History of ICH: The Common Technical Document structure and contents

DCVMN Common Technical Document (CTD) Workshop

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- The realisation of the importance of an independent evaluation of medicinal products before entry into the market was reached at different times in different regionsof the world.
- In many cases the realisation was driven by tragedies, such as the Cutter incident in USA in 1955 and that with thalidomide in Europe in the 1960s.

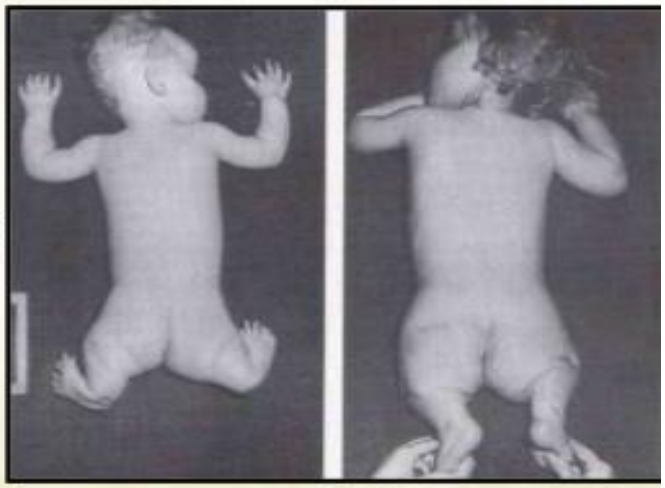
Cutter incident with IPV

In 1955, the production of the vaccine at industrial facilities operated by Cutter, led to the tragedy that occurred when 200,000 people were inadvertently injected with live virulent polio virus

- **70,000 became ill,**
- **200 were permanently paralyzed and,**
- **10 died.**

Thalidomide tragedy

- 1958: Thalidomide markated in West Germany as a non barbiturate hypnotic & for morning sickness during pregnancy based on animal toxicity report.



1959-61 thalidomide disaster

(4000-100000 case)

- In 1959 - 1961, it was reported in that there was an outbreak of **PHOCOMELIA** (**hypoplastic and aplastic limb deformities**) in the new born babies.

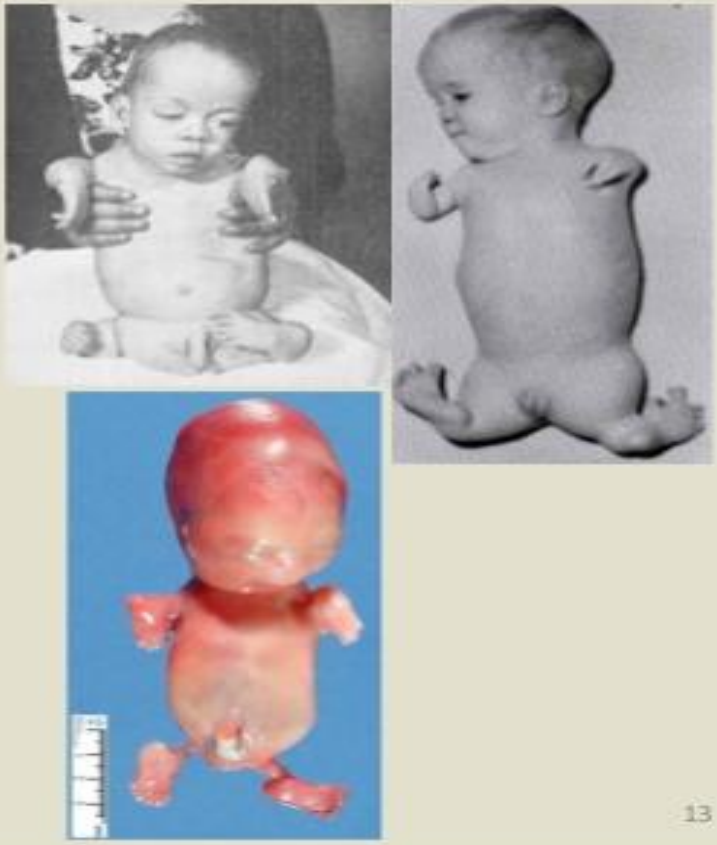
Thalidomide tragedy

Importance of Pharmacovigilance

•Thalidomide tragedy (1961-62): The greatest of all drug disasters. Thalidomide had been introduced and welcomed as a safe and effective hypnotic and antiemetic. It rapidly became popular for the treatment of nausea and vomiting in early pregnancy.

•Tragically the drug proved to be a potent human teratogen that caused major birth defects in an estimated 10,000 children

•Phocomelia was a characteristic feature



Thalidomide tragedy

Thalidomide Tragedy

- Approved as a sedative in Europe in 1950s
- Not FDA approved in United States
  - Manufacturer supplied it to physicians and paid them to do "research" to study its safety and efficacy
- By 1961 recognized that use in first trimester pregnancy caused abnormal development of arms and legs
- Banned world-wide
- Lead to 1962 Drug Amendments Act
  - Must now prove efficacy, not just safety

VA COACH
Center On Advice & Compliance Help

Impact of Thalidomide tragedy

History of Drug Regulation

- Kefauver Amendments to Food, Drug and Cosmetics Act (1962)
  - Response to thalidomide tragedy
  - Drug manufacturers are required to provide to FDA "substantial evidence" of efficacy and safety of their products before marketing them
  - FDA gains authority to regulate Rx promotion and clinical testing
  - Manufacturers must demonstrate the efficacy of products approved prior to 1962

History of drug regulation

- ✓ For other countries, whether or not they had initiated product registration controls earlier, the 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products.
- ✓ Industry, was becoming more international and seeking new global markets; however the divergence in technical requirements from country to country was such that industry found it necessary to duplicate many time-consuming and expensive test procedures, in order to market new products, internationally.
- ✓ Hence urgent need to rationalise and harmonise regulation

Initiation of ICH

- ✓ Harmonisation of regulatory requirements was pioneered by the EC in the 1980s,
- ✓ Europe moved towards the development of a single market for pharmaceuticals
- ✓ The success achieved in Europe demonstrated that harmonisation was feasible.
- ✓ Discussions started between Europe, Japan and the US on possibilities for harmonisation
- ✓ Plans for action began to materialise at the WHO Conference of Drug Regulatory Authorities (ICDRA), in Paris, in 1989
- ✓ Soon afterwards, authorities approached the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to discuss a joint regulatory-industry initiative on international harmonisation, and ICH was conceived.

ICH: Intl. Council for harmonization of technical requirements for pharmaceuticals for human use

The evolution of ICH

Since its inception in 1990, the ICH process has gradually evolved:

First decade:

- MedDRA (Medical Dictionary for Regulatory Activities),
- development of ICH Guidelines on Safety, Quality and Efficacy topics,
- CTD

Second decade:

- Communication and dissemination of information on ICH Guidelines with non-ICH regions,
- Focus on implementation of ICH Guidelines in ICH's own regions and updating existing ICH Guidelines as needed,

Third decade:

- Extending the benefits of harmonisation beyond the founding ICH regions and introducing structural, organizational and other changes to achieve this goal .

ICH Mission

- To make recommendations towards harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration and the maintenance of such registrations;
- To maintain a forum for a constructive dialogue on scientific issues between regulatory authorities and the pharmaceutical industry
- To contribute to the protection of public health in the interest of patients from an international perspective;
- To monitor and update harmonised technical requirements
- To avoid divergent future requirements through harmonisation of selected topics
- To facilitate the adoption of new or improved technical research and development approaches which update or replace current practices;
- To encourage the implementation and integration of common standards
- to develop policy for the ICH (MedDRA) as a standardised dictionary which facilitates the sharing of regulatory information internationally for medicinal products used by humans.

Membership

Members

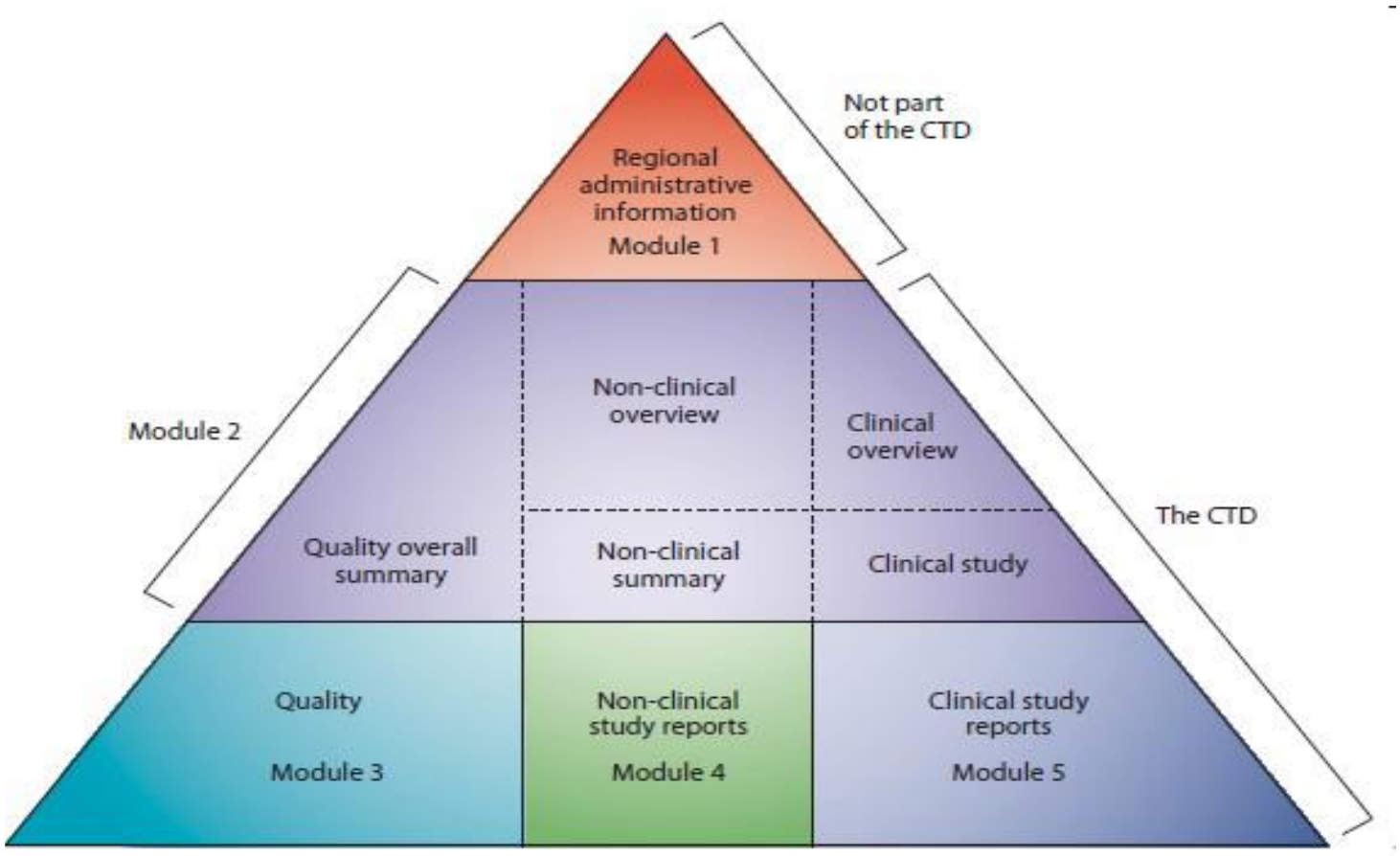
- Brazil, China, EU, USA, Canada, Singapore, Korea, Japan, Switzerland, plus certain organizations such as

Observers

- India, Cuba, Mexico, Kazakhstan, South Africa, Chinese Taipei and TGA plus certain organizations such as IFPMA, WHO, PICs, PANDRH, CIOMS, EDQM and certain blocks such as EAC and SADC

NOTE: The list is not-exhaustive

ICH CTD



ICH developed the Common Technical Document as a harmonized dossier both in format and contents

CTD Module 2

- **Module 2. Common Technical Document Summaries**
- Module 2 should contain seven sections in the following order :
- 2.1 Table of Contents
- 2.2 Introduction
- 2.3 Quality Overall Summary
- 2.4 Nonclinical Overview
- 2,5 Clinical Overview
- 2.6 Nonclinical Written and Tabulated Summaries
  - 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.

- 2.7 Clinical Summary including Synopsis of Clinical trial reports
  - 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.

CTD Module 3

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. Body of data.

3.2.S. Drug 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

3.2.S.2. Manufacture

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.

3.2.S.3. Characterization

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

3.2.S.3.2. Impurities.

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

3.2.S.4.1. Specifications.

3.2.S.4.2. Analytical procedures.

CTD Module 3 (cont)

3.2.S.4.3. Validation of analytical procedures.
3.2.S.4.4. Batch analyses.
3.2.S.4.5. Justification of specification.
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.
3.2.P. Drug product:
3.2.P.1. Description and composition of the drug product.
3.2.P.2. Pharmaceutical development:
3.2.P.2.1. Composition of drug product.
3.2.P.2.2. Formulation, overages, properties
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
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.

CTD Module 3 (Cont)

3.2.P.3.4. Controls of critical steps and intermediates.
3.2.P.3.5. Process validation and/or evaluation.
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.
3.2.P.5. Control of drug product:
3.2.P.5.1. Specifications.
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 specifications.
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
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. Regional information.
3.3. Key Literature references.

CTD Module 4

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 drug interactions.
4.2.2. Pharmacokinetics:
4.2.2.1. Analytical methods and validation reports.
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 drug interactions
4.2.2.7. Other pharmacokinetic studies.
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.

CTD Module 5

Module 5: Clinical Study Reports

5.1. Comprehensive 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 human pharmacokinetics
5.3.3. Reports of human pharmacokinetic studies.
5.3.4. Reports of human pharmacodynamic studies
5.3.5. Reports of efficacy and safety studies.
5.3.6. Reports of post-marketing experience.
5.3.7. Case Report Forms (CRF)/Individual Patient Listings
5.4. Literature references.

THANK YOU