The Changed Context of Drug Discovery and Development

The 1800s: natural sources; limited possibilities; prepared by individuals; small scale; not purified, standardised or tested; limited administration; no controls; no idea of mechanisms.

The 1990s: synthetic source; unlimited possibilities; prepared by companies; massive scale; highly purified, standardised and tested; world-wide administration; tight legislative control; mechanisms partly understood.

How Are Drugs Discovered?

- Random screening of natural products
- Rational drug design (combinatorial chemistry, pharmacology, bioinformatics, etc.)
- Biotechnology and cloning using genes to make proteins
- Luck!

Pre-clinical studies

- To assess primary safety & activity
- In vitro models, in vivo models
- Battery of screens, dose response tests,
- PK, PD

Levels of Pre-clinical Activity Testing

- DRUG + receptor + transduction system (second messenger; enzyme)
- BIOCHEMICAL TESTING
- Anaesthetised or conscious animals
- WHOLE ANIMAL EXPERIMENTS
Preclinical Safety and Toxicology Testing

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Safety Tests</th>
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Limitations of Preclinical Testing

- Time consuming and expensive.
  - Approximately $41 million per successful drug
- 2-5 years to collect and analyze data
- Large numbers of animals used to obtain data.
- Extrapolation of toxicity data from animals to humans is not completely reliable.
- For statistical reasons, rare adverse effects are unlikely to be detected.

Evaluation in Humans

Clinical Trials

- When ready to study in humans, a Notice of Claimed Investigational Exemption for a New Drug (IND) must be filed with the FDA, which includes:
  1. Information on the composition and source of the drug.
  3. All data from animal studies.
  5. Names and credentials of M.D.’s who will conduct the trials.
- FDA-30 day Safety Review

Clinical Trials

- Phase 1
- Phase 2
- Phase 3
- Phase 4
Phase 1
- Effects of the drug as a function of dosage are established in a small number (25-50) of healthy volunteers.
- Establish limits of safe clinical dosage range.
- Pharmacokinetic measurements: absorption, half-life, metabolism.
- Short term

Phase 2
- Drug is tested for the first time in patients with the target disease to determine efficacy, safety, optimum dose.
- Small number of patients studied in great detail (10-300).

Phase 3
- Large numbers of patients (thousands) to further establish safety and efficacy.
- Designed to minimize errors by placebo effects and variable course of the disease. Done in multicenters.
- Difficult to design and execute.
- Expensive.

Clinical Trial Designs
- double-blind
- randomised
- placebo-controlled
- crossover
- washout

Clinical Trials
- controlled or uncontrolled
- open or blind
- parallel
- sequential
- cross-over

New Drug Application (NDA)
- After the three clinical phases.
- Full reports of all preclinical and clinical testing pertaining to the drug under review for FDA approval.
- Approval may take 1-3 years (50-400 volumes, 30,000-150,000 pages)
Clinical Trials: Main Questions

- **Phase I**
  - What are the side effects?
  - Is it safe enough to test?
- **Phase II**
  - Does it work at all?
  - What is the dosage range?
- **Phase III**
  - Is it better than placebo?
  - Is it better than other treatments?
  - What are the side-effects

**The Long Road to a New Medicine**

**Drug Discovery Approaches**

**Very Costly & Long Process:**
11-15 Years, $800MM+

- Millions of Compounds Screened
- Preclinical Pharmacology
- Preclinical Safety
- Clinical Pharmacology & Safety

**New Drugs Sales Curve**

**Classic sales curve**

- Unit sales
- Time
- Serious side effects
- Not always effective
- Balanced view of advantages & problems
- Appreciate where best used and risks

**When a drug goes to market, we know everything about its safety!**

**WRONG**

**Phase IV studies**

- Occurs after approval to market drug
- Long term safety, efficacy under actual conditions of use in large numbers of patients: **ADR**
- Special populations
- New formulations
- Marketing
Adverse Drug Reactions

Any response to a drug that is noxious and unintended
- Significant
  - fatal
  - life-threatening
  - disabling
  - hospitalization or prolonged hospitalization
  - teratogenic effect

Postmarketing Surveillance
- Because of the small numbers of patients in Phase 1-3, drug effects with very low incidence will generally not be detected.
- Phase I-III studies:
  - Narrow population
  - Narrow set of indications
  - Short term studies
- Establishing the association between ADR with a drug requires large numbers of subjects: ~15-20 times the number of people in which the ADR would be expect to occur 1 time (statistical Significance).

SUMMARY OF TIME LAGS AFTER U.S. MARKETING BEFORE ADVERSE DURG REACTIONS WERE WIDELY RECOGNIZED

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Reaction</th>
<th>Time Lag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives</td>
<td>Pulmonary embolism</td>
<td>3</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Myocardial infarction</td>
<td>5</td>
</tr>
<tr>
<td>Sympathomimetic aerosols</td>
<td>Deaths from asthma</td>
<td>4</td>
</tr>
<tr>
<td>Halothane</td>
<td>Jaundice</td>
<td>7</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>Colitis</td>
<td>6</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Colitis</td>
<td>5</td>
</tr>
</tbody>
</table>

MedWatch
- FDA’s “postmarketing surveillance”
- Depends on Doctors, dentists, nurses, pharmacists to pass on info to FDA about serious adverse reactions
- Formed in 1993
- Voluntary
- Confidential
Sources of Data For Post-Marketing Safety Assessment

- Spontaneous reports to FDA by the MD’s
- Case series
- Observational studies
- Formal epidemiological studies
- Others

Safety-Based Drug Marketing Withdrawals in the U.S., 1980-2000

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Reason</th>
</tr>
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<tbody>
<tr>
<td>1980</td>
<td>Selacryn</td>
<td>Acute liver failure</td>
</tr>
<tr>
<td>1982</td>
<td>Oraflex</td>
<td>Acute liver failure</td>
</tr>
<tr>
<td>1983</td>
<td>Zomax</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>1986</td>
<td>Merital</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>1987</td>
<td>Suprol</td>
<td>Flank-pain</td>
</tr>
<tr>
<td>1991</td>
<td>Calban</td>
<td>Esophageal obstruction</td>
</tr>
<tr>
<td>1991</td>
<td>Enkaid</td>
<td>Excess mortality</td>
</tr>
<tr>
<td>1992</td>
<td>Omniflex</td>
<td>Hemolytic-uremic synd</td>
</tr>
<tr>
<td>1993</td>
<td>Manoplax</td>
<td>Excess mortality</td>
</tr>
<tr>
<td>1997</td>
<td>Pondimin</td>
<td>Valvular disease</td>
</tr>
<tr>
<td>1997</td>
<td>Redux</td>
<td>Valvular disease</td>
</tr>
<tr>
<td>1998</td>
<td>Seldane</td>
<td>Interactions; Torsades</td>
</tr>
<tr>
<td>1998</td>
<td>Duract</td>
<td>Acute liver failure</td>
</tr>
<tr>
<td>1998</td>
<td>Posicor</td>
<td>Interactions; Torsades</td>
</tr>
<tr>
<td>1999</td>
<td>Trovan</td>
<td>Acute liver failure</td>
</tr>
<tr>
<td>2000</td>
<td>Rezulin</td>
<td>Acute liver failure</td>
</tr>
<tr>
<td>2000</td>
<td>Propulsid</td>
<td>Sudden death, Torsades</td>
</tr>
</tbody>
</table>

HOW DID WE GET THERE?

Laws Regulating Availability & Distribution of Drugs

A Historical Perspective

Prescription Drug Regulation

- Good Old Days
  - In the Early 1900s You Could Get Anything You Wanted: Medicine men in traveling wagons shows or doctors
  - No Concern for People Poisoning Themselves: not required to list ingredients on label
  - Few Effective Drugs
  - Limited Rationale for Physician Supervision
  - Heroin Was the Hero Drug Because It Saved People From Morphine
Drug Regulation: A Historical Perspective

- **Federal Food and Drug Act of 1906**
  - Labeling accuracy to eliminate adulteration
  - Interstate transport of foods and drugs
  - Purity & strength (USP, NF)

- **Amended Act in 1938**
  Truthful labeling and safety of drugs.
  New Drug Application (NDA) required for safety.
  NO EFFICACY DATA required.

Thalidomide

- Hypnotic drug used in the 1960’s.
- No obvious advantage over other drugs in its class.
- Increased incidence of limb defects.
- Retrospective study established Thalidomide as cause.

Harris-Kefauver Amendments

- Require sufficient pharmacological and toxicological research in animals before testing in humans.
- Data from these studies submitted to FDA in form of Investigational New Drug (IND) Application.
- **Proof of EFFICACY.**
- Documentation of relative safety in terms of risk-to-benefit ratio.
- Increased the time and cost to market a new drug.

More Recent Legislation

- The Orphan Drug Act, 1983: grants to encourage research to find drugs for rare chronic diseases (leprosy, Cystic fibrosis, rare cancers) - 500 new drugs
- Prescription Drug Marketing Act, 1987
- Analogue (Designer Drug) Act, 1986
- Anti-Drug Abuse Act, 1988 (ONDCP)
- Anabolic Steroids Control Act, 1990

Laws Regulating Manner of Drugs Dispensing

A Historical Perspective
### Laws Regulating Manner of Drugs Dispensing

- **The Durham-Humphrey Amendment of 1952**
  - Establish "legend" drugs: "Caution: Federal laws prohibits dispensing without prescription"
  - Prescriptions refill
  - Recognized the OTC drugs

- **Controlled Substances Act in 1970**
  - Classified controlled substances into schedules (flexible)
  - Requires that prescribers and dispensers register with the Drug Enforcement Agency (DEA)

### Schedules

- **Schedule I**: Highest abuse potential, no medical use in the U.S.
  - Potential for Abuse: HIGH
  - No accepted medical use
  - Prescriptions may not be written for this class.
  - Possession or use are illegal
  - Examples: heroin, marijuana, PCP, LSD

- **Schedule II**: High abuse potential, but, may be used medicinally
  - Potential for Abuse: HIGH
  - Current accepted medical use.
  - Abuse may lead to severe psychological or physical dependence
  - Written prescriptions necessary
  - Examples: Oxycodone, morphine, methylphenidate, cocaine, $\Delta^9$-THC
  - NO REFILLS
  - Cannot be "called in"

- **Schedule III**: Limited dependence potential
  - Potential for abuse: Less than I or II
  - Current accepted medical use.
  - Limited potential for dependence.
  - Five refill maximum.
  - May not be refilled after 6 months from date of prescribing
  - Examples: Lortab, Tylenol #3,

- **Schedule IV**: Lower abuse potential than I & II
  - Potential for abuse: less than III.
  - Current accepted medical use.
  - Limited potential for dependence.
  - Five refill maximum.
  - Cannot be refilled after 6 months from date of writing prescription
  - Examples: Xanax, Valium

- **Schedule VI (Virginia)**: all legend drugs not included in other schedules
Schedule V

- Limited Abuse Potential
- No refill limitations
- Examples: Lomotil

Questions????