Clinical Trials and the Food and Drug Administration

Objectives

- To be informed about the process of clinical trials
- Understand the FDA regulations guiding the process
- Prepare a clinical trials game for students to play

What do you know about Clinical Trials ?

- a) vocabulary:

  GMP, FDA, IND, CDER, NIH, NDA
- b) do you know anyone who went through a clinical trial?
- c) FDA : covers food, drugs, biological products, medical processes, cosmetics

What Would You Like to Find Out ?

- How is a clinical trial carried out?
- Who is responsible for conducting these trials ?
- Drugs must be effective/safe
- Foreign drugs?

Five Basic Components of Clinical Trials for Investigational New Drug

- Pre-clinical trials: Animals or Tissue Culture
- Phase 1 clinical studies: Small, healthy groups
- Phase 2 clinical studies: Larger, sick population
- Phase 3 clinical studies: Broad trial with a large sick population
- Phase 4 clinical studies: Retrospective look at drug after released

History of FDA and CDER

- FDA established in 1906 with Pure Food and Drug Act
  - list ingredients in medicine
  - examine samples for adulterated food and drugs
  - federal control via interstate commerce

Following information is available at-
http://www.fda.gov/cder/about/history/default.htm

CDER Timeline

- 1906 Food and Drug Act
- 1938 Food, Drug, and Cosmetic Act
- 1953: Factory Inspection; manufacturers must provide information about analysis of samples
- 1962: Thalidomide causes widespread birth defects in other countries. Congress institutes supervision over drug safety
- 1968 : Drug trafficking is now under the control of the treasury's department of narcotics and dangerous drugs

Pre-1906 Sales of Medicines

Brain Centers

Glands Wear Out!

Epilepsy Treatment

Throat and Lung

Consumption Remedy

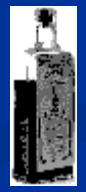
Certificate of Purity

Energizing Tonic

Lose Weight

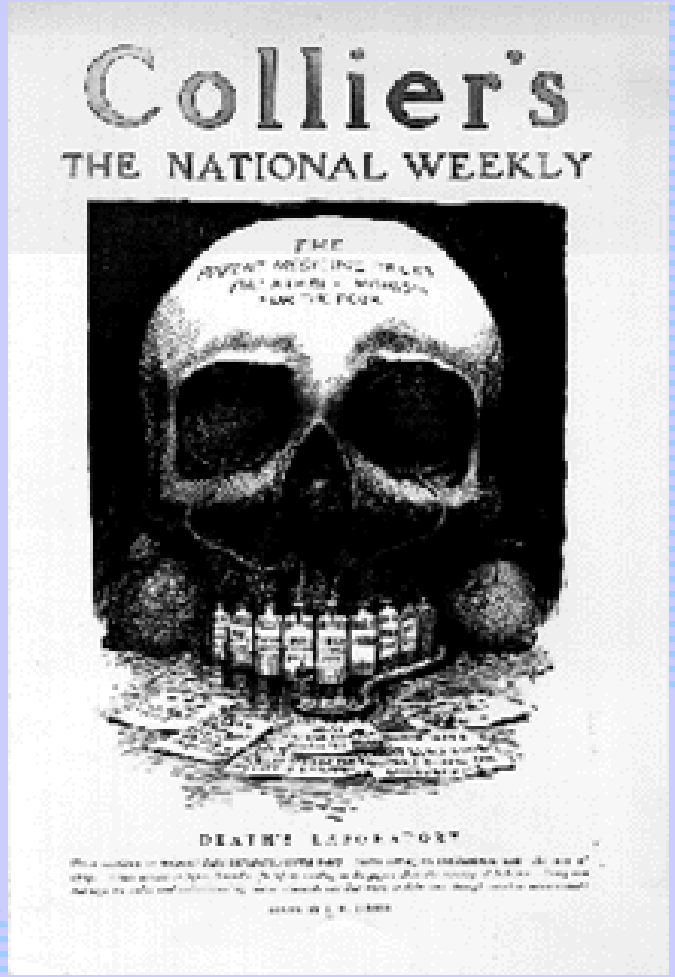
Snake Oil

Germ Killer



Renovator

Heart Remedy



One of the covers Collier's used in its campaign for the Pure Food and Drugs Act of 1906.

Initially, the Drug Laboratory worked on a variety of projects. One of the first was an investigation of the reagents used by the Bureau, which Kebler soon learned were not completely pure. The Laboratory spent much of its time in search of methods to improve pharmaceutical analyses. Kebler also alerted the public to problems with the drug supply in general.

fda/gov/cder/about/history/time.1htm

Elixir Sulfanilamide
1937

- Previous Law did not address safety of drugs
- This drug was dissolved in diethylene glycol
- Over 100 people died, mostly children
- Led to a demand for redefining FDA laws

1938 Food, Drug & Cosmetic Act

- Drugs must be tested for safety before being marketed
- Drug maker must submit a New Drug application to obtain approval to sell drug
- This application must include results of safety regulations
- Drugs must have adequate labeling

FDA in the 1940's

- Insulin amendment act: all batches must be tested for purity, strength, quality and identity
- Penicillin must be assigned a strength and assessment of purity

FDA in the 1950's

- Adverse reaction reported to Chloromycetin
  - Dycrasia, bleeding, lack of platelets, and white blood cells
  - Voluntary drug adverse effects reporting to FDA
- Big expansion of the FDA to Include 7 different divisions

The Thalidomide Story

- Drug approved for sleep and nausea in Europe and Canada
- Dr. Francis Kelsey was awarded medal of honor
- Was submitted to the FDA but not approved as a new drug application:
  - Insufficient safety data
  - Was not approved for marketing

1962 Drug Amendments

- Drugs must both be safe and effective prior to being marketed
- Antibiotics must be certified
- FDA was given control over marketing of drugs

Popular Influence on FDA Procedures

- Coalition of activists for Aids cure was formed 1987
- Sought to expand and expedite new treatments
- Orphan drug act instituted 1983
- Anti-tampering act 1982

Further Expansion of FDA 1987

- Center for Drugs /Biologics was split into Several Separate Units

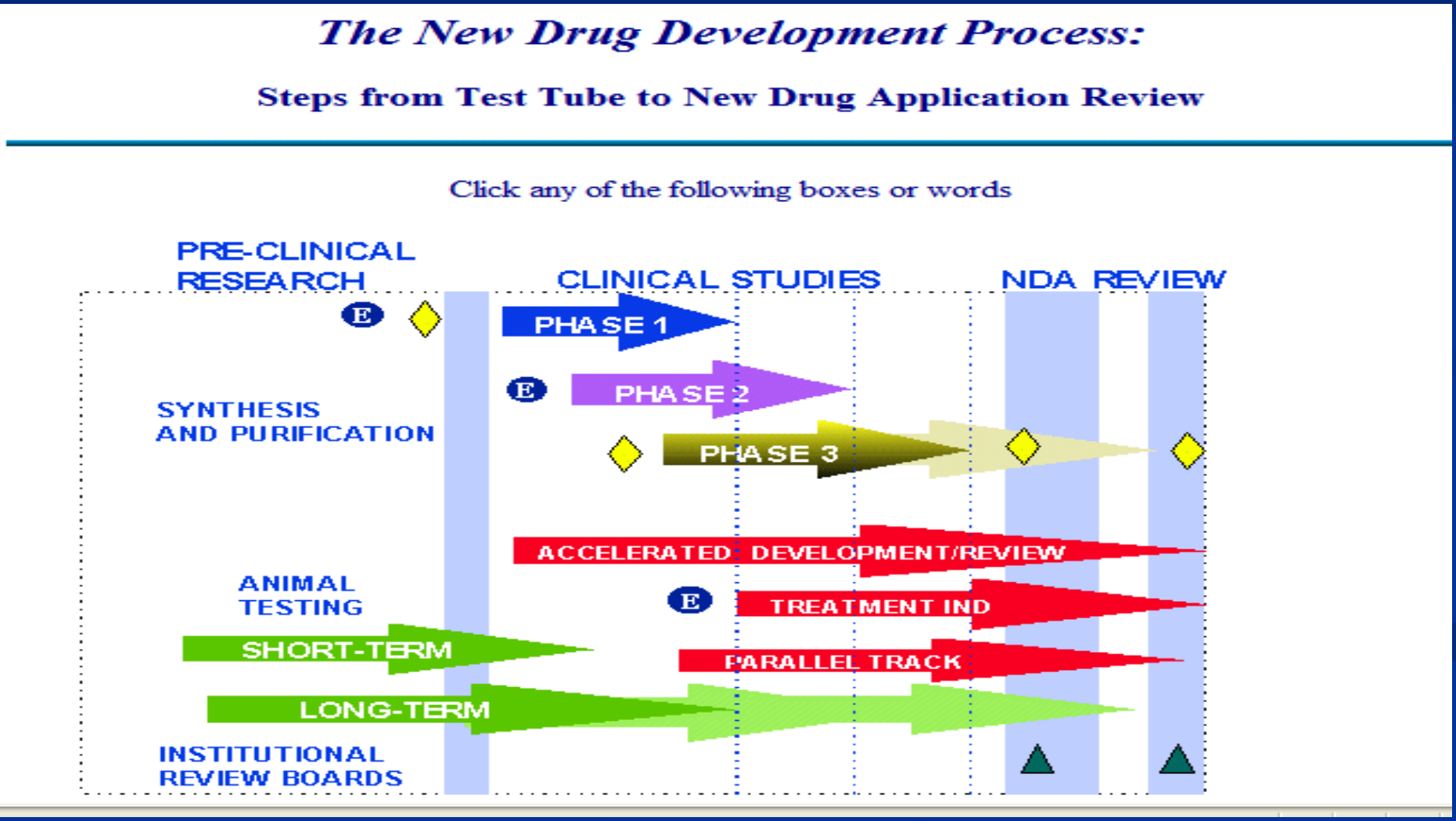
Center for Drug Evaluattion and Research

Center for Biologic Evaluation and Research

Hatch/Waxman Amendments 1984

- 50% of all prescription drugs are generic with cost 50$ less per prescription than name brand
- 2000 : 44% of drugs are filled with generic varieties
- Generic drug makers can rely on previous safety & efficacious findings of original drug application
- Same application as for NDA but is amended NDA

FDA.gov/cder/handbook/develop.htm



Pre-Clinical Trials

- Based on fundamental scientific findings
- Consists of short-term testing in animals using the compound of interest
- Usually takes from 2 weeks to 3 months
- Tests toxicity, absorption, clearance of drug
  compound must be biologically safe for initial administration to humans

Clinical Trials

- Pre-Investigational New Drug (IND)
  - NDA = new drug application
- Two trial types: observational & interventional
- Discussion begins about testing phases
  - Including data requirements
  - Scientific issues
- Required for further testing:
  - Compound must be biologically active
  - Compound must be safe for data shown

What Drugs Make it to Clinical Trials?

- Synthesis and Purification of Product
  - 1/1000 are successful
  - Up to 8 ½ years to go through trials
  - Drug selection is made by using test models for a disease/adding drug to determine its effect
  - Selection by screening – microorganisms/plants
  - Other forces, price, marketing etc.

Institutional Review Boards (IRB)

- Ensures rights for public participation
- Patient must be fully informed
- Written consent obtained before trial
- Consists of 5 experts + lay people
- Must understand specific drug action, law, constitutional involvement

Phase 1 Clinical Studies of IND

- Drugs used in humans
- Subjects are usually healthy volunteers
- Double blind studies
- Is subject to a clinical hold, 483 warning is issued
- Monitors the following:
  - Toxicity
  - Drug metabolism
  - Mechanism of action

Phase 2 Clinical Studies of IND

- Obtain preliminary data about effectiveness of the drug
- Determines the common short term side effects
  - Risks associated with drug
- Well controlled, closely monitored
  - Usually 100 hundred carefully selected people

Controlled Trials

- Designed to permit valid comparisons with a placebo
- Dose response curve is created
- Control is concurrent with tested substance
- Comparison can be made to earlier studies
- Sometimes there is no control: Requires special approach
  - Multiple resistant pathogens
    - Example extremely drug resistant TB (XDR TB)

Phase 3 Clinical Trials

- Expanded controlled trials
- Measures effectiveness and safety of drug
- Includes hundreds-thousands of patients
- Evaluates risk/benefit for majority of people
  - Requires statistical analysis

Phase 4 Clinical Trial

- A retrospective view of overall effects of drug on a large population over time
- Statistical analysis of effects of preventative or palliative drugs on overall health of individual
  - Example : Framingham Nurses Health Study

Women's Health Initiative
15 year analysis of 161,000 women 50-79 years of age

- Benefits
  - 57% reduction in colon cancer
  - Better bone density
  - Relieves symptoms of menopause
  - Improves HDL cholesterol levels
- Risks
  - 24% increase in breast cancer
  - 24% increase in heart disease (stroke, clots)
  - Increased level of dementia
  - Statistically insignificant increase in heart attacks

http://www.whi.org/findings/ht/eplusp_pad.php

Epidemiologic Studies

- Unknown factors might be driving results
  (statistics can be misleading)
- Is not as significant as a blind study with controlled groups
- Contradicts other evidence about heart disease

Gene Therapy

- How does one carry out clinical trials for gene therapy ?
- Jessie Gelsinger had genetic disorder (OTC) Ornithine transcarbamylase
- Died within days of being injected with a healthy gene attached to an adenovirus September 17,1999

Reforms Instituted

- Clear, pertinent information about toxic effects seen in animal trials at U Penn was not disclosed
- Many other studies were discovered that had withheld adverse effects from reports to FDA
- The FDA withheld adverse effects from patient
- All gene therapy trials were suspended in the US

Conflict of Interest ?

- Paul Gelsinger said that regulators are aiming in the wrong direction if they don't correct the undue influence of business interests on gene therapy research.

- Business argued that they need to keep adverse effects under wraps due to competition and and fear of frightening the public

Exploring the FDA website

- www.fda.gov/cder/about/default.htm

- Go to section on CDER that is titled
  - What do we do?
    - Go to MAPP [Manual of Policy and Procedures]
    - Office of drug safety Chapter 6000
      - Review Management 6010.1

6010.1 New Drug Application

- Pre-approval Safety Conference: insures communication before approval alerts everyone to potential problems
- How frequent would an adverse drug reaction have to be to gain notice?
- What must the project manager do to review a new chemical entity or drug?

Let's Make Our Game

- Choose a game which most like to play
  - Monopoly
  - Shoots and Ladders
  - Clue
- Make up rules that require all three phases of
- Design a board that will allow players to travel around the board to obtain approval for all 3 phases of Trials
- Create cards to be drawn determine how to use dice to allow players to move

FDA Drug Approval Game