Teaching an Old Candyman New Tricks: Reforming the FDA

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Bioc118q Final Presentation
May 24, 2002

The Problem

- 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

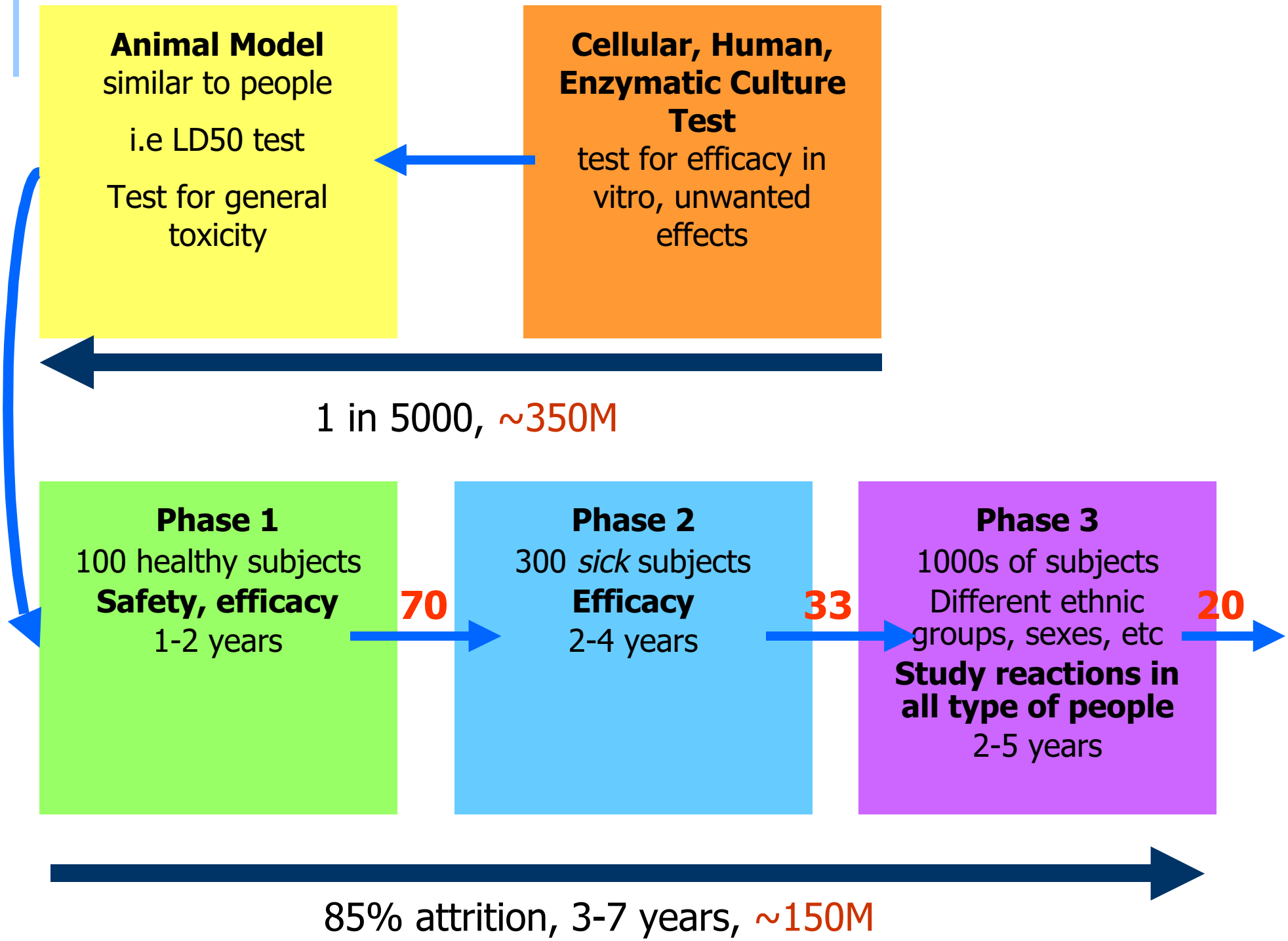
History of Drug Regulation

- 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

FDA and Drug Regulation

- Defined standards
  - Purity
  - Quality
  - Cleanliness
  - Production
- Pre-approval process
  - Safety
  - Efficacy
  - Prescription/over-the-counter
  - Dosing instructions

Modern Drug Approval Process



Post Approval Process

- 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

	Drug is Beneficial	**Drug is Harmful**
FDA Approves Drug	Correct Decision	**Type 1 Error: Highly Visible Self Correcting**
FDA Does Not Approve Drug	**Type 2 Error: Not Visible Not Self-Correcting**	Correct Decision

Reform to Drug Process

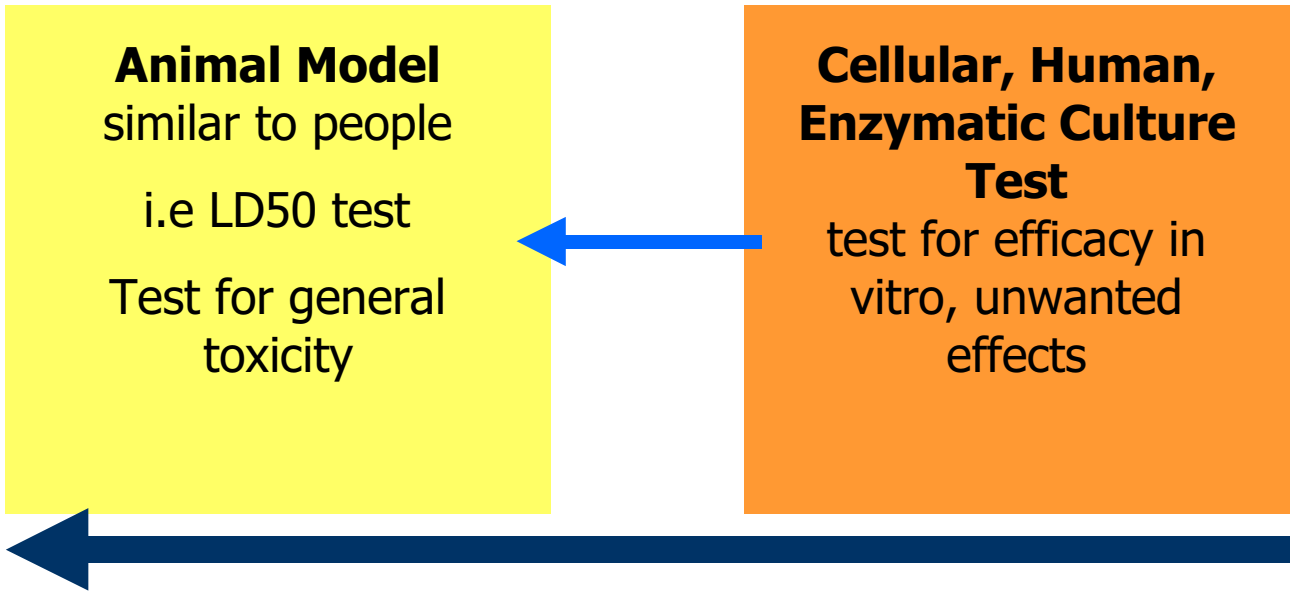
- With growing size/membership of HMOs and greater standard of care given to disadvantaged groups, costs **must** decrease
- Cannot compromise current standards or information release
- Type 1 and Type 2 error balance
- Minimizing Type 2 is current goal, and most current critique

Advancements of Bioinformatics

- 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

Applications – Drug Companies

- 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 - FDA

- 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

CEI Proposal for FDA Reform

- 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

Patent Law and Generic Drugs

- 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

Suggested Bioinformatics use in FDA

- 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

Movement of Drug Industry

- 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
- "CEI: Competitive Enterprise Institue: FDA vs. Reform" http://www.cei.org/gencon/025,01454.cfm
- "FDA Backgrounder: Milestones in U.S. Food and Drug Law History" http://vm.cfsan.fda.gov/mileston.html
- "FDA Drug Approval: Reform Considered" http://www.aegis.com/pubs/atn/1988/ATN06201.html
- "FDA Ensures Equivalency of Generic Drugs" http://www.fda.gov/fdac/special/newdrug/generic.html
- "FDA Review.org" http://www.fdareview.org/
- "From the Test Tube to the Patient: Drug Development in the United States" http://www.fda.gov/fdac/special/newdrug/ndd_toc.html
- "History of FDA" http://www.fda.gov/oc/history/historyoffda/default.htm
- "Proposal to Reform FDA's Approval Process" http://www.banned-books.com/truth-seeker/1995archive/122_2/ts222w.html
- "Pharmaceutical Research and Manufacturers of America" http://phrma.org/policy/