), founded in 1902, is the world's oldest international public health agency. It provides technical cooperation and mobilizes partnerships to improve health and quality of life in the countries of the

Americas. PAHO is the specialized health agency of the Inter-American System and serves as the Regional Office for the Americas of the World Health Organization (WHO). Together with WHO, PAHO is a member of the United Nations system.

World Trade Organization (WTO) ^[9]

The WTO is a rules-based, member-driven organization - all decisions are made by the member governments, and the rules are the outcome of negotiations among members.

International Conference on Harmonization (ICH) ^[10]

ICH's mission is to make recommendations towards achieving greater harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines. Launched in 1990, ICH is a unique undertaking that brings together the drug regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States.

Regulatory harmonization offers many direct benefits to both regulatory authorities and the

pharmaceutical industry with beneficial impact for the protection of public health.

PROGRESS IN INTERNATIONAL HARMONIZATION

There have been enormous changes in the technical and scientific requirements for the dossier, as the work of the ICH has continued to devise and approve new guidelines in the categories of Quality, Safety, Efficacy, and Multidisciplinary. The CTD harmonized structure and modular format for new medicinal product registration files that were adopted in San Diego, is now the obligatory format in the European Union (EU), Japan, Canada, Switzerland, and Australia. It is the recommended format in the United States.

THE CTD—A COMMON FORMAT, NOT A HARMONIZED CONTENT FOR SUBMISSIONS

Enormous efforts have been expended by the staffs of the regulatory agencies and the pharmaceutical industry in the work of the ICH, and this has achieved a remarkable degree of harmonization in many scientific and technical areas of the dossier. Despite this there are still national differences in the content of submissions not only in Module 1, the administrative and prescribing information, but also in other areas of the dossier. These arise from differences in regulatory practice and procedures, different practices of medicine and pharmacy, and differences in access to diagnostic and therapeutic procedures. We are, however, still far from a genuinely global single registration dossier.

INCREASED COOPERATION BETWEEN AGENCIES BASED ON ICH

Mutual Recognition Agreements between agencies in relation to Good Manufacturing Practice (GMP) are in operation between the EU and Canada, Australia, New Zealand, Switzerland, and Japan. Arrangements exist between many countries (including the ICH members) for exchange of pharmacovigilance and defect information. The confidentiality arrangements between the EU and the FDA now allow for exchange of information on legal and regulatory issues, scientific advice, orphan drug designation, inspection reports, marketing authorization procedures, and post-marketing surveillance. In September 2004, the European Medicines Agency (EMA) and the Food

and Drugs Administration (FDA) instituted a pilot program of parallel scientific advice meetings for sponsors to obtain advice on scientific issues during the development phase of new medicinal products. Orphan indication products and pediatric products have been targeted in particular. Bilateral and trilateral collaboration has increased in 2008. Health Canada has agreed to exchange information with the European Commission and EMA about the authorization and safety of drugs. Canada and Australia have started their parallel review project for biologicals (originally launched in 2006). All of this has only been possible based on the prior work that has been done in harmonization of regulatory requirements and in the development of the CTD format of the dossier in ICH.

SPREADING THE ICH MESSAGE—THE ICH GLOBAL COOPERATION GROUP

The ICH-affiliated and other developed countries, which have adopted the CTD format (the United States, EU, Japan, Canada, Switzerland, and Australia), comprise in total approximately 15% of the current (2008) world population of 6650 million people. The ICH Global Cooperation Group (GCG) was formed on March 11, 1999 as a subcommittee of the ICH Steering Committee. Its purpose is to make information available on ICH, ICH activities, and any ICH guideline to a wider group of countries.

REGIONAL HARMONIZATION INITIATIVES

A number of regional harmonization initiatives (RHIs) have been set up where a geographic grouping of countries harmonizes technical and scientific requirements and in some cases the format of submissions for member countries. These groups have been invited to designate permanent representatives to the GCG. They currently comprise:

Asia-Pacific Economic Cooperation (APEC): 21 countries in the Asia-Pacific region.

Association of Southeast Asian Nations (ASEAN): Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam.

Gulf Cooperation Countries (GCC): Saudi Arabia, Kuwait, United Arab Emirates, Oman, Bahrain, Qatar and Yemen.

Pan American Network on Drug Regulatory Harmonisation (PANDRH): Argentina, Barbados, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Guatemala, Jamaica, Mexico, Panama, Trinidad and Tobago and Venezuela.

South African Development Community (SADC): Angola, Botswana, Democratic Republic of Congo, Lesotho, Malawi, Mauritius, Madagascar, Namibia, Seychelles, South Africa, Swaziland, Tanzania, Zambia and Zimbabwe.

The regional groups review the applicability of the ICH guidelines in their own specific countries. Particular topics of interest include the ICH stability guideline, GMP guidances, requirements for bioavailability and bioequivalence studies, clinical trials, export/import of medicines, traditional medicines, and market surveillance.

The following are the various regions as per regulatory guidelines having CTD structure / format for registration product-^[11-13]

* ASEAN Region (ACTD Format): Brunei, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam.

* African Region (CTD Format): Nigeria, Kenya, South Africa, Zimbabwe, Tanzania, Ethiopia, Namibia, & Mauritius.

* CIS Region (CTD Format) (country specific resemble to CTD): Moldova, Russia, Ukraine, Georgia, Kazakhstan, Uzbekistan.

* WHO & India (CTD Format)

* LATAM region (Country specific): Mexico, Panama, Venezuela, Chile, Costa-Rica, Brazil, Dominican Republic & Jamaica.

* GCC Region (CTD Format) and Australia (ICH-CTD Format)

The registration procedure is differs from region to region. Thus some follow the ICH guidelines and some WHO guidelines for the registration of the drug product. But some regions have the country specific guidelines for registration of the FPP. Drug

regulatory affairs in pharmaceutical industries have mandated two types of dossier namely CTD (Common Technical Dossier) and ACTD (ASEAN Common Technical Dossier) .

Regulated pharmaceutical markets (eg. USA, Europe) require submission of dossier in CTD format which require clinical trial and bioequivalence studies. As against this, semi-regulated pharmaceutical markets (South East Asian) require ACTD format which does not require exhaustive details like CTD. All of these guidelines will consider the safety, quality and efficacy of Finished Pharmaceutical Product (FPP).

ORGANIZATION OF ICH-CTD FORMAT ^[14-18]

The CTD is organized into five modules. Module 1 is region-specific. Modules 2, 3, 4 and 5 are be common for all regions. Conformance with ICH guidelines should ensure that these four modules are provided in a format acceptable to WHO and regulatory authorities. An overview of module contents for a multisource product in greater details.

The five Modules are:

- Module 1: Administrative and prescribing information
- Module 2: Overview and summary of module 3 to 5
- Module 3: Quality (Pharmaceutical documentation)
- Module 4: Safety (Toxicology/ Non-clinical studies)
- Module 5: Efficacy (Clinical studies)

The diagram below represents the above information as a modular structure which is known as CTD Triangle.

The modular structure of ICH-CTD shows that Module 1 is not a part of CTD, it contain only the regional information or administrative information of the one who right to file the dossier for getting market authorization.

The modular structure is detailed with the help of technical data of common technical document (CTD) which is mentioned in all module as module of contents.

This format is explained with an examples of two selected countries Zimbabwe and Australia from different continents which follow the ICH-CTD format for dossier preparation for selected drug(s) Regorafenib and Roflumilast respectively.

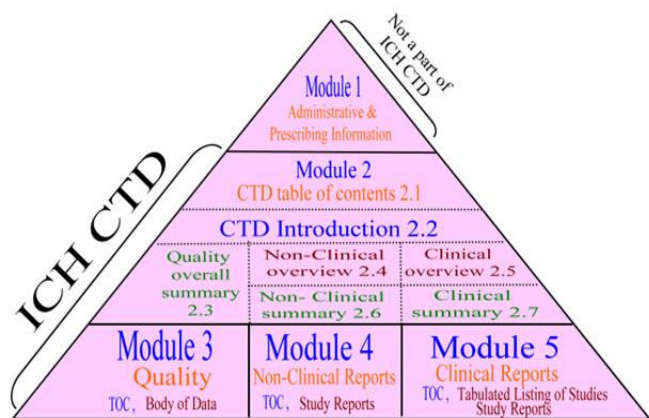


Fig 2 : Modular Structure of ICH CTD

CATEGORIES OF PHARMACEUTICAL PRODUCT THAT CAN BE SUBMITTED AS A CTD REGISTRATION FILE

Most categories of product can be submitted in all of the ICH regions as a CTD registration file. This includes the following:

- New drug substance (NCE) products
- New biological/biopharmaceutical products
- Radiopharmaceuticals
- Phytopharmaceuticals (herbal medicines)

In the case of the United States, CTD registration files may also be submitted for generic and OTC products and this format would be obligatory in the European Union for these products.

DIFFERENCES IN CTD CONTENT BETWEEN THE ICH REGIONS

As mentioned in the Preface, the CTD is a harmonized format for registration files; however, the content is not yet completely harmonized. There are still national or regional differences in the content of submissions—not only in Module 1 but also in other parts of the dossier. These arise from differences in regulatory practice and procedures, differences in practices of medicine and pharmacy, and differences in access to diagnostic and therapeutic procedures. What are the major differences in content and how can companies cope with them to make filings in the major developed world markets?

Module 1 Differences

Although the ICH CTD refers to Module 1 as comprising “Regional Administrative Information” (such as the application form, labeling, text of prescriber, and patient information), in practice there are other differences and some of key ones are summarized in table 2. It is usual for companies to prepare a common Core Data Sheet for information to health practitioners that could then be used to prepare draft Prescribing Information and Patient Information for the United States, the Summary of Product Characteristics (SmPC), and Patient Information Leaflet for the European Union.

Nation/region	Key differences
European Union	1.4 Information about the Experts (who sign the Module 2 Summaries)
	1.5 Specific Requirements for Different Kinds of Application (summaries to support generics, hybrid applications, bibliographic applications, extended market exclusivity applications, conditional marketing authorizations, etc.)
	1.6 Environmental Risk Assessment
	1.7 Information relating to Orphan Market Exclusivity
	1.8 Information relating to Pharmacovigilance
	1.9 Information relating to Clinical Trials
United States	1.3.5 Patent and exclusivity information
	1.9 Pediatric administrative information
	1.16 Risk management plans
Japan	Patent status
	Background of origin, discovery, and development
	List of related products
	Data for review of designation as poisons, deleterious substances, etc.
	Draft of basic protocol for postmarketing surveillance
Canada	1.2.4 Patent information
	1.4 Health Canada Summaries

	1.4.1 Certified Product Information Document (CPID) 1.4.2 Comprehensive Summary of BE
	1.5 Environmental Assessment Statement
Australia	1.4.1 Information about the Experts (who sign the Module 2 Summaries)
	1.5 Specific requirements about different types of application (literature based, orphan drug products, genetically modified organisms, comarketed medicines, etc.)
	1.6 Drug and Plasma Master Files and Ph Eur Certificates of Suitability
	GMP clearance letters
	Summary Biopharmaceutic Studies
	Pediatric Development Program
	Environmental Risk for non-GMOs containing medicines
	Antibiotic resistance data

CPID: This is a condensed summary of current and specific chemistry and manufacturing information attested by the manufacturer and sponsor. There is no requirement for Expert signatures for the Module 2 Summaries in registration filings in the United States, Japan, and Canada.

Module 2 Differences

Although the formal ICH requirements for the Module 2 Summaries are identical in all ICH and other countries, there are likely to be national or regional differences particularly in relation to the contents of the Module 3: Quality and Module 5: Clinical Studies modular files, and these will be reflected in these high-level summaries. For example, where a pharmacopoeial drug is the subject of a DMF, there will be just a reference to the DMF in Module 2 of a U.S. or Japanese dossier, whereas in the European Union there will be a summary of the Open Part of the European Union Active Substance Master File (DMF).

Module 3 Differences

Some of the key national or regional differences in content of Module 3 in relation to the drug substance and drug product are summarized in Table 3 and Table 4.

In addition, there are the 3.2.R Regional Differences. Examples quoted in the ICH CTD are as follows:

- Executed Batch Records for Drug Substance and Drug Product (the United States only): Copies of records with equipment specified, manufacturing conditions, packaging records, and batch reconciliation information (theoretical yield, actual yield, and packaged yield).
- Method validation package for drug substance and drug product (the United States only)
- Comparability protocols (the United States only)
- Process validation scheme (the European Union only), including a process validation protocol where validation studies on the manufacturing process for the drug product are not complete
- Medical device used in combination with the drug product (the European Union only)

In addition, highly abbreviated documentation (a “lite” document) on the manufacture of the drug substance in 3.2.S.2.2 Description of the Manufacturing Process and on 3.2.P.3.3 Description of the Manufacturing Process and Process Controls for the drug product may need to be supplied in countries where regulatory agencies do not always respect the confidentiality of data.

There may also be differences in marketing needs for different countries. Thus, blister or foil packs are usually the packaging material of choice for tablets or capsules in the European Union whereas in the United States high-density polyethylene (HDPE) bottles are much more commonly used. In such a case, 3.2.P.7 Container Closure will include different information and also the primary stability data in 3.2.P.8 Stability for the European Union will be in blister or foil packs and in the United States it will be in HDPE bottles.

Table 3: Summary of Some Key National or Regional Differences in Module 3.2.S

Nation/region	Key differences
European Union	3.2.S Drug substance data may be submitted as an EU 2-part DMF (Open Part to be reproduced in 3.2.S) or as a reference to a Ph. Eur Certificate of Suitability (for Ph Eur monograph substances)
	3.2.S.7 Stability: Storage requirements to be stated in accord with CHMP guideline
United States	3.2.S Reference may be made in the dossier to DMF information supplied directly by the drug substance manufacturer to FDA
	3.2.S.7 Stability: Storage requirements to be stated in accord with FDA labeling requirements
Japan	3.2.S Reference may be made in the dossier to DMF information supplied directly by the drug substance manufacturer
Canada	3.2.S Reference may be made in the dossier to DMF information supplied directly by the drug substance manufacturer
Australia	3.2.S Drug substance data may be submitted as a 2-part DMF (Open Part to be reproduced in 3.2.S) or as a reference to a Ph. Eur Certificate of Suitability (for Ph Eur monograph substances)

Table 4: Summary of Some Key National or Regional Differences in Module 3.2.P

Nation/region	Key differences
European Union	3.2.P.1 Description and Composition: Colors to be on the European Union permitted list. Excipients to be designated as conforming to Ph Eur or a European national pharmacopoeia where there is a monograph.
	3.2.P.4 Excipients: To conform to Ph Eur/European national pharmacopoeia if described in a monograph.
	3.2.P.5 Control of Drug Product: Assay limits to be $\pm 5\%$ unless justified. A different manufacturing and shelf-life specification may be required. Products to conform to general monographs of the Ph Eur.
	3.2.P.7 Container Closure System: Name of manufacturer(s) not required unless product is critical (e.g., parenteral).
	3.2.P.8 Stability: Storage requirement to be in accord with CHMP guideline.
United States	3.2.P Reference may be made in the dossier to DMF information supplied directly to FDA by excipient and container/closure manufacturers.
	3.2.P.1 Description and Composition: Colors to be on FDA permitted list. Excipients to be designated as conforming to USP/NF where there is a monograph.
	3.2.P.4 Excipients: To conform to USP/NF if described in a monograph.
	3.2.P.5 Control of Drug Product: Assay limits allowed to be up to $\pm 10\%$. A single regulatory (shelf-life) specification is allowed.
	3.2.P.7 Container Closure System: Name of manufacturer(s) required.
3.2.P.8 Stability: Storage requirement to be in accord with FDA requirements for wording.	
Japan	3.2.P.1 Description and Composition: Colors to be on Japanese permitted list.
	3.2.P.4 Excipients: To conform to monographs of the Japanese Pharmacopoeia or Japanese Pharmaceutical Excipients.
Canada	3.2.P.7 Container/Closure: Reference may be made to a DMF from the supplier.
	3.2.P.8 Stability: Storage conditions to refer to Health Canada requirements (e.g., storage at controlled room temperature).
Australia	3.2.P.1 Description and Composition: Colors to be on Australian permitted list for colors in oral products.
	3.2.P.8 Stability: Storage conditions to refer to TGA list of acceptable storage conditions (e.g., Store below 30°C).

Module 4 Differences

There are usually no major differences in this module.

Module 5 Differences

Some of the key differences are summarized in Table 5.

Table 5: Summary of Some Key National or Regional Differences in Module 5: Clinical Studies

Nation/region	Key differences
Europe	Where required BE studies for generic products need to use a European batch of reference product.
	Clinical trials should normally comply with CHMP Efficacy guidances where these exist.
	Clinical trials of new drug products versus European authorized “gold standard treatment” are important as well as placebo studies
United States	Clinical trials should normally comply with FDA regulatory guidances where these exist.
	FDA Integrated Summaries of Safety and Efficacy (ISS/ISE) to be included in 5.3.5.3 Reports of Analyses from More than One Study (these are normally required in addition to the Clinical Overview and Clinical Summary in 2.5 and 2.7)
Japan	“Bridging” pharmacokinetic and clinical studies may be needed to allow foreign data to be extrapolated to the Japanese population if the clinical studies performed outside Japan
Other Non-ICH countries	“Bridging pharmacokinetic and clinical studies may be needed to allow foreign data to be extrapolated to the national population if the clinical studies are performed outside these countries

Managing the Differences

If companies wish to file simultaneously in a number of the major developed world markets, the chemical, pharmaceutical, nonclinical, and clinical development program needs to be designed to meet all of the individual market regulatory needs. For example, additional “bridging” pharmacokinetic or clinical trials may be needed to support a foreign registration file in Japan. Most of the documentation in Modules 2 to 5 for a major new drug registration file can be identical, but where there are national differences in requirements (e.g., differences in 3.2.P.5.1 Drug Product Specification in terms of assay limits for the European Union and U.S. markets), it is usually more efficient to prepare the two versions of the document at the same time. The Module 2.3 Quality Overall Summary and the Module 2.5 Clinical Overview could be prepared as identical “core documents” but they should then be reviewed by in-country staff and customized as necessary to meet any different technical or regulatory requirements of the different agencies.

ADOPTION OF THE CTD FORMAT OUTSIDE THE ICH REGION

The CTD format is being adopted with local modifications as needed by other national regulatory agencies and regional groupings of agencies. The Association of Southeast Asian Nations (ASEAN) comprises Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. These countries have a combined population of over 550 million. They have published the ASEAN CTD (10). The ICH format is allowed for NCE and Biological products, but compliance is needed with ASEAN technical requirements [e.g., the ASEAN guideline on Stability Study of Drug Product (10)] and the ASEAN CTD (ACTD) administrative requirements. The ACTD will be implemented across the whole region by January 1, 2009.

ASEAN COMMON TECHNICAL DOCUMENT [ACTD] [19-22]

ASEAN Introduction

The Association of South-East Asians Nations (ASEAN) is a regional organization consisting of ten member countries, namely, Brunei Darussalam, Cambodia, Indonesia, Laos, Myanmar, Malaysia, Philippines, Singapore, Thailand and Vietnam.

ASEAN was established in 8 August 1967 by the governments of five countries - Indonesia, Malaysia, Philippines, Singapore and Thailand. In 1984, Brunei Darussalam joined its neighbors in the association. As a group, these early participants are dubbed the ASEAN6. Vietnam has become member since 1995, Laos and Myanmar since 1997 and Cambodia since 1999. These four new members are usually referred to as the CLMV group. In 1992, the governments of ASEAN member countries agreed to create the ASEAN Free Trade Area (AFTA) to set common tariff scheme. The agreement on Common Effective Preferential Tariff Scheme (CEPT) has been effective since 2003. Pharmaceutical trade among the members now enjoy import duties of 0-5 % under CEPT, provided that the products has no less than 40% local content.

A Pharmaceutical Product Working (PPWG) was established to work on the details in the development of harmonization guidelines for technical procedures and requirements partially applicable to the ASEAN pharmaceuticals have been identified for harmonization - quality, efficacy, safety and administrative data.

Key documents resulted from work of PPWG include :

- ASEAN Common Technical Requirements (ACTR) for pharmaceutical product registration (for human use).
- ASEAN Common Technical Dossier (ACTD) for pharmaceutical product registration (for human use).
- ASEAN Guidelines on the following areas: analytical validation, bioavailability and bioequivalence studies, process validation, stability.

While ASEAN was working on its harmonized pharmaceutical registration, another international collaboration for harmonization of pharmaceutical registration was taking place in parallel called the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). It was established in 1990 and works for development for technical guidelines for registration of pharmaceutical products to achieve greater harmonization.

ASEAN Pharmaceutical Product ^[24]

At the first PPWG meeting the terms of reference were agreed and it was decided that the topics selected for harmonization would be divided into safety, quality and efficacy to reflect the three criteria which would be the basis for approving medicinal products. One of the PPWGs key topic is the idea of an 'ASEAN pharmaceutical product'. This means that same regulatory requirements apply for the registration of a medicinal product among the ASEAN member countries. The PPWG developed the ASEAN Glossary of terms, the ACTD, the ACTR and their guidelines.

The ACTD gives information on the format and structure of the dossier that shall be commonly used for applications in the ASEAN region. The ACTD should serve as a locator for documentation that has been compiled for a marketing authorization application. It does not give any recommendations on the actual content of the dossier. The ACTD is similar to the European Notice to Applicants Volume 2B Presentation and Format of the dossier (EU-CTD).

The ACTR is as set of written material intended to guide applicants to prepare an application in a way that is consistent with the expectations of all ASEAN Drug Regulatory Authorities. It is a guide for preparation of the ACTD.

For Pharmaceuticals, efforts to develop harmonization schemes of pharmaceutical regulations in ASEAN to facilitate trade in pharmaceuticals continued and for this ATCD, covering administrative data, quality, safety and efficacy and an ASEAN Common Technical Requirements (ATCRs), covering quality, safety and efficacy had developed. The ACTD is the part of marketing authorization application dossier that is common to all ASEAN member countries while the ATCR is the set of written materials, intended to guide applicant(s) to prepare application dossiers in a way that is consistent with the expectations of all ASEAN Drug Regulatory Authorities. Series of guidelines for the implementation of the ATCR are being finalized. The ASEAN Standards and Quality Bulletin is regularly published with a view to ensure dissemination of information and promote transparency on standards, technical regulations and

conformity assessment procedures in ASEAN member countries.

Regulatory Agencies in South East Asia

Table 6 : List of countries and their Regulatory Authority (ACTD) [19-20]

Country	Regulatory Agencies
Indonesia	National Agency of Drug & Food Control
Malaysia	Drug Control Authority, NCE Unit
Philippines	Department of Health
Thailand	Thai FDA Drug Control Division
Singapore	Health Sciences Authority (HSA)
Brunei	Ministry of Health
Vietnam	Drug Administration of Vietnam
Myanmar	Food and Drug Administration
Cambodia	Department of Drug, Food and Cosmetics
Laos PDR	Ministry of Health, Food And Drug Department (FDD)

ORGANIZATION OF ASEAN CTD (ACTD) FORMAT ^[23]

ACTD is a guideline for the preparation of a well-structured CTD applications that would be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals for human use. This guideline describes a CTD format that would significantly reduce the time and resources needed to compile applications for registration and in the future, would ease the electronic document submissions.

Four parts are :

- Part I : Table of Contents, Administrative Data and Product Information
- Part II : Quality Document
- Part III : Nonclinical Document
- Part IV : Clinical Document

Presenting above information in the organizational structure which is known as ACTD Triangle.

Table 7 : DOCUMENTS LOCATION IN FORMAT OF ICH-CTD & ASEAN CTD ^[13]

ICH CTD	ASEAN CTD	Description	Remarks
Module 1 -Regional and Administrative Information	Part I	Contains documents that are specific to each region. This module is not part of CTD. Basically consists of administrative documents like Application form, legal documents (GMP, Licenses etc.), labeling etc.	Required for generics and New Drug.

The organizational structure is detailed with the help of technical data of ASEAN common technical document (ACTD) which is mentioned in all part of respective dossier.



* upon request

Fig. 2 Organizational Structure of ACTD

This format is explained with selected drug Alogliptin for Singapore.

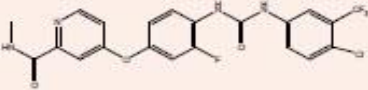
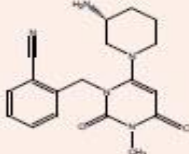
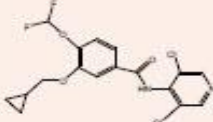
Overview of ICH-CTD and ACTD

In this thesis an attempt has been made to compare the drug regulatory approval procedure and requirements for the registration of pharmaceuticals for human use in ICH countries and ASEAN. The main points of divergence are in the content and format of the registration dossier.

The ACTD consists of Parts I to IV which have subsections A to F whereas ICH-CTD has 5 Modules with subsections that are numbered. The administrative data of Part I is part of ACTD whereas Module 1 of ICH-CTD is purely country specific. The summaries of the quality (Part II), nonclinical (Part III) and clinical (Part IV) are located at the beginning of each part of the ACTD. The ICH-CTD dedicates these summaries in a separate Module 2. As the ACTD does not have such summary part, it consists of only 4 Parts. The major differences between the ICH-CTD and ACTD are listed below in Table.

Module 2 - Overall Summary	Incorporated in Parts II, III and IV	This module summarizes the Module 3, 4 and 5. It includes Quality Overall summary, Non Clinical Overview and Summary and Clinical Overview and Summary. The summary provides reviewer the abstract of documents provided in the whole application.	Required for generics and New Drug. For generics summary on Quality part only required.
Module 3 - Quality	Part II	The documents related to Chemistry, manufacturing and Control of both Drug Substance and Drug Product is included in this module.	Required for generics and New Drug.
Module 4 - Safety	Part III	Non Clinical Study Reports – Data on pharmacologic, pharmacokinetic, and toxicological evaluation of the pharmaceutical product is provided.	Not required for generics.
Module 5 -Efficacy	Part IV	Clinical Study Reports - A critical assessment of the clinical data and related reports is provided in this module.	Not required for generics except Bioequivalence study.

Drug Profile[24-35]

Name of drug	Regorafenib	Alogliptin	Roflumilast
Trade Name	STIVARGA	NESINA	DALIRESP
FDA Approval	27 September 2012	25 January 2013	1 March 2011
CDSCO Approval	1 July 2014	17 July 2014	27 August 2014
Category	Anti-neoplastic Agents	Dipeptidyl peptidase-4 (DPP-4) inhibitor, Antidiabetic Agents	Selective Phosphodiesterase 4 (PDE4) inhibitor
Structure			
CAS Reg. no.	755037-03-7	850649-61-5	162401-32-3
Mol. Formula	C ₂₁ H ₁₅ ClF ₄ N ₄ O ₃ · H ₂ O	C ₁₈ H ₂₁ N ₅ O ₂	C ₁₇ H ₁₄ Cl ₂ F ₂ N ₂ O ₃
Mol. Weight	500.83	339.39	403.22
Chemical Name	4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl} amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide monohydrate	2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl}methyl)benzotrile	3-Cyclopropylmethoxy-N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy benzamide
Seeking for market approval*	Zimbabwe ^[21]	Singapore ^[22]	Australia ^[23]

*As of May 2015

CONCLUSION

From the study it could be understood that getting a market authorization for registration of a drug in any territory requires a particular format, and that each country follows a specific guideline in addition to its own regulations which are laid down by the respective drug regulatory authority. There are basically two formats available in most of the countries of world one is, ICH-CTD and the other is ACTD. ICH-CTD is followed by ICH countries where as ACTD is usually adopted by ASEAN countries. The ICH-CTD has five modules, in which module 1 is country specific presenting administrative information of the country but the other four modules which are framed for drugs. They include descriptive scientific details information and are common to all the countries which follow the format. Module - 2,3,4,5 have summary of quality, nonclinical and clinical information, respectively. The ACTD has parts instead of module. They are four in number. These include summary of quality, nonclinical and clinical in part II, III, IV, respectively.

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