Drug Development Process

*Original Arthur:* Addie D. Anderson
CRB Consulting Engineers, Inc.
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

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

BioPharm Guide to Biopharmaceutical Development