Growing health care cost
- Grew from 8% of personal expenditure to over 20%
- Services are increasing in cost
- Drugs and goods are both increasing in cost

This creates prospect of only the rich receiving the best healthcare
History of Drug Regulation

- Modern FDA instituted in 1906 with Federal Food and Drugs Act
- Food Cosmetics and Drugs Act (1938)
- Durham Humphrey Amendment (1951)
- Kefauver-Harris Amendment (1962)
- Accelerated drug approval process
- Extension of patent term
• Defined standards
  – Purity
  – Quality
  – Cleanliness
  – Production

• Pre-approval process
  – Safety
  – Efficacy
  – Prescription/over-the-counter
  – Dosing instructions
Modern Drug Approval Process

**Phase 1**
- 100 healthy subjects
- Safety, efficacy
- 1-2 years

**Phase 2**
- 300 sick subjects
- Efficacy
- 2-4 years

**Phase 3**
- 1000s of subjects
- Different ethnic groups, sexes, etc
- Study reactions in all type of people
- 2-5 years

Animal Model
- similar to people
- i.e. LD50 test
- Test for general toxicity

Cellular, Human, Enzymatic Culture Test
- test for efficacy in vitro, unwanted effects

1 in 5000, ~350M

85% attrition, 3-7 years, ~150M
After finishing trial, apply for a New Drug Approval

Time limit of approval process
- 6 months for advantage drug
- 12 months for new drug

Once NDA is received, begin marketing process

Adverse Reaction Reporting

Testing/Sampling Drugs For Efficacy

Marketing claims and Advertising
Accelerated Approval

- Treatment INDs (Zidovudine (AZT) was approved fully in 107 days)
- Parallel track approval
- Accelerated Approval
  - Surrogate Endpoint (post-marketing assessment required)
  - Restricted distribution is a necessary part of the drug (drug requires clinical expertise to dose or advise)
Critiques

- Drug development costs (350M)
- Speed of process (drug lag)
- Selectivity of process (vs. Europe)
- Patent Law and generic equivalents

<table>
<thead>
<tr>
<th>FDA Approves Drug</th>
<th>Drug is Beneficial</th>
<th>Drug is Harmful</th>
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<tbody>
<tr>
<td>Correct Decision</td>
<td><strong>Type 1 Error:</strong></td>
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<td><strong>Type 2 Error:</strong></td>
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</table>
• With growing size/membership of HMOs and greater standard of care given to disadvantaged groups, costs must decrease

• Cannot compromise current standards or information release

• Type 1 and Type 2 error balance

• Minimizing Type 2 is current goal, and most current critique
• 3D protein structure databases
• Working on the amino acid sequence to protein shape
• Protein/molecule docking
• Allow us to match molecules against each other through fast computational processes
Use of bioinformatics to discover or de novo design drugs

- Reduces cost of development
- Boost percentage of drugs that make it through phase 1

Applications – Drug Companies

- Animal Model
  - similar to people
  - i.e LD50 test
  - Test for general toxicity

- Cellular, Human, Enzymatic Culture Test
  - test for efficacy in vitro, unwanted effects

1 in 5000, ~350M
• With ever growing database and docking algorithms, toxic interactions could be quickly determined
• From FDA’s point of view, little change to drug approval process – nothing beats human testing
• Make protein database securely public domain to aid drug development among all institutions, and to create common standards
• FDA veto power changed to certification
• Unapproved drugs could still be marketed
• Emergence of secondary/competing approval institutions, i.e. British approval

• Does not address stated critiques, including those from CEI
• Additional problems arise:
  – Generation of unproven, unreliable drugs: ‘tonics’, ‘elixirs’
  – Standard of care in hospitals
• Purpose of patent law: moves knowledge into public domain
• Important to maintain motivation for research and development of drugs
• Reasons for shortening patent term:
  – Obsolescence of drugs in 20 years?
  – Reduced costs of development and shortened approval process
  – Aggressive pricing models characteristic of monopolies until generics crop up
• Study genetic makeup of common ethnic/social backgrounds to produce a database of common genetic motifs that might be faced
• private company vs. FDA managed
• In combination with drug absorption and effect models, could provide an even more in depth look at efficacy of drugs before testing begins
• However, still not a replacement for actual testing
Suggested Policy Change in FDA

• More aggressive funding of certain parts of the approval process to aid drug development

• Closer monitoring of price controls (i.e. average total cost pricing to provide incentive for more efficient drug discovery process)

• More rigorous phase-4 (post marketing) tests to check toxicology, learn body systems
• Drug discovery/synthesis will shift away from high throughput discovery to more targeted development

• Discovery and synthesis will happen as small start-up/research firms

• Big pharmaceutical firms will specialize in developing, seeking approval and marketing drugs

• Paradigm shift driven by research, aided by larger availability of molecule reactivities
Selected Readings

- “Background” [http://www.bipolarworld.net/Research/background.htm](http://www.bipolarworld.net/Research/background.htm)
- “History of FDA” [http://www.fda.gov/oc/history/historyoffda/default.htm](http://www.fda.gov/oc/history/historyoffda/default.htm)
- “Pharmaceutical Research and Manufacturers of America” [http://phrma.org/policy/](http://phrma.org/policy/)