INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Review Article

COMPARATIVE STUDY OF REGULATORY REQUIREMENTS FOR THE COMPILATION AND APPROVAL OF DOSSIER; AS PER CTD, ACTD AND ECTD FORMATS

Sunil L. Harer[1]*, Yuvraj D. Aher[2], Vikas S. Kokane[3] and Priyanka A. Sonar[4]

*[1]R. L. Tawde Foundation's Sarojini College of Pharmacy, Kolhapur, Maharashtra, India.
[2]Sharadchandra Pawar College of Pharmacy, Otur, Pune, Maharashtra, India.
[3]MITCON Institute of Management, Pune, Maharashtra, India.
[4]PES's Modern College of Pharmacy, Nigdi, Pune, Maharashtra, India.

ABSTRACT

This present article discusses the rules & regulations which are followed for drug approval process in USA, Europe & ASIAN country and India. Data required for the compilation of the dossier for various countries include the formats like CTD, e-CTD and ACTD.Regulatory affairs as a profession have important positions to play in positively impacting medication policy, use, results and other aspects of medical proper care. In many such cases this will be through cooperation and support with other wellness care professionals at a community stage. Pharmaceutical product approval process should be a critical step in ensuring access to safe and effective drugs. If performed, they will result in added value to medication treatment and development by making a beneficial participation to the safe, inexpensive and affordable use of drugs, leading to significant resources and results and improve the growth of the industry. Obtain and maintain medication records, results and relevant wellness details, if they do not already exist. These detailsare essential to evaluate personalized medication treatment. Identify, develop, evaluate and assess: Medication related problems, Symptoms described by patients, self-diagnosed conditions. Implementation of CTD is expected to significantly reduce time and resources needed by industry to compile applications and reports for global registration. The pharmacologist must use his clinical reasoning and data to determine the stage of drug proper care and effects that is needed for each patient.

Keywords: Regulatory affairs, CTD, ACTD, eCTD, Drug approval.

INTRODUCTION

Dossier is a file document which is been submitted for the approval of drug product in various regulatory countries as per their need. It is submitted in various forms like CTD, e-CTD, ACTD, CTD is a harmonized format (template) for presenting data in the ICH regions by following the guidelines. Generic drug product is comparable to an innovator drug product in following cases:

1. Dosage form
2. Strength
3. Route of administration
4. Quality
5. Use etc.

eCTD (Electronic Common Technical Document)

The eCTD is standard format of submitting regulatory information suchasa applications, supplements and reports to the concerned health authorities (HAs). It provides a harmonized solution to implement common technical document electronically. An eCTD consists of individual documents in PDF format which are arranged in hierarchical form as per the CTD structure. It also has an XML backbone which cross-links required documents and provides information regarding the submission. The purpose of introducing eCTD was to reduce

the burden on the reviewer's of the HAs. It also simplifies the process of submission as all the regulatory authorities use it as standard format.[1]There are five modules in eCTD as mentioned here-

1. Region-specific information.
2. Summary documents.
3. Information related to quality.
4. Non-clinical study reports.
5. Clinical study reports (CSRs).

eCTD submissions are accepted for the following applications-

1. Investigational New Drugs (INDs).
2. New Drug Applications (NDAs).
3. Abbreviated New Drug Applications (ANDAs).
4. Biologics license Applications (BLAs).
5. All the applications following submission of above stated applications.
6. All the Master Files (MFs) which are part of any above mentioned applications.

Content specification– as defined by ICH specified below-

1. Technical specification-Electronic software's
2. CTD ⟶ TOC [pdf][paper]
3. eCTD ⟶ XML Backbone

The eCTD is the electronic document similar to the CTD. Is an eCTD backbone describing the structure of the submission, the XML file (Extensible Mark-up Language) it includes links to files and other metadata such as checksum information.[2]

1. The schema for the XML is very rigid.
2. Easy to distribute and review.
3. More efficient use of resources with less cost and stress to the organization.
4. Self-validating.

ACTD (ASEAN Common Technical Document)

The ASEAN Common Technical Document is standardized into four parts. The ACTD generally consists of Parts I to IV whereas ICH – CTD has 5 Modules.[3] The authoritative data of Part I is part of ACTD whereas Module 1 of ICH– CTD is purely country specific. The analysis of the quality (Part II), nonclinical (Part III) and clinical (Part IV) are at the beginning of each part of the ACTD. The ICH –CTD favourable these summarises in a separate Module 2. As the ACTD does not have such summary part, it consists of only 4 Parts and not 5.[4]

1. ASEAN abbreviates Association of South East Asian Nations.
2. ASEAN is established in 08 August 1967.
3. Ten Member states are Brunei, Cambodia, Indonesia, Lao, Malaysia, Myanmar, Philippines, Singapore, Thailand, Viet Nam.

CTD (Common Technical Document)

CTD isa format set by ICH which was agreed and approved by the Regulatory Agencies of Europe, Japan & the U.S. The FDA singularize the CTD as an information package of clinical, non-clinical, manufacturing, technical data in the same content that would be submitted for registering new drugs in all 3ICH regionsi.e .U.S, European Union and Japan.[5] (Fig. 1: CTD triangle describing different modules)

Joint regulatory agencies of CTD

1.European Medicines Agency (EMEA, Europe).
2. Food and Drug Administration (FDA, USA).
3. Ministry of Health, Labour and Welfare (MHLW, Japan).

CTD is maintained by ICH

The CTD became the mandatory format for new drug applications in July 2003 in the EU and Japan, and the strongly recommended type and format of choice for NDAs submitted to the FDA. It has been mostly adopted by several other countries including Australia, Canada and Switzerland (2004).[6]

Objective of ICH to prepare CTD

1. The arch of ICH is ignored todepictive testing of animal and human and to reach a common understanding of the technical requirements to support the registration process in the three ICH regions.
2. These purposesare accomplishing through harmonized guidelines and result in a more economical use of human, animal and material resources, as well as the elimination of unnecessary delays in comprehensiveaccession and proposal of new medicines, while maintaining quality efficacy and safety, and regulatory obligations to protect public health.
3. With the development of the Common Technical Document (CTD), the ICH hopes to accomplish many of its objectives.

Any guideline which is given by ICH passes through different steps. These different steps are called "Guideline Status".[7] Fig. 2:"Guideline Status" of ICH showing different steps

Advantages of CTD

1. To make the reviewing of each application easierand to avoid omission of critical data or analyses. Omissions of such data can result in unnecessary delays in approvals.
2. To save time and resources.
3. To facilitate regulatory review and communications.
4. Appropriate format for the data.
5. Easy to understand and evaluation of data.
6. Applicable to all types of products (NCE, radiopharmaceuticals, vaccines, herbals, etc.).

Silent benefits of the CTD

1. More "reviewable" applications.
2. Complete and well-organized submissions.
3. More predictable format.
4. More consistent reviews.
5. Easier analysis across applications.
6. Easier exchange of information.
7. Facilitates the electronic submissions and reports.

Limitations of CTD

1. CTD is only a format and it's not a single dossier with a single content.
2. Legal requirements various in the various regions.
3. ICH guidelines have not yet harmonized in all requirements.
4. Pharmacopoeias are not harmonized.
5. Applicant may have regional preferences**.**
6. The eCTD has proved critical and comprehensive to improve the application submission efficiencies as well as reviewer efficiency.

Types of submissions required CTD

CTD is mandatory for all types of submissions as discussed below-

1. Manufacture and marketing approval of new drugs (New chemical entity and indication, new dosage forms and new route of administration etc.), as a finished pharmaceutical product, for firsttime finalise with reviewer and for subsequent applications until 4 years.
2. Modified release formulations and development (even after 4 years of approval by CDSCO).
3. Fixed Dose Combinations of drugs under item (a) of Appendix VI of Schedule Y of Drugs and Cosmetics Act and Rules 1945.

Ultimately, CTD took many years, for finalising the wish list realisation as there is now a common format for the submission and approval of marketing authorizations applications across the 3 ICH regions as Europe, Japan and the USA. (Fig. 3: eCTD file structure, Fig. 4: eCTD recommendation to all procedures, Fig. 5: eCTD file structure, Fig. 6: eCTD file structure and Fig. 7: Overview on benefits of eCTD)

Benefits of eCTD

The challenges of eCTD

1. In the US, eCTD is only accepted however NDAs, BLAs and INDs are allowedand no paper is used.
2. eCTD plus paper is still needed for medical authorities in EU.
3. Paper is still the official archival copy of the EU Marketing Authorization.
4. EU wants eCTD as preferred type format for all Marketing Authorization Applications(MAAs) and variations.
5. Only eCTD is allowed for all EU member states by 1 Jan 2010.
6. Health Canada needs eCTD format on CD/DVD plus paper.

Electronic Submission Needs[9]

1. Creation
2. Review
3. Assists project management and information management
4. Lifecycle management(the history of a product application)
5. Archiving
6. Drug development planning

eCTD CHARACTERISTICS

1. Structure of eCTD

2. All Modules 1 to 5 have granularity options.
3. PDF documents linked via XML backbone.
4. Increased document granularity.
5. Transparency of entire submission.
6. Ease of navigation and review.

2. QC of eCTD

a. Pre-compilation

1. QC inter-document links.
2. 100% QC that all bookmarks and hyperlinks are live.
3. 100% QC that all bookmarks and hyperlinks point to the correct targets.

4. Check all documents for presence and location.
5. Check all the document titles in eCTD viewer.

b. Post-compilation

1. Validate eCTD.
2. Recheck for broken links.

c. Submitting the eCTD

The Cover letter (From the ICH eCTDspecification, v. 3.2.2) as paper copy with any non-electronic portions and as cover pdf.[10]

1. A description and composition of the submission including appropriate regulatory information.
2. A listing of the sections and files of the submission filed as paper, electronic, or both paper and electronic.
3. A description of the electronic submission including type and number of electronic media.
4. Approximate size of the submission, and, if appropriate, characteristics concerning the media (e.g. Format used for DLT tapes) based onsub-regional guidance.
5. A statement of filing that the submission is virus free with a description of the software used to check the files for viruses.
6. The regulatory requirements and information technology points of contact for the submission.
7. Copy eCTD to CD-ROM, DVD or DLT master.
8. Reload eCTD from CD, DVD or DLT master and revalidate.
9. Create eCTD copies from master.
10. Number of copies determined by each EU MS.

Points to remember for eCTD

1. Files are referenced in the XML Backbone(s).
2. eCTD submissions mostly include module 1.
3. Application numbers are always 6 digits.
4. Sequence serial numbers are 4 digits.
5. Ensure we receive what your intended.
6. Never forward in one submission to be applied tomultiple applications.
7. XML must be standard components.
8. PDF contains recognizable texts.
9. PDF hyperlinks, TOC and bookmarks are correct.
10. PDF documents include TOCs.

Closing Remarks

The end is near for the traditional paper base era for managing, abstracting, reviewing, and submitting regulatory submissions. Successful transition to eCTD provides competitive advantages:

1. Increased review efficiency.
2. Decreased risk of refusal to file.
3. Faster time to market.
4. Happier stockholders
5. Greater employee & management satisfaction.
6. Lower cost of production.
7. Simultaneous ease global submissions.
8. Healthier patients.
9. Healthier patients.

COMPARISON of CTD and eCTD

Table 1: Comparative statements ofCTD and eCTD.

Sr. No.	Paper CTD	eCTD
1	Compiledelectronicallywithvolumes,tabs, slip-sheetsthen printedtopaper	Compiled electronically withe-documents infolders
2	PapervolumesmustbeA4	e-Documentscanbe A4orUSlettersize
3	CTDnavigation byTOCsand volume	eCTD navigationbyXMLbackbone
4	Crossreferencesincludetarget CTD sectionnumber	Crossreferencesare hyperlinkedto targets
5	Manualdocumentnavigation by TOCs,pagenumbers,andcaptioncross references	Electronic documentnavigationby TOCs , bookmarksandhyperlinks
6	Submittedinbindersinboxes onpallets Bytrucks	SubmittedonCD [or DVD]or by email portal

CTD Structure

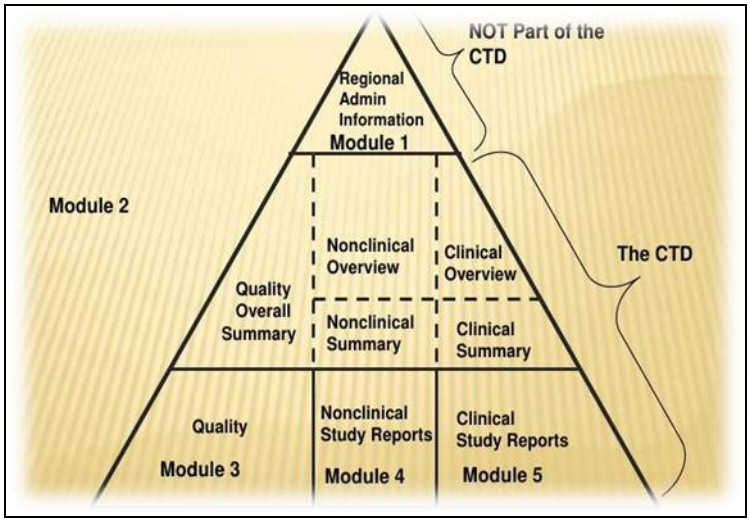

Fig. 1: CTD triangle describing different modules

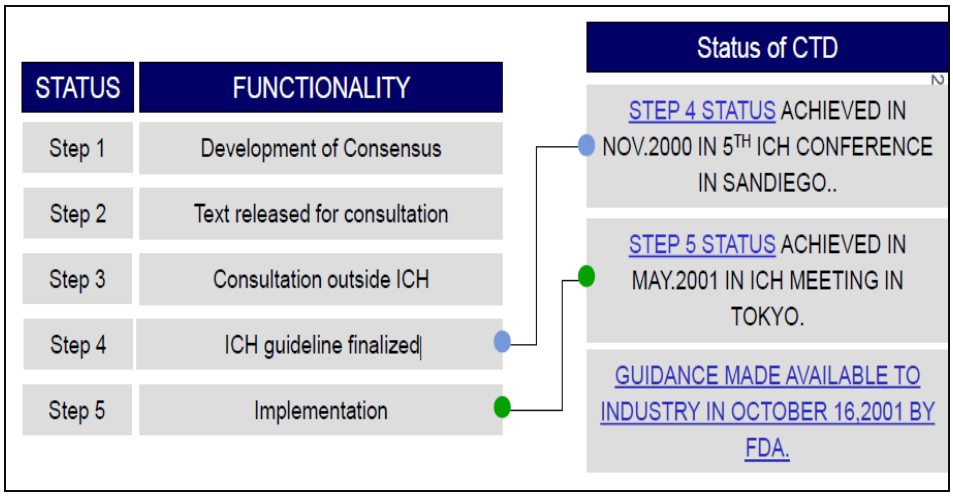

Fig. 2:"Guideline Status" of ICH showing different steps

eCTD FILE STRUCTURE[8]

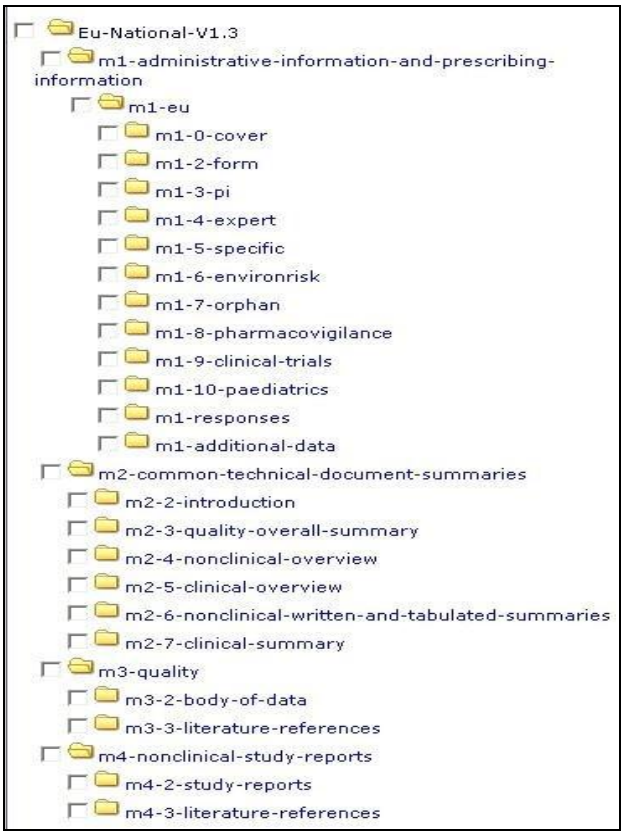

Fig. 3: eCTD file structure

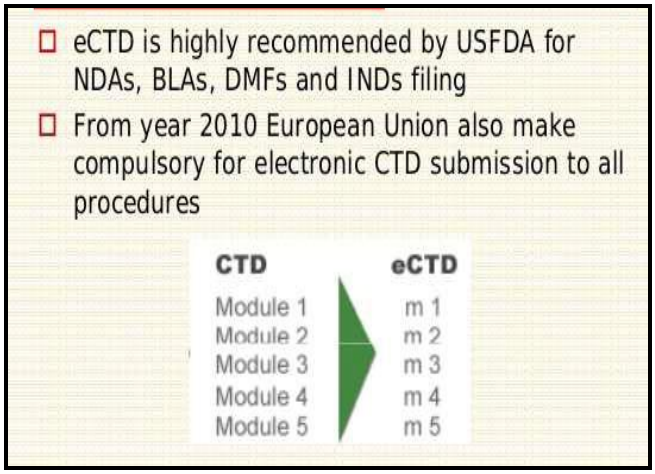

Fig. 4: eCTD recommendation to all procedures

Fig. 5: eCTD file structure

Fig. 6: eCTD file structure

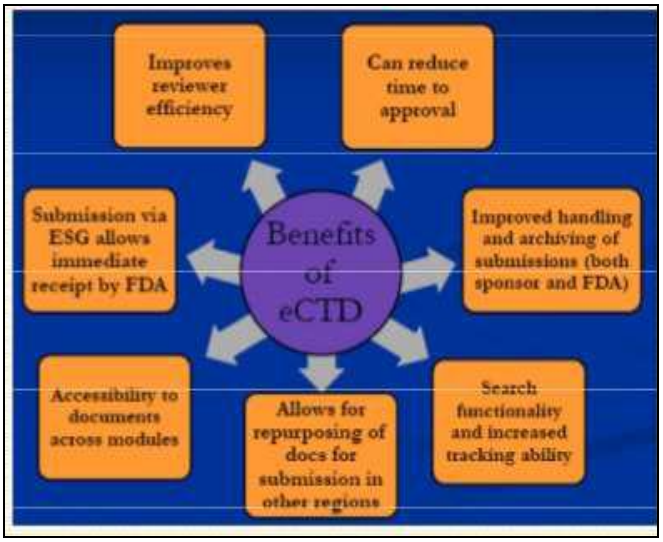

Fig. 7: Overview on benefits of eCTD

Fig. 8: eCTD closing remark

ORGANIZATION OF ACTD

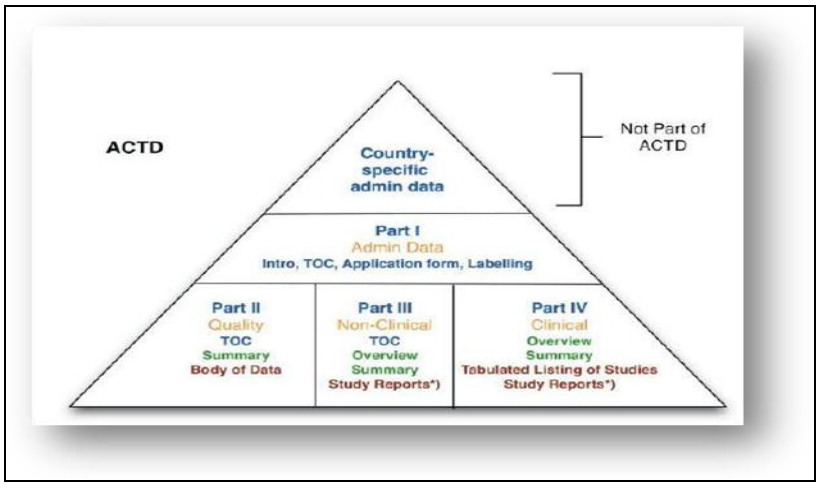

Fig. 9: ACTD triangle in hierarchy

ASEAN Economic Community (AEC)

ASEAN will be Single Market and Single Production Base in the year 2015.

1. Free flow of goods.
2. Free flow of services.
3. Free flow of investment.

4. Free flow of capitals.
5. Free flow of skilled labour.

ASEAN Requirement

Agreed "ACTR, ACTD, Technical guidelines"

1. ACTR (ASEAN Common Technical Requirement).
2. ACTD (ASEAN Common Technical Dossier).
3. Technical "Quality, Safety, Efficacy" guidelines – adopted guidelines (from WHO, ICH, and IP).

Objectives of ASEAN

To establish harmonization scheme of pharmaceuticals regulations of ASEAN member countries, to maintain, complement and facilitate the objective of AFTA, the elimination of technical barriers to trade and development posed by regulations, without compromising on drug quality,& facilitateand safety & efficacy the AEC.[11]

Scope of ASEAN[12]

1. This document is intended to provide guidance on the format for a registration application for drug products regarding ASEAN COUNTRY. forNew Chemical Entity, (NCE) Biotech (Biotechnological Products), MaV (Major Variations), MiV (Minor Variations) and G (Generics).
2. The applicability of this format to be determined fora product, applicant should consult with appropriate National Regulatory Authorities (NRA). In guideline, the body of data merely navigate where information should be located.
3. The neither type nor extent of a specific supporting data has been addressed in this guideline and both may depend upon the national guidance and or accepted leading international references (Pharmacopoeias).
4. For NCE and Biotech requirements please refer to the relevant ICH Guidelines.

List of documents required for administrative section writing of a Part I

1. Application form (details to be filed in)
2. Letter of authorization
3. Certifications
   a) Manufacturing license
   b) Certificate of Pharmaceutical Product
   c) GMP certificate of the Manufacturer
   d) Site Master File of manufacturer
4. Labelling
   a) Mock-up for Inner Carton
   b) Mock-up for outer carton
   c) Mock-up for Label
5. Product Information
   a) Package inserts
   b) SPC (Summary of Product Characteristics) (Product Data Sheet)
   c) Summary of product characteristics is required for NCE and Biotechnology products.
   d) Patient Information Leaflet (PIL)PIL is required for Over-the-Counter Products.
   e) Product Information.

List of documents required for Part II Quality section writing[13]

1. DMF of API
2. BMR Finished product
3. BPR Finished product
4. Critical manufacturing steps, reviews and justifications.
5. Process validation protocol, schemes and reports.
6. Flow chart (Detailed and simple)
7. Process development report
8. Impurity profile with justifications
9. Excipients details
   a. Specification and testing method.
   b. COA.
   c. TSE/BSE declaration from supplier/manufacturer.
10. Specification and method of Analysis (MOA):
    a. Intermediates and in-process specification & MOA.
    b. Finished product release specification & MOA.
    c. Finished product Stability specification & MOA.
    d. API specification & MOA from finished product manufacturer.
    e. Packaging material (primary, secondary and tertiary).
11. Analytical method validations report at release and stability (if different methods are used):
    a. Assay.
    b. Related substance.
    c. Dissolution (if applicable).
    d. Preservative content (if applicable).
    e. Sterility (if applicable).
    f. Endotoxins (if applicable).

g. MLT.
h. Forced degradation.

12. COA's
    a. API from FP manufacturer (3 consecutive batches).
    b. All the raw materials (excipients and coating materials).
    c. Reference and working standards.
    d. Impurity standards.
    e. Packaging material (primary, secondary and tertiary).
13. IR spectra of PVC/PVDC sheets &aluminium foil if used.
14. Soft copy of labels (PDF).
15. Food grade certificate from a primary packaging material manufacturer for its primary packaging Material.
16. Preparation of reference standard in brief.
17. Stability protocol.
18. Stability data and photo stability data (if applicable).
19. Bioequivalence studies (if applicable)

ABBREVIATIONS

1. CDSCO: Central Drugs Standard Control Organization.
2. CTD: Common Technical Document.
3. DCGI: Drug Controller General of India.
4. eCTD: Electronic Common Technical Document.
5. FDA: Food and Drug Administration.
6. ICH: International Conference on Harmonisation.
7. IND: Investigational New Drug application.
8. NDA: New Drug Application.
9. USFDA: US Food and Drug Administration.
10. TGA: Therapeutic Goods Administration.
11. EMA: European Medicines Agency.

REFERENCES

1. ICH M8 Guideline. Electronic Common Technical Document [cited 2010 Nov 8]. Available from: http://www.ich.org/products/guidelines/multidisciplinary/multidisciplinary single/ article/ electronic-commontechnical-document-ectd.html.
2. ICH M2 EWG – eCTD specifications ICH M2 EWG Electronic Common Technical Document Specification version 3.2.2. (PDF). ICH. Retrieved 29 October 2015.
3. Jain A, Venkatesh MP and Kumar TM. ACTD: Bridge between regulatory requirements of developed and developing countries. International Journal of Drug Regulatory Affairs. 2013;1(4): 1-11.
4. The ASEAN common technical dossier (ACTD) for the registration of pharmaceuticals for human use; September 2002.
5. Molzon J. The Common Technical Document: the changing face of New Drug Application. Nature Reviews – Drug Discovery. 2003;2:71-74.
6. Roth IR. Preparing the Common Technical Document (CTD) for registration of pharmaceuticals for human use– insight and recommendations. Drug Information Journal. 2008;42:149-159.
7. Jordan D. An overview of the Common Technical Document (CTD) regulatory dossier. Med Writ. 2014;23(2):101-105.
8. Providing Regulatory Submissions in Electronic Format - Certain Human PharmaceuticalProduct Applications and Related Submissions Using the eCTD Specifications(PDF). US FDA.
9. Available from: http://www.xmlpharma.org/iriss/wp-content/ uploads/20120326Japan-eCTD-IRISS-2011_02_16.pdf. [Last accessed on 2017 Mar 18].
10. Available from: http://www.estri.ich.org/new-eCTD/index. htm. [Last accessed on 2017 Jun 20].
11. Foote M. Using the biologic license application or new drug application as a basis for the common technical document. Biotechnol Annu Rev. 2004;10:251-258.
12. ICH M4 Guideline: General Questions and Answers Document (R3) [2004 Jun]. Available from: http://www.ich.org/fileadmin/Public_ Web_Site/ICH_Products/CTD/M4_R3_Organisation/M4_QAs.pdf.
13. Regulation of pharmaceuticals in the EU. [Internet].[cited 2013 November]available from: http://www.echamp.eu/regulation.html.