Drug Development & the FDA
Pharmacy 309 – November 2004

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TOXICOLOGY vs MECHANISM

GOVERNMENT AGENCIES INVOLVED
- FDA - Food and Drug Administration
- DEA - Drug Enforcement Administration
- EPA - Environmental Protection Agency
- OSHA - Occupational Safety and Health Administration
- CPSC - Consumer Product Safety Commission
- CMS - Center for Medicare/Medicaid Services

REGULATORY DEMANDS
- GLPs - Good Laboratory Practices
- GMPs - Good Manufacturing Practices
- GCPs - Good Clinical Practices
- ICH – EC, MHW,* FDA

*Japanese Ministry of Health and Welfare

NEW DRUG ATTRITION RATE
- 100,000 New Compounds
- 100 Tested in Humans
- 10 Marketed Drugs
- 2 Drugs Return a Profit
- CRO
  - Accelerates selection
  - Refines efficacy
  - Saves time & money

100 Tested in Humans
2 Drugs Return a Profit

10 Marketed Drugs
CRO
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100,000 New Compounds

Preclinical Evaluation
Clinical Evaluation

100 Tested in Humans
2 Drugs Return a Profit
10 Marketed Drugs
CRO
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100,000 New Compounds
##### DRUG APPROVAL PROCESS

<table>
<thead>
<tr>
<th>Years</th>
<th>6.1</th>
<th>1.5</th>
<th>2.4</th>
<th>3</th>
<th>2.3</th>
<th>Total=15.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Population</td>
<td>Lab and Animal Studies</td>
<td>20-80 Healthy Volunteers</td>
<td>100-300 Patient Volunteers</td>
<td>1000-3000 Patient Volunteers</td>
<td>Post-Marketing Safety</td>
<td></td>
</tr>
<tr>
<td>Purpose</td>
<td>Safety and Biological Activity</td>
<td>Determine Safety and Dosage</td>
<td>Efficacy and Safety</td>
<td>Efficacy and Safety of Long Term Use</td>
<td>Review Process</td>
<td></td>
</tr>
<tr>
<td>File IND</td>
<td>File NDA</td>
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Goal - reduce preclinical development to 3-4 years by employing state of the art biological sciences & technology

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##### An History of Disasters -- Drug Emphasis

- **Vaccine Act 1813**
  - fraudulent smallpox vaccines
- **Food & Drugs Act 1906**
  - Upton Sinclair, *The Jungle*
  - truthful label (strength & purity)
- **Food, Drug & Cosmetic Act 1938**
  - “elixir” of sulfanilamide
  - safety, IND, NDA, 60-day review

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##### History (2)

- **Durham-Humphrey Amendment 1951**
  - collateral measures necessary for “safe” use
  - “Caution: Federal law prohibits ...”
  - Rx to OTC switch
- **Kefauver-Harris Amendment 1962**
  - Thalidomide
  - effectiveness; 180 day NDA review
- **Guidelines for Reproductive Studies 1966**
  - public pressure

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##### History (3)

- **Orphan Drug Act 1983**
  - rare diseases
  - tax break; patent protection
- **ANDA 1984**
  - bioequivalence for generic drugs
- **Codification of IND Regulations 1987**
- **Expedited Approval, Serious & Life-Threatening Diseases (AIDS) 1994 [“Subpart E”]**
  - Phase 4
History (4)

- 1992 Prescription Drug User Fee Act
- 1994 Dietary Supplement Health And Education Act
- 1997 Food And Drug Administration Modernization Act reauthorizes PDUFA, advertising of unapproved uses of approved drugs and devices, and regulate health claims for foods, compounding
- 2000 Washington Legal Foundation [65 Federal Register 14286]
- 2002 Supreme Court ruling on First Amendment violations in FDAMA
- 2002-3 Pediatric Labeling – legislation / rulemaking / legal challenges

http://www.fda.gov/opacom/backgrounders/miles.html

Drug/Biologic History Summary

- truthful label (strength & purity)
- safety under conditions of intended use
- effectiveness under conditions of intended use
- adequate directions for use ... for almost everyone

Other “Interesting” Web Sites

- PhRMA – www.phrma.org
- Public Citizen – www.citizen.org

FDA Consumer
From Test Tube To Patient:
New Drug Development in the United States
Second Edition
January 1995
What is worse?

- regulators mistakenly ...
  - approve a dangerous or ineffective drug
  - fail to approve a beneficial drug

Olson MK. Pharmaceutical Policy Change and the Safety of New Drugs. *J Law Econ* 2002;45:615

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**Phases of Drug Development**

- idea
- “preclinical”
- Investigational New Drug Application (IND)
  - Phase 1
  - Phase 2
  - Phase 3
- New Drug Application (NDA)
  - Phase 4

http://www.fda.gov/oder/handbook/

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**Idea**

- objective: synthesis, isolation of active compound
- modes of discovery
  - "combinatorial" chemistry, Affymax
  - "traditional sources" -- Shaman Pharmaceuticals
  - human genome project
  - targeted discovery
  - dumb luck

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Idea (2)

- types of studies
  - purification
  - identification of impurities
  - computer simulations
  - validation, validation, validation
- time: years
- survival: 500,000 → 5,000

Pre-Clinical Development

- objective: pharmacology & toxicology in animals
- types of studies
  - acute toxicity
  - sub-acute toxicity (<3 months)
  - chronic toxicity (6-18 months)
  - reproductive, teratology, mutagenicity

Pre-Clinical (2)

- LD<sub>50</sub> Tissue culture methods
- ADME
  - Absorption, Distribution, Metabolism, Excretion
- study size: hundreds of animals
- time: 6.5 years
- survival: of 5000 pre-clinical → 5 INDs

Phase 1

- objective: safety, dose ranging, pk/pd in “normals”
- types of studies
  - first exposure in humans
  - single dose tolerability
  - multiple dose tolerability
  - dose-ranging based on animal doses
Phase 1 (2)

- study size: 20-80
- time: 2-3 years
- survival
  - 80% proceed to Phase 2
  - 5 \rightarrow 4

Phase 1 Failures

- pre-clinical animal models \neq behavior in humans
- inadequate preclinical data
- change in drug formulation between time of pre-clinical and clinical testing
- pk/pd relationships
- poorly designed clinical studies
- drug too toxic in humans

Phase 2 Clinical Studies

- objectives: testing an hypothesis of no difference; safety
- types of studies: small controlled trials in patients
- dose ranging
- study size: 100-300
- time: months - 2 years
- survival: 2 go on to Phase 3

Phase 3 Clinical Studies

- objective: testing an hypothesis of no difference; safety
- targeted patients
- "well controlled" studies
  - placebo-controlled
  - double blinded
  - multi-centered (bias)
- size: 100’s - 1000’s
- time: 1-4 years
- survival: 1
Phase 2 & 3 Failures

- infrequent adverse reactions observed; but ...
- drug-drug interactions
- drug-disease interactions in ill patients
- genetic
- effectiveness insufficient (20%)
- economic (24%)

Application Types

- **New Drug Application** (NDA) (Center for Drug Evaluation and Research - CDER)
  - manufacturing facility approval included in application review
  - includes some "well characterized biologicals"
- **Biologics License Application** (BLA)(Center for Biologics - CBER)
- **510(k) | Premarket Approval** (PMA)(Center for Devices and Radiological Health - CDRH)
- Office of Combination Products

NDA | BLA

- FDA has 180 days for review
  - FDA judges both benefit (efficacy) and risks (safety)
  - one specific indication is approved
- Average drug approval story
  - 1:350,000 approved
  - cost ~ $500 million
  - time ~ 15 years

Phase 4

- post marketing surveillance
  - negotiation
  - accelerated approval for therapies for serious and life-threatening diseases (Subpart E)
  - targeted studies for cause
  - other stages of diseases, other sub-populations, drug-drug interactions, "off-label" uses
- Prescription Drug User Fee Act (PDUFA3) "mandates"
Safety & Efficacy

- **Under conditions of intended use**
  - limitations of “well controlled” studies
  - relevance of clinical trial information to alternate (“off label”) uses
- “promotion” of off label uses
- domestic (dis)incentives to conduct studies of alternate uses
- PDUFA

International Conference on Harmonisation

- US, European Union & Japan
  - efficacy (human clinical trials)
  - safety (animal pharmacology / toxicology)
  - quality (manufacturing)
  - regulatory communication