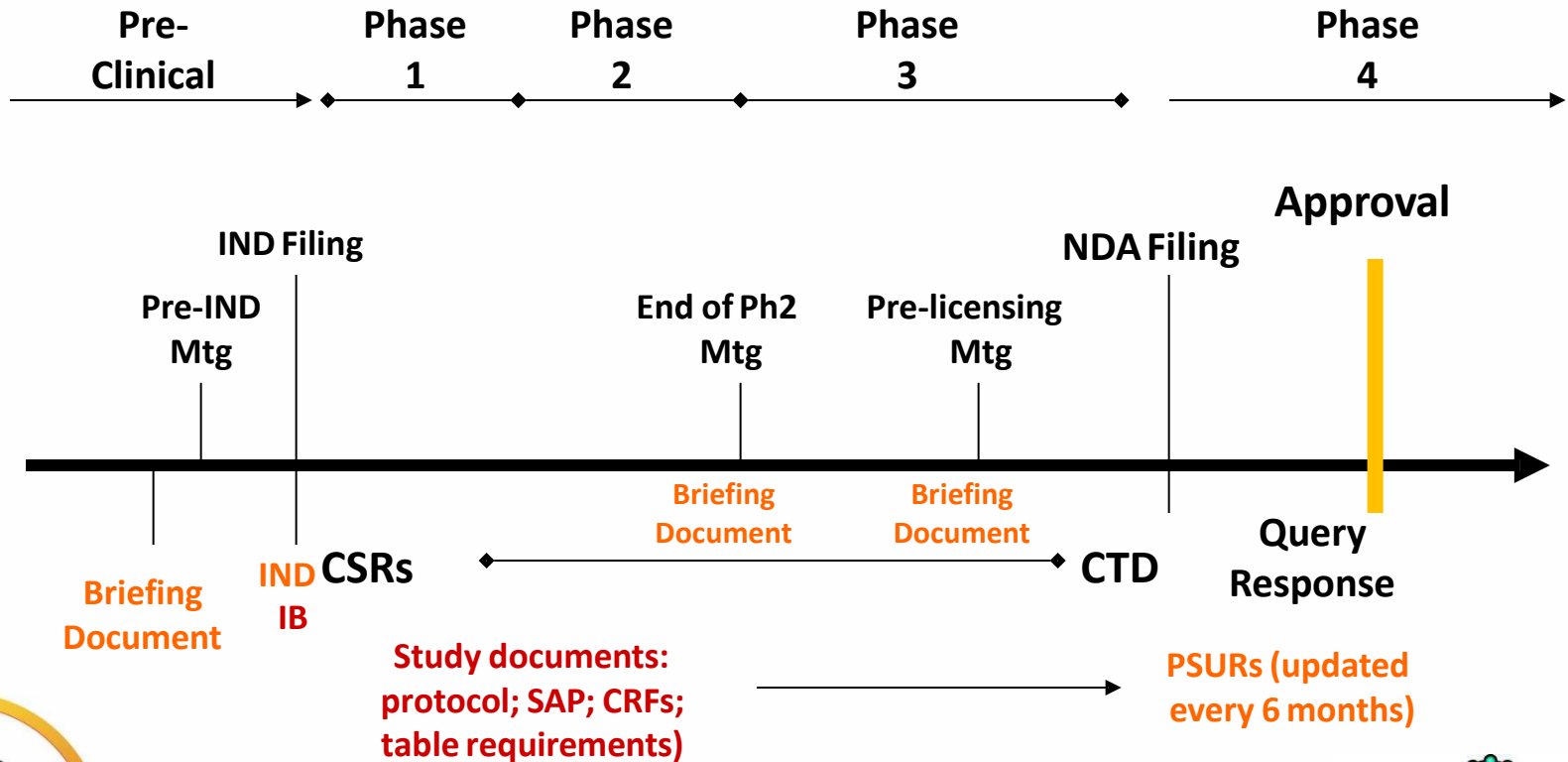


Regulatory Writing – e CTD, Clinical study reports

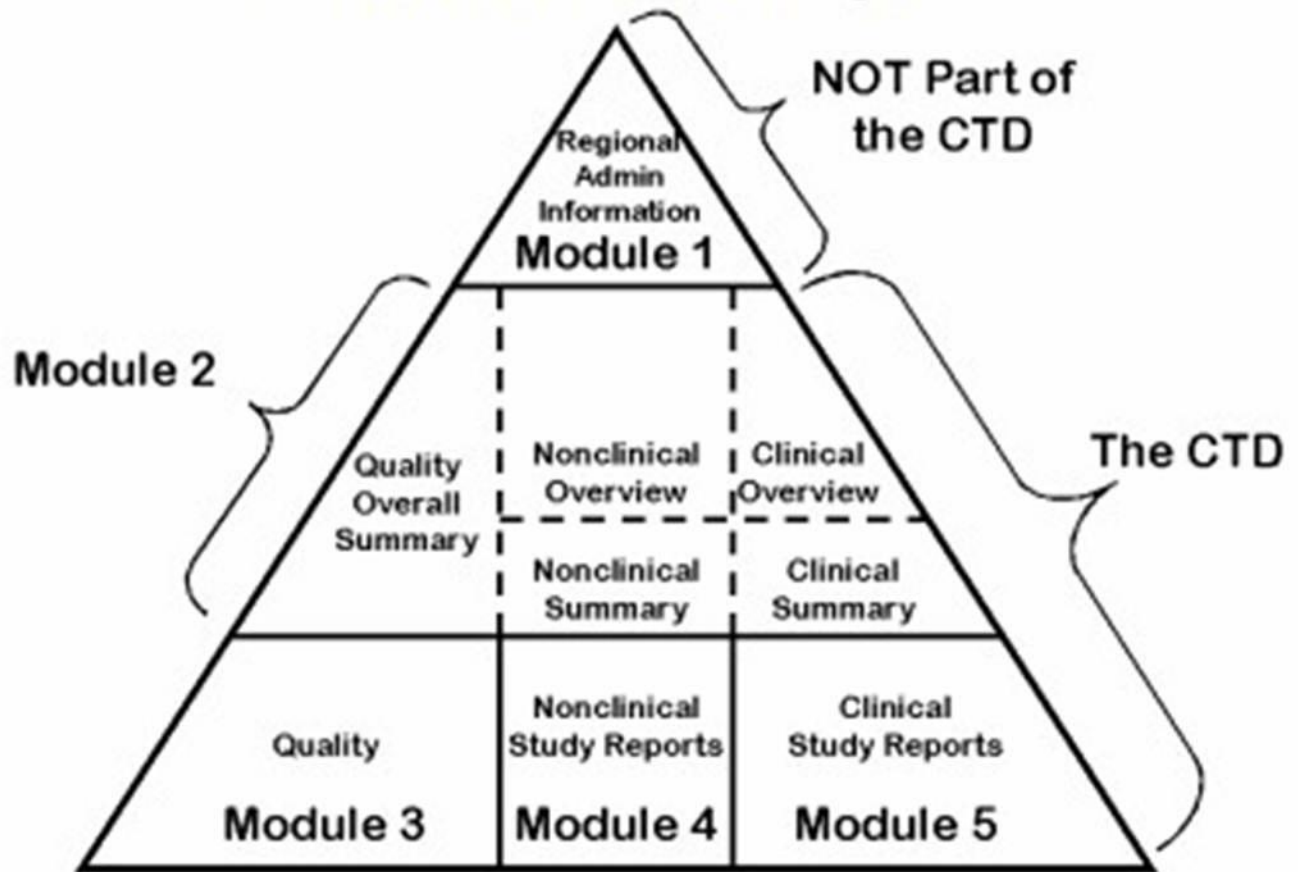


Drug Approval Process



Application for marketing authorization

The CTD Triangle



CTD is a joint effort of 3 regulatory agencies:

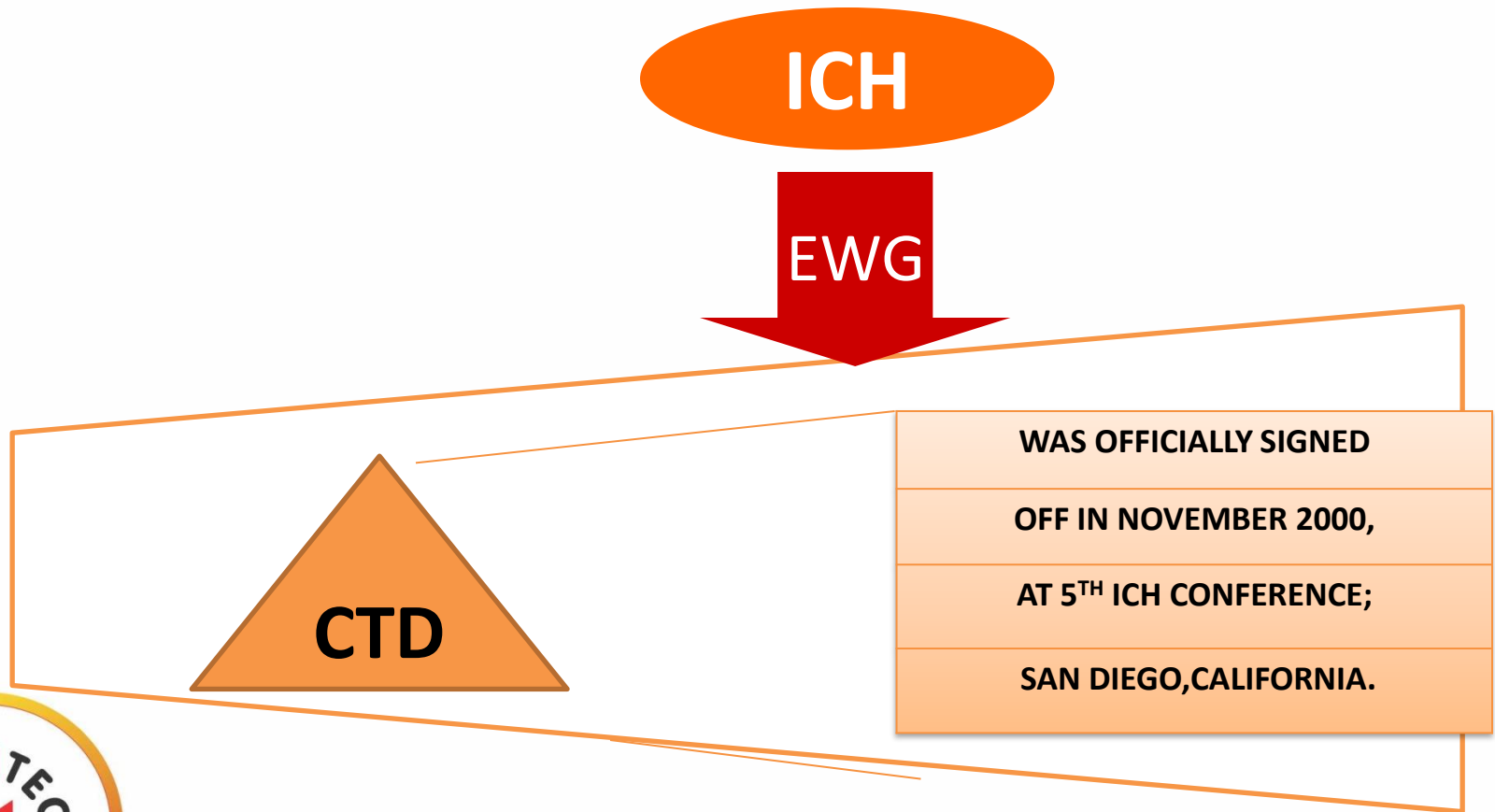
- European Medicines Agency (EMA, Europe),
- Food and Drug Administration (FDA, USA) and
- Ministry of Health, Labour and Welfare (MHLW, Japan)

**Ministry of Health, Labour and Welfare
(MHLW, Japan)**

CTD is maintained by ICH through EWG (Electronic Working Group)



Origin of CTD...

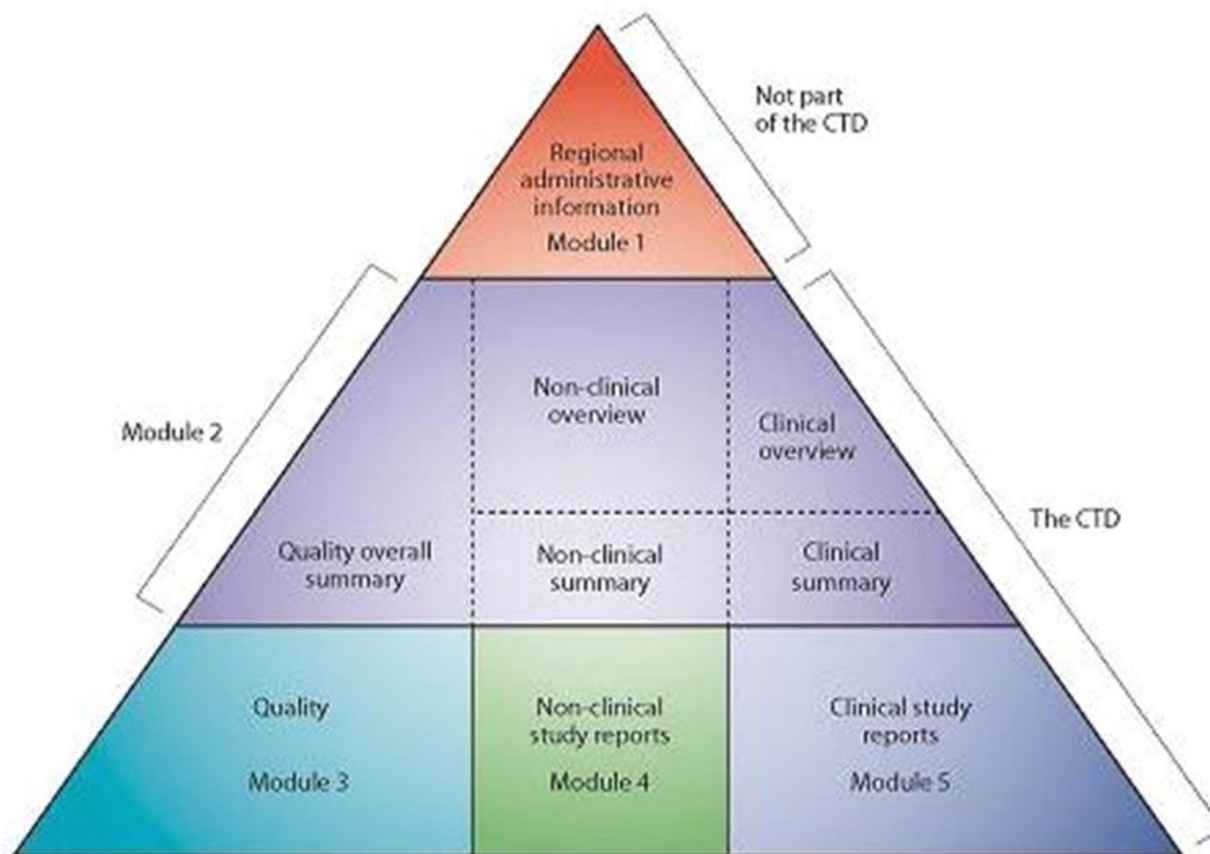


Significance Of CTD:

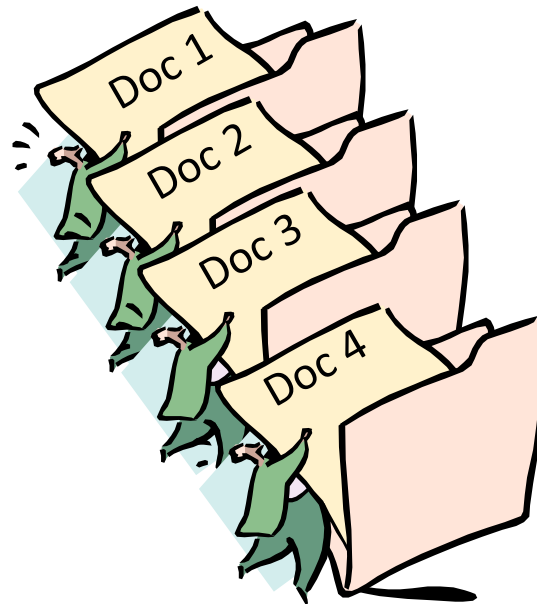
- Avoid generating and compiling different registration dossiers
- Common format will significantly reduce the time and resources
- Facilitates simultaneous submission in three regions
- Facilitates exchange of information among regulatory authorities
- Faster availability of new medicines



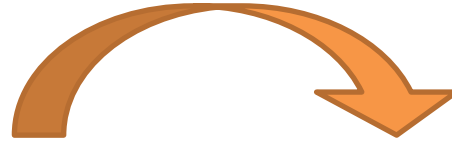
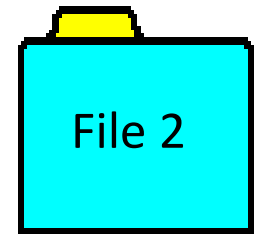
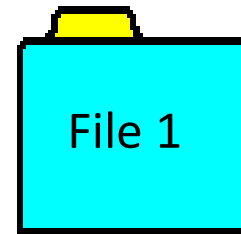
CTD Triangle



Paper CTD



eCTD



eCTD:electronic CTD

- Developed by M2 EWG (Multidisciplinary 2 Expert Working Group) of ICH.
- Industry <-----> Message <-----> Agency



Paper submission has been replaced by electronic submission



eCTD:electronic CTD

- The Electronic Common Technical Document (eCTD) allows for the electronic submission of the Common Technical Document (CTD) from applicant to regulator
- While the table of contents is consistent with the harmonized CTD, the eCTD also provides a harmonized technical solution to implementing the CTD electronically based on XML technology
- The ICH Electronic Working Group (EWG) has published specifications for eCTD Submissions (ICH M2 EWG, version 3.2.2)



eCTD Benefits

- Easy to distribute and review
- More efficient use of resources, less cost and stress to the organization
- Highly organized electronic table of contents
- Searchable
- Self-validating
- Integrated document and life-cycle management
- Cross submission integration
- Living document
 - New, replace, append & delete



Characteristics of eCTD:-

- Files Referenced in the XML Backbone(s)
(Extensible Markup Language)
- It manages the large data for the entire submission and for each document within the submission
- This XML backbone allows the eCTD submission to be viewed via a web browser and can be loaded on a Web server



The file formats that can be included in the eCTD are Portable Document Format (PDF) and XML.

However other formats can be used for graphs and images.

JPEG

PNG

GIF

-may be used for higher resolution



All eCTD Submissions Include Module 1

Module 1 Identifies following important information:

- Company Name
- Drug Name
- Submission Type
- Submission Date
- Application Number
- Sequence Number



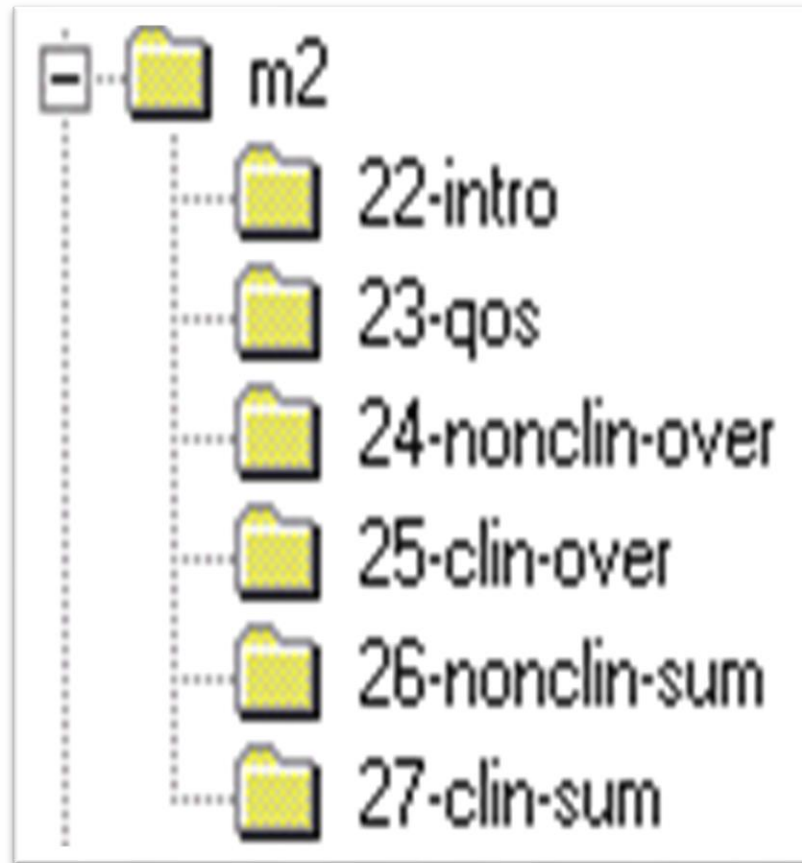
Nomenclature for files and eCTD submission

EXAMPLE:- MODULE 2 FILE NOMENCLATURE AND eCTD submission

| Description | File Name |
|---|------------------------|
| 2.2 Introduction | <i>22-intro</i> |
| 2.3 Quality overall summary | <i>23-qos</i> |
| 2.4 Non clinical Overview | <i>24-nonclin-over</i> |
| <i>2.5 Clinical Overview</i> | <i>25-clin-over</i> |
| <i>2.6 Non clinical Written and Tabulated Summaries</i> | <i>26-nonclin-sum</i> |
| <i>2.7 Clinical summary</i> | <i>27-clin-sum</i> |



Nomenclature for files and eCTD submission (contd)



Agency Sites with eCTD submission Information

- FDA:
<http://www.fda.gov/cder/regulatory/ersr/ectd.html>
- EMEA(EU): <http://esubmission.eudra.org/>
- MHLW(JP):
<http://www.mhlw.go.jp/english/index.html>



Module 1: Administrative information

1.1 Table of contents

1.2. Application form

1.3. Summary of product characteristics, labelling and instructions for medical use:

- 1.3.1. Summary of product characteristics
- 1.3.2. Labelling
- 1.3.3. Instructions for medical use
- 1.3.4. Mock-ups and specimens
- 1.3.5. Summary of product characteristics already approved in the manufacturer/applicant-country



Module 1: Administrative information (contd)

1.4. Information about the independent experts:

- 1.4.1. Information about the quality expert
- 1.4.2. Information about the pre-clinical expert
- 1.4.3. Information about clinical expert

1.5 Specific requirements for different types of applications

Annex to Module 1. Environmental risk assessment



Module - 2: CTD Summary

- 2.1. Table of contents of Modules 2 – 5
- 2.2. Introduction
- 2.3. Quality overall summary
- 2.4. Pre-clinical overview:
- 2.5. Clinical overview



Module - 2: CTD Summary

2.6. Pre-clinical summary

- 2.6.1. Pharmacology written summary
- 2.6.2. Pharmacology tabulated summary
- 2.6.3. Pharmacokinetics written summary
- 2.6.4. Pharmacokinetics tabulated summary
- 2.6.5. Toxicology written summary
- 2.6.6. Toxicology tabulated summary



Module - 2: CTD Summary

2.7. Clinical summary:

- 2.7.1. Summary of biopharmaceutical studies and associated analytical methods
- 2.7.2. Summary of clinical pharmacology studies
- 2.7.3. Summary of clinical efficacy
- 2.7.4. Summary of clinical safety
- 2.7.5. Literature references
- 2.7.6. Synopses of individual studies



Module 3: Quality

Chemical, Pharmaceutical And Biological Information
For Medicinal Products Containing Chemical And/Or
Biological Active Substances

3.1. Table of contents

3.2. Basic data

- 3.2.S. Active substance(s)
- 3.2.S.1. General information:
 - 3.2.S.1.1. Nomenclature
 - 3.2.S.1.2. Structure
 - 3.2.S.1.3. General properties



Module 3: Quality (contd)

- 3.2.S.2. Manufacture of active substance(-s):
 - 3.2.S.2.1. Manufacturer(s)
 - 3.2.S.2.2. Description of manufacturing process and process controls
 - 3.2.S.2.3. Control of materials
 - 3.2.S.2.4. Controls of critical steps and intermediates
 - 3.2.S.2.5. Process validation and/or evaluation
 - 3.2.S.2.6. Manufacturing process development



Module 3: Quality (contd)

3.2.S.3. Characterization of active substance(-s)

- 3.2.S.3.1. Elucidation of structure and other characteristics.
- 3.2.S.3.2. Impurities.

3.2.S.4. Control of active substance(s).

- 3.2.S.4.1. Specification.
- 3.2.S.4.2. Analytical procedures.
- 3.2.S.4.3. Validation of analytical procedures.
- 3.2.S.4.4. Batch analyses.
- 3.2.S.4.5. Justification of specification.



Module 3: Quality (contd)

3.2.S.5. Reference standards or materials

3.2.S.6. Container/closure system

3.2.S.7. Stability:

- 3.2.S.7.1. Stability summary and conclusions
- 3.2.S.7.2. Post-approval stability protocol and stability commitment
- 3.2.S.7.3. Stability data



Module 3: Quality (contd)

- 3.2.P. Finished medicinal product:
- 3.2.P.1. Description and composition of the medicinal product
- 3.2.P.2. Pharmaceutical development:
 - 3.2.P.2.1. Composition of the medicinal products
 - 3.2.P.2.1.1. Active substance(s)
 - 3.2.P.2.1.2. Excipients
 - 3.2.P.2.2. Medicinal product
 - 3.2.P.2.2.1. Formulation development
 - 3.2.P.2.2.2. Overages
 - 3.2.P.2.2.3. Physicochemical and biological properties



Module 3: Quality (contd)

- 3.2.P.2.3. Manufacturing process development.
 - 3.2.P.2.4. Container/closure system.
 - 3.2.P.2.5. Microbiological attributes.
 - 3.2.P.2.6. Compatibility.
- 3.2.P.3. Manufacture of the medicinal product:
 - 3.2.P.3.1. Manufacturer(s)
 - 3.2.P.3.2. Batch formula
 - 3.2.P.3.3. Description of manufacturing process and process controls.
 - 3.2.P.3.4. Controls of critical steps and intermediates.
 - 3.2.P.3.5. Process validation and/or evaluation.



Module 3: Quality (contd)

- 3.2.P.4. Control of excipients:
 - 3.2.P.4.1. Specifications
 - 3.2.P.4.2. Analytical procedures
 - 3.2.P.4.3. Validation of analytical procedures
 - 3.2.P.4.4. Justification of specifications
 - 3.2.P.4.5. Excipients of human or animal origin
 - 3.2.P.4.6. Novel excipients



Module 3: Quality (contd)

- 3.2.P.5. Control of medicinal product:
 - 3.2.P.5.1. Specification(s)
 - 3.2.P.5.2. Analytical procedures
 - 3.2.P.5.3. Validation of analytical procedures
 - 3.2.P.5.4. Batch analyses
 - 3.2.P.5.5. Characterization of impurities
 - 3.2.P.5.6. Justification of specification(s)



Module 3: Quality (contd)

- 3.2.P.6. Reference standards and materials.
- 3.2.P.7. Container/closure system.
- 3.2.P.8. Stability:
 - 3.2.P.8.1. Stability summary and conclusion
 - 3.2.P.8.2. Post-approval stability protocol and stability commitment
 - 3.2.P.8.3. Stability data



Module 3: Quality (contd)

- 3.2.A. Appendices:
 - 3.2.A.1. Facilities and equipment.
 - 3.2.A.2. Adventitious agents safety evaluation.
 - 3.2.A.3. Novel excipients.
- 3.2.R. Additional information.
- 3.3. Literature references.



Module 4: Pre-clinical study reports

4.1. Table of contents

4.2. Study reports

- 4.2.1. Pharmacology:
 - 4.2.1.1. Primary pharmacodynamics
 - 4.2.1.2. Secondary pharmacodynamics
 - 4.2.1.3. Safety pharmacology
 - 4.2.1.4. Pharmacodynamic interactions
- 4.2.2. Pharmacokinetics:
 - 4.2.2.1. Analytical methods and validation reports



Module 4: Pre-clinical study reports (contd)

- 4.2.2.2. Absorption
- 4.2.2.3. Distribution
- 4.2.2.4. Metabolism
- 4.2.2.5. Excretion
- 4.2.2.6. Pharmacokinetic interactions (pre-clinical)
- 4.2.2.7. Other pharmacokinetic studies



Module 4: Pre-clinical study reports (contd)

- 4.2.3. Toxicology:
 - 4.2.3.1. Single-dose toxicity
 - 4.2.3.2. Repeated dose toxicity
 - 4.2.3.3. Genotoxicity
 - 4.2.3.4. Carcinogenicity
 - 4.2.3.5. Reproductive and developmental toxicity
 - 4.2.3.6. Local tolerance
 - 4.2.3.7. Other toxicity studies

4.3. Literature references



MODULE 5: Clinical study reports

5.1. Table of contents.

5.2. Tabular listing of all clinical studies.

5.3. Clinical study reports:

- 5.3.1. Reports of biopharmaceutical studies.
- 5.3.2. Reports of studies pertinent to pharmacokinetics using human biomaterials.
- 5.3.3. Reports of human pharmacokinetic studies



MODULE 5: Clinical study reports

- 5.3.4. Reports of human pharmacodynamic studies
- 5.3.5. Reports of efficacy and safety studies
- 5.3.6. Reports of post-registration experience
- 5.3.7. Samples of case reports forms and individual patient listings

5.4. Literature references



eCTD Implementation - FDA

- Jan 1, 2008, eCTD became CDER's standard for electronic submission.
- FDA has made it mandatory for all ELECTRONIC submissions to be in eCTD format since 2007-08. However, paper copies are still accepted. Suitable waivers will have to be taken before hand.
- The number of ANDA submissions to FDA has increased from 72 in the year 2006 to 1550 in 2009



eCTD Implementation - EU

- Requirements on Electronic submissions (Nees (Non-eCTD electronic submission, Version 2.0 March-2010) and eCTD) and paper documentation for New Application within MRP, DCP or National procedure – Refer CMDh/085/2008/Rev7 October 2010)



eCTD Implementation – EU (contd)

- From 1st July 2010, the EU Mv1.4 must be used for all eCTD submissions for all European procedures,

Key dates

| Date | Milestone |
|---------------|---|
| January 2010 | Mandatory eCTD for the centralised Procedure |
| January 2010 | Target for all NCAs to be able to accept eCTD- only submissions |
| August 2009 | EU eCTD Module specification v1.4 released |
| July 2009 | eCTD strongly recommended as a submission format for Centralised procedure applications |
| May 2009 | Publication of EU Harmonised eCTD Guidance |
| March 2009 | DES v2.7 release |
| February 2009 | Guidelines for non-eCTD electronic submissions for the Centralised Procedure must be followed |
| January 2009 | PIM Data Validation Engine (PDVE) v2.0 release |
| January 2009 | e-only submission by all Member States for Centralised Procedure Application |
| January 2009 | EU eCTD Module 1 specification v1.3 must be used for all eCTD submissions. See EU M1 |

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Last update: 14-04-2010 Contact: esubmission@ema.europa.eu



eCTD Implementation - MHRA

- The preferred format for new marketing authorization (MA) applications is the electronic Common Technical Dossier (eCTD)
- eCTD applications must be created according to the current specifications: eCTD specification v 3.2.2



eCTD Implementation – MHRA (contd)

- MHRA will accept applications in PDF-only format (Note that all PDF files included in an eCTD [irrespective of the module] should be v1.4, except where there is an agency-specific requirement for a later version (e.g. for an application form))
- The Summary of Product Characteristics (SmPC) will need to be prepared using the Word template
- Use the MHRA Adobe Application form which is available via the MHRA Portal. This will produce an XML file that MHRA can upload directly into their database



Some eCTD Management Software

- eCTDXPress – Image Solutions –
<http://www.imagesolutions.com>
- MasterControl Submissions Gateway™ - Master Control, <http://www.mastercontrol.com>
- Liquent's EZsubs® software solution,
[http://www.liquent.com /](http://www.liquent.com/)
- Take solution : www.PharmaReady.com
- Lorenz Life Sciences : www.lorenz.cc



Summary

- CTD was introduced with the aim to harmonize submission of technical data for registration of human use in different regions
- Considerable harmonization has been achieved in various regions for submission of technical data
- More and more regulatory agencies have started association with this implementation



Clinical Study Report

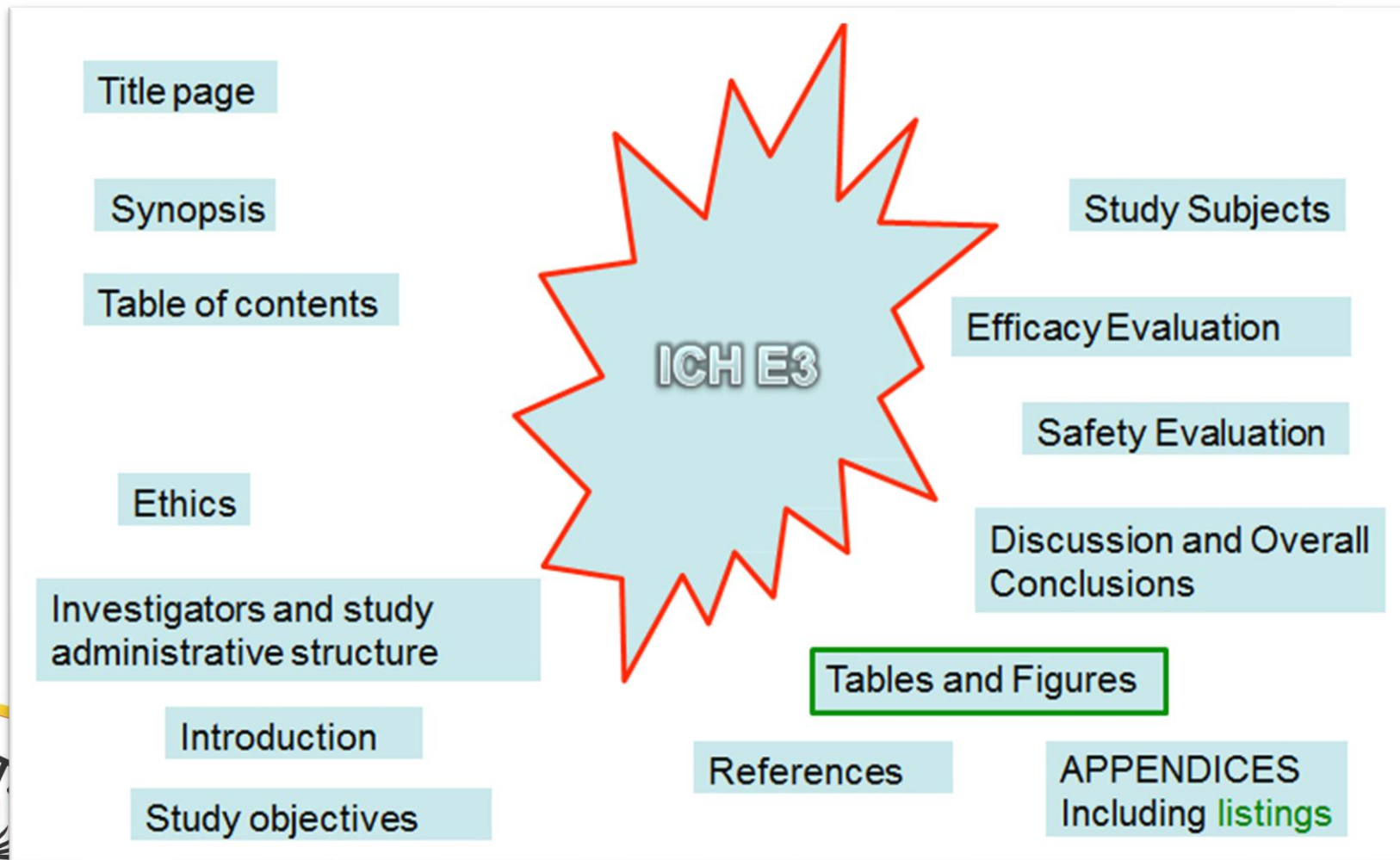


Clinical Study Reports

- CSRs describe the background, rationale, methodology and full results for a clinical study
- Called integrated reports as they cover clinical and statistical aspects
- Guideline ICH E3 on structure and content of CSRs:
- Main text often around 80-200 pages; complete reports with tables and figures plus appendices (including listing of all recorded data) are usually 1000s of pages
- Move over time from all paper to completely electronic reports – which involve ‘publishing’
- Elapsed time: 2-12 months; writing time 3-8 weeks



Contents of a CSR

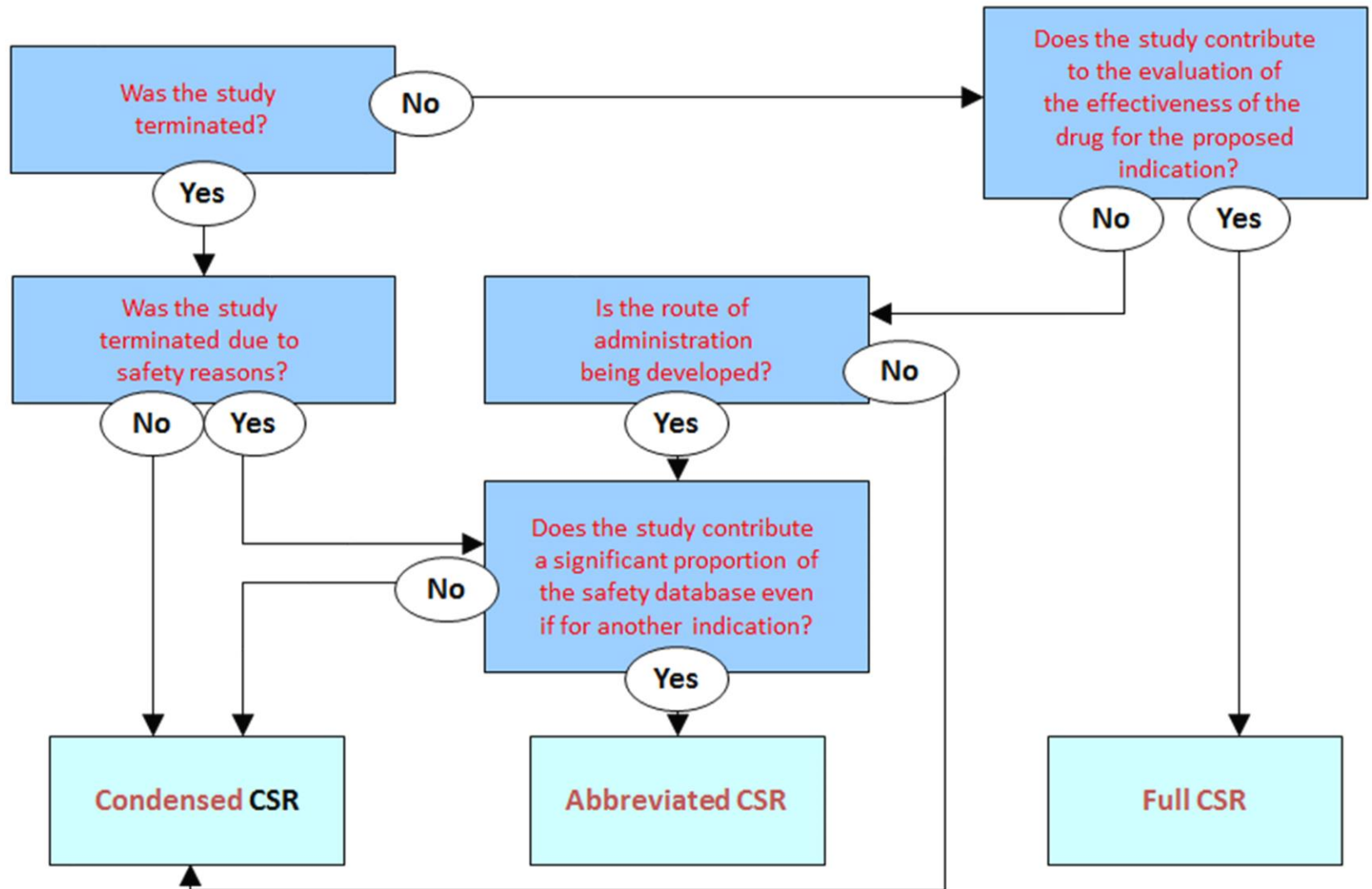


Clinical Study Report

- Types of Clinical Study Reports
 - Full Clinical Study Report (CSR)
 - Abbreviated Clinical Study Report (ACSR)
 - Condensed Clinical Study Report (CCSR)
 - Clinical Pharmacology Study Report (CPSR)



Decision tree for CSR types



The CSR

- Every pre-clinical and clinical study in drug development has to be agreed with the authorities before execution and written up afterwards - as a CSR
- CSRs are the building blocks of a Marketing Authorization Application (MAA)
- <http://www.emea.europa.eu/pdfs/human/ich/013795en.pdf>



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Who writes CSRs

- Medical writing groups within Pharma companies, e.g.: Astra-Zeneca (Alderley Edge), Genzyme (Cambridge)
- Clinical research organisations: multiple
- Specialist companies, e.g.:
 - Constella Group (Milton Park): www.constellagroup.com
 - Insight Medical Writing (Finstock): www.insightmw.com

