Introduction

Cmc [chemistry manufacturing and control.]

- CMC Regulatory Affairs is a specific area with RA that has ultimate responsibility for providing CMC regulatory leadership and strategy required to achieve regulatory approvals.

• CMC RA provides knowledge, understanding, interpretation and utilization of regulatory guidance and regulations, as well as industry and government agency best practice and trends.

• CMC RA is a high value-added function within a company that is critical to successful development, registration, approval and life

cycle management of pharmaceutical product.

Example: CMC regulatory submission may contain information associated with API and the finished dosage form, including.

✓Names and location of manufacturing and testing sites .

✓Characterization of the API and composition of the dosage form .

✓Raw materials used to manufacture the API and finished dosage form .

✓Description of the product and process development.

✓Description of the manufacturing process.

✓Analytical methods and specifications used for testing and release of raw materials, in-process controls, container and closure system,

API and dosage form.

✓Quality testing, bio equivalence testing .

✓Release and stability testing data for both API and the dosage form.

Post approval Regulatory Affairs :

✓ The FDA may require a post-approval study at the time of approval of a Premarket Approval (PMA), Humanitarian Device Exemption (HDE), or product development protocol (PDP) application to help assure continued safety and effectiveness (or continued probable benefit, in the case of an HDE) of the approved drug product of medical device.

✓ A sponsor's failure to comply with any post-approval requirement may be grounds for withdrawing approval i.e. whether the post approval study will be terminated or revised/replaced.

✓ The safety surveillance is designed to detect any rare or long-term adverse effect s over the much larger population and longer time period.

✓ Harmful effects shown in this trial may result in drug ban or restricted in certain usages.

Post approval studies.

- ✓ Drug-drug interaction
- ✓ Drug-food interaction
- ✓ Drug- herbal interaction
- ✓ Pharmacoeconomic
- ✓ Expanded efficinency/safety
- ✓ Additional indication
- ✓ Strategies for minimization of adverse effect.
- ✓ Strategies for dose indivisuilization
- ✓ Optimization of surrogate lab test
- ✓ Special populations
- ✓ New formulation

Regulation for combination product & medical devices .

A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product.

Example: -

-Monoclonal antibody combined with a therapeutic drug

-Device coated or impregnated with a drug or biologic

-pacing lead with steroid-coated tip, catheter with antimicrobial coating, condom with spermicide, transdermal patch

Prefilled drug delivery systems (syringes, insulin injector pen, metered dose inhaler)

- Medical Devices are instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory.
- Medical devices does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

In US, FDA has 3 assigned centers for regulation:

1. Center for Drug Evaluation and Research (CDER) (for combination product)
2. Center for Devices and Radiological Health (CDRH) (for Devices)
3. Center for Biologics Evaluation and Research (CBER)

Example:

1) Wound dressing with antimicrobial – typically a device (CDRH)
2) asthma inhaler or medicinal patch – typical a drug (CDER)

CTD and ECTD

INTRODUCTION:

CTD was agreed in November 2000 in San Diego, USA.

It provides for a harmonized structure and format for new product applications.

CTD is a set of specification for application dossier for the registration of medicines and designed to be used across Europe, Japan & US

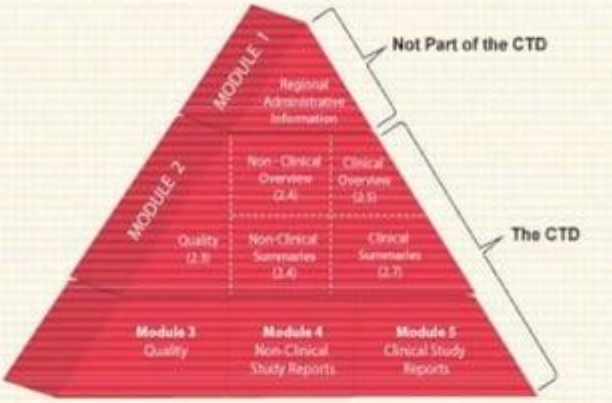
CTD was developed by the European medicines agency(EMEA),

Food& Drug Administration(FDA),the ministry of health, labour&welfare(Japan).

CTD is maintained by the ICH (International Conference on Harmonization) of technical requirement for registration of pharmaceuticals for human use.

The FDA characterized the CTD as "An information package of clinical ,non-clinical, manufacturing, technical data in the same format and with the same content, that would be submitted for registering new drugs in all three ICH regions i.e.; US, European Union and Japan.

The CTD Triangle



CTD Modules

Module 1 – Administrative Information (Region Specific)

Module 2 – CTD Summaries (QOS)

Module 3 – Quality (CMC)

Module 4 – Non-Clinical Study Reports

Module 5 – Clinical Study Reports

Module 1

administrative information (Region specific)

should contain document contain specific to region

- For USA
- Application form 356 h
- Product label
- Patient certificate/ Information
- Department certificate
- Letter of authurization (Loa)/Dmf letter
- Labelling text

- For EU
- Application form
- Summry of characteristic product.
- Labelling text and mocks up
- Information about experts
- Risk management plan

Module 2 CTD Summaries (QOS)

It contain 7 sections in the following order:

2.1 CTD TOC (Module 2-5)

2.2 CTD Introduction

2.3 Quality Overall Summary

2.4 Non clinical Overview

2.5 Clinical Overview

2. 6 Non Clinical Summary

2.7 Clinical Summary

Module 3 Quality (CMC)

3.1 TOC of Module 3

3.2 Body of Data-

S - Drug substance

P - Drug product

A - Appendices

R - Regional Information

3.3 Literature references

Module 4 Non-Clinical Study Reports.

4.1 TOC of Module 4

4.2 Study reports

- 4.2.1 Pharmacology
- 4.2.2 Pharmacokinetics
- 4.2.3 Toxicology

4.3 Literature References

Module 5 Clinical Study Reports

5.1 TOC of Module

5 .2 Tabular listing of Clinical Studies

5.3 Clinical study reports

- 5.3.1 Reports of Biopharmaceutical (BA-BE) Study
- 5.3.2 Reports of Pharmacokinetic (biomaterial) study
- 5.3.3 Reports of Pharmacokinetic (PK) Studies
- 5.3.4 Reports of Pharmacodynamic (PD) Studies
- 5.3.5 Reports of Efficacy and Safety studies

5.3.6 Reports of Post-Marketing experience p g p

5.3.7 Case Report Forms & Individual patient listings

5.4 Literature References.

eCTD

Its electronic version of CTD so called as CTD, electronic Common Technical Document (eCTD).

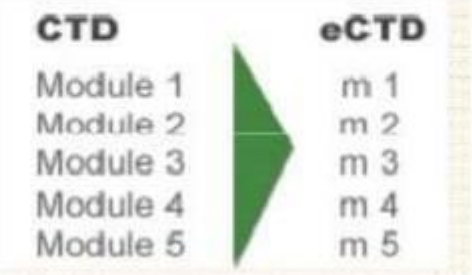
eCTD composed of two types of specification

✓Content specification – As defined by ICH

✓Technical specification – Electronic softwares

✓CTD is highly recommended by USFDA for NDAs, BLAs, DMFs and INDs filing.

✓From year 2010 European Union also make compulsory for electronic CTD submission to all procedures.



eCTD Characteristics

Structure

✓All Modules 1 to 5 have granularity options.

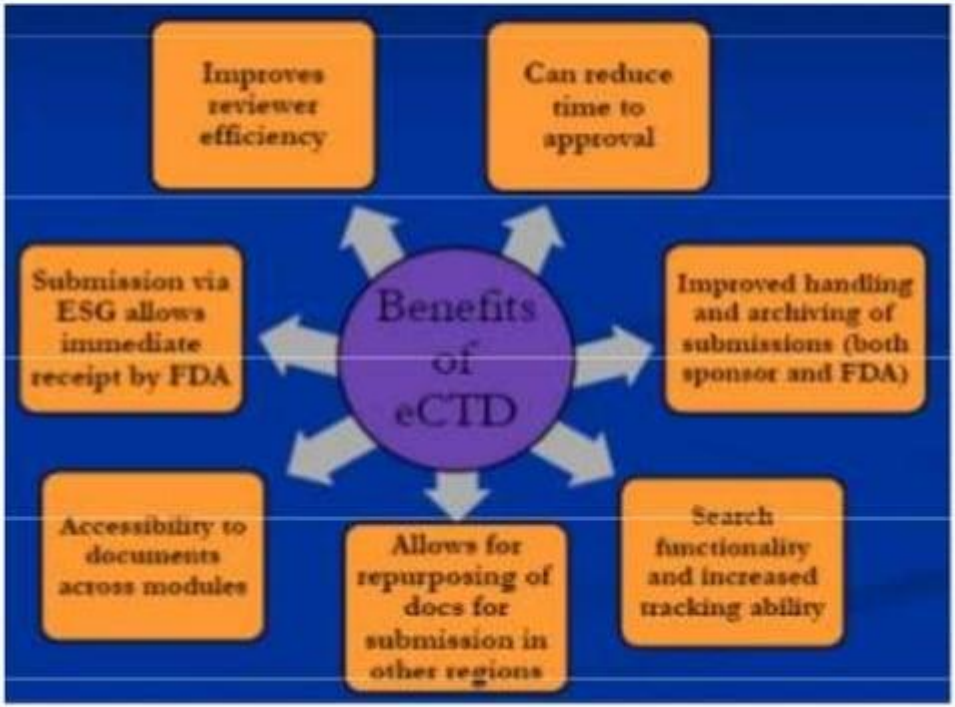
✓PDF documents linked via XML backbone.

✓Increased document granularity.

✓Transparency of entire submission.

✓ Ease of navigation and review.

Benefits of eCTD



Industry and FDA liaison.

- Experienced Drug Regulatory Affairs [DRA] personnel are essential in the process of new product development.
- They are largely responsible for establishing a liaison with their counterparts at the U.S. Food and Drug Administration [FDA] and other regulatory agencies globally.
- FDA is one of our nations oldest consumer protection agencies dating back to 1862.

U.S. FDA

The U.S. FDA [Food and Drug Administration] is an agency of the US Department of Health

and Human services [DHHS] that is responsible for the safety regulation of :

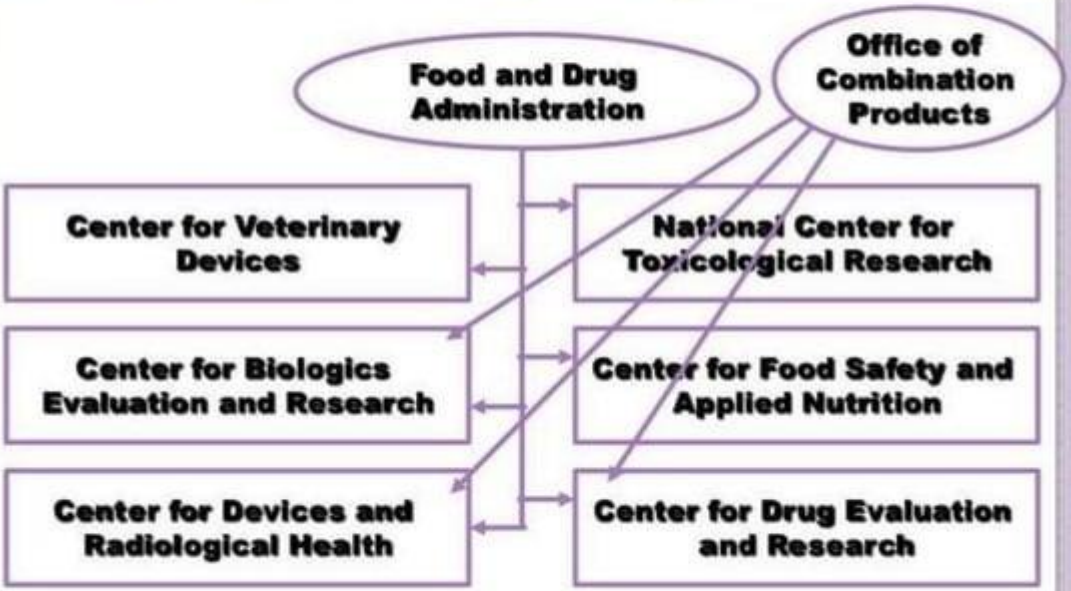
- most type of foods
- Vaccines
- Drugs
- Blood products
- dietary supplements
- biological medical products
- cosmetics

The FDA also enforces other laws ,notably Section 361 of the Public Health service Act and associated regulations, many of which are not directly related to food or drugs•

They include sanitation requirements on interstate travel and control of disease on products ranging from certain household pets to sperm donation for assisted reproduction.

The FDA has its headquarters at White oak, Maryland . The agency also has 223 field offices and 13 laboratories located throughout 50 states.

FDA Structure / Organization



Responsibility of FDA organization

FDA Center	Areas of Responsibility
Center for Drug Evaluation and Research	Safety and effectiveness of Rx and over the counter drugs
Center for Biologics Evaluation and Research	Safety and effectiveness of vaccines, nations blood supply, other biologics
Center for Devices and Radiological Health	Safety and effectiveness of medical devices, diagnostic tests, radiation emitting devices
Center for Food Safety and Applied Nutrition	Safety of domestic and imported food supply, cosmetics, dietary supplements
Center for Veterinary Medicine	Safety and effectiveness of veterinary drugs
Center for Tobacco Products	Implementation of the Family Smoking Prevention and Tobacco Control Act
National Center for Toxicological Research	Research to support regulatory decisions and reduce risks associated with FDA-regulated products
Office of Regulatory Affairs	Enforcement of laws and regulations

Ich guideline

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

- ✓Quality (Q1-Q 11)
  - chemical & Pharmaceutial QA
- ✓ Safety (S1-S10,M3)
  - dealing with invitro & invivo preclinical testing
- ✓ Efficacy (E1-E16, Except E13)
  - clinical studies in human beings
- ✓Multidiscilplinary (M1-M8)
  - terminology, electronic standards common documents

QUALITY

"Harmonization achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management."

- Q1-Stability
- Q2-Analytical Validation
- Q3-Impurities
- Q4-Pharmacopoeias
- Q5Qualityof Biotechnological Products
- Q6-Specifications
- Q7-Good Manufacturing Practice
- Q8-Pharmaceutical Development
- Q9-Quality Risk Management
- Q10-Pharmaceutical Quality System

SAFETY

"ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years."

- S1-Carcinogenicity Studies
- S2-Genotoxicity Studies
- S3-Toxicokinetics and Pharmacokinetics
- S4-Toxicity Testing
- S5-Reproductive Toxicology
- S6-Biotechnological Products
- S7-Pharmacology Studies
- S8-Immunotoxicology Studies
- S9-Nonclinical evaluation for anticancer pharmaceuticals
- S10-Photosafety Evaluation

EFFICACY

"The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines."

- E1&E2-Clinical Safety
- E3-Clinical Study Reports
- E4-Dose-Response Studies
- E5-Ethnic Factors
- E6-Good Clinical Practice
- E7,E8,E9,E10&E11-Clinical Trials
- E12-Guidelines for Clinical Evaluation by Therapeutic Category
- E14-Clinical Evaluation
- E15&E16-Pharmacogenomics

MULTIDISCIPLINARY

"Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for theTransfer of Regulatory Information (ESTRI)."

M1-MedDRA Terminology
M2-Electronic Standards
M3-Non-clinical Safety Studies
M4-CTD
M5-Data elements & Standards for Drug dictonaries
M6-Gene Theraphy
M7-Genotoxic Impurities
M8-eCTD

Regulatory requirements of EU MHRA TGA

The Agency is responsible for the scientific evaluation, supervision and safety monitoring of the medicines developed by pharmaceutical companies for the use in EU.

EMA and the Member States cooperate and share expertise in the assessment of new medicines and of new safety information.

By working closely together, Member States reduce duplication, share the workload and ensure the efficient and effective regulation of medicines across the EU.

T HE ROLE OF EMA

EMA plays an important role in the regulation of medicines in the EU. On the basis of scientific assessments carried out, it grants or refuses, changes or suspends marketing authorizations for medicines that have been submitted via the centralized procedure.

The European Commission can also take action concerning other aspects of medicine regulation:

- Right of initiative – it can propose new or amended legislation for the pharmaceutical sector;

- Implementation – it can adopt implementing measures as well as oversee the correct application of EU law on pharmaceuticals;
- Global outreach – it ensures appropriate collaboration with relevant international partners and promotes the EU regulatory system globally.

MHRA

Medicines and Healthcare products Regulatory Agency is an executive agency of the Department of Health of United Kingdom. MHRA was set up in April, 2003 bringing together the function of medicines Control Agency (MCA) and the Medical Devices Agency (MDA).

MHRA is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

MHRA functions when the company wants to start clinical trials in patients.

ROLES

- Licensing
- Manufacturer and dealer licenses
- Clinical trial licences
- Parallel import licenses

✓ Safety and efficacy monitoring

✓ Enforcements of laws

✓ Regulation of clinical trials

✓ Providing information to public and health professionals

MHRA does not regulate dietary supplements, veterinary products and cosmetics.

TGA

- Therapeutics Goods Administration is the regulatory body for therapeutic goods in Australia.
- TGA is responsible for conducting assessment and monitoring activities to ensure that therapeutic goods available in Australia are of an acceptable standard.
- The objectives of Therapeutic Goods Act 1989, which came into effect on 15 Feb, 1991 is to provide a national framework for the regulation of therapeutic goods in Australia to ensure quality, safety and efficacy of the medicines and ensure quality, safety and performance of medical devices.

REGULATORY REQUIREMENTS IN ROW COUNTRIES

❖ Key function of RA:

1. Product registration.
2. Regulation of drug manufacturing, importation and distribution. Adverse drug reaction monitoring.
3. Licensing of premises, person and practices.
4. Main goal of the agency is to guarantee the safety, efficacy and quality of the available drug product