CTD STRUCTURE: FROM IND TO NDA

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Coming together is a beginning.
Keeping together is progress.
Working together is success.
— Henry Ford
Agenda

+ Typical Drug Development Timelines & Costs
+ CTD and its Role in Drug Development
+ CTD Origin and Purpose
+ CTD Structure
+ Evolution of the CTD from IND to NDA
+ Rest of World Awareness
+ Messaging: The Value of Storyboards
+ Agency Reviewer Perspective
+ Authorship and QC
+ Contributions of Each Functional Area
+ Team Dynamics
+ Timelines & Quality versus Expediency
+ Tracking Progress
+ Example CTD Structure for an NDA
+ Following NDA Submission
Typical Drug Development Timeline

**BASIC RESEARCH**
- 5,000 – 10,000 compounds

**DISCOVERY RES / CLINICAL**
- 250 volunteers

**DEVELOPMENT RESEARCH**
- 20 – 100 volunteers
- 100 – 5,000 volunteers
- > 5,000 volunteers
- 3 – 6 years
- 6 – 7 years

**PHASE I**
- MARKET AUTHORIZATION

**PHASE II**
- MARKET ACCESS

**PHASE III**
- POSTMARKETING
- 0.5 – 2 years
- 0.5 – 1.5 years

**5,000 – 10,000 compounds**

**250 volunteers**

**20 – 100 volunteers**

**100 – 5,000 volunteers**

**> 5,000 volunteers**
The Tufts Center for the Study of Drug Development (CSDD) calculates the cost of developing a prescription drug that gains market approval at $2.6 billion—a 145% increase, correcting for inflation, over the estimate the center made in 2003. Another $312 million is spent on post-approval development—studies to test new indications, formulations, and dosage strengths—for a life-cycle cost of $2.9 billion.
What is the CTD and its role in drug development?

+ The Common Technical Document (CTD) is an internationally agreed format for the preparation of applications regarding new drugs intended to be submitted to regional regulatory authorities in participating countries.

+ Used to build a dossier from the start of a drug development program—i.e., from Investigational New Drug (IND) application through New Drug Application (NDA) submission.
CTD Origin & Purpose

+ Developed by the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, US) and the Ministry of Health, Labour and Welfare (Japan)
  + Subsequently adopted by Canada, Switzerland, and other countries (Brazil, Republic of Korea, Singapore, China, Taipei)
+ Maintained by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
  + Now ICH stands for “International Council on Harmonisation”
The CTD Structure
Evolution Of The CTD From IND To NDA

- **IND Submission**
- **Clinical Start**
- **End of Phase 1 Meeting** (accelerated programs only)
- **End of Phase 2 Meeting**
- **Pre-NDA Meeting**
- **NDA Submission**

- **IND Review**
- **Annual Reports**
- **IND Amendments**

- **30-day Clinical hold**
- **Phase 1**
- **Phase 2**
- **Phase 3**
Pre-IND Meeting

FDA is particularly focused on:

- Problems with drug substance, drug product, or formulation intended for human use
- Questions regarding the adequacy of preclinical toxicology studies
- PK issues, e.g. related to dosing schedules, known/unidentified metabolites
- Novel dose-escalation scheme is proposed
- Questions regarding clinical monitoring for an anticipated end organ toxicity
Evolution Of The CTD From IND To NDA, Cont.

+ After IND submission, IND amendments update and continue to build out the CTD
+ Compliance requirement to update IND when additional data are available to inform clinical investigators
  + e.g., new tox data that justifies extended clinical dose duration; new nonclinical pharmacokinetic & drug metabolism (PKDM) data
+ Non-critical updates can go into the annual IND update
While the CTD is intended to serve as a common global structure for drug development documentation, regional differences exist in requirements.

In Europe, clinical trials are preceded by a Clinical Trial Application (CTA)

- An Investigational Medicinal Product Dossier (IMPD) is required for approval of clinical trials by competent authorities in the European Union (EU)—the IMPD follows CTD structure.

- Paediatric investigation plan (PIP) may be required by European Medicines Agency (EMA)
  - Can be preceded by a request for Scientific Advice from EMA.
Messaging: The Value Of Storyboards

+ Alignment of messaging up front, to be carried through the CTD
+ Have all important issues been addressed?
  + Class effects and safety signals have been explored and discussed
+ Do the data align across all sources?
  + Cross-document agreement in messaging
  + Data tables and listings
+ The importance of quality control (QC) cannot be overstated
Agency Reviewer Perspective

+ Throughout CTD life cycle, important to keep in mind the Agency reviewer perspective
  + Where does the sponsor want me to go?
  + Where does the science tell me to go?
  + What does common sense tell me?

Leslie Ann Furlong, MD – Clinical Reviewer, FDA

Authorship & QC

+ Cross-functional teams need to generate high-quality documents that are then improved by a series of reviews
+ Pre-approval document quality control (QC) review
  + General content review and group consensus
  + Consensus on how external cross-references are cited in text
  + Cross-reference and data accuracy check
  + Document formatting check
Contributions Of Each Functional Area

+ Authors (subject matter experts) and reviewers stay in “swim lanes”
  + Each sub-team needs to define the responsibilities of each member
    + Each individual addresses his/her responsibilities; leaves others to theirs
+ Document review
  + Some redundancy may be built in, but every reviewer should not evaluate all aspects of a document
  + Include reviewers with the most project familiarity and reviewers who are naïve to the project
Team Dynamics During IND & NDA Preparation

+ Multiple overlapping demands are made on key people, especially during critical review of documents
+ Recognize there will be simultaneous preparation of CSRs, summary documents and labeling
+ Recognize interdependency of various documents (if making a change in ISS, make sure same change occurs in SCS)
+ Helpful to have a key clinical person assigned to the safety documents and a (different) key clinical person assigned to the efficacy documents to funnel up and down the line
+ Very stressful time – Need to be flexible and supportive of team members
Team Dynamics, cont.

+ Recommendation: Require functional areas to provide collated comments so that the message within the functional line is consistent
  + Work out any differences in interpretation before trying to finalize the document
+ Pre-plan as much as possible
  + Someone in a key leadership role for the team should map out review schedules of documents and have the working group, contributors, reviewers, and signatories protect time on calendars for review and signature cycles
+ Review timelines need to be respected
Timelines & Quality Versus Expediency

+ How long does it take? (fit for purpose)
  + “Right” answer: It depends on how much time is left
  + Reality: Quality must be part of process
+ Resource constraints and conflicting priorities are to be expected for authors and reviewers
+ Quality control (QC) checks need to be built into the timelines
+ When is a document “Done”? Most assume “When approved”
+ Often, the regulatory publishing and eSubmission preparation stages are left to compensate for missed deadlines during document authoring/review/approval
Tracking Progress

+ Project tracking tools such as Smartsheet (or Microsoft Project) and Visio can be used to depict documents, resources (authors/reviewers/QCers/approvers/publishers), timelines, and interdependencies
Example CTD Structure For An NDA Mapped In Visio
Following NDA Submission – It’s Not Over Yet…

+ Preparation for Agency questions
  + Gap analysis
  + Preparation of responses to anticipated questions
    + Post-hoc analyses and write-up
+ If required by FDA, Advisory Committee meeting
  + When a scientific, technical, or policy question arises regarding an unapproved product, FDA often relies on Ad Comm
  + Ad Comm provides independent, expert advice and votes whether to recommend product approval
  + Recommendations of the Ad Comm are not binding but are high-stakes
FDA Advisory Committee — Sponsor Preparation

+ Briefing book
+ Slides addressing anticipated questions
+ Mock Ad Comm sessions (typically 2-3)
  + Numerous companies provide coaching and strategic input on preparation
  + Prior to mock session, briefing book provided to advisors
+ Mock session conducted as per actual Ad Comm Meeting
  + Sponsor presentation: summary of key messages on compound
  + FDA presentation: current interpretation of data submitted in NDA
  + Ad Comm/sponsor Q&A
+ Break
+ Sponsor responses to questions requiring additional preparation
+ Public comment
References & Resources

+ Relevant US Laws
  + Federal Food, Drug, and Cosmetic Act
  + Public Health Service Act—Part F, Licensing of Biological Products and Clinical Laboratories

+ Relevant US Regulations
  + IND regulations (both drugs and biologics) – 21 CFR 312
  + NDA (drugs) regulations – 21 CFR 314
  + Product licensing (biologics) – 21 CFR 601

+ Resources
  + ICH – https://www.ich.org