Common Technical Documents, IND and NDA Requirements

Module 5 Topic 2

Common Technical Document (CTD)

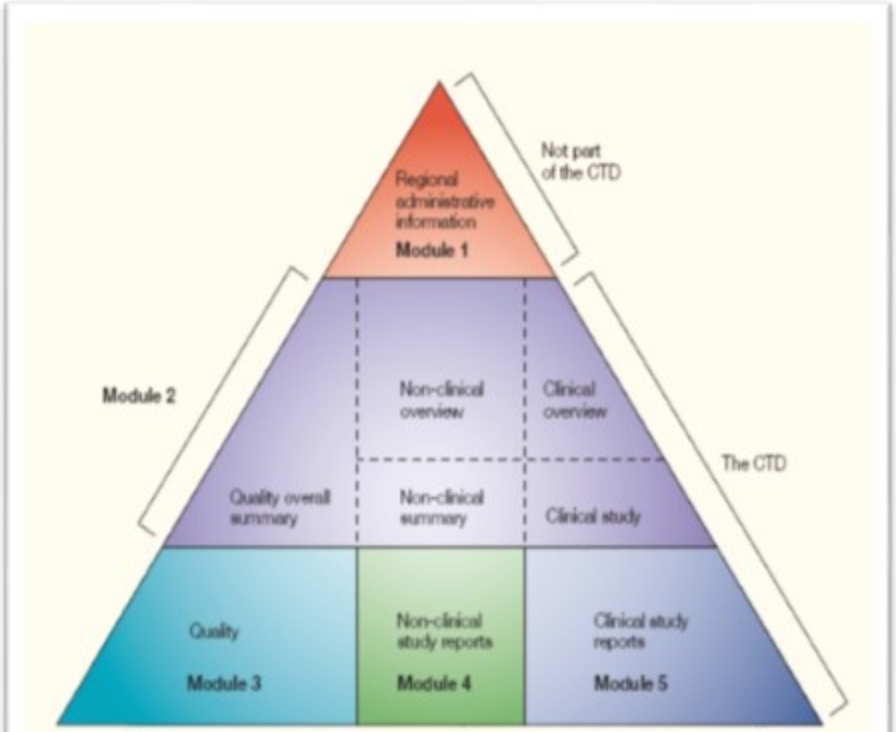
- Drug approval is the goal of the long process of drug development. Once preclinical and clinical trial data have been collected, a New Drug Application (NDA) must be submitted to the regulatory authority for approval
- Although the requirements for this submission have similarities around the world, until now, the applications have been different
- Regulatory authorities worked under the umbrella of the International Conference on Harmonisation (ICH) for development of the CTD which has harmonized the application procedure, and made this process simpler for applicants

Common Technical Document (CTD)

- The agreement to assemble all the Quality, Safety and Efficacy information in a common format called CTD revolutionized the regulatory review processes, led to harmonized electronic submission that, in turn, enabled implementation of good review practices
- For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities

Common Technical Document (CTD)

In July 2003, the CTD became the mandatory format for new drug applications in the EU and Japan, and the strongly recommended format of choice for NDAs submitted to the FDA, US



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions. CTD, Common Technical Document.

CTD Assembly

M4(R4): Organisation

M4 Q(R1): Quality

Module 2: Quality Overall Summary (QOS)
Module 3: Quality

M4S(R2): Safety

M4E(R2): Efficacy

Module 2: Clinical Overview and Clinical Summary
Module 5: Clinical Study Reports

CTD: M4(R4): Organisation

- **Organisation Including the Granularity document that provides guidance on document location and paginations**
- The CTD is organised into five modules:
  - **Module 1** is for administrative information and prescribing information, and should contain documents that are specific to each region; for example, application forms or the proposed label for use in the region.
  - **Module 2** contains the CTD summaries and should begin with a general introduction to the drug, including its pharmacological class, mode of action and proposed clinical use.

CTD: M4(R4): Organisation (contd)

- **Module 2** should also provide the overall summary of the 'quality' information provided, the non-clinical overview and the clinical overview, as well as the non-clinical written summaries and the tabulated summaries, and the clinical summary as a foundation for the aforementioned material.
- **Module 3** contains information on quality topics
- **Module 4** contains the nonclinical study reports
- **Module 5** contains the clinical study reports

CTD: M4Q(R1): Quality

- **The section of the application covering chemical and pharmaceutical data including data for biological/ biotechnological products**
- The Quality section of the Common Technical Document (M4Q) provides a harmonised structure and format for presenting CMC (Chemistry, Manufacturing and Controls) information in a registration dossier
- The table of contents includes sections on Drug Substance and Drug Product. There are also sections for regional specific information as well as some appendices

CTD: M4 Q(R1): Quality (contd)

- Due to the fact that many CMC topics have not yet been the subject of ICH guidelines (e.g. drug substance synthesis, drug product manufacture, container closure), the content of M4Q is not totally harmonised
- A new section on Pharmaceutical Development has been included to replace the Development Pharmaceutics Report (currently a part of the EU submission requirements)
- Also, a new CMC summary document, the Quality Overall Summary, has been developed

CTD: M4 S(R2): Safety

- The CTD Safety (M4S) Guideline delineates the structure and format of the nonclinical summaries in Module 2 of the Common Technical Document and provides the organisation of Module 4, the Nonclinical Study Reports
- The Nonclinical Overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic and toxicological evaluation of the pharmaceutical and generally should not exceed 30 pages

CTD: M4 S(R2): Safety (contd)

- The Nonclinical Written Summaries (100 - 150 pages) are recommended to provide more extensive summaries and discussion of the nonclinical information on pharmacology, pharmacokinetics and toxicology
- Thirty-four templates are provided for the preparation of the Non-clinical Tabulated Summaries, and 31 example tables are provided. Finally, the organisation of the Nonclinical Study Reports in Module 4 is described

CTD: M4 S(R2): Safety (contd)

- Preparation of the nonclinical sections of the Common Technical Document according to the M4S Guideline results in a single harmonised dossier of the nonclinical information that is acceptable in all three ICH regions

CTD: M4 E(R2): Efficacy

- CTD-Efficacy (M4E) describes the structure and format of the clinical data in an application, including summaries and detailed study reports
- There are two high level clinical summaries in Module 2 of the CTD : the Clinical Overview, a short document that provides a critical assessment of the clinical data; and the Clinical Summary, a longer document that focuses on data summarisation and integration
- Clinical Study Reports and raw data (where applicable) are included in Module 5 of the CTD

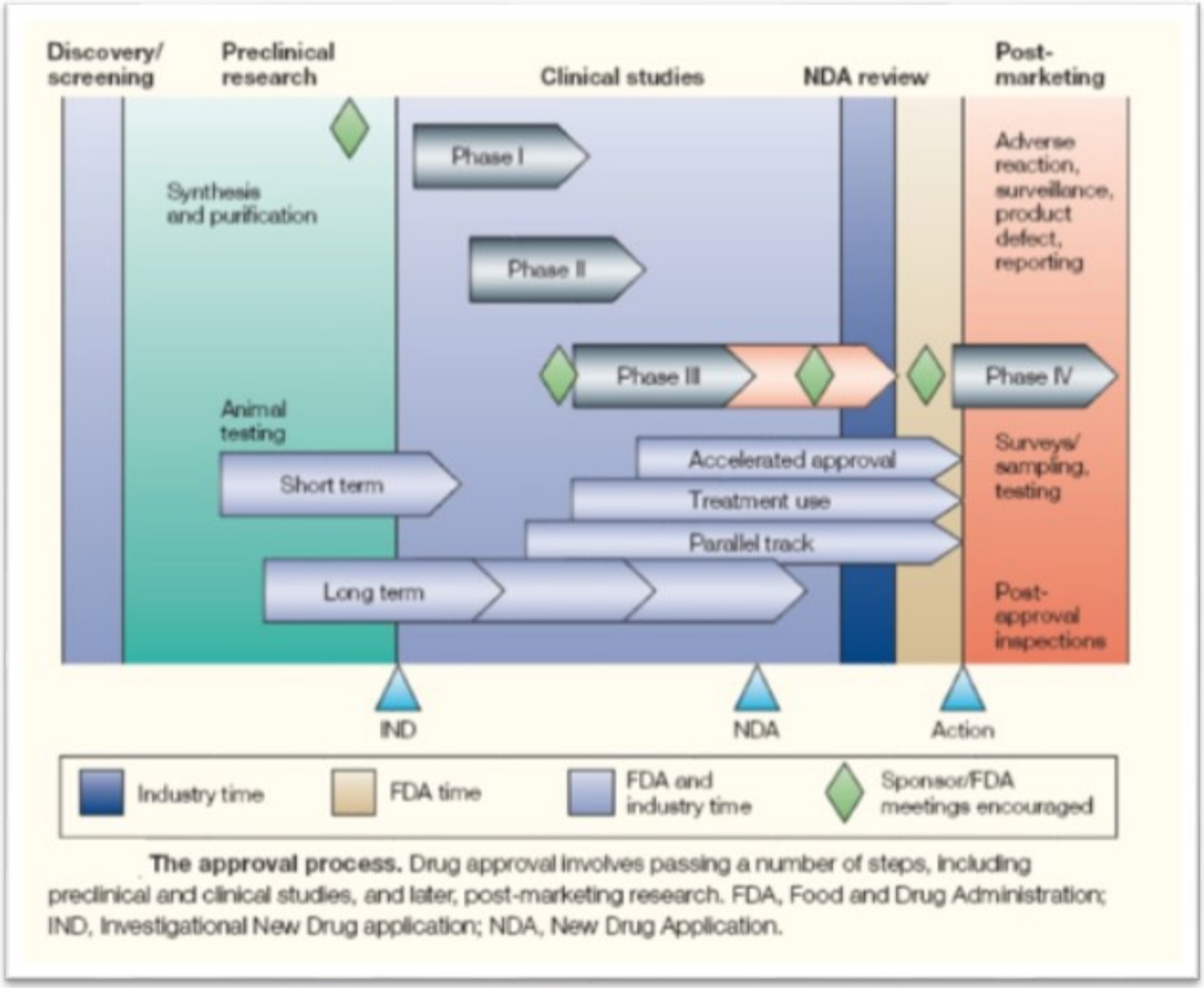
CTD: M4 E(R2): Efficacy (contd)

- The revised version of the ICH M4 E(R1) Guideline on Enhancing the Format and Structure of Benefit-Risk Information in ICH was approved by the Assembly under Step 4 of the ICH Process at the Lisbon meeting in June 2016, and now enters the implementation period (Step 5)
- The M4 E(R2) Guideline includes greater specificity on the format and structure of benefit-risk information, harmonising the presentation of this information in regulatory submissions. This topic was endorsed by the ICH Steering Committee in April 2015

CTD: M4 E(R2): Efficacy (contd)

- The M4 E(R2) Concept Paper proposed a review and revision in some parts of the Section 2.5 Clinical Overview of the Module 2 of the Common Technical Document (CTD) (Section 2.5.1 and 2.5.6) to ensure the guideline is both harmonised and sensible in its entirety

Drug Approval Process



The approval process. Drug approval involves passing a number of steps, including preclinical and clinical studies, and later, post-marketing research. FDA, Food and Drug Administration; IND, Investigational New Drug application; NDA, New Drug Application.

Investigational New Drug Application

- After investigating the pharmacological activity and acute toxicity potential of a drug product in animals, a Sponsor will proceed with assessing safety and therapeutic potential in humans
- In general, to perform clinical studies of a drug product in the United States, a Sponsor is legally required to first submit an Investigational New Drug (IND) application to the FDA
- The IND serves as the primary mechanism for Sponsors to communicate with the FDA during the entire drug development program

Investigational New Drug Application (contd)

- Each document filed to the Sponsor's IND becomes a part of the official record and is considered a formal message to the FDA
- Communications to the IND build a story that starts when a Sponsor expresses intent to dose a patient and may continue beyond the time a product is marketed
- The procedures and requirements for the submission and review of an IND by the FDA are described in Title 21 of the CFR Section 312
- The basic structure, format, and content of an IND should follow the ICH M4 guideline

Investigational New Drug Application (contd)

- Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines
- Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement
- The IND is the means through which the sponsor technically obtains this exemption from the FDA

Investigational New Drug Application (contd)

- During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development
- When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies

Investigational New Drug Application (contd)

- FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer), having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans
- At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system

IND: Types and Categories

- There are three IND types:
  - An Investigator IND
  - Emergency Use IND
  - Treatment IND
- There are two IND categories:
  - Commercial
  - Research (non-commercial)

IND: Types- Emergency Use IND

- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR, Sec. 312.23 or Sec. 312.20.
- It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist

IND: Types-Investigator IND

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed
- A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population

IND: Types- Treatment IND

- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place

IND: Categories- Commercial IND

- Commercial INDs are sponsored by a company that financially supports the conduct of clinical trials and may involve multiple clinical sites
- This is usually the most direct path to negotiations with the Regulatory Agency and approval for marketing, even for rare conditions with significant unmet medical need

IND: Categories- Research (non-commercial)

- Investigator-sponsored INDs are generally financed and conducted by a physician at one study site
- For Investigator-sponsored INDs, the Investigator not only conducts the clinical investigation (i.e., under whose direction the investigational drug is administered or dispensed) but is also considered the Sponsor of the IND and assumes all legal responsibility for the conduct of the study, which must be compliant to all elements of Good Clinical Practice

IND: Regulatory Scenario

- Treatment INDs, described in 21 CFR 312.320 (Subpart I), are used to make promising new drugs available to desperately ill patients as early in the drug development process as possible and before marketing of the product begins
- The FDA will permit an investigational drug to be used under a treatment IND if there is preliminary evidence of drug efficacy and the drug is intended to treat a serious or life-threatening disease with no comparable alternative drug or therapy available to treat that stage of the disease in the intended patient population

IND: Regulatory Scenario (contd)

- The IND application must contain information in three broad areas:
  - **Animal Pharmacology and Toxicology Studies** - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
  - **Manufacturing Information** - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

IND: Regulatory Scenario (contd)

- **Clinical Protocols and Investigator Information** - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

IND: Regulatory Scenario (contd)

- Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials
- During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk

Resources for IND Applications

- The following resources include the legal requirements of an IND application, assistance from CDER to help you meet those requirements, and internal IND review principles, policies and procedures
  - Pre-IND Consultation Program
  - Guidance Documents for INDs
  - Laws, Regulations, Policies and Procedures
  - Code of Federal Regulations (CFR)
  - Manual of Policies and Procedures (MaPPs)

Resources for IND Applications: Pre-IND Consultation Program

- CDER's Pre-Investigational New Drug Application (IND) Consultation Program fosters early communications between sponsors and new drug review divisions to provide guidance on the data necessary to warrant IND submission
- The review divisions are organized generally along therapeutic class and can each be contacted using the designated Pre-IND Consultation List

Resources for IND Applications: Guidance Documents for IND

- Guidance documents represent the Agency's current thinking on a particular subject. These documents provide FDA review staff and applicants/sponsors with guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products
- They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures

Resources for IND Applications: Guidance Documents for IND (contd)

- Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if it satisfies the requirements of the applicable statute, regulations, or both
- For information on a specific guidance document, investigator or representative may contact the originating office

Resources for IND Applications: Laws, Regulations, Policies and Procedures

- The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook
- The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the U.S.
- The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive

IND: Code of Federal Regulations (CFR)

- The final regulations published in the Federal Register (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the Code Of Federal Regulations (CFR).
- The CFR is divided into 50 titles that represent broad areas subject to Federal regulations.
- The FDA's portion of the CFR interprets the The Federal Food, Drug, and Cosmetic Act and related statutes.
- Section 21 of the CFR contains most regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under Federal law.

IND: Code of Federal Regulations (CFR)

- The following regulations apply to the IND application process:

Regulation	Type of Application
21CFR Part 312	Investigational New Drug Application
21CFR Part 314	INDA and NDA Applications for FDA Approval to Market a New Drug (New Drug Approval)
21CFR Part 316	Orphan Drugs
21CFR Part 58	Good Lab Practice for Nonclinical Laboratory [Animal] Studies

IND: Code of Federal Regulations (CFR) (contd)

- The following regulations apply to the IND application process:

Regulation	Type of Application
21CFR Part 50	Protection of Human Subjects
21CFR Part 56	Institutional Review Boards
21CFR Part 201	Drug Labeling
21CFR Part 54	Financial Disclosure by Clinical Investigators

IND: Manual of Policies and Procedures (MaPPs)

- CDER's Manual of Policies and Procedures (MaPPs) are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities
- All MAPPs are available for the public to review for a better understanding of office policies, definitions, staff responsibilities and procedures

IND: Manual of Policies and Procedures (MaPPs) (contd)

- CDER's Manual of Policies and Procedures (MaPPs) are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities
- All MAPPs are available for the public to review for a better understanding of office policies, definitions, staff responsibilities and procedures

New Drug Application (NDA)

- For decades, the regulation and control of new drugs in the United States has been based on the New Drug Application (NDA). Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization
- The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S.
- The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA

New Drug Application (NDA) (contd)

- The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:
  - Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks
  - Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain
  - Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity

New Drug Application (NDA) (contd)

- The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged

Resources for NDA Submissions

- The following resources provide summaries on NDA content, format, and classification, plus the NDA review process:
  - Guidance Documents for NDAs
  - Laws, Regulations, Policies and Procedures
  - Code Of Federal Regulations (CFR)
  - CDER's Manual of Policies and Procedures (MaPPs)
  - The resources provide the similar guidance as referred for IND in earlier slides

Resources for NDA Submissions

- Guidance documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and applicants/sponsors to provide guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products
- They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures. Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts

Resources for NDA Submissions (contd)

- An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations or both

References

- Justina Molzon, The Common Technical Document: The changing face of the New Drug Application. Nature Reviews | Drug Discovery Volume 2 | January 2003 | 71.
- http://www.ich.org/products/ctd.html
- https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/UCM166356.pdf