An Introduction to Clinical Research and Development

The Complex Process by which New Drugs are Tested in Humans

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Outline of Presentation

- Definitions
- Essential Tools of Clinical Research
- Phases of Clinical Research
- The Critical Path of Clinical R&D
- Interactions with Regulatory Agencies
- Products of Clinical R&D
- Challenges for Clinical R&D in the 21st century
- Improving the Chances of Success
- Considerations for Effective Clinical R&D
Clinical Research and Development (Clinical R&D) is the part of the drug development that attempts to define the test compound's characteristics in humans. Clinical research in its modern format (with emphasis in well-controlled and powered studies) is a relatively young field of endeavor, being established mostly after the 1960’s.
What does Clinical R&D Accomplish?

- Clinical R&D defines the important pharmacological properties of therapeutic compounds (drugs or biologics)
  - Efficacy
  - Safety
  - How the human body affects the drug (Pharmacokinetics)
  - How the drug affects physiological and pathological processes in the human body (Pharmacodynamics)
  - How the human genetic phenotype affects the actions of the drug (Pharmacogenetics)
Where does Clinical R&D Fit in the Drug Development Process?

- **Discovery**
- **Non-Clinical Development**
  - IND Related Pre-Clinical Development
  - NDA-Related Non-Clinical Development
- **Clinical R&D**
  - Phase 1
  - Phase 2
  - Phase 3
- **IND**
- **NDA**
- **NDA Action**
  - Approval
  - Approvable
  - Complete Response
  - Rejection
- **Regulatory**
  - Chemistry
  - Manufacturing
  - Controls
  - Toxicology
  - ADME Studies
  - Animal Pharmacology
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
What does **Efficacy** Mean in Clinical Research?

- **Efficacy** has a legal definition
  - It is included in section SEC. 505. [21 USC §355] New Drugs section of the Federal Food, Drug and Cosmetics Act.
    - “Substantial evidence" of efficacy means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.
    - In practice, substantial evidence of efficacy consists of two well-controlled, adequately powered clinical trials (pivotal) that provide consistent findings for the efficacy of the drug.
  - What does **well** mean?
    - Blinded
      - Study personnel and patients are unaware of the identity of the drug assignments
    - Randomized
      - Patients allocated to study arms in a random fashion
What does **Efficacy** Mean in Clinical Research? (continued)

- **Pivotal (Phase 3) studies test hypotheses**
  - Null Hypothesis (H₀): The test drug does not work better than the control
  - Alternate Hypothesis (Hₐ): The test drug works better than the control

- **Pivotal (Phase 3) studies support the marketing application if they:**
  - Are appropriately powered
    - Power relates to the sample size required to avoid accepting the null hypothesis when the null hypothesis is not true (avoids Type II error)
    - Typical power of pivotal studies is ≥ 80%
  - Reach statistically significant conclusions
    - Level of Significance (alpha, α) is the frequency level at which an event is unlikely to have arisen by chance
    - The test of significance generates a number (p-value) which must be lower than the level of significance for the results of the study not to have arisen by chance
    - “Popular” significance level is 0.05 (or 5%)
What does **Efficacy** Mean in Clinical Research? (continued)

- **Controls**
  - **None**
    - Most phase 1 studies are uncontrolled
    - Certain phase 2 studies may be uncontrolled
  - **Historical**
    - The drug efficacy is compared to prior data
    - Mostly utilized in phase 2 studies
  - **Placebo**
    - The test drug efficacy and safety is compared to that of the drug “vehicle” or another inert preparation
  - **Active**
    - The drug efficacy and safety is compared to those of an already approved drug for the indication
      - But does the older drug work?
• **Endpoints**
  - Endpoints are disease symptoms, vital signs, biomarkers, clinical laboratory parameter, pharmacodynamic measures, disease progression, or treatment outcomes, which when set at certain levels define the target outcome of a clinical study.
  - Endpoints must define:
    - Clinical benefit of treatment
      - These endpoints are typically utilized in Phase 3 clinical trials
      - Overall survival (OS) is such an endpoint
    - Disease progression
      - These endpoints are utilized in both Phase 2 and Phase 3 trials
      - Progression-free survival (PFS) or Time to Progression (TTP) are such endpoints
  - **Surrogate Endpoints**
    - Usually utilized in Phase 2 clinical studies. They consist of biomarkers or pharmacodynamic measures that have some correlation to the clinical benefit endpoint.
What does **Safety** Mean in Clinical Research

- **Safety is assessed by:**
  - Adverse events (AEs)
  - Changes in vital signs (heart rate, temperature, respiration)
  - Laboratory parameters (hematology, blood chemistry)

- **Definition, assessment and reporting of AEs**
  - Regulatory bodies have adopted harmonized guidelines
    - ICH E1-E2xx guidelines

- **Structured presentation of AEs**
  - There is a special “dictionary” for the presentation of AEs in regulatory applications (MedDRA)

- **Standardized assessment of AEs**
  - NCI Toxicity Grades:
Essential Tools of Clinical R&D

- **Clinical R&D requires the following “instruments”:**
  - Investigator’s Brochure
  - Clinical Study Protocol
  - Case Report (and Forms)
  - Statistical / Database Plan

- **Supporting “Toolboxes”**
  - Publications in scientific journals
  - Statistical methodologies
  - Consensus documents on current state indication under consideration
  - Regulatory guidance documents
  - Prior regulatory actions in the area of development
  - Internal data for the compound under development
Essential Tools of Clinical R&D
(continued)

• Investigator’s Brochure
  - Outlines what is known about the drug
    - Chemistry
    - Composition
    - Preclinical testing
      - Animal toxicology
      - Animal pharmacology
    - Results of previous clinical studies
    - Summary of patient spontaneous reports (if already marketed)
    - Description of likely adverse drug reactions (ADRs)
    - Method of administration
    - Shipping and storage conditions
    - Drug disposition
Clinical Protocol

- Outlines the design and methods of the clinical study
  - Study Design
  - Objective
  - Study Population
    - Enrollment Criteria
  - Procedures
    - Patient Treatment Algorithm
    - Assessments of Safety and Efficacy
  - Methods
    - Methodology of Assessments
  - Statistical considerations
    - Sample size
    - Analysis of Results
  - Obligations of Sponsors and Investigators
Essential Tools of Clinical R&D
(continued)

- **Case Report**
  - Contains the information collected for each subject during the clinical study as requested by the protocol
  - This information is usually structured in forms (CRFs) issued by the sponsor to investigative sites

- **Statistical Plan**
  - Defines in detail how the data collected during the clinical trial will be analyzed
  - Must be completed prior to unblinding

- **Database Plan**
  - Defines in detail the allowable parameters and rules for the data that would be collected during the clinical study. Data that fail these “rules” are queried.
Phases of Clinical R&D

- **Phase 0**
  - Pharmacokinetics and pharmacodynamics of drugs and imaging agents are examined in patients or normal volunteers following a “microdose”, a subtherapeutic dose.

- **Phase 1**
  - Safety, pharmacokinetics and pharmacodynamics are examined in normal volunteers. Toxic drugs (such as chemotherapeutic compounds) or potentially infectious agents are tested in patients
    - **Phase 1b**: Safety and pharmacokinetics in enhanced and longer lasting treatment regimens

- **Phase 2**
  - Safety, detailed pharmacokinetics, efficacy (usually with surrogate endpoints), dose ranging, drug-drug interactions, drug-food interactions are determined in limited studies in patients
    - **Phase 2a**: an early phase 2 to set the parameters for other phase 2 studies
    - **Phase 2b**: a more definitive phase 2 study
• **Phase 3 (Pivotal Phase)**
  - Efficacy is determined on pre-specified endpoints by testing the null and alternate hypotheses at a level of statistical significance and with power consistent with legislation and regulations. Extensive safety information is collected and analyzed

• **Phase 4**
  - Usually mandated by regulatory agencies as an element of conditional approval. These studies expand drug testing in patient groups and clinical presentations not covered by the pre-NDA development (but in which the test drug/biologic is likely to be used)
The "Critical Path" of Clinical R&D

The manner in which the drug affects the body

Pharmacokinetics

Preclinical

Defined in dose-escalation Phase 1 studies

Maximum Tolerable Dose (MTD)

Defined in dose-ranging Phase 2 studies

Minimum Effective Dose (MED)

Efficacy (proof of concept)

Efficacy (Regulatory Standard of Proof)

Safety

Pharmacodynamics

The manner in which the body affects the drug

Phase 1

Phase 2

Phase 3

Regulatory Review
Interactions with Regulatory Authorities

- **Pre-IND Meeting**
  - Essential to avoid a clinical hold but may be difficult to arrange

- **End-of-Phase 1 Meeting**
  - Usually not held, sometimes substituted for an End-of-Phase 2a Meeting

- **End-of-Phase 2 Meeting**
  - Critical meeting: Issues regarding the upcoming Phase 3 discussed in this meeting

- **Pre-NDA Meeting**
  - Crucial meeting to discuss the elements that will be included in the NDA

- **Phase 1**
- **Phase 2**
- **Phase 3**
- **Regulatory Review**
“Products” of Clinical R&D

- **Clinical Study Reports (CSR)**
  - Findings of clinical studies in a standardized format (ICH – E3 Guideline)

- **Specific Sections of the Common Technical Document**
  - Section 2
    - Clinical Overview
    - Clinical Summary
  - Section 5
    - CSRs
    - Integrated Summary of Efficacy
    - Integrated Summary of Safety
Challenges of Clinical R&D in the 21st Century

- **Declining Productivity**
  - Fewer Compounds Approved
  - Rising Costs

- **High Attrition Rates**
  - 45% of all pivotal studies fail
  - Only 8 – 12% of drugs entering development obtain marketing approval

- **Limited Patient Populations**
  - Expansion of clinical study enrollment in India, China, South America, South Africa
  - Challenges in integrating data from diverse populations

*Figure 1: Increase in pharmaceutical R&D expenditures and drop in NME approvals between 1993 and 2003. The graphs and data are derived from the “Challenges and Opportunities Report” published by the FDA in March 2004.*
Improving The Chances of Success in Drug Development

• Acceptance of industry conditions and restrictions
  - Highly regulated
  - Expensive
    • With a variety of drugs in most diseases, development is expected to become more challenging, not less
  - Erratic
  - Competitive

• Extensive and Tedious Planning
  - There can never be too much planning in clinical R&D
    • Dispersed activities and teams
      o Multiple investigative sites
      o Multiple CROs with medium to low team stability
      o Remote Central Laboratories
      o Remote (usually) drug supply management
  - Murphy’s law prevails. Risk management is essential for success.
• Assembling teams with the right expertise
  - This is a “knowledge-driven” enterprise
    - Expertise in therapeutic area
      - But manage the “experts”
    - Expertise in the regulatory environment
      - Prior development highlights challenges, problems, opportunities and regulatory approach
    - Expertise in operations management
      - Complex and “open” systems
      - Variability in training among participants
      - Constant competition with other projects
      - Various regulatory and ethics boards
      - Demanding timelines
    - Expertise in data flow and data management
      - Regulatory guidelines on computer systems utilized
      - Demanding database standards, structure and integrity
      - Regulatory requirements for datasets and statistical processes
Considerations for an Effective Clinical R&D

• **Definition of the Desired Final Product (Slide 23)**
  - Assemble a Target Product Profile (TPP)
    - A TPP is a summary of the drug development program described in terms of labeling concepts

• **Effective Study Protocols (Slide 24, 25)**
  - Maintain internal consistency
  - Utilize the appropriate design and endpoints
  - Remain faithful to the TPP and the overall clinical plan

• **Awareness of New Methodologies (Slide 26)**
  - Investigate improved statistical methodologies
  - Investigate improved and flexible study designs
Considerations for Effective Clinical R&D (continued)

- **Assembling a Target Product Profile (TPP)**
  - Detailed information on a Target Product Profile can be found in:

- **Regulatory bodies strongly advocate the use of TPPs**

- **TPP templates are included in recent FDA guidance documents**
• Checking Clinical Protocol Consistency
  - Clinical protocols must be checked for internal consistency and for consistency against the TPP and clinical plan
Considerations for Effective Clinical R&D (continued)

- Structuring clinical studies to provide accurate and pertinent information
  - Phase 2 studies usually fail to provide reliable information in “go/no go” decisions to initiate pivotal studies
    - Inappropriate study designs
    - Inappropriate endpoints
      - Surrogate or alternate endpoints may not correspond well to the “clinical benefit” endpoint utilized in Phase 3
  - Phase 3 studies fail because they do not address the concerns of the regulators
    - Inaccurate estimate of the event rate (if primary endpoint)
    - No consideration on how enrollment criteria modify the event rate
    - Inadequate “assay sensitivity”
    - Endpoints do not provide an estimate of “clinical benefit”

Considerations for Effective Clinical R&D (continued)

- Utilizing Adaptive Clinical Trial Designs
  - Received a lot of attention recently because they may:
    - Limit costs
    - Speed up clinical development
  - They require
    - Additional planning
    - Clinical study teams with:
      - High level of expertise
      - High level of motivation
  - Significant up-front funding
  - Willingness to allow third parties (data and safety monitoring committees) to guide the program
  - Link:
Summary

- Clinical R&D is a rigorously regulated activity with strong ethical guidelines
- Its measure of success is defined by law and regulation
- Proceeds along a well-defined path (phases) in constant interaction with regulatory authorities
- Requires substantial planning and expertise
- Requires expert understanding and management of a variety of complex systems