Dr. Flexner is disclosing the following potential conflicts as required by the University:

- Research grants and contracts: NIH, GSK, Merck, Xceleron
- Consulting: Boehringer-Ingelheim, BMS, Clinton Foundation, Gates Foundation, Genzyme, Inhibitex, Merck, Roche, Schering-Plough, Tibotec, Virostatics
- Honoraria: NIH, Abbott
- Stockholder and equity: none to report.
- Patents and intellectual property: none to report.
WHAT YOU SHOULD KNOW

Learning Objectives:
1. Differences between Phase I, II, III, and IV studies.
2. Definition of an IND and an NDA, and when each is used in drug development.

OBJECTIVES OF DRUG DEVELOPMENT:

Who Wants What???
OBJECTIVES OF DRUG DEVELOPMENT:

CONSUMERS

• Rapid access to effective, affordable, and safe drugs
OBJECTIVES OF DRUG DEVELOPMENT:

INDUSTRY
• Make a profit

OBJECTIVES OF DRUG DEVELOPMENT:

THE FDA
• Don’t make a mistake

OBJECTIVES OF DRUG DEVELOPMENT:

ACADEMIA
• Gain scientific and professional notoriety
  – (i.e., become famous)
THE HISTORY OF DRUG DEVELOPMENT

• Chance Observation
• Trial-and-Error
• Targeted Screening
  - The “Magic Bullet” (Paul Ehrlich)
  - The “Lock and Key” Model of Drug Effect
    (Louis Pasteur and “anti-bodies”)

DRUG DISCOVERY

• Identify the “lock”
• Develop a panel of chemical “keys”
• Rapid-throughput screening
• Use in \textit{in vitro} or \textit{in vivo} model systems
• Exploit a chance observation

ECONOMICS OF DRUG DEVELOPMENT*

• Only 1 in 30,000 screened chemicals becomes a licensed drug.
• Only 1 in 10 drugs that enter clinical testing becomes a licensed drug.
• Only 1 in 5 licensed drugs ever generates enough revenue to cover research and development (R&D) expenditures.

*Source: Pharmaceutical Research and Manufacturers Assoc.
ECONOMICS OF DRUG DEVELOPMENT

• It costs on average $0.8-1.0 billion to get a new drug developed and licensed.*
• Average length of time from patent filing to NDA approval is 8-10 years.*
• Expected annual revenues must be $50 – 100 million.
• Focus on “blockbuster” drugs.

*Source: Pharmaceutical Research and Manufacturers Assoc.

TOP SELLING DRUGS -2003*

<table>
<thead>
<tr>
<th>DRUG (Trade Names)</th>
<th>INDICATION</th>
<th>U.S. SALES (Billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipitor</td>
<td>High cholesterol</td>
<td>$6.3</td>
</tr>
<tr>
<td>Zocor</td>
<td>High cholesterol</td>
<td>$4.2</td>
</tr>
<tr>
<td>Prevacid</td>
<td>Acid reflux</td>
<td>$3.7</td>
</tr>
<tr>
<td>Procrit</td>
<td>Anemia</td>
<td>$3.2</td>
</tr>
<tr>
<td>Zyprexa</td>
<td>Schizophrenia</td>
<td>$3.1</td>
</tr>
<tr>
<td>Prilosec</td>
<td>Acid reflux</td>
<td>$2.9</td>
</tr>
<tr>
<td>Epogen</td>
<td>Anemia</td>
<td>$3.0</td>
</tr>
<tr>
<td>Zoloft</td>
<td>Depression</td>
<td>$2.6</td>
</tr>
<tr>
<td>Celebrex</td>
<td>Pain</td>
<td>$2.6</td>
</tr>
<tr>
<td>Paxil</td>
<td>Depression</td>
<td>$2.3</td>
</tr>
</tbody>
</table>

*Source: IMS Health, Ltd.

ECONOMICS OF DRUG DEVELOPMENT

• 15-25% of overall health care expenditures, but a moving target:
  ➢ Standards of care/drugs-of-choice change from year to year.
  ➢ Prescribing practices/formularies are easily regulated.
  ➢ Trade-off between the cost of expensive new treatments, and savings from reduced hospital days and reduced patient morbidity.
ECONOMICS OF DRUG DEVELOPMENT

• $420 billion spent on prescription drugs in the U.S. in 2005.
• Estimated $820 billion will be spent on prescription drugs in the U.S. in 2016.
• Increasing markets for generic drugs
  – $70 billion estimated in 2009
• Major sales growth is outside the U.S.
  – Europe, China, India
  – Source: U.S. Bureau of Economic Analysis

ECONOMICS OF DRUG DEVELOPMENT

• Competition between generic and “branded” prescription drugs:
  – 2003: Generics are 54% of treatments dispensed in the U.S.
  – 2008: Generics are 69% of treatments dispensed in the U.S.

Globalization of Drug Development

THE ECONOMIC TIMES

Ranbaxy set to launch India’s first malaria drug

NEW DELHI: India may have its own anti-malaria drug soon. Drug major Ranbaxy has successfully completed the phase II clinical trials for the first malaria drug being developed in the country. The company is expected to start marketing the drug three to five years from now.

“The proof-of-phasing for phase II of the trials have been successfully undertaken and the drug will now undergo phase III of trials before being introduced in the market,” Ranbaxy’s senior VP for new drug discovery research Pradip Bhatnagar said on the sidelines of a seminar. Ranbaxy has been working on the anti-malaria segment since May 2003. Earlier, it was a collaborative research project with the Geneva-based Medicines for Malaria Venture (MMV) to develop the synthetic peroxide anti-malarial drug but MMV walked out of the joint project in November 2007.

The company has not yet decided on any trade name for the drug research. The company plans to export the anti-malaria drug to Asian, African and South American countries at an affordable cost. Despite having a huge market for malaria in developing countries, the market segment has very limited resources.
PHASES OF DRUG DEVELOPMENT

• Pre-Clinical/Non-Clinical
• Phase 1
• Phase 2
• Phase 3
• Phase 4

PRE-CLINICAL DRUG DEVELOPMENT

• Efficacy and Mechanism of Action
• Toxicology (including teratogenicity and carcinogenicity)
• Pharmacokinetics/ADME
  – Absorption, Distribution, Metabolism, Excretion
• Pharmaceutics (including formulation development)

CLINICAL DRUG DEVELOPMENT

PHASE I

➢ Objectives:
  • Short-term Safety and Tolerance
  • Pharmacokinetics
➢ Subjects: Healthy Volunteers (usually)
➢ Sample Size: Tens
➢ Duration: Days or Weeks
**CLINICAL DRUG DEVELOPMENT**

**PHASE II**
- Objectives:
  - Medium-term Safety and Tolerability
  - Initial evidence of beneficial activity
- Subjects: Patients (usually)
- Sample Size: Hundreds
- Duration: Weeks or Months

**CLINICAL DRUG DEVELOPMENT**

**PHASE III**
- Objectives:
  - Long-term Safety and Tolerability
  - Clinical Efficacy
- Subjects: Patients
- Sample Size: Thousands
- Duration: Years

**CLINICAL DRUG DEVELOPMENT**

**PHASE IV**
- Objectives:
  - Post-marketing surveillance
  - Develop new indications
  - Study special patient populations
  - Study “real world” effectiveness and toxicity
- Subjects: Patients
- Sample Size: Thousands (usually)
- Duration: Often retrospective
DRUG REGULATION: THE FDA

• History:
  • 1906, Upton Sinclair’s The Jungle
    - The Federal Food and Drug Law
  • 1938, Massengill’s Sulfanilamide
    - Federal Food Drug and Cosmetic Act
  • 1962, Thalidomide
    - Kefauver-Harris Drug Amendment

DRUG REGULATION: THE FDA

RECENT HISTORY

• Vioxx recall
• E. coli, tainted beef recall
• Salmonella outbreak mismanagement
• “Fen-Phen” toxicity recall
• Ephedra recall
• Pacemaker and heart valve recalls

Drug Development:

Some definitions
WHAT IS A DRUG?
• Any chemical administered with therapeutic intent.
• Distinct from:
  - Foods
  - Health foods
  - GRAS substances
• Orphan drugs
  – Intended for conditions affecting <200,000

DRUG REGULATION: THE IND
• Required for investigational new drugs
• Required for approved drugs if:
  - Change in the drug label (package insert)
  - Significant changes in advertising claims
  - A new route of administration, formulation, dose or patient population with significant increase in risk
  - IRB (Human Subjects Board) requirement

DRUG REGULATONS: THE NDA
• New Drug Application = data submitted to support marketing approval of an investigational new drug.
• Reviewed by an Advisory Committee (mostly academicians) who make a recommendation for approval or disapproval.
• FDA not obliged to follow Advisory Committee recommendations.
THE FUTURE OF DRUG DEVELOPMENT

- Competition from Generic Drugs – YES
- Privatization of Drug Development - YES
- Globalization of Drug Development - YES
- Combinatorial Chemistry - ?
- Pharmacogenomics - ?
- Simulated Clinical Trials - ?