Drug Development Process

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Overview

- Important milestones establishing our current system of regulations
- Step-by-step overview of the drug development process
- Fast-track drug development
- More Information

Milestones

1800s

- **U.S. became the world's dumping ground for counterfeit, contaminated, diluted, and decomposed drug materials.**

- **U.S. Customs Laboratories were established to administer the Import Drugs Act of 1848.**
  - **Mission: Enforce purity and potency standards**

State of Food and Drug Supply Late 1800s

- Agricultural to industrial economy
- Principle means of refrigeration – ICE
- Unpasteurized milk
- Cows weren't tested for TB
- Pioneers of bacteriology just starting string of victories over infectious diseases
- "Kick-a-poo Indian Sagwa"
- "Warner's Safe Cure for Diabetes"
- Opium, morphine, heroin, and cocaine – no restrictions or labeling

Medicine Men vs Circus

http://www.fda.gov

Pure Food and Drug Act of 1906

- Prohibited interstate commerce of misbranded and adulterated foods and drugs.
- Allowed for seizure and criminal penalties.
- Did not address:
  - Food or drug standards
  - False advertising
  - Inspection of food and drug facilities.
- Enforced by Division of Chemistry

1937 – Elixir of Sulfanilamide

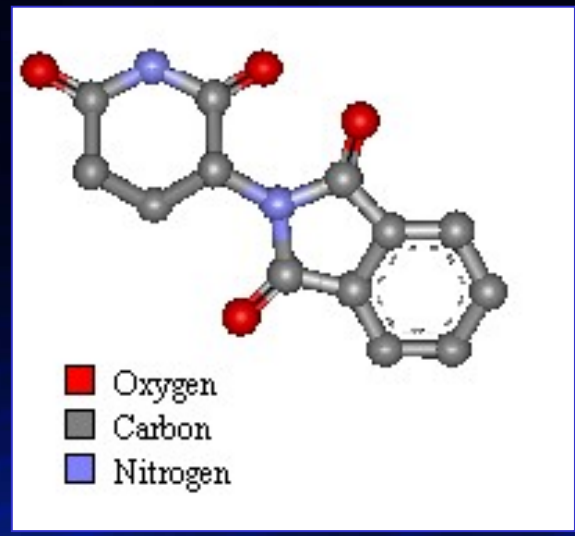
- Liquid form of Sulfanilamide produced using diethylene glycol as solvent.
- Diethylene glycol = Antifreeze
- Administered to mostly children to treat streptococcal infections.
- Existing laws did not require any kind of pharmacological studies demonstrating that a drug is safe.
- 107 people died.

1938- Food, Drug and Cosmetic Act

- Extended control to cosmetics and therapeutic devices.
- Required new drugs to be demonstrated as safe before marketing.
- Eliminated requirement to prove intent to defraud in drug misbranding cases (fraudulent claims).
- Provided standards and safe tolerances.
- Authorized factory inspections.

1961- Thalidomide Crisis

- Hailed as a wonder drug for sleeplessness.
- Relieved many morning sickness symptoms in pregnant women.
- Unknown that Thalidomide crossed the placental wall.
- Catastrophic results:
  - Peripheral neuritis – nerve disorder
  - Birth defects – deafness, blindness, disfigurement, cleft palette, internal defects, phocomelia

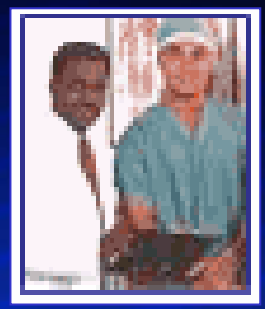


1962- Kefauver-Harris Amendments

- Drug Manufacturers were required to prove drug effectiveness and safety to FDA before marketing.
- Advertisements must show complete info on benefits and risks.
- Adverse effects must be reported to the FDA.
- Since 1962, thousands of drugs have been removed from the market because of these amendments.

Overview of Development Process

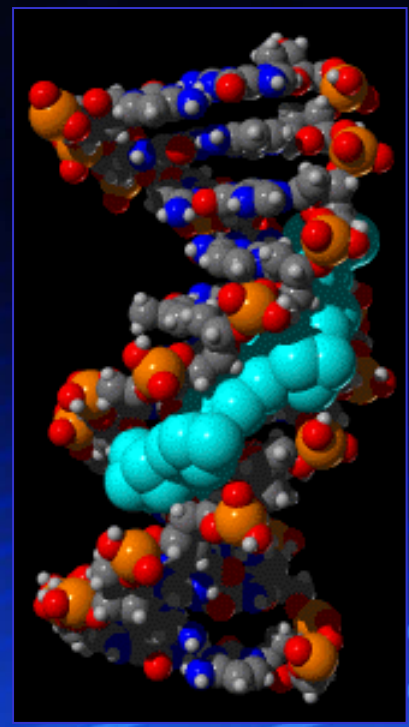
- Drug Discovery
- Screening
- Pre-Clinical Testing
- IND Application
- Phase I Clinical Trials
- Phase II Clinical Trials
- Phase III Clinical Trials
- New Drug Application (NDA) / Biologics License Application (BLA)
- Phase IV and Beyond



Therapeutic Drug Discoveries

(R & D – Careers: Scientists, Management, Finance, Accounting, HR)

- Determine target disease.
- Develop hypothesis for a mechanism of treatment.
- Use CAD and 3-D modeling software to begin evaluating hypothesis.
- Determine feasibility of producing and evaluating the selected compound.



Screening

(Careers: Scientists, Management, Finance, Accounting, HR, Quality Assurance/Control, Regulatory)

- Combination Chemistry
  - Make many possible compounds at one time.
  - Focus on quantity of possible compounds, not purity of each.
- High Throughput Screening
  - Test hundreds at a time for activity.
- Process requires serious technology.
- 1 in 10,000 makes it to the market.

Pre-Clinical Testing

(Careers: Scientists, Management, Finance, Accounting, HR, Quality Assurance/Control, Regulatory, Vet Med)

- Evaluate acute and short term toxicity in animals (one rodent, one non-rodent).
  - Dose at increasingly high levels to induce toxicity.
  - Determine lethal dose.
  - Dose at normal levels for short and long term.
- Assess how drug is absorbed, distributed, metabolized, and excreted in animals.

Investigational New Drug (IND) Application

(Careers: Quality Assurance/Control, Regulatory – people who love to write and document in detail, Legal)

- Request submitted to FDA to allow human exposure to the experimental drug.
- IND is an ongoing file at FDA containing data on drug as it passes through the development process.
- Inexperienced companies often hire consultants to help.

Clinical Trials

	Preclinical		Phase I	Phase II	Phase III		FDA		Phase IV
Years	3.5-6.5		1-1.5	2	3-3.5		1.5-2.5	**15 Total**	
Test Population	Laboratory and Animal Studies		20-80 healthy volunteers	100-300 patient volunteers	1,000-3,000 patient volunteers				
Purpose	Assess safety and biological activity	**File IND with FDA**	Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions for long term use	**File NDA with FDA**	Review process / approval		Additional post-marketing testing
Success Rate	5,000 compounds evaluated			5 enter clinical trials			1 approved		

Phase I Clinical Trials

(Careers: Scientists, Management, Finance, Accounting, HR, Quality Assurance/Control, Regulatory, Medical)

- **Begin 30 days after submission of IND providing FDA has not placed a “clinical hold” on development.**
- **20-80 healthy subjects**
- **Duration: 1 year**
- **Cost: $100,000 - $1,000,000**
- **Determine bioavailability.**
- **Determine side effects associated with increasing doses.**
- **Gain early evidence on effectiveness.**

Phase II Clinical Trials

(Careers: Scientists, Management, Finance, Accounting, HR, Quality Assurance/Control, Regulatory, Medical)

- **Not necessary to consult with FDA to begin Phase II.**
- **Assess a drug's effectiveness in treating a particular disease or medical condition.**
- **Safety and side effects are monitored.**
- **100-300 patient volunteers**
- **Duration: 2 years**
- **Cost: $10-100 million**
- **Less than 1/3 of INDs survive Phase II.**

Phase III Clinical Trials

(Careers: Scientists, Management, Finance, Accounting, HR, Quality Assurance/Control, Regulatory, Medical)

- Company must consult with the FDA before beginning Phase III.
- 1,000-3,000 patient volunteers
- Multiple testing sites
- Duration: 3-3.5 years
- Cost: $10-500 million
- Confirm effectiveness and safety of drug.

New Drug Application (NDA) / Biologics License Application (BLA)

(Careers: Quality Assurance/Control, Regulatory – people who love to write and document in detail, Legal, Pharmacists, Statisticians)

- Formal proposal for the FDA to approve a new drug for sale in the U.S.
- Must provide sufficient evidence for the FDA to decide:
  - Drug is safe and effective.
  - Benefits outweigh the risks.
  - Proposed labeling is appropriate.
  - Manufacturing methods and controls maintain drug identity, strength, quality, and purity.

NDA / BLA Review Process

(Careers: Quality Assurance/Control, Regulatory – people who love to write and document in detail, Legal, Pharmacists, Statisticians)

- **Biologics**
  - Center for Biologics Evaluation and Research (CBER)
- **All other drugs**
  - Center for Drug Evaluation and Research (CDER)

NDA Review Process

(Careers: Quality Assurance/Control, Regulatory – people who love to write and document in detail, Legal, Pharmacists, Statisticians)

- **Medical - clinical protocols, safety**
- **Biopharmaceutical - absorption, distribution, metabolism, and excretion**
- **Pharmacology - toxicity, therapeutic value**
- **Chemistry - chemical properties**
- **Microbiology - anti-infective drugs**
- **Statistical - results must be significant**

Registration and Market Launch

(Careers: Marketing and Sales)

- NDA must be approved.
- Must prove to FDA that you can safely produce drug.
  - Pre-approval inspection
  - 3 production batches
  - Development group justifies development process

For More Information…

www.fda.gov

FDA
U.S. Food and Drug Administration

BioPharm Guide to Biopharmaceutical Development