Lecture 1

Clinical Development, Regulatory Approval Process

Outline

- History of Clinical Trial
- Regulatory Process
- IND (Investigational New Drug)
- NDA (New Drug Application)
- IRB (Institutional Review Board)
- Advisory Committee

Drug Development - Objectives

- Before approval
  - Efficacy
  - Safety

Drug Development - Objectives

- After approval
  - Identity
  - Strength
  - Quality
  - Purity
  - Stability
  - Reproducibility
  - etc

Drug Development - Process

- Discovery
- Formulation
- Laboratory development
- Animal studies
- Clinical development (Phases 1-3 trials)
- Process validation/stability/QA
- Regulatory submission
- Post-marketing (Phases 3B and 4 trials)

Drug Development - Process

- It is a lengthy process
  - On average, it will take about 12 and half years.
- It is a very costly process
  - An estimate of 300 to 450 millions for development of a new drug product.
- Is it necessary for such a lengthy and costly process?
  - Safety and efficacy
  - Identity, strength, purity, quality, and stability

Recalled drugs

A series of prescription drugs being pulled from the market has renewed concerns that government's process for approving drugs moves too quickly. Here are some recently recalled drugs.

Name of drug	Year recalled	Company	Type of drug	Reason for recall
Propulsid	2000	Johnson & Johnson	Heartburn	Cardiac problems
Rezulin	2000	Parke-Davis/Warner-Lambert	Diabetes	Liver toxicity
Raxar	1999	Glaxo Wellcome PLC	Antibiotic	Cardiovascular problems
Hismanal	1999	Johnson & Johnson	Allergy	Cardiac problems
Duract	1998	American Home Products	Arthritis	Liver failure
Posicor	1998	Roche Laboratories	Blood pressure	Dangerous drug interactions
Seldane	1998	Hoechst Marion Roussel	Allergy	Dangerous drug interactions
Redux	1997	American Home Products	Diet	Possible heart valve damage
Pondimin	1997	American Home Products	Diet	Possible heart valve damage
Manoplax	1993	Boots Pharmaceuticals	Congestive heart failure	Increased risk of death

Mostly Recently

- Merck withdrew Vioxx due to the safety concern of increased risk of heart attack and stroke
- Vioxx – a COX-2 inhibitor drug for arthritis approved by the FDA in 1999
- Merck's stock went down almost 30% in one day

Drug Regulatory Milestones

1906 - U.S. Pure Food and Drug Act

1912 - Sherley Amendment

Prohibited labeling medicines with **false and fraudulent claim**

1931 - First randomization of patients to treatments in clinical trials

- U.S. Food and Drug Administration formed

1938 - U.S. Federal Food, Drug and Cosmetic Act

Extended coverage to cosmetics and **therapeutic devices**

Required pre-distribution clearance of the safety of new drugs

1952 - Publication of *Elementary **Medical Statistics***

(Mainland, 1952)

Drug Regulatory Milestones

1962 - Kefauver-Harris Amendment

Strengthened the safety requirements for new drugs

Established an efficacy requirement for the first time

Publication of ***Statistical Methods in Clinical and Preventive Medicine*** (Hill, 1962)

1966 - Mandated creation of the local boards (IRB)

1976 - Medical Device Amendment

1977 - Publication of General Considerations for Clinical Evaluation of Drugs

1984 - Drug Price Competition and Patent Term Restoration Act (Waxman and Hatch, 1984)

Drug Regulatory Milestones

1985 - NDA Rewrite
Major revisions in the format and approval process related to NDAs

1987 - Treatment IND (FDA, 1987)

1988 - Publication of *Guidelines for the Format and Content of Clinical and* ***Statistical*** *Section of an Application* (FDA, 1988)

1990 - Publication of *Good Clinical Practice for Trials on Medicinal Products in the European Community* (EC Commission, 1990)

1992 - Parallel track and accelerate approval (FDA, 1992)

1997 - FDA Modernization Act (FDAMA)

- Publication of *Good Clinical Practice: Consolidated Guidelines* (ICH, 1997)
- *Good Statistics Practice* (Chow, 1997)

What are clinical trials?

- FDA (21 CFR 312.3)

  A clinical trial is the clinical investigation of a drug which is administered or dispensed to, or used involving one or more human subjects.

- Chow and Liu (1998)

  A clinical trial is the clinical investigation in which treatments are administered, dispensed or used involving one or more human subjects for evaluation of the treatments.

Three Key Components

- Experimental unit
  - A subject from a targeted population under study. For example
    - Healthy human subjects
    - Patients with certain diseases at certain stages
- Treatment
  - It could be a placebo or any combinations of
    - A new pharmaceutical entity
    - A new diet
    - A surgical procedure
    - A diagnostic test
    - A medical device
    - or no treatment

Three Key Components

- Evaluation
  - Efficacy analysis
    - Clinical endpoints
  - Safety assessment
    - Adverse experience
    - Laboratory test results
  - Others
    - Quality of life assessment
    - Pharmacoeconomics and outcomes research

Phases of Clinical Trials

- Phase 1 studies
  - Objectives
    - To determine the metabolism and pharmacological activities, the side effects associated with increasing dose, and early evidence on the effectiveness of the drug
    - To obtain sufficient information about pharmacokinetics and pharmacological effects for planning of phase 2 studies

Phase 1 Studies

- Include
  - **Drug metabolism**
  - **Bioavailability**
  - **Dose ranging**
  - **Multiple dose**
- Sample size
  - **20-80 normal volunteers or patients**
- Comments
  - **Less detailed and more flexible**
  - **Safety is the focus**

Phase 2 Studies

- Objectives
  - To first evaluate the effectiveness of the drug based on clinical endpoints
  - To determine the common short-term side effects and risks associated with the drug
  - To determine the dosing ranges and doses for phase 3 studies

Phase 2 Studies

- Include
  - Studies for evaluation of dosing (phase 2A)
  - Studies for determination of effectiveness (phase 2B)
- Sample size
  - Usually no more than several hundreds, e.g., 100-200 patients
- Comments
  - First controlled clinical studies
  - Expanded phase 2 studies may involve up to several thousand patients
  - Some pharmaceutical companies classify phase 2A and 2B depending upon study endpoints

Phase 3 Studies

- Objectives
  - **To gather the additional information about effectiveness and safety for evaluation of overall benefit-risk of the drug**
  - **To provide an adequate basis for physician labeling**
- Sample size
  - **Several hundred to several thousand patients**
- Comments
  - **Most rigorous and extensive clinical investigation**
  - **Studies performed after submission before approval called phase 3B**

Phase 4 Studies

- Objectives
  - To further evaluate the incidence of adverse reactions
  - To determine the effect of the drug on morbidity and mortality
  - To study a patient population not previously studied
- Include
  - Post-marketing surveillance
  - Spontaneous adverse drug reporting
  - Prescription survey

FDA Regulations

- Pharmaceutical entities
  - Drugs (CDER)
  - Biological products (CBER)
  - Medical devices (CDRH)
- Remarks
  - For evaluation and marketing approval of a pharmaceutical entity, the sponsors are required to submit substantial evidence of effectiveness and safety accumulated from adequate and well-controlled clinical trials to the FDA
  - For a combination product consisting of different pharmaceutical entities, FDA requires that each of entities should be reviewed separately by appropriate center at the FDA (Safety Medical Devices Act, 1990)

FDA Regulations

- Drugs (CDER)
  - IND (Investigational New Drug Application)

    NDA (New Drug Application)
    - **New drugs**
    - **Orphan drugs**
    - **Over-the-counter (OTC) drugs**
  - ANDA (Abbreviated New Drug Application)
    - **Generic drugs**

FDA Regulations

- Biological Products (CBER)
  - **ELA (Establishment License Application)**
  - **PLA (Product License Application)**
- Medical Devices (CDRH)
  - **IDE (Investigational Device Exemptions)**
  - **PMA (Premarket Approval of Medical Devices)**

Regulatory Process

- IND (Investigational New Drug Application)
- NDA (New Drug Application)
- IRB (Institutional Review Board)
- Advisory Committee

Code of Federal Regulations

21 CFR 50	Protection of Human Subjects
21 CFR 56	Institutional Review Boards (IRB)
21 CFR 312	Investigational New Drug Application (IND)
21 CFR 314	New Drug Application (NDA)
21 CFR 316	Orphan Drugs
21 CFR 320	Bioavailability and Bioequivalence Requirements
21 CFR 330	Over-the-Counter (OTC) Human Drugs
21 CFR 812	Investigational Device Exemptions (IDE)
21 CFR 814	Premarket Approval of Medical Device (PMA)
21 CFR 60	Patent Term Restoration
21 CFR 201	Labeling
21 CFR 202	Prescription Drug Advertising

IND

- Principle
  - Before a drug can be studied in humans, its sponsor must submit an IND to the FDA
  - The sponsor may begin to investigate the drug 30 days after the FDA has received the application
- Type of IND (Kessler, 1989)
  - Commercial IND
  - Non-commercial IND

IND

- Commercial IND
  - Permits the sponsor to gather the data on clinical safety and effectiveness that are needed for an NDA
  - If the drug is approved, the sponsor is allowed to market the drug for specific uses
- Non-commercial IND
  - Allows the sponsor to use the drug in research or early clinical investigation to obtain advanced scientific knowledge of the drug
- Remark
  - FDA itself ***does not*** investigate new drugs or conduct clinical trials

Content of an IND

- A cover sheet (FDA-1571)
- A table of contents
- An investigational plan
- An investigator's brochure
- Protocols
- Chemistry, manufacturing, and control information
- Pharmacology and toxicology information
- Previous human experiences with the investigational drug
- Additional information
- Relevant information

NDA

- For approval of a new drug, the FDA requires at least two adequate well-controlled clinical studies be conducted in humans to demonstrate substantial evidence of the effectiveness and safety of the drug
  - What are adequate well-controlled studies?
  - What is substantial evidence?
  - How to submit an NDA?

Adequate and Well-controlled Study

- Objective
- Methods of analysis
- Design
- Selection of subjects
- Assignment of subjects
- Participants of studies
- Assessment of responses
- Assessment of the effect

Adequate and Well-controlled Study

- Objective **(clear)**
- Methods of analysis **(appropriate statistical methods)**
- Design **(valid for addressing scientific questions)**
- Selection of subjects **(assurance of the disease under study)**
- Assignment of subjects **(minimize bias)**
- Participants of studies **(minimize bias)**
- Assessment of responses **(well-defined and reliable)**
- Assessment of the effect **(accurate and reliable)**

Content and Format of an NDA

Cover letter

A. Application form (365H)

B. Index

C. Summary

D. Technical Sections

- **1. Chemistry, manufacturing, and controls**
- **2. Nonclinical pharmacology and toxicology**
- **3. Human pharmacology and bioavailability**
- **4. Microbiology (for anti-infective drugs)**
- **5. Clinical data**
- **6. Statistical**

E. Samples and Labeling

F. Case Report Forms and Tabulations

Institutional Review Board

- **It is required since 1971**
- **Responsibility**
  - To evaluate the ethical acceptability
  - To examine the scientific validity
  - To avoid unreasonable risk
- **Composition (21 CFR 56.107)**
  - At least 5 members
  - No IRB may be entirely composed of one gender
  - No IRB may be entirely composed of one profession
  - At least one member are in the scientific area
  - At least one member are in the non-scientific are
  - No IRB should have a member participate in IRB's initial or continuous review of any project in which the member has a conflicting interest

Advisory Committee

- Composition
  - Clinical expert
  - Pharmacological expert
  - Statistical expert
  - One consumer advocate (not employed by the FDA)
- Responsibility
  - To review data presented in NDA's
  - To advise FDA as to whether there exists substantial evidence of safety and effectiveness

Advisory Committee

- Advantages
  - Supplement to the FDA's expertise
  - Allow an independent peer review during the regulatory process
- Remark
  - FDA will usually follow the recommendations made by the Advisory Committee, though they do not have to legally

Advisory Committee

A list of questions for Advisory Committee

Are there two or more adequate and well-controlled trials?

Have the patient populations been well enough characterized?

Has the dose-response relationship been sufficiently characterized?

Do you recommend the use of the drug for the indication sought by the sponsor for the intended patient population?

Good Clinical Practice

- Definition
  - A set of standards for clinical studies to achieve and maintain high quality clinical research in a sensible and reasonable manner
- Concerns
  - Patient protection
  - Responsibilities of sponsors, monitors, and investigators
  - Quality of clinical data
  - Appropriate design and valid statistical evaluation

Good Clinical Practice

- Actions
  - Guidelines/Regulations
    - European Community (Committee for Proprietary Medical Products)
    - U.S. (Food and Drug Administration)
    - Japan (Ministry of Health and Welfare)
    - e.g., 21 CFR Parts 50, 56, 312, and 314
  - Standard Operating Procedures
    - Protocol
    - Clinical monitoring
    - Data management/biostatistics
    - Document review

Good Clinical Practice

- **GCP packet assembled by Alan B. Lisook, M.D.**
  - (a) Information concerning FDA regulation
  - (b) CDER publications
  - (c) Clinical investigations
  - (d) Protection of human subjects; informed consent
  - (e) New drug, antibiotic, and biologic drug product regulations; final rule
  - (f) Investigational new drug, antibiotic, and biologic drug product regulations; treatment use and sale; final rule
  - (g) Guideline for monitoring of clinical investigations
  - (h) Investigational new drug, antibiotic, and biological drug product regulations; procedures intended to treat life-threatening and severely debilitating illnesses; interim rule

Good Clinical Practice

- **GCP packet assembled by Alan B. Lisook, M.D.**

  - (i) FDA IRB information sheets
  - (j) FDA clinical information sheets
  - (k) Reprint of Alan B. Lisook, M.D. "FDA Audits of Clinical Studies: Policy and Procedure" *Journal of Clinical Pharmacology*, 30(4), 296-302, 1990
  - (l) Federal Policy for the protection of human subjects; notices and rules
  - (m) FDA compliance program guidance manual - clinical investigators
  - (n) FDA compliance program guidance manual - sponsors, contract research organizations and monitors

Good Clinical Practice

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