DRUG EVALUATION & REGULATION

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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!

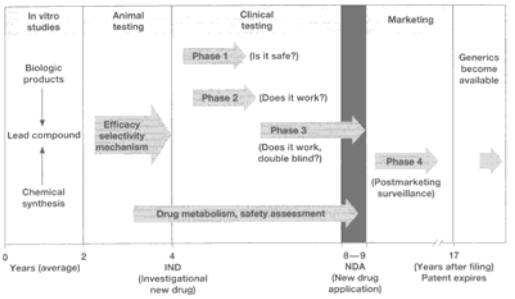
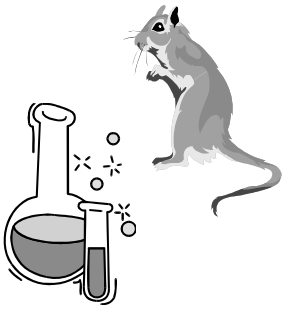


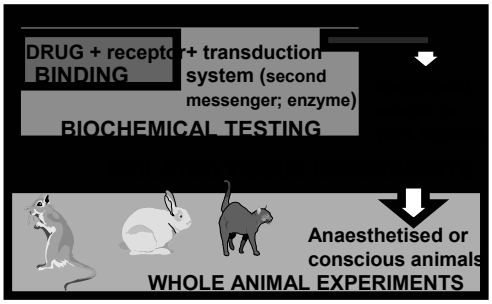
Figure 5–1. The development and testing process required to bring a drug to market in the USA. Some requirements may be different for drugs used in life-threatening diseases. (Reproduced, with permission, from Katzung BG [editor]: *Basic and Clinical Pharmacology*, 6th ed. Appleton & Lange, 1995.)

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



Preclinical Safety and Toxicology Testing

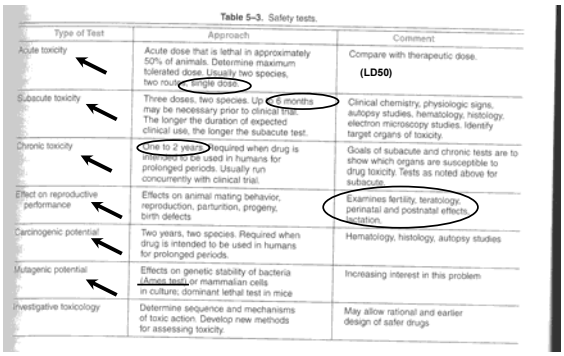


Table 5–3. Safety tests.

Type of Test	Approach	Comment
Acute toxicity	Acute dose that is lethal in approximately 50% of animals. Determine maximum tolerated dose. Usually two species, two routes, single dose.	Compare with therapeutic dose. (LD50)
Subacute toxicity	Three doses, two species. Up to 6 months may be necessary prior to clinical trial. The longer the duration of expected clinical use, the longer the subacute test.	Clinical chemistry, physiologic signs, autopsy studies, hematology, histology, electron microscopy studies. Identify target organs of toxicity.
Chronic toxicity	One to 2 years required when drug is intended to be used in humans for prolonged periods. Usually run concurrently with clinical trial.	Goals of subacute and chronic tests are to show which organs are susceptible to drug toxicity. Tests as noted above for subacute.
Effect on reproductive performance	Effects on animal mating behavior, reproduction, parturition, progeny, birth defects	Examines fertility, teratology, perinatal and postnatal effects, lactation.
Carcinogenic potential	Two years, two species. Required when drug is intended to be used in humans for prolonged periods.	Hematology, histology, autopsy studies
Mutagenic potential	Effects on genetic stability of bacteria (Ames test) or mammalian cells in culture; dominant lethal test in mice	Increasing interest in this problem
Investigative toxicology	Determine sequence and mechanisms of toxic action. Develop new methods for assessing toxicity.	May allow rational and earlier design of safer drugs

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.
  2. Manufacturing information.
  3. All data from animal studies.
  4. Clinical plans and protocols.
  5. Names and credentials of M.D.'s who will conduct the trials.
- FDA-30 day Safety Review

U.S. Department of Health and Human Services
Food and Drug Administration

Clinical Trials

- Usually requires 4-6 years accumulate data.
- Can only begin after animal toxicity studies have been completed.
- Volunteers or patients must be informed of the investigational status of the drug and possible risks and must give informed consent.
- Institutional Review Board at the facility where trial will be conducted must review and approve plans for testing in humans.

Clinical Trials

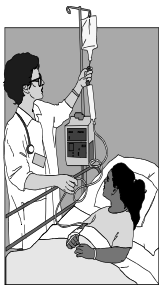
- Phase 1
- Phase 2
- Phase 3
- Phase 4

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

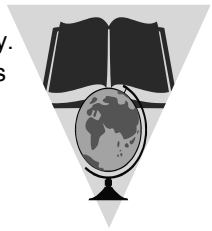
Phase 2

- 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).



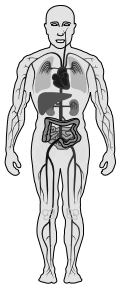
Phase 3

- 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

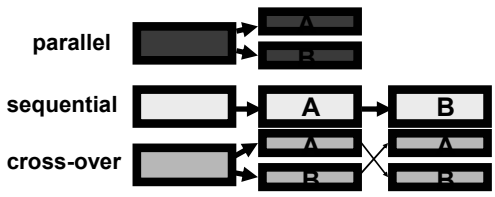
- double-blind
- randomised
- placebo-controlled
- crossover
- washout



Clinical Trials

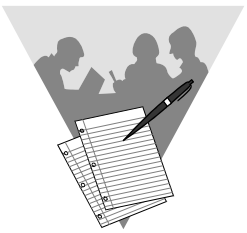
controlled or uncontrolled

open or blind



New Drug Application (NDA)

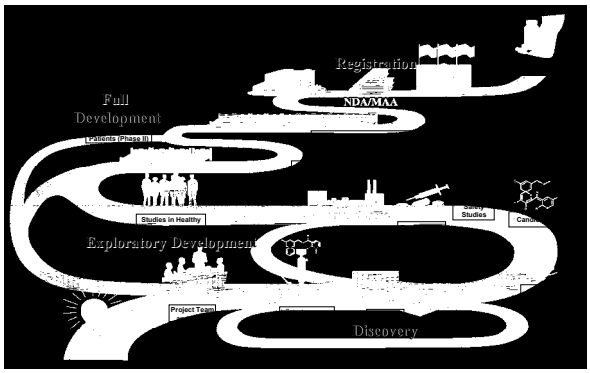
- After the three clinical phases.
- Full reports of all preclincial and clinical testing pertaining to the drug under review for FDA approval.
- Approval may take 1-3 years (50-400 volumes, 30,000-150,000 pages)

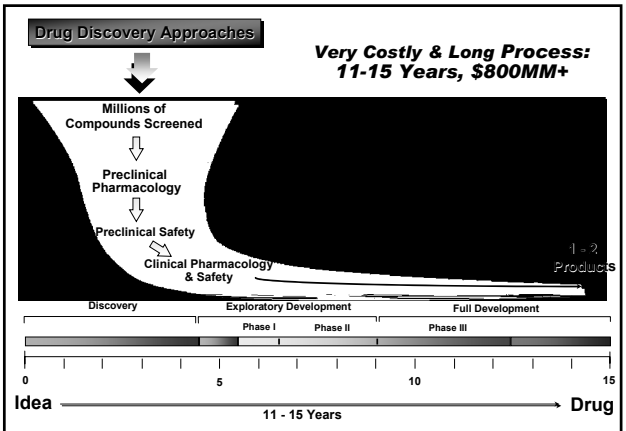


Clinical Trials: Main Questions

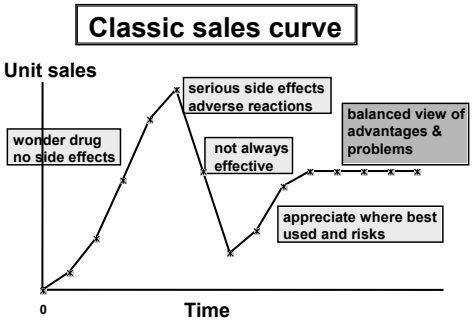
- Phase I
  - What are the side effects?
  - Is it safe enough to test?
- Phase II
  - Does it work at all?
  - What is the dosage range?
- Phase III
  - Is it better than placebo?
  - Is it better than other treatments?
  - What are the side-effects

The Long Road to a New Medicine

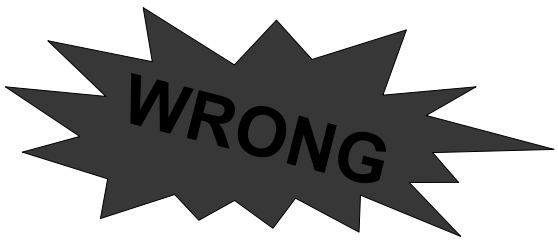




New Drugs Sales Curve

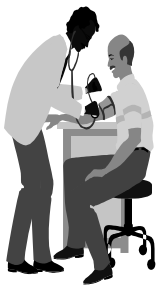


When a drug goes to market, we know everything about its safety!



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

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

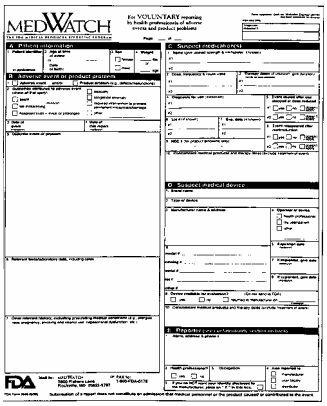
- Because of the small numbers of patients in Phase 1-3, drug effects with very low incidence will generally not be detected.
- Phase I-III studies:
  - Narrow population
  - Narrow set of indications
  - Short term studies
- Establishing the association between ADR with a drug requires large numbers 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

Drug (yr)	Adverse Reaction	Time Lag
Oral contraceptives	Pulmonary embolism	3
Oral contraceptives	Myocardial infarction	5
Sympathomimetic aerosols	Deaths from asthma	4
Halothane	Jaundice	7
Lincomycin	Colitis	6
Clindamycin	Colitis	5

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

1980	Selacryn	Acute liver failure
1982	Oraflex	Acute liver failure
1983	Zomax	Anaphylaxis
1986	Merital	Hemolytic anemia
1987	Suprol	Flank-pain
1991	Calban	Esophageal obstruction
1991	Enkaid	Excess mortality[1]
1992	Omniflox	Hemolytic-uremic synd
1993	Manoplax	Excess mortality[1]
1997	Pondimin	Valvular disease
1997	Redux	Valvular disease
1998	Seldane	Interactions; Torsades
1998	Duract	Acute liver failure
1998	Posicor	Interactions; Torsades
1999	Trovan	Acute liver failure
2000	Rezulin	Acute liver failure
2000	Propulsid	Sudden death,Torsades

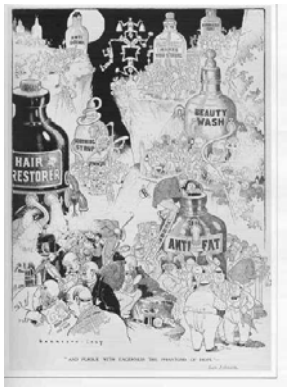
HOW DID WE GET THERE?

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

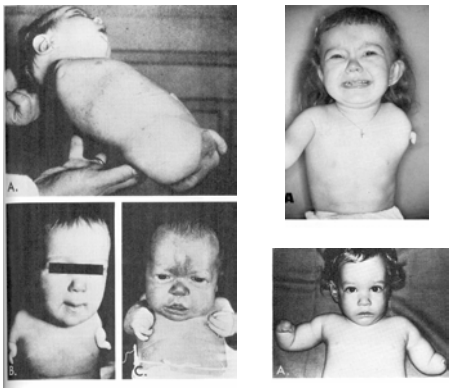


Drug Regulation: A Historical Perspective

- **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**
  Food, Drug, and Cosmetic Act.
  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.
- Resulted in **Harris-Kefauver Amendments** to the Food, Drug and Cosmetic Act in 1962.



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
- http://www.druglibrary.org/schaffer/History/drug_law_timeline.htm

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.
- *Schedule II:* High abuse potential, but, *may be used medicinally*
- *Schedule III:* Limited dependance potential
- *Schedule IV:* Lower abuse potential than I & II
- *Schedule V:* Lowest potential for abuse
- *Schedule VI (Virginia): all legend drugs not included in other schedules*

Schedule I

- 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

- 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, Δ^9-THC
- NO REFILLS
- Cannot be "called in"

Schedule III

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

Schedule IV

- 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 V

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