From Bench to Bedside : Getting New Drugs Approved by the FDA

Drug Discovery Facts & Figures

- It takes 12 to 15 years to develop a single drug
- Only 1 in 10,000 potential medications makes it completely through the process
- Only 5 in 5,000 (est.) possible formulations make it to human testing and out of these only 1 in 5 make it through the clinical test phase and FDA approval
- In 2000 it cost more than $800 million to develop a single drug for the market
- An estimated $51.3 billion were spent by the biopharmaceutical industry on developing new drugs in 2005

The FDA: Basic Facts

Center for Drug Evaluation and Research (CDER)
- Approves and regulates drugs or pharmaceuticals
- Approves generics
- Maintains a system for reporting adverse events or reactions
- Checks bioequivalency to the name brand (*e.g.,* do they react in the same way?)
- Only 1 in 20 new drugs make it through to full approval
- In 2005:
  - ~ Approved 80 new medicines (78 drugs and 2 biologics)
  - ~ 20 were totally new medicines which were never marketed in any form (15 were priority approvals)
  - ~ Priority approvals are used for drugs that represent significant improvement over current therapies for life-threatening diseases
  - ~ Approved 344 generic versions of drugs
- Medwatch
  - ~ Warnings and safety information
  - http://www.fda.gov/medwatch/index.html
- Maintains websites with information for consumers
  - ~ http://www.fda.gov/cder/drug/DrugSafety/drugSafetyConsumer.htm
  - ~ Drug safety and information sheets website
  - http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm

Center for Devices and Radiological Health
- Approves and regulates medical devices
- Oversees research in gene therapy

Center for Biological Evaluation & Research (CBER)
- Regulates Biologics including vaccines and blood

Center for Veterinary Medicine regulates veterinary pharmaceuticals
- Publishes List of Approved Animal Drug Products (Green Book)

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Getting a New Drug Approved : The Procedure

Researchers must submit an Investigational Drug Application (IDA)

Investigational New Drug Application Process (IND) :
- Must be completed and submitted to FDA before clinical trials
- If not disapproved within 30 days Phase I Clinical Trials can begin
- The IND includes:
  - ~ Results of preclinical studies
  - ~ Chemical formulations tested
  - ~ Computer models and/or laboratory assays to check chemical actions of formulas
  - ~ Test: Add each compound to enzymes, cell cultures or cellular substances to see if there is an effect
  - ~ Manipulate the chemical structure of the compound until the desired reaction occurs
  - ~ Test results in animal models:
    - How the compound is absorbed by or reacts in the body
    - Toxicological or toxicity of compound
    - Is it safe to administer to human test subjects?
  - ~ Complete information on the formulation and manufacturing
  - ~ Detailed protocols for proposed clinical trials
  - ~ Progress reports on clinical trials must be sent to the institution's IRB and FDA annually

FDA can halt the clinical trials if:
- Trial's design does not meet the study's objectives
- Unsafe to administer new drug to humans or other safety issues for participants

FDA provides manual of regulations investigators must follow when running clinical trials

Clinical Trial Phases:
- FDA inspects trial sites to ensure the safety of the volunteer patients and the integrity and validity of the data
- Inspects 300 to 400 clinical investigators annually
- Phase I (6 months to 1 year):
  - ~ 20 to 100 Healthy participants are given the drug to check safety in humans
- Phase II (6 months to 1 year):
  - ~ 100 to 500 patients who have the disease are given either placebo or drug to check the new drug's effectiveness
  - ~ Still checking for adverse or toxic reactions in humans and optimum dosing
- Phase III (1 to 4 years):
  - ~ Large-scale testing on 800 to 5,000 volunteer patients at multiple sites
  - ~ Randomized controlled trial (some patients get placebo instead of drug)
  - ~ Effectiveness and safety in a large, varied population
  - ~ Interactions with other medications
- Phase IV Trials (After New Drug Application is approved)
  - ~ FDA may request these studies after the new drug has been approved and is available on the market
  - ~ Studies adverse effects or safety, optimal use and efficacy

New Drug Application (NDA)

- Drug developers meet with the FDA before submitting the NDA
- Submitted to the FDA for review before a drug can go on the market
- FDA has 60 days to decide whether or not to file an application for review
  - ~ Incomplete applications are rejected
- The NDA includes:
  - ~ All the preclinical and clinical data and its analysis
  - ~ Chemical formulation
  - ~ How it reacts within the body (pharmacokinetics and pharmacology)
  - ~ Clinical study sites and manufacturing sites and details
    - Inspects manufacturing sites to ensure they comply with guidelines
    - Ensures quality and purity of the drug
  - ~ Labeling information
- Reviewed by a team of staff members
  - ~ Evaluates the research on safety and effectiveness
  - ~ May convene an advisory committee of specialists depending on the medication or disease
- Median review and approval times for 2005:
  - ~ Regular drug applications:
    - Review time: 11.8 months
    - Approval time: 13.1 months
  - ~ Priority drug applications:
    - 6 months for review and approval
- Accelerated New Drug Application
  - ~ Generics
    - Are they bioequivalent to the original formulation?
      - ~ They must act in the same manner in the body as the original formulation
    - Listed in *Approved Drug Products With Therapeutic Equivalence* (Orange Book)

Bibliography

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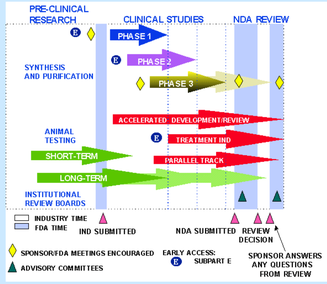
The New Drug Development Process: **Steps from Test Tube to New Drug Application Review**



http://www.fda.gov/cder/handbook/develop.htm