

# DRUG DEVELOPMENT EVALUATION AND CONTROL

- regulatory issues (eg, drug development, scheduling)

# Basic & Clinical Evaluation of New Drugs



- **Regulatory issues (eg, drug development, approval, scheduling)**
- **For collateral reading, see Katzung Chapter 5**

- **During the past 60 years, new drug developments have revolutionized the practice of medicine, and allowed doctors to effectively treat many once fatal diseases.**
- **One cause of this medical advance has been a fundamental improvement in the means of developing and testing new drugs.**
- **This process has been greatly accelerated by new technology, by financial motivation, and by governmental support of medical research.**
- **In most countries, the testing of drugs is now regulated by legislation and closely monitored by governmental agencies.**
- **This lecture summarizes the process by which new therapeutic agents are discovered, developed, and regulated. While the examples used reflect the USA experience, the pathway of new drug development generally is the same worldwide.**

- **The first step in the development of a new drug is the discovery or synthesis of a potential new drug molecule.**
- **By law, the safety and efficacy of drugs must be defined before they can be marketed.**
- **In addition to in vitro studies, most of the biologic effects of the molecule must be characterized in animals before human drug trials can be started.**
- **Human testing must then go forward in three conventional phases before the drug can be considered for approval for general use.**
- **A fourth phase of data gathering follows after approval for general use.**

- **Enormous costs, from \$100 million to over \$500 million, are invested by pharmaceutical companies in the development of a single successful new drug.**
- **These costs include the labor invested in searching for useful new molecules— 5000— 10,000 may be synthesized for each successful new drug introduced—and the costs of detailed basic and clinical studies and promotion of the ultimate candidate molecule.**
- **On the other hand, it has been estimated that during the second half of the 20th century, medications produced by the pharmaceutical industry saved more than 1.5 million lives and \$140 billion in the costs of treatment for tuberculosis, poliomyelitis, coronary artery disease, and cerebrovascular disease alone.**

# ● DRUG DISCOVERY

● Most new drug candidates are identified through one or more of four approaches:

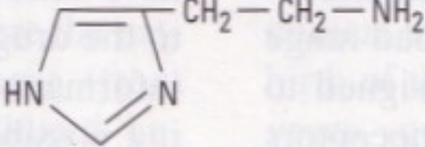
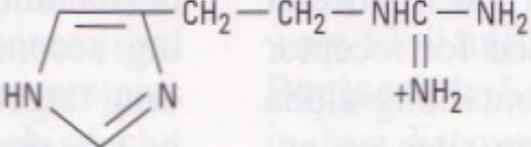
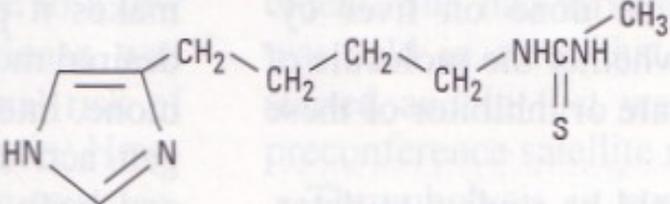
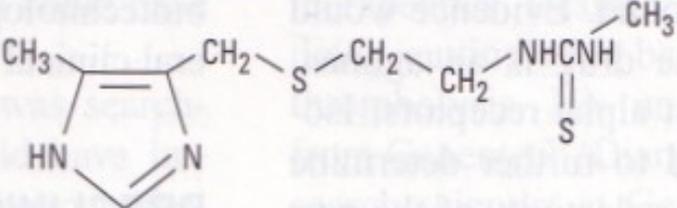
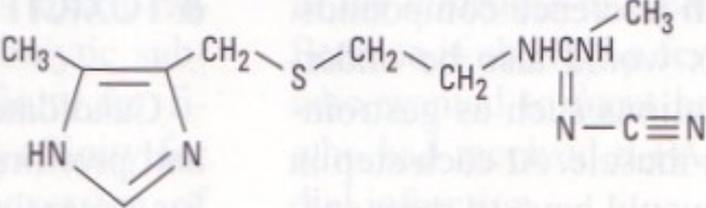
● (1) **chemical modification of a known molecule**; the development of the thiazide diuretics by chemical modification of the much less useful carbonic anhydrase inhibitors is an example of this approach.

● (2) **random screening for biologic activity of large numbers of natural products**, banks of previously discovered chemical entities, or large libraries of peptides, nucleic acids, or other organic molecules; **the discovery of many antibiotics and cyclosporine, an immunosuppressant drug, by random screening of soil samples illustrates the second approach.**

● (3) **rational drug design based on an understanding of biologic mechanisms and chemical structure**; and, increasingly,

● **An early example of this third approach was the development of H<sub>2</sub> histamine antagonists. Based on the suspected existence of different types of histamine receptors, rational molecular modification led to the gradual improvement of antagonist selectivity and potency, culminating in the introduction of cimetidine (Table 5—1).**

# A history of the development of H<sub>2</sub> blockers

Compound and Characteristics	Structure	Antagonist Activity (in vivo ID <sub>50</sub> μmol/kg) <sup>1</sup>
<b>Histamine</b> The starting point.		Agonist
<b>N-Guanylhistamine</b> The first lead compound. A weak partial agonist.		800
<b>Burimamide</b> Thiourea compound with a longer side chain. Weakly active in humans.		6.1
<b>Metiamide</b> Active in humans but toxic.		1.6
<b>Cimetidine</b> Replaces the thiourea with an N-CN substituent. Retains high potency with decreased toxicity. Launched the major series of drugs for the treatment of acid-peptic disorders.		1.4

- Rational design has made major strides recently, as illustrated by the development of angiotensin-converting enzyme inhibitors from a study of the structure-activity relationships of enzyme active site inhibitors and by the current development of hypothetical drug structures with computer assistance.
- **(4) biotechnology and cloning using genes to produce larger peptides and proteins.**
- **Moreover, automation has generated the process known as “high through-put screening;” which permits millions of assays per month. In addition to these efforts, major attention is now being given to the discovery of entirely new targets for drug therapy, eg, the intracellular receptors for second messengers.**
- The fourth approach is illustrated by the development of recombinant tissue plasminogen activator (rt-PA).

# • How are new drugs found?

- Work directed towards finding new drugs is carried out mainly in the pharmaceutical industry.
- The starting point may be the structure of a newly identified endogenous chemical or an enzyme or a receptor.
- Drugs are evaluated on a range of model systems from isolated cellular components to whole animals. Some effects are easier to measure than others e.g. lowering of blood pressure compared with a reduction in anxiety.
- After a potential new drug is identified there will usually be further work to ensure it is orally active and has an acceptable level of side effects (toxicity, mutagenicity and teratogenicity). Eventually the drug goes into clinical trials
- Discovery of drugs/medicines is usually due to increased
- knowledge in biomedical sciences
- availability of novel chemicals
- testing procedures (bioassays)
- Usefulness of drugs/medicines is due to
- appropriate use required for powerful drugs
- clinical trials for evaluation of effects versus risks (evidence-based medicine)

# Discovery and Development of a drug may follow the scheme below

---

- **The idea**
- **The clinical need**
- **The biologic hypothesis**
- **The chemical hypothesis:**
- **Research and development**
- **Postscript**

- Regardless of the source of the candidate molecule, **testing it involves a sequence of experimentation and characterization called drug screening.**
- **A variety of biologic assays at the molecular, cellular, organ, and whole animal levels are used to define the activity and selectivity of the drug.**
- **The type and number of initial screening tests depend on the pharmacologic goal.**
- Anti-infective drugs will generally be tested first against a variety of infectious organisms, hypoglycemic drugs for their ability to lower blood sugar, etc.

- **The molecule will also be studied for a broad array of actions to establish the selectivity of the drug. This has the advantage of demonstrating unsuspected toxic effects and occasionally discloses a previously unsuspected therapeutic action.**
- **The selection of molecules for further study is most efficiently conducted in animal models of human disease.**
- **Where good models exist (eg, hypertension or thrombotic disease), we generally have adequate drugs. Good drugs are conspicuously lacking for diseases for which models are not yet available, eg, Alzheimer's disease.**
- **Some of the studies performed during drug screening are listed in Table 5—2 and define the pharmacologic profile of the drug.**

# Pharmacological Profile Test

Table 5-2. Pharmacologic profile tests.

Experimental Method or Target Organ	Species or Tissue	Route of Administration	Measurement
Molecular Receptor binding (example: β-adrenoceptors)	Cell membrane fractions from organs or cultured cells; cloned receptors	In vitro	Receptor affinity and selectivity
Enzyme activity (examples: tyrosine hydroxylase, dopamine-3-hydroxylase, monoamine oxidase)	Sympathetic nerves adrenal glands; purified enzymes	In vitro	Enzyme inhibition and selectivity
Cytochrome P450	Liver	In vitro	Enzyme inhibition; effects on drug metabolism
Cellular Cell function	Cultured cells	In vitro	Evidence for receptor activity—agonism or antagonism (example: effects on cyclic nucleotides)
Isolated tissue	Blood vessels, heart, lung, ileum (rat or guinea pig)	In vitro	Effects on vascular contraction and relaxation; selectivity for vascular receptors; effects on other smooth muscles
Systems/disease models Blood pressure	Dog, cat (anesthetized)	Parenteral	Systolic-diastolic changes
	Rat, hypertensive (conscious)	Oral	Antihypertensive effects
Cardiac effects	Dog (conscious)	Oral	Electrocardiography
	Dog (anesthetized)	Parenteral	Inotropic, chronotropic effects, cardiac output, total peripheral resistance
Peripheral autonomic nervous system	Dog (anesthetized)	Parenteral	Effects on response to known drugs and electrical stimulation of central and peripheral autonomic nerves
Respiratory effects	Dog, guinea pig	Parenteral	Effects on respiratory rate and amplitude, bronchial tone
Diuretic activity	Dog	Oral, parenteral	Natriuresis, kaliuresis, water diuresis, renal blood flow, glomerular filtration rate
Gastrointestinal effects	Rat	Oral	Gastrointestinal motility and secretions
Circulating hormones, cholesterol, blood sugar	Rat, dog	Parenteral, oral	Serum concentration
Blood coagulation	Rabbit	Oral	Coagulation time, clot retraction, prothrombin time
Central nervous system	Mouse, rat	Parenteral, oral	Degree of sedation, muscle relaxation, locomotor activity, stimulation

- For example, on a drug designed to act as an antagonist at vascular alpha adrenoceptors for the treatment of hypertension a broad range of tests would be performed thus.
- **At the molecular level, the compound would be screened for receptor binding affinity to cell membranes containing alpha receptors, other receptors, and binding sites on enzymes.**
- **Early studies would be done on liver cytochrome P450 to determine whether the molecule of interest is likely to be a substrate or inhibitor of these enzymes.**
- **Effects on cell function would be studied to determine the efficacy of the compound.**
- **Evidence would be obtained about whether the drug is an agonist, partial agonist, or antagonist at alpha receptors.**
- **Isolated tissues would be utilized to further determine the pharmacologic activity and selectivity of the new compound in comparison with reference compounds.**
- **Comparison with other drugs would also be under taken in other in vitro preparations such as gastrointestinal and bronchial smooth muscle. At each step in this pathway, the compound would have to meet specific performance criteria to be carried further.**

- **Whole animal studies are generally necessary to determine the effect of the drug on organ systems and disease models.**
- **Cardiovascular and renal function studies would be first performed in normal animals.**
- **For the hypothetical antihypertensive drug, animals with hypertension would then be treated to see if blood pressure was lowered and to characterize other effects of the compound.**
- **Evidence would be collected on duration of action and efficacy following oral and parenteral administration.**
- **If the agent possessed useful activity, it would be further studied for possible adverse effects on other major organ systems, including the respiratory, gastrointestinal, endocrine, and central nervous systems.**
- **These studies might suggest the need for further chemical modification to achieve more desirable pharmacokinetic or pharmacodynamic properties.**
- **For example, oral administration studies might show that the drug was poorly absorbed or rapidly metabolized in the liver; modification to improve bioavailability might be indicated.**

- **Advances in molecular biology and biotechnology have introduced new approaches and new problems to the drug discovery and development process.**
- **New information about the structure of receptors is making possible more rational drug design. A better understanding of second messenger processes is revealing second messenger receptors as a new class of drug targets.**
- **Insertion of the genes for active peptides or proteins into bacteria, yeast, or mammalian cells makes it possible to prepare large quantities of the desired molecule.**
- **Human insulin, human growth hormone, interferon, hepatitis vaccines, tissue plasminogen activator, erythropoietin, antihemophilic factor, and bone marrow growth factors produced by these biotechnology approaches are now available for general clinical use.**

## • **PRECLINICAL SAFETY & TOXICITY TESTING**

• **Candidate drugs that survive the initial screening and profiling procedures must be carefully evaluated for potential risks before clinical testing is begun.** Depending on the proposed use of the drug, preclinical toxicity testing includes most or all of the procedures shown in table 5-3.

• **While no chemical can be certified as completely “safe” (free of risk), since every chemical is toxic at some dosage, it is usually possible to estimate the risk associated with exposure to the chemical under specified conditions if appropriate tests are performed.**

# Safety Test

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.
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

- The major kinds of information needed from the preclinical toxicity study are
- **(1) acute toxicity**— effects of large single doses up to the lethal level;
- **(2) subacute and chronic toxicity**—effects of multiple doses which are especially important if the drug is intended for chronic use in humans;
- **(3) effects on reproductive functions, including teratogenicity;**
- **(4) carcinogenicity;**
- **(5) mutagenicity; and**
- **(6) investigative toxicology.**

- In addition to the studies shown in Table 5—3, several quantitative estimates are desirable. **These include the “no-effect” dose—the maximum dose at which a specified toxic effect is not seen; the minimum lethal dose—the smallest dose that is observed to kill any animal; and, if necessary, the median lethal dose (LD 50 dose that kills approximately 50% of the animals.**

# • **EVALUATION IN HUMANS**

- **Less than one-third of the drugs tested in clinical trials reach the marketplace, because laws requires that the study of new drugs in humans be conducted in accordance with stringent guidelines.**
- **The need for careful design and execution is based upon the three major factors listed in the next slide.**

# EVALUATION IN HUMANS

```
graph TD; Title[EVALUATION IN HUMANS]; Title --- L1[ ]; Title --- L2[ ]; Title --- L3[ ]; L1 --> A[A. The Variable Natural History of Most Diseases:]; L2 --- B[B. The Presence of Other Diseases and Risk Factors]; L3 --- B; B --> C[C. Subject and Observer Bias:];
```

**A. The Variable Natural History of Most Diseases:**

**•B. The Presence of Other Diseases and Risk Factors**

**C. Subject and Observer Bias:**

## • **Confounding Factors in Clinical Trials**

### • A. The Variable Natural History of Most Diseases:

- Many diseases tend to wax and wane in severity; some disappear spontaneously with time; even malignant neoplasms may on occasion undergo spontaneous remissions.
- A good experimental design must take into account the natural history of the disease under study by evaluating a large enough population of subjects over a sufficient period of time.
- Further protection against errors of interpretation caused by fluctuations in severity of the manifestations of disease is provided by utilizing a crossover design, which consists of alternating periods of administration of test drug, placebo preparation (the control), and the standard treatment (positive control), if any, in each subject.
- **These sequences are systematically varied, so that different subsets of patients receive each of the possible sequences of treatment. An example of such a design is shown in the next slide.**

# Crossover Design

---

Patient Group	Medication Given		
	Week 1	Week 2	Week 3
I	Aspirin	Placebo	Novent
II	Placebo	Novent	Aspirin
III	Novent	Aspirin	Placebo

# **B. The Presence of Other Diseases and Risk Factors:**

- Known or unknown diseases and risk factors (including life-styles of subjects) may influence the results of a clinical study. For example, some diseases alter the pharmacokinetics of drugs .**

- Concentrations of a blood component being monitored as a measure of the effect of the new agent may be influenced by other diseases or other drugs.**

- Attempts to avoid this hazard usually involve the crossover technique (when feasible) and proper selection and assignment of patients to each of the study groups.**

- This requires that careful medical and pharmacologic histories (including use of recreational drugs) be obtained and that statistically valid methods of randomization be used in assigning subjects to particular study groups.**

# Subject and Observer Bias:

- Most patients tend to respond in a positive way to any therapeutic intervention by interested, caring, and enthusiastic medical personnel.
- The manifestation of this phenomenon in the subject is the placebo response (Latin “I shall please”) and may involve objective physiologic and biochemical changes as well as changes in subjective complaints associated with the disease.
- The placebo response is usually quantitated by administration of an inert material, with exactly the same physical appearance, odor, consistency, etc, as the active dosage form. The magnitude of the response varies considerably from patient to patient.
- However, the incidence of the placebo response is fairly constant, being observed in 20—40% of patients in almost all studies.
- Placebo “toxicity” also occurs but usually involves subjective effects: stomach up set, insomnia, sedation, etc.
- Subject bias effects can be quantitated—and discounted from the response measured during active therapy—by the single-blind design. This involves use of a placebo or dummy medication, as described above, which is administered to the same subjects in a crossover design, if possible, or to a separate control group of subjects.
- Observer bias can be taken into account by disguising the identity of the medication being used—placebo or active form—from both the subjects and the personnel evaluating the subjects’ responses (double-blind design). In this design, a third party holds the code identifying each medication packet, and the code is not broken until all of the clinical data have been collected.

- **The Food & Drug Administration**

- **The Food and Drug Administration (FDA) is the administrative body that oversees the drug evaluation process in the United States and grants approval for marketing of new drug products. The FDA's authority to regulate drug marketing derives from several pieces of legislation (shown in the next slide). If a drug has not been shown through adequately controlled testing to be "safe and effective" for a specific use, it cannot be marketed in interstate commerce for this use.\***

- **Unfortunately, "safe" means different things to the patient, the physician, and society. As noted above, complete absence of risk is impossible to demonstrate (and probably never occurs), but this fact is not understood by the average member of the public, who assumes that any medication sold with the approval of the FDA must indeed be free of serious, if not minor, "side effects." This confusion continues to be a major cause of litigation and dissatisfaction with medical care.**

- **Although** it is impossible to certify that a drug is absolutely safe, ie, free of all risk, it is possible, however, to identify most of the hazards likely to be associated with use of a new drug and to place some statistical limits on frequency of occurrence of such events in the population under study.
- **As a result**, an operational and pragmatic definition of “safety” can usually be reached that is based upon the nature and incidence of drug-associated hazards as compared to the hazard of nontherapy of the target disease.

# Drug legislation

Law	Purpose and Effect
Pure Food and Drug Act of 1906	Prohibited mislabeling and adulteration of drugs.
Opium Exclusion Act of 1909	Prohibited importation of opium.
Amendment (1912) to the Pure Food and Drug Act	Prohibited false or fraudulent advertising claims.
Harrison Narcotic Act of 1914	Established regulations for use of opium, opiates, and cocaine (marijuana added in 1937).
Food, Drug, and Cosmetic Act of 1938	Required that new drugs be safe as well as pure (but did not require proof of efficacy). Enforcement by FDA.
Durham-Humphrey Act of 1952	Vested in the FDA the power to determine which products could be sold without prescription.
Kefauver-Harris Amendments (1962) to the Food, Drug, and Cosmetic Act	Required proof of efficacy as well as safety for new drugs and for drugs released since 1938; established guidelines for reporting of information about adverse reactions, clinical testing, and advertising of new drugs.
Comprehensive Drug Abuse Prevention and Control Act (1970)	Outlined strict controls in the manufacture, distribution, and prescribing of habit-forming drugs; established programs to prevent and treat drug addiction.
Orphan Drug Amendments of 1983	Amended Food, Drug, and Cosmetic Act of 1938, providing incentives for development of drugs that treat diseases with less than 200,000 patients in USA.
Drug Price Competition and Patent Restoration Act of 1984	Abbreviated new drug applications for generic drugs. Required bioequivalence data. Patent life extended by amount of time drug delayed by FDA review process. Cannot exceed 5 extra years or extend to more than 14 years post-NDA approval.
Expedited Drug Approval Act (1992)	Allowed accelerated FDA approval for drugs of high medical need. Required detailed postmarketing patient surveillance.
Prescription Drug User Fee Act (1992)	Manufacturers pay user fees for certain new drug applications. FDA claims review time for new chemical entities dropped from 30 months in 1992 to 20 months in 1994.

# • **Clinical Trials:** The IND & NDA

- **Once a drug is judged ready to be studied in humans, a Notice of Claimed Investigational Exemption for a New Drug (IND) must be filed with the FDA as shown in the next slide.**
- The IND 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, and
- (5) the names and credentials of physicians who will conduct the clinical trials.

# Overview Developing & Testing

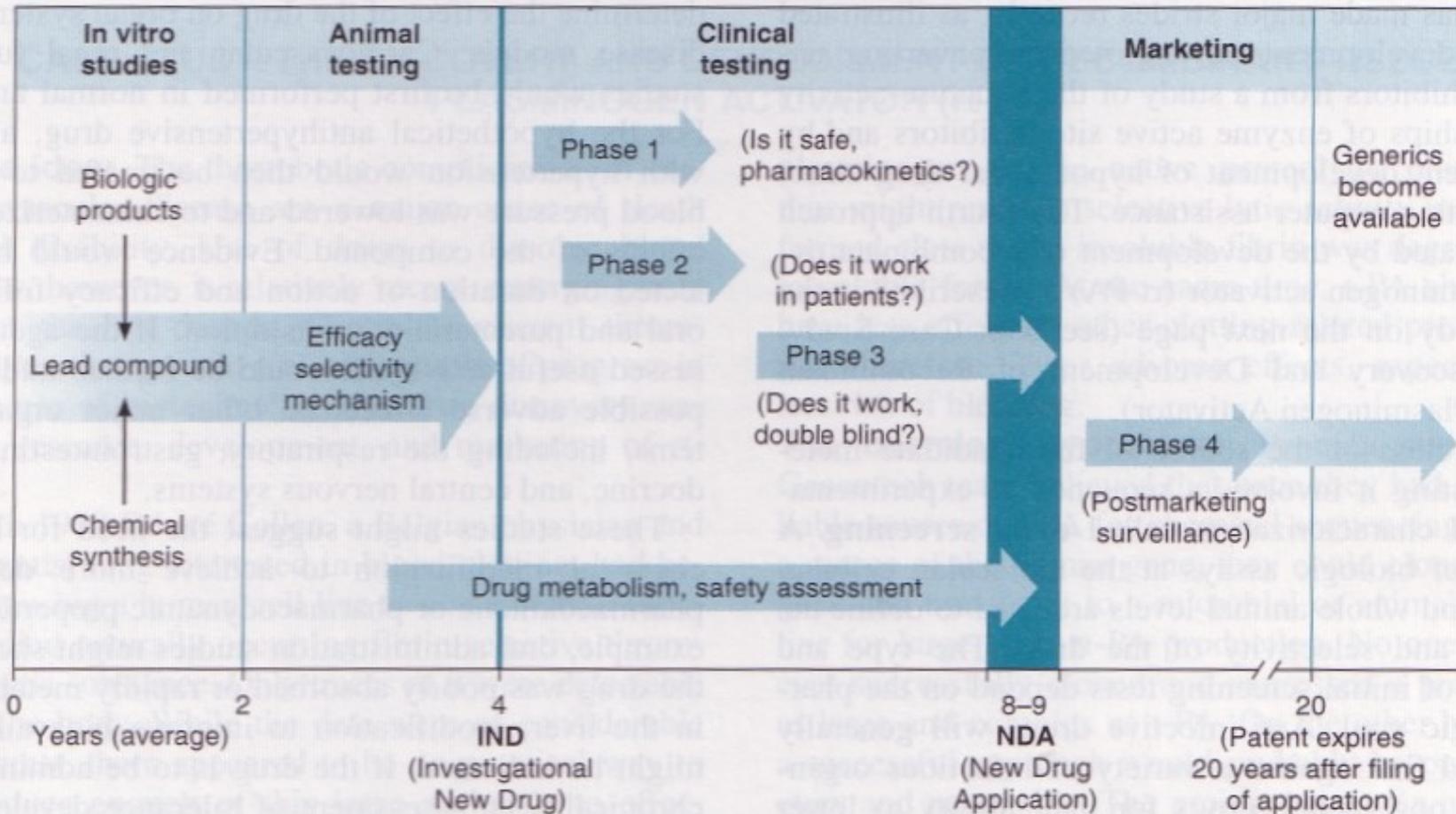


Figure 5-1. The development and testing process required to bring a drug to market in the USA. Some of the requirements may be different for drugs used in life-threatening diseases.

- It often requires 4—6 years of clinical testing to accumulate all required data.
- **Testing in humans is begun after sufficient acute and subacute animal toxicity studies have been completed.**
- **Chronic safety testing in animals is usually done concurrently with clinical trials.**
- In each of the three formal phases of clinical trials, **volunteers or patients must be informed of the investigational status of the drug as well as possible risks and must be allowed to decline or to consent to participate and receive the drug.** These regulations are based on the ethical principles set forth in the Declaration of Helsinki .
- In addition to the approval of the sponsoring organization and the FDA, an interdisciplinary institutional review board at the facility where the clinical drug trial will be conducted must review and approve the plans for testing in humans.

# • **Clinical trials**

- There are a number of important features in the evaluation of the effects of drugs in clinical trials:
- 1) **The new drug is compared to an existing remedy (a standard drug) and/or placebo.**
- **Comparison with a standard shows whether the new drug is more effective, has fewer side effects or needs to be taken less frequently.**
- **The placebo ("I will please") is a biologically inert preparation which looks identical to the active drug.**
- **The clinician sees how many patients improve on this treatment; it may be 50% of the sample.**
- **It is important that the active drug has a significantly better success rate than the placebo.**

- **2) Patients are placed at random into the different treatment groups.**
- **This reduces the possibility of biasing the results by selection e.g. less serious cases for the new drug.**
- **Note the ethical issue of assigning some patients to treatment with an inert preparation.**
  
- **3) The trial is carried out double-blind i.e. neither the patient nor the person measuring the effects should know whether the drug given is the new one or the standard or the placebo.**
  
- **Trials that are not carried out double-blind may report excellent effects for a new drug but often these are not confirmed in properly controlled trials.**

- **4) There is statistical evaluation of the results in order to determine whether two treatments are significantly different one from the other.**
- **If there is no statistically significant difference between e.g. the new drug and the placebo, it cannot be concluded that there is no difference between the treatments but only that this clinical trial has not shown one.**
- **On the other hand, if the new drug was significantly more effective than the placebo it doesn't mean the result is biologically important.**
- **For example, a new hypnotic (sleep-inducing) drug significantly increased time asleep in patients to 6 hours and 5 minutes from 6 hours on a placebo.**
- **This was statistically significant but the new drug doesn't appear to be a very good hypnotic.**

- **5) Some clinical trials compare single doses of drugs but this allows very limited conclusions to be drawn.**
- **It is preferable that several doses of a drug are evaluated so that dose-response curves can be plotted.**
- **Usually the logarithm of the dose is used so that the middle part of the curve becomes linear.**

# Clinical Trials

---

- Phase I
- Phase II
- Phase III
- Phase IV

- **PHASE 1**

- In phase 1, the effects of the drug as a function of dosage are established in a small number (25—50) of healthy volunteers.
- If the drug is expected to have significant toxicity, as is often the case in cancer and AIDS therapy, volunteer patients with the disease are used in phase I rather than normal volunteers.

- **Phase I trials are done to determine whether humans and animals show significantly different responses to the drug and to establish the probable limits of the safe clinical dosage range.**
- **These trials are nonblind or “open,” ie, both the investigators and the subjects know what is being given.**
- **Many predictable toxicities are detected in this phase.**
- **Pharmacokinetic measurements of absorption, half-life, and metabolism are often done in phase 1.**
- **Phase 1 studies are usually performed in research centers by specially trained clinical pharmacologists.**

## • **PHASE 2**

- **In phase 2, the drug is studied for the first time in patients with the target disease to determine its efficacy.**

- **A small number of patients (10—200) are studied in great detail.**

- **A single-blind design is often used, with an inert placebo medication and an older active drug (positive control) in addition to the investigational agent.**

- **Phase 2 trials also are usually done in special clinical centers (eg, university hospitals). A broader range of toxicities may be detected in this phase**

## • **PHASE 3**

- **In phase 3, the drug is evaluated in much larger numbers of patients—sometimes thousands—to further establish safety and efficacy.**
- **Using information gathered in phases 1 and 2, phase 3 trials are designed to minimize errors caused by placebo effects, variable course of the disease, etc.**
- **Therefore, double-blind and crossover techniques (like that set out in Table 5—4) are frequently employed.**

**Table 5–4.** Typical crossover design for comparing a mythical new analgesic, “Novent,” with placebo and a known active drug, aspirin, in the management of chronic pain. Each therapeutic period lasts 7 days, with 1 week between each treatment period for washout of the preceding medication.

Patient Group	Medication Given		
	Week 1	Week 3	Week 5
I	Aspirin	Placebo	“Novent”
II	Placebo	“Novent”	Aspirin
III	“Novent”	Aspirin	Placebo

- **Phase 3 trials are usually performed in settings similar to those anticipated for the ultimate use of the drug.**
- **Phase 3 studies can be difficult to design and execute and are usually expensive because of the large numbers of patients involved and the masses of data that must be collected and analyzed.**
- **The investigators are usually specialists in the disease being treated. Certain toxic effects—especially those caused by immunologic processes—may first become apparent in phase 3.**
- **If phase 3 results meet expectations, application will be made for permission to market the new agent. The process of applying for marketing approval requires submission of a New Drug Application (NDA) to the FDA.**
- **The application contains, often in hundreds of volumes, full reports of all preclinical and clinical data pertaining to the drug under review.**

- **The FDA review of this material and a decision on approval may take 3 years or longer.**
- **In cases where an urgent need is perceived (eg, cancer chemotherapy), the process of preclinical and clinical testing and FDA review may be greatly accelerated.**
- **For serious diseases, the FDA may permit extensive but controlled marketing of a new drug before phase 3 studies are completed; for life-threatening diseases, it may permit controlled marketing even before phase 2 studies have been completed.**

## • PHASE 4

• Phase 4 which has no fixed duration, begins when approval to market a drug has been obtained.

Phase 4 constitutes monitoring the safety of the new drug under actual conditions of use in large numbers of patients.

• Final release of a drug for general prescription use should be accompanied by a vigilant postmarketing surveillance program.

• The importance of careful and complete reporting of toxicity by physicians after marketing begins can be appreciated by noting that many important drug-induced effects have an incidence of 1:10,000 or less.

- The table in the next slide shows the sample size required to disclose drug-induced increases of events that occur with different frequencies in the untreated population (and some examples of such events).
- **Because of the small numbers of subjects in phases 1—3, such low- incidence drug effects will not generally be detected before phase 4 no matter how carefully the studies are executed.**
- **Phase 4 has no fixed duration.**

# Study Size as a function of effect frequency

---

Frequency of Effect in Non exposed controls	Example	Number of Exposed Subjects required
1/100	Any Congenital Cardiac Effect	1800
1/1000	Facial Clefts	18,000
1/10,000	Triscuoid atresia	180,000
1/100,000	Myocardial Infarction	1,800,000

- The time from the filing of a patent application to approval for marketing of a new drug may be 5 years or even longer.
- Since the lifetime of a patent is 20 years in the USA, the owner of the patent (usually a pharmaceutical company) has exclusive rights for marketing the product for only a limited time after approval of the NDA.
- Because the FDA review process can be lengthy, the time consumed by the review process is sometimes added to the patent life. However, the extension (up to 5 years) cannot increase the total life of the patent to more than 14 years post NDA approval.
- **After expiration of the patent, any company may produce and market the drug as a generic product without paying license fees to the original patent owner.**
- **However, a trademark (the drug's proprietary trade name) may be legally protected indefinitely.**

- Therefore, pharmaceutical companies are strongly motivated to give their new drugs easily remembered trade names.
- For example, “Librium” is the trade name for the antianxiety drug “chlordiazepoxide.”
- For the same reason, the company’s advertising material will emphasize the trade name.

## Orphan Drugs

- Drugs for rare diseases—so-called orphan drugs— can be difficult to research, develop, and market. Proof of drug safety and efficacy in small populations must be established, but doing so effectively is a complex process. For example, clinical testing of drugs in children is severely restricted, even for common diseases, and a number of rare diseases affect the very young.

- Furthermore, because basic research in the pathophysiology and mechanisms of rare diseases tends to receive little attention or funding in both academic and industrial settings, recognized rational targets for drug action may be relatively few.

- In addition, the cost of developing a drug can greatly influence decisions and priorities when the target population is relatively small.

- **Orphan Drugs** are thus drugs that are effective for certain illnesses but for some reason are not profitable for manufacturers to produce.

# Adverse Reactions to Drugs

- Severe adverse reactions to marketed drugs are uncommon, though less dangerous toxic effects, are frequent for some drug groups. Life-threatening reactions probably occur in less than 2% of patients admitted to medical wards.

- The mechanisms of these reactions fall into two main categories. **Those in the first group are often extensions of known pharmacologic effects and thus are predictable. These toxicities are generally discovered by pharmacologists, toxicologists, and clinicians involved in phase 1—3 testing.**

- **Those in the second group, which may be immunologic or of unknown mechanism are generally unexpected and may not be recognized until a drug has been marketed for many years. These toxicities are therefore usually discovered by clinicians.**

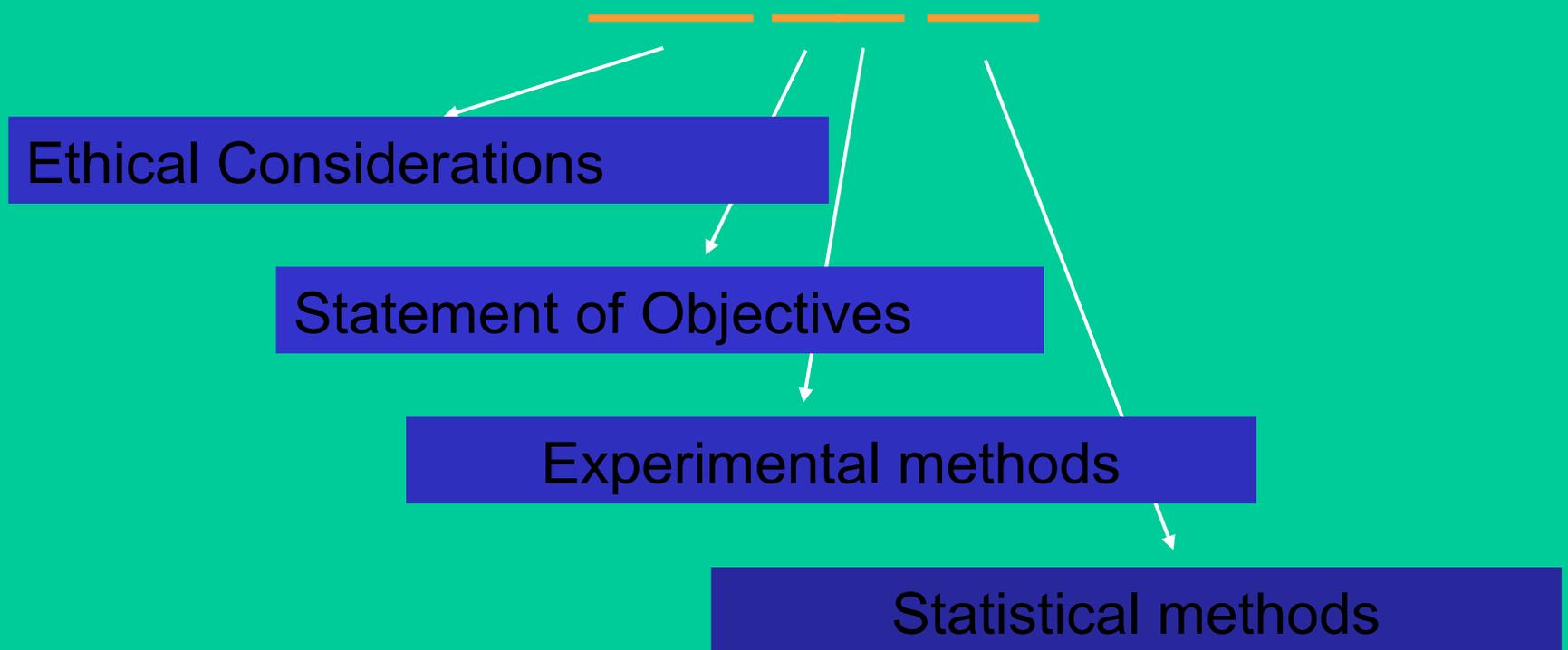
- It is thus important that practitioners be aware of **the various types of allergic reactions to drugs.** These include

- IgE-mediated reactions such as anaphylaxis, or urticaria, and angioedema; IgG- or

- IgM-mediated reactions of the lupus erythematosus type; IgG mediated responses of the serum sickness type, which involve vasculitis; and cell-mediated allergies involved in contact dermatitis.

# *Evaluating a Clinical Drug Study*

---



- **The periodical literature is the chief source of clinical information about new drugs, especially those very recently released for general use. (Much of this information is also currently available on the internet.)**
- Such information may include new indications or major new toxicities and contraindications.
- **Therefore, health practitioners should be familiar with the sources of such information and should be prepared to evaluate it.**
- Certain general principles can be applied to such evaluations.
- These principles are conveniently stated in the form of questions every reader should ask while examining the information in the journals about new drugs.

- **A. Ethical Considerations:** Was informed consent obtained? Were appropriate ethical and procedural safeguards available to the patients?
- **B. Statement of Objectives:** What were the objectives of the study? Are the goals clearly defined and stated? A poorly defined goal such as “to study the effects of minoxidil” (an antihypertensive drug) is much less likely to lead to useful results than a clearly defined objective such as, “to measure the effect of minoxidil on renal function in severely hypertensive women.”
- **C. Experimental Methods:** Were the experimental methods appropriate to the study goals? Does the author state the accuracy (precision) and reliability (reproducibility) of the methods? Are the methods sensitive enough so that small but biologically important changes could be detected?

- **D. Statistical Methods:** How were the patients selected? Were there enough subjects? Are the subjects representative of the population most likely to receive the drug or of the population for which the reader would like to use the drug? If the project was a long-term or outpatient study, were any patients lost to follow-up? How was this accounted for? Were placebo and positive control treatments included? How were patients assigned to the various groups or subgroups, and were patients properly randomized between treatment groups? Was a crossover design feasible, and was one used? Were patients receiving any other therapy during the trial? How was this controlled or accounted for? Were appropriate statistical tests applied?

- **E. Conclusions:** Do the data, even if sound, justify the conclusions? Does the drug offer significant advantages of cost, efficacy, or safety over existing agents, or is it merely new? Extrapolation from the study population to other groups must be very carefully scrutinized.

- A well-written report in a journal subject to peer review usually provides explicit answers to all of the above questions. Absence of clear answers to these questions justifies skepticism about the investigation and the authors' **conclusions**.

## • **Development of New Drugs**

- 1. Before a drug is marketed, subjected to lab and clinical study.
- a) Before used on humans, must establish LD50 and ED50 , and side effects.
- 2. Assessed for short and long term use
- 3. Must be carried out on at least three different species.
- 4. Then taken to clinical trial conducted on normal volunteers and patients (phase 1).
- 5. Then controlled study: utilize placebos and eliminate investigator bias (phase 2).
- 6. If promising, period of extended clinical evaluation; made available to investigators for variety of uses (phase 3).
- 7. If OK, FDA approval received for broad use by physicians and medical centers who agree to report on therapeutic results, limitations, and problems (phase 4).
- Costs manufacturer more than \$30 million to take new compound through testing to marketing stage.

# SUMMARY FOR REVISION PUPOSES

# Drug Evaluation & Regulation

New drugs are usually developed by large pharmaceutical companies.

They are regulated (in the United States) by the US Food and Drug Administration (FDA).

These notes provide an overview of the development process and how drugs are regulated.

## **SAFETY & EFFICACY**

Because society expects prescription drugs to be safe and effective, governments regulate the development and marketing of new drugs.

The FDA is the regulatory body in the United States that proposes and administers these regulations.

**Current regulations require evidence of relative safety (derived from acute and sub-acute toxicity testing in animals) and probable therapeutic action (from the pharmacologic profile in animals) before human testing is permitted.**

**Some information about the pharmacokinetics of a compound is also required before clinical evaluation is begun.**

**Chronic toxicity test results are generally not required before human studies are started.**

**The development of a new drug and its pathway through various levels of testing and regulation are illustrated in Figure 5—1.**

The cost of development of a new drug, including false starts and discarded molecules, is currently several hundred million dollars.

# ANIMAL TESTING

The amount of animal testing required before human studies begin is a function of the proposed use and the urgency of the application.

Thus, **a drug proposed for occasional nonsystemic use requires less extensive testing than one destined for chronic systemic administration.**

**Anticancer drugs and drugs proposed for use in AIDS,-because of the urgent need for new agents, require less evidence of safety than do drugs used in treatment of less threatening diseases and are often investigated and approved on an accelerated schedule.**

## **A. acute toxicity**

**Acute toxicity studies are required for all drugs.** These studies involve administration of single doses of the agent up to the lethal level in at least 2 species (eg, 1 rodent and 1 nonrodent).

## **B. SUBACUTE AND CHRONIC TOXICITY**

Subacute and chronic toxicity testing are required for most agents, especially those intended for chronic use. Tests are usually conducted for at least the length of time proposed for human application, ie, 2—4 weeks (subacute) or 6-24 months (chronic), in at least 2 species.

# TYPES OF ANIMAL TESTS

Tests done with animals often include general screening tests for pharmacologic effects, hepatic and renal function monitoring, blood and urine tests, gross and histopathologic examination of tissues, and tests of reproductive effects and carcinogenicity.

## A. pharmacologic profile

The pharmacologic profile is a description of all the pharmacologic effects of a drug (eg, effects on blood pressure, gastrointestinal activity, respiration, renal function, endocrine function, CNS).

## **B. reproductive toxicity**

Reproductive toxicity testing involves the study of the fertility effects of the candidate drug and its teratogenic and mutagenic effects.

Teratogenesis can be defined as the induction of developmental defects in the somatic tissues of the fetus (eg, by exposure of the fetus to a chemical, infection, radiation).

Teratogenesis is studied by treating pregnant female animals of at least 2 species at selected times during early pregnancy when organogenesis is known to take place and later examining the fetuses or neonates for abnormalities.

Examples of drugs known to have teratogenic effects include thalidomide, isotretinoin, valproic acid, ethanol, glucocorticoids, war-farin, lithium, and androgens.

Mutagenesis is induction of changes in the genetic material of animals of any age and therefore induction of heritable abnormalities.

The Ames test, the standard in vitro test for mutagenicity, uses a special strain of salmonella bacteria that naturally depends on specific nutrients in the culture medium.

Loss of this dependence during exposure to the test drug signals a mutation. The dominant lethal test is an in vivo mutagenicity test carried out in mice. Male animals are exposed to the test substance before mating.

Abnormalities in the results of subsequent mating (eg, loss of embryos, deformed fetuses) signal a mutation in the male's germ cells.

Many carcinogens (eg, aflatoxin, cancer chemotherapeutic drugs, and other agents that bind to DNA) have mutagenic effects.

## TERMS TO LEARN

<b>Single-blind study</b>	A clinical trial in which the investigators—but not the subjects—know which subjects are receiving active drug and which are receiving placebos
<b>Double-blind study</b>	A clinical trial in which neither the subjects nor the investigators know which subjects are receiving placebos; the code is held by a third party
<b>IND</b>	Investigational New Drug Exemption; application for FDA approval to carry out new drug trials in humans; requires animal data
<b>NDA</b>	New Drug Application; seeks FDA approval to market a new drug for ordinary clinical use. Requires data from clinical trials as well as preclinical (animal) data.
<b>Placebo</b>	An inactive “dummy” medication made up to resemble the active investigational formulation as much as possible
<b>Phases I, II, and III of clinical trials</b>	Three parts of a clinical trial that are usually carried out before submitting an NDA to the FDA
<b>Positive control</b>	A known standard therapy, to be used along with placebo, to fully evaluate the safety and efficacy of a new drug in relation to the others available
<b>Mutagenic</b>	An effect on the inheritable characteristics of a cell or organism—a mutation in the DNA; tested in microorganisms with the Ames test
<b>Teratogenic</b>	An effect on the development of an organism resulting in abnormal structure or function; not generally heritable
<b>Carcinogenic</b>	An effect of inducing malignant characteristics
<b>Orphan drugs</b>	Drugs developed for diseases in which the expected number of patients is small. Some countries bestow certain commercial advantages on companies that develop drugs for uncommon diseases

## c.carcinogenesis

Carcinogenesis is the induction of malignant characteristics in cells. Because carcinogenicity is difficult and expensive to study, the Ames test is often used to screen chemicals, since there is a moderately high degree of correlation between mutagenicity in the Ames test and carcinogenicity in some animal tests.

Agents with known carcinogenic effects include coal tar, aflatoxin, dimethylnitrosamine and other nitrosamines, urethane, vinyl chloride, and the polycyclic aromatic hydrocarbons in tobacco smoke (eg, benzo[\*z]pyrene).

## CLINICAL TRIALS ;

Human testing in the United States requires the prior approval of an Investigational New Drug Exemption application (IND), which has been submitted by the manufacturer to the FDA (see Figure 5-1).

The IND includes all of the preclinical data collected up to the time of submission and the detailed proposal for clinical trials.

The major clinical testing process is informally divided into 3 phases that are carried out to provide information for a New Drug Application (NDA).

The NDA constitutes the request for approval of general marketing of the new agent for prescription use and includes all of the results of preclinical and clinical testing.

A fourth phase of study (the surveillance phase) follows NDA approval.

## **A. phase I**

A phase I trial consists of careful evaluation of the dose-response relationship in a small number of normal human volunteers (eg, 20-30).

An exception is in phase I trials of cancer chemotherapeutic agents and other highly toxic drugs; these are carried out by administering the agents to patients with the target disease.

In phase I studies, the acute effects of the agent are studied over a broad range of dosages, starting with one that produces no detectable effect and progressing to

## **B. phase II**

A phase II trial involves evaluation of a drug in a moderate number of patients (eg, 100-300) with the target disease.

A placebo or positive control drug is included in a single-blind or double-blind design. The study is carried out under very carefully controlled conditions, and patients are very closely monitored, often\* in a hospital research ward.

The goal is to determine whether the agent has the desired therapeutic effects at doses that are tolerated by sick patients.

### **C. phase III**

A phase III trial consists of a large design involving many patients (eg, 1000-5000 or more in many centers) and -many clinicians who are using the drug in the manner proposed for its ultimate general use (eg, in outpatients). Such studies usually include placebo and positive controls in a double-blind crossover design.

The goal is to explore further the spectrum of beneficial actions of the new drug, to compare it with older therapies, and to discover toxicities, if any, that occur so infrequently as to be undetectable in phase II studies.

### **D. phase IV**

Phase IV represents the postmarketing surveillance phase of evaluation, in which it is hoped that toxicities that occur very infrequently will be detected and re-reported early enough to prevent major therapeutic disasters.

Unlike the first 3 phases, phase IV is not rigidly regulated by the PDA.

## **DRUG LEGISLATION**

In the United States, many laws regulating drugs have been passed during this century. Refer to Table 5-1 for a partial list of this legislation.

## **ORPHAN DRUGS**

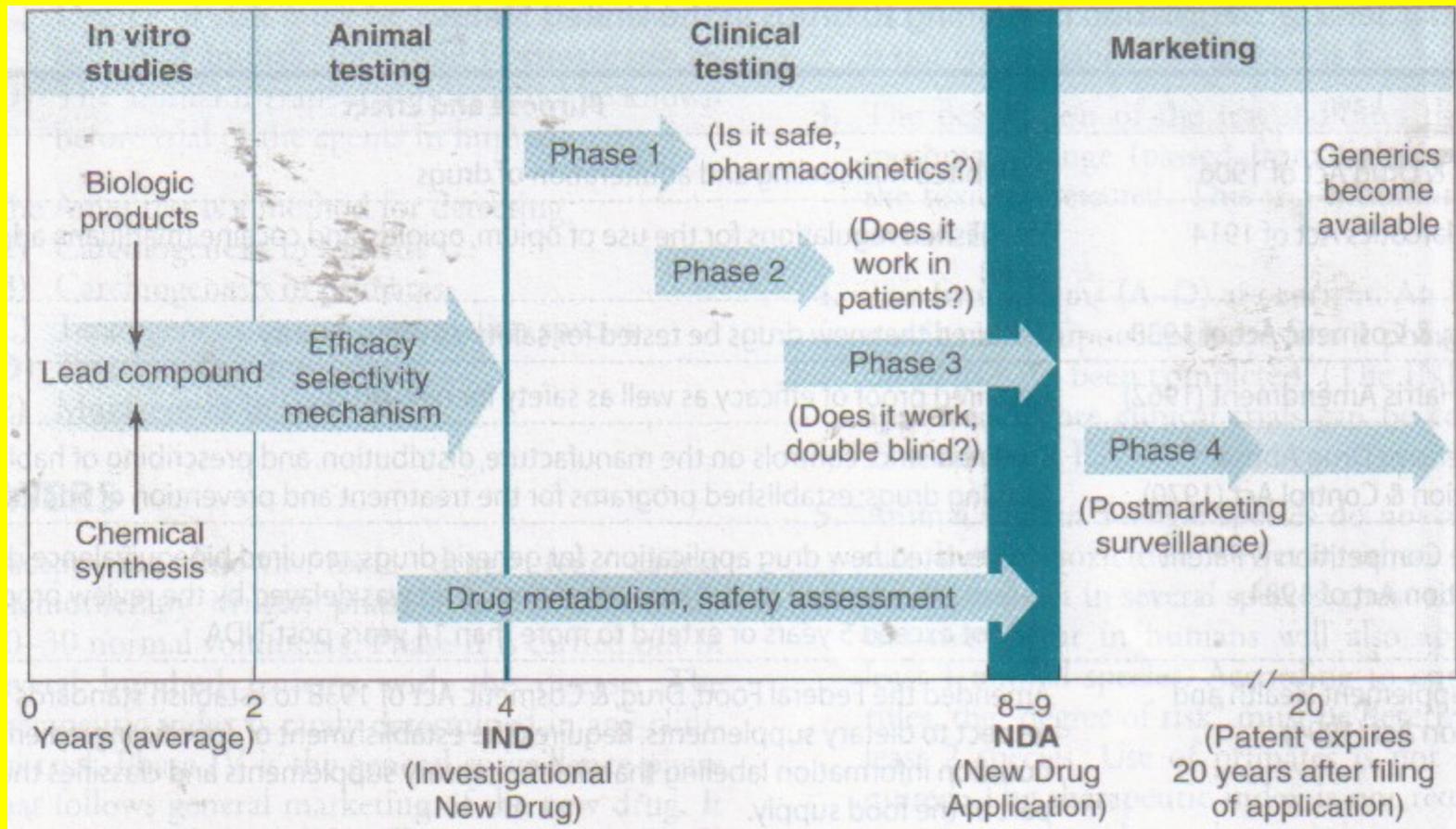
An orphan drug is a drug for a rare disease (one affecting fewer than 200,000 people in the United States).

The study of such agents has often been neglected because the sales of an effective agent for an uncommon ailment might not pay the costs of development.

In the United States, current legislation provides for tax relief and other incentives designed to encourage the development of orphan drugs.

**Figure 5-1.** The development and testing process required to bring a new drug to market in the United States. Some requirements may be different for drugs used in life-threatening diseases.

(Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.)



Law	Purpose and Effect
Pure Food & Drug Act of 1906	Prohibited mislabeling and adulteration of drugs
Harrison Narcotics Act of 1914	Established regulations for the use of opium, opioids, and cocaine (marijuana added in 1937)
Food, Drug, & Cosmetic Act of 1938	Required that new drugs be tested for safety as well as purity
Kefauver-Harris Amendment (1962)	Required proof of efficacy as well as safety for new drugs
Comprehensive Drug Abuse Prevention & Control Act (1970)	Outlined strict controls on the manufacture, distribution, and prescribing of habit-forming drugs; established programs for the treatment and prevention of addiction
Drug Price Competition & Patent Restoration Act of 1984	Abbreviated new drug applications for generic drugs; required bioequivalence data; patent life extended by the amount of time drug was delayed by the review process; cannot exceed 5 years or extend to more than 14 years post-NDA
Dietary Supplement Health and Education Act (1994)	Amended the Federal Food, Drug, & Cosmetic Act of 1938 to establish standards with respect to dietary supplements. Requires the establishment of specific ingredient and nutrition information labeling that defines dietary supplements and classifies them as part of the food supply.
Bioterrorism Act of 2002	Enhances control on dangerous biologic agents and toxins. Seeks to protect safety of food, water, and drug supply.

Modified and reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.