The discovery and development of new drugs

Development and testing process

- Drugs are regulated in almost all countries by governmental agencies.
- In the United States, regulation is by the Food and Drug Administration (FDA)

Safety & Efficacy

- Because society expects prescription drugs to be safe and effective, governments regulate the development and marketing of new drugs.
- In the United States, the FDA proposes and administers these regulations.
- Current regulations require evidence of **relative safety** (derived from acute and subacute 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 but must be underway before human studies are started.

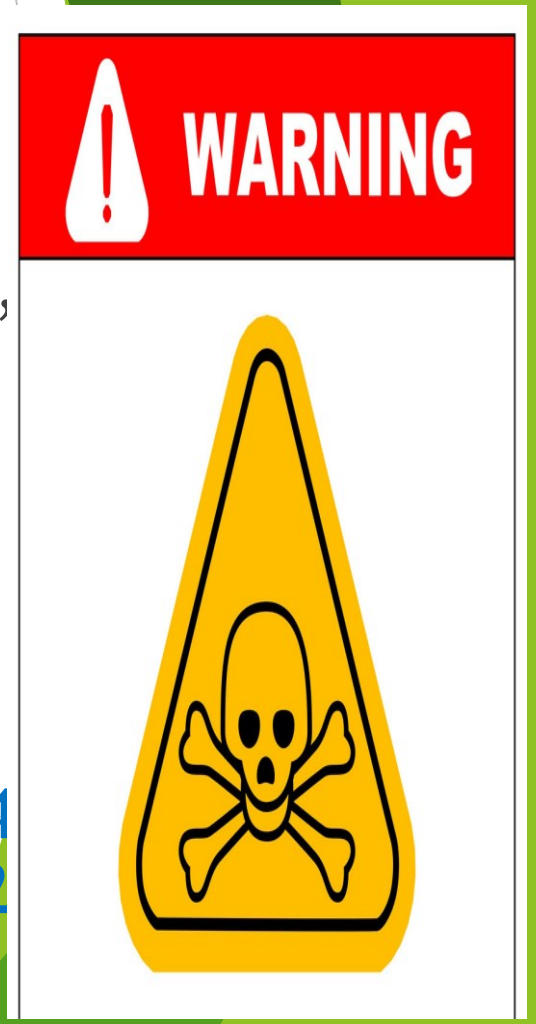
Animal Testing

- **Acute Toxicity**

1. required for all new drugs.
2. 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).

- **Subacute and Chronic Toxicity**

1. required for most agents, especially those intended for chronic use.
2. Tests are usually conducted for a duration in proportion to the time proposed for human application, that is, 2–4 weeks (subacute) or 6–24 months (chronic), in at least 2 species.



Types of Animal Tests

Tests done with animals usually include general screening tests

- Pharmacologic profile,
- Reproductive effects
- Carcinogenicity.

Pharmacologic Profile

- Pharmacologic effects of a drug (eg, effects on cardiovascular function, gastrointestinal activity, respiration, renal function, and endocrine function, CNS).
- Both graded and quantal dose-response data are gathered.

Reproductive toxicity testing

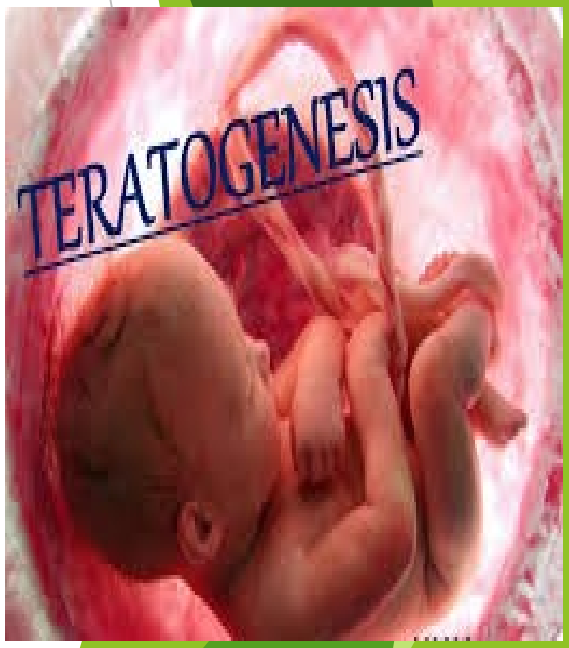
Need to check either the drug is

1. teratogenic
2. mutagenic toxicity.

- The FDA uses a 5-level descriptive scale to summarize information regarding the safety of drugs in pregnancy

Teratogenesis

- defined as the **induction of developmental defects** in the somatic tissues of the fetus (eg, by exposure of the fetus to a chemical, infection, or radiation).
- It 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 by later examining the fetuses or neonates for abnormalities.
- Examples of drugs known to have teratogenic effects include thalidomide, isotretinoin, valproic acid, ethanol, glucocorticoids, warfarin, 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.

It uses a special strain of salmonella bacteria that naturally depends on specific nutrients in the culture medium.

Loss of this dependence as a result of exposure to the test drug signals a mutation.

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

- The **dominant lethal test** is an in vivo mutagenicity test carried out in mice.

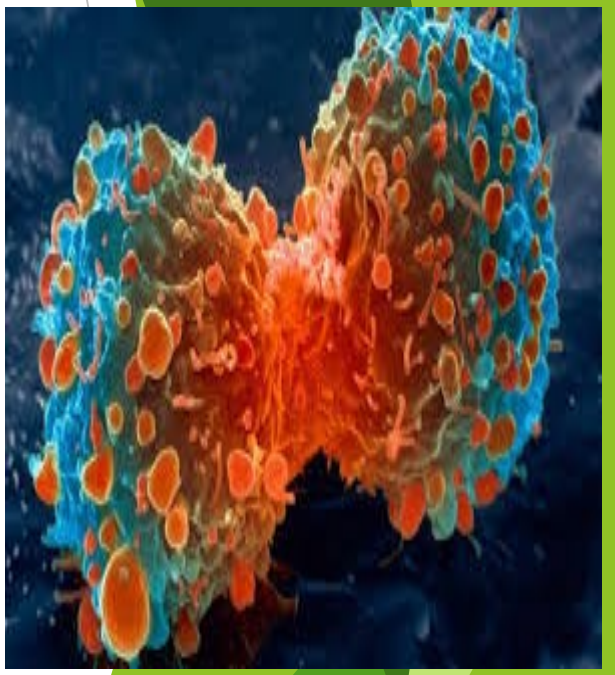
Male animals are exposed to the test substance before mating. Abnormalities in the results of subsequent mating (eg, loss of embryos, deformed fetuses) signal a mutation in the male's germ cells.

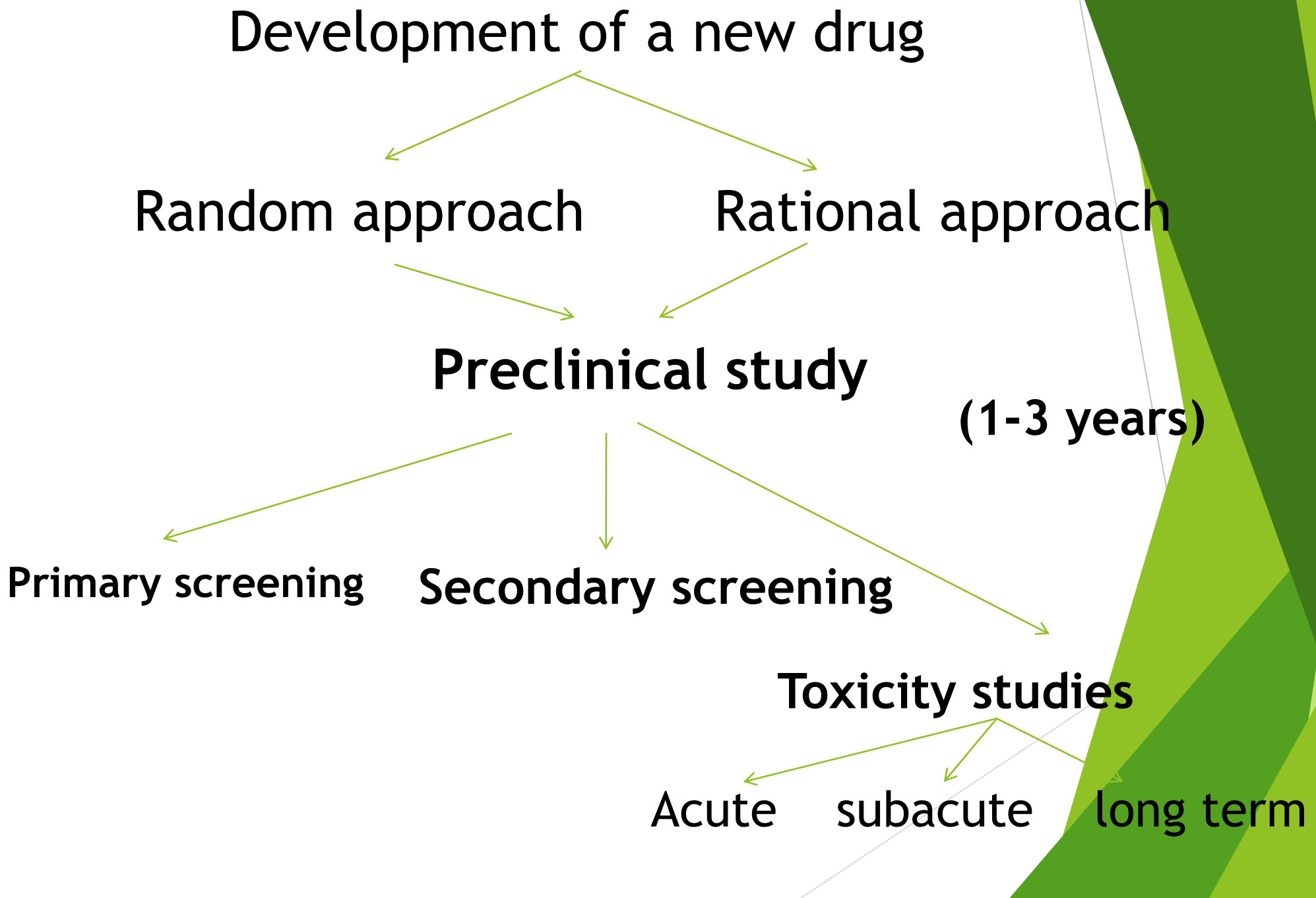
Table 1. FDA Drug Risk Classification

Category	Description
A	Controlled studies in humans show no risk to the fetus
B	No controlled studies have been conducted in humans; animal studies show no risk to the fetus
C	No controlled studies have been conducted in animals or humans
D	Evidence of human risk to the fetus exists; however, benefits may outweigh risks in certain situations
X	Controlled studies in both animals and humans demonstrate fetal abnormalities; the risk in pregnant women outweighs any possible benefit

Carcinogenesis

- Carcinogenesis is the induction of malignant characteristics in cells.
- Carcinogenicity is difficult and expensive to study
- **Ames test** is often used
- 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[*a*]pyrene) and other tobacco products.




Development of a new drug
Random approach
Rational approach
Preclinical study
(1-3 years)
Primary screening
Secondary screening
Toxicity studies
Acute
subacute
long term

Clinical trials

- Human testing of new drugs in the United States requires approval
- An **Investigational New Drug Exemption application (IND)**, which is submitted by the manufacturer to the FDA
- The IND includes all 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 the results of preclinical and clinical testing.
- A fourth phase of study (the surveillance phase) follows NDA approval.

Development and testing process

- Preclinical study
  - In vitro studies
  - Animal testing
- Clinical testing
- New drug application and registration
- Marketing
- Post marketing surveillance
- Years after filling expires
  - generics become available

Preclinical testing (1-5 years)

- Studies in vitro --- biological products and chemical synthesis
- Animal testing
  - Efficacy, selectivity & mechanism
  - Pharmacokinetics, pharmacodynamics, & toxic properties

Clinical testing

- (phase 1, phase 2, phase 3)
  - 2-10 years (average 5.6 years)

Clinical testing (**phase 1**)

- **Open trial in research center**
- By whom? -- Clinical pharmacologist
- Why ? ---- Is it safe, pharmacokinetics?
- Who? --- Normal **volunteers** (**25-50**)
  - Volunteer patients --- Cancer , AIDs
  - special population (renal & hepatic impairment)

Clinical testing (phase 2)
Single blind trial (inert placebo, active drug)

- By whom? -- Clinical pharmacologist & clinical investigators
- Why ?
  - Does it work in patients
  - Therapeutic efficacy, dose range, kinetics , metabolism
- Who? --- **Selected patients** (100-200)

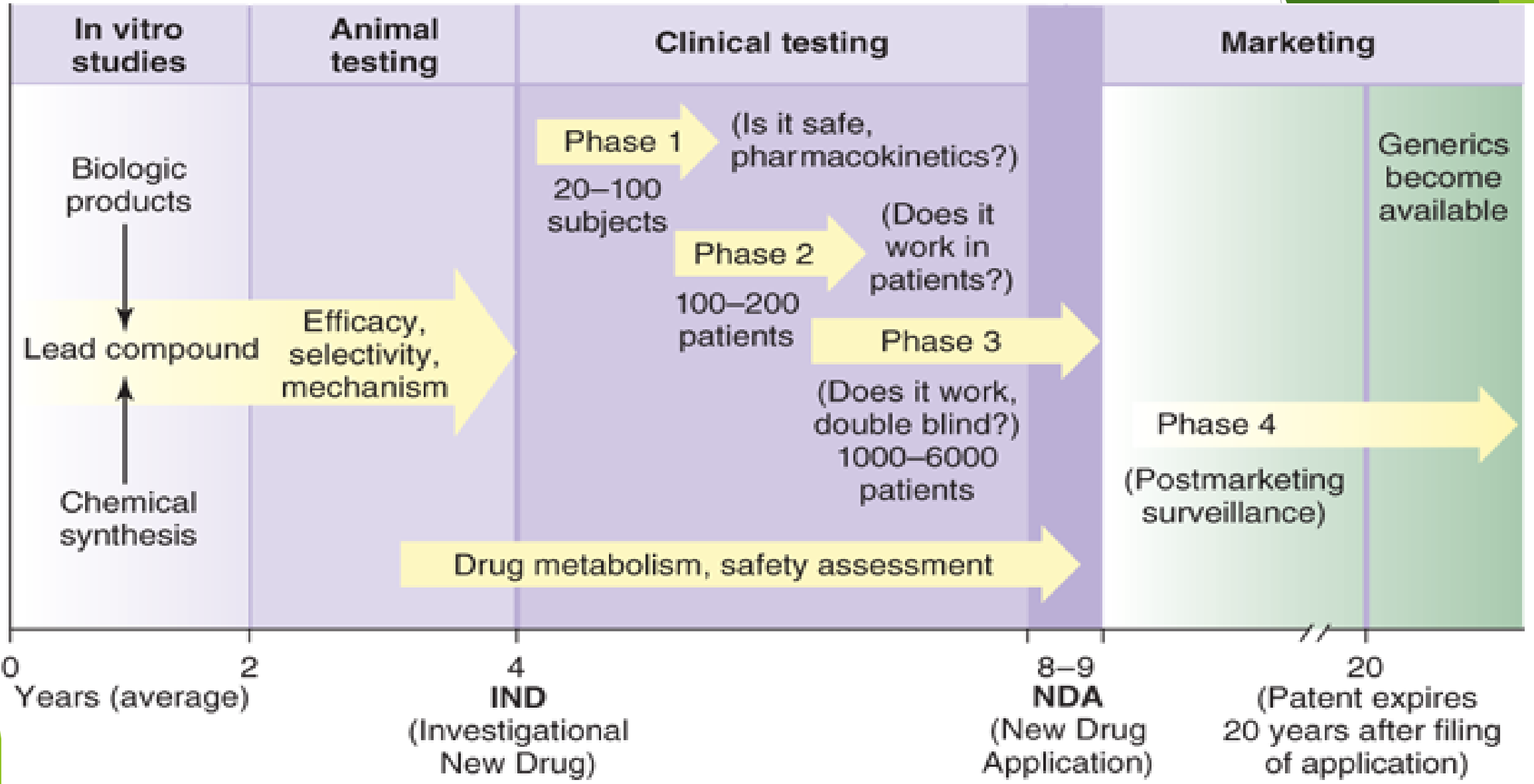
Clinical testing (**phase 3**)
Double blind & cross over techniques

- By whom? -- Clinical investigators
- Why ?
  - Does it work (**efficacy**) & **Safety**
- Who?
  - **Large sample of selected patients** (may be in thousands) (200-1000)

Post marketing surveillance (**phase 4**)

- By whom? -- All physicians
- Why ?
  - Adverse reactions, patterns of drug utilization, additional indications discovered
- Who?
  - **Patients given drugs for therapy** (2000 ---10,000)

- New drug application and registration (NDA)
  - NDA review - (average 12 months) - NDA approved
- Marketing and Post marketing surveillance (Phase 4)
- Years (20years) after filing expires (generics available)



Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.
www.accesspharmacy.com

An example

- **The idea**
- Histamine is potent stimulant of gastric acid secretion
- Classic antihistamines did not inhibit this action
- There might be a distinct type of histamine receptors

The Clinical Need

- Peptic ulcer can be treated by suppressing gastric acid secretion

The Biological Hypothesis

- Histamine could be selectively blocked at the receptors that mediate histamine effect on histamine secretion

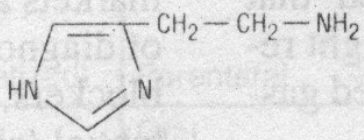
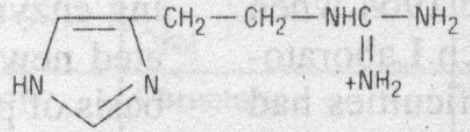
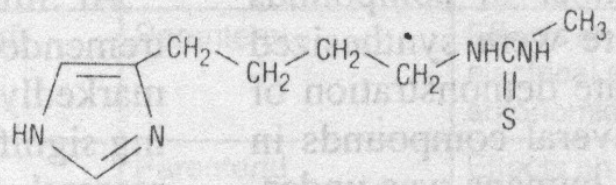
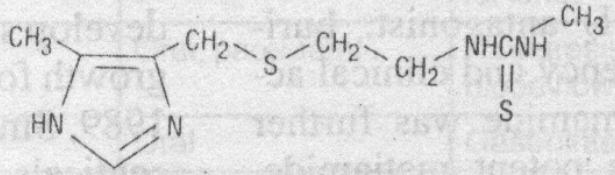
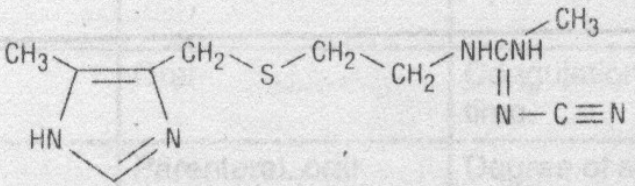
The Chemical Hypothesis

- Classic antihistamines(H_1 blockers) are ineffective
- Chemical modification of histamine itself might result in a selective antagonist for the postulated gastric histamine receptors

Development

- Pre clinical models and animal testing
  - A large number of compounds based on histamine structure were synthesized and tested
- The first selective H_2 antagonist, burimamide, lacked adequate potency and clinical activity
- Burimamide --- metamide --- **cimetidine**

- **Cimetidine** First selective H_2 receptor antagonist in 1974
- The research had taken 12 years
- In 1992 the sale of H2 receptor antagonist exceeded $ 4 billion

Compound and Characteristics	Structure	Antagonist Activity (in vivo ID_{50}, μmol/kg)[1]
Histamine The starting point.		Agonist
N-Guanylhistamine The first lead compound. A weak partial agonist.		800
Burimamide Thiourea compound with a longer side chain. Weakly active in humans.		6.1
Metiamide Active in humans but toxic.		1.6
Cimetidine 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

Approaches to develop new drugs

- **The clinical need**
  - Corticosteroids too toxic for chronic use
  - Need of anti-inflammatory drugs
- **The idea --** Identification of a new drug target
  - Mediators of inflammation especially prostaglandins (PG)
- **The hypothesis**
  - Inhibitors of prostaglandins
- **Development**
  - NSAIDs developed (1950-1980)

Aspirin to COX-2 inhibitors

- **The idea**
- Willow bark --- used since centuries
  - Analgesic & antipyretic
  - Active ingredient --- **Salicin** (1897)
- Salicin derivative developed in 1897
  - Aspirin(acetylsalicylic acid)
  - Analgesic ,antipyretic + **anti-inflammatory effect**
  - Adverse effects-- -GI bleed

The clinical need of anti-inflammatory drugs

- Corticosteroids too toxic for chronic use
- Based on better understandings of mediators of inflammation especially prostaglandins (PG) NSAIDs developed (1950-1980)
  - More potent than aspirin but had similar toxicities especially of GI adverse effects

The biological hypothesis

- Aspirin and NSAIDs inhibit **PG** synthesis
- Prostaglandins are mediators of inflammation
  - Enzyme cyclooxygenase (COX) involved in synthesis of specific PG is increased in inflamed tissue and stimulated by certain cytokines
- Isoforms of COX
  - COX 1 ----- maintain the integrity of lining of the stomach
  - COX2 --- inducible cox that is upgraded in inflammation

The chemical hypothesis

- Cox 2 cloned and expressed in 1991
- Screening and rational drug design an inhibitor much more selective for COX2 than for COX 1 was discovered
- Celecoxib --- rofecoxib --- valdecoxib
- Celcoxib approved in December 1998 for treatment of osteoarthritis and rheumatoid arthritis

Development

- NDA for rofecoxib filed in 1998
  - Clinical trials for clonic polys and Alzheimer's disease started
- In1999, the FDA approved the rofecoxib for OA, acute pain, and painful menstruation

Development about 1 year later

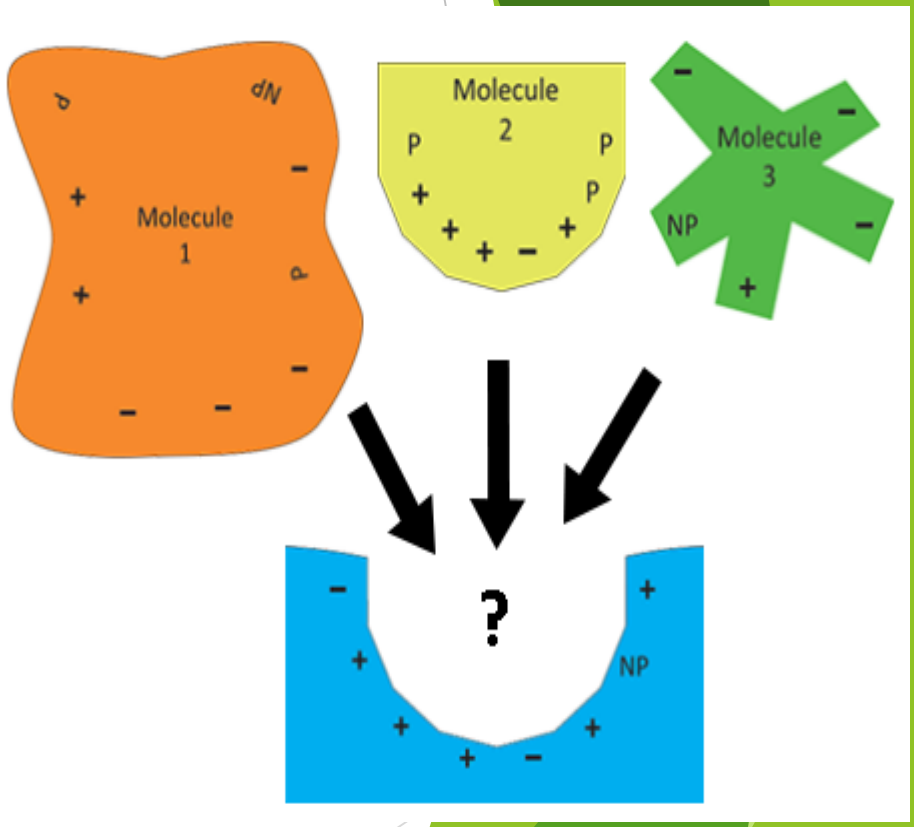
- First large comparison trial showed a **4 fold risk of heart attack** than non selective Cox inhibitors
- In 2002--- label indicating increased CV risk, GI benefit, new use to treat RA
- **In 2004 second** large trial showed twice the risk of hearts an compared to placebo
- The manufacturer then voluntarily withdraw rofecoxib

Drug development

- **Modification of structure of known drug**
  - Aim is to develop a new drugs which are **more active, less toxic or easier to use** than the original drug
- **Repositioning** of a known drug for a new therapeutic use
  - Amantadine for parkinsonism
- **Rational drug design**

Rational Drug Design

It is the designing of the drug molecule to fit into its receptor on the basis of known **three dimensional structure** of the receptor



Modification of structure of known drug

- Homatropine from atropine
- Hyoscine butylbromide from hyoscine
- Thiazide diuretics from cabonic anhydrase inhibitors
- Modification of histamine structure to form H_2 receptor antagonist

Drug act

An act to regulate the import, export, manufacture, storage, distribution and sale of drugs

Why need of drug Act ?

- To ensure the availability of standard **quality, safety, efficacy, and Supply of** drugs in hospitals, dispensaries, pharmacies and clinics so that patients get the maximum benefit from the modern drugs.
- A basic requirement of any control system is that no medicine may be sold or supplied without prior licensing or registration by government

- Health care professionals must understand the implications of this act &
- **Should avoid violation of the act during performance of their professional duties.**

DRUGS ACT

- **Drugs Act 1940** and its rules were enforced in India. These rules remained applicable for many years in Pakistan.
- In **1972 Generic Drugs Act** was enforced.
- According to it the drugs were to be sold under Generic Names and not under Trade Names (Proprietary, Patent Names).

DRUGS ACT

Generic Drugs Act was replaced by ***DRUGS ACT 1976*** and at present this act and rules made there under are enforced in **Pakistan.**

National essential drug list (NEDL)

- **Essential drug** as defined by WHO are those that satisfy the health care need of majority of the population.
  - They should, therefore, be available at all times in adequate amounts and in appropriate dosage form
- NEDL of Pakistan was first prepared in 1994. present list is the 3rd revision containing **425 drugs** of different pharmacological classes

Pakistan National Formulary (PNF)

- Federal Ministry of Health, Govt of Pakistan registers drugs (both manufactured in Pakistan or imported from abroad) for marketing in the country.
- The registered drugs are published in Pakistan National Formulary (P.N.F.).

Adverse drug reaction monitoring

The form for reporting to drug controller Pak. Secretariat, Block C, Ministry of heath Islamabad

The form

Sr. No

REPORT ON SUSPECTED SERIOUS ADVERSE DRUG REACTION

1. PARTICULARS OF PATIENT

Name of patient.

Age Weight (kg) Patient address

Sex Male Race

Female

Pregnant Yes No Not applicable

Relevant Medical History

- **2. ADVERSE EVENT**
- Reason for reporting
- Requires or prolongs hospitalization Life threatening Death
- Permanently disabling or incapacitating Congenital anomaly Overdose
- Other (Please Specify)
-
-

3. SUSPECTED DRUG

- Name of suspected Drug Generic Name
- Name of manufacturer
- Date of occurrence Duration of Event
- Starting date of Medication
- Route of administration
- Discontinuation of Drug because of event No Yes Dated

4. **REPORTING DOCTOR'S / PHARMACIST'S / NURSE'S**

- **SIGNATURE**
- Institution
- Date
- **<u>GUIDELINES TO FILL SERIOUS ADVERSE EVENT REPORT FORM</u>**
- **<u>An adverse event is "Serious", if it</u>**
- •Is life threatening
- •Results in hospitalization
- •Prolongation of hospitalization
- •Causes malignancy
- •Is an overdose resulting in clinically
- Relevant signs and / or symptoms
- Results in permanent disability
- Is associated with death
- Causes a birth defect
- Causes a relevant organ toxicity
- ***An adverse drug event can be a manifestation of various etiologies such as***
- •Complication of an underlying disease
- •Coincidental accident
- •Concomitant medication
- Intercurrent disease
- Drug associated effect

Duties of **Drug Inspectors**

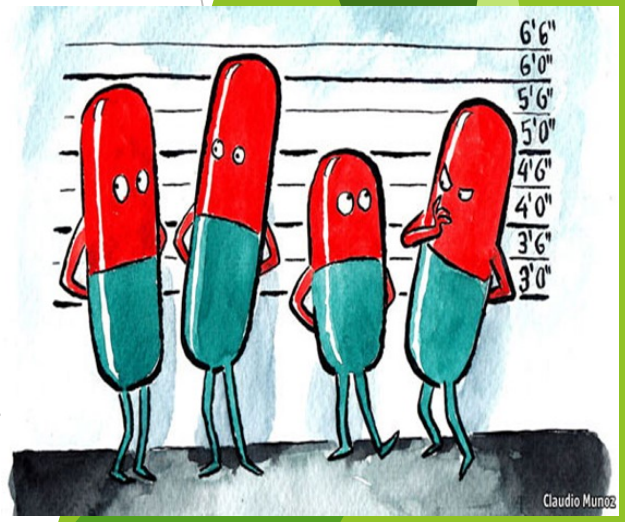
- To ensure that standard drug are being manufactured and sold in the country.
- They take samples of drugs and send to **Drugs Testing Laboratory** for analysis.
  - If drugs are not of standard quality, they register case against the defaulter in the **Drugs Court** established by the Govt, for this purpose.
  - If found guilty, the defaulter is punished under the Drgs Act 1976.

Definitions in the drug act

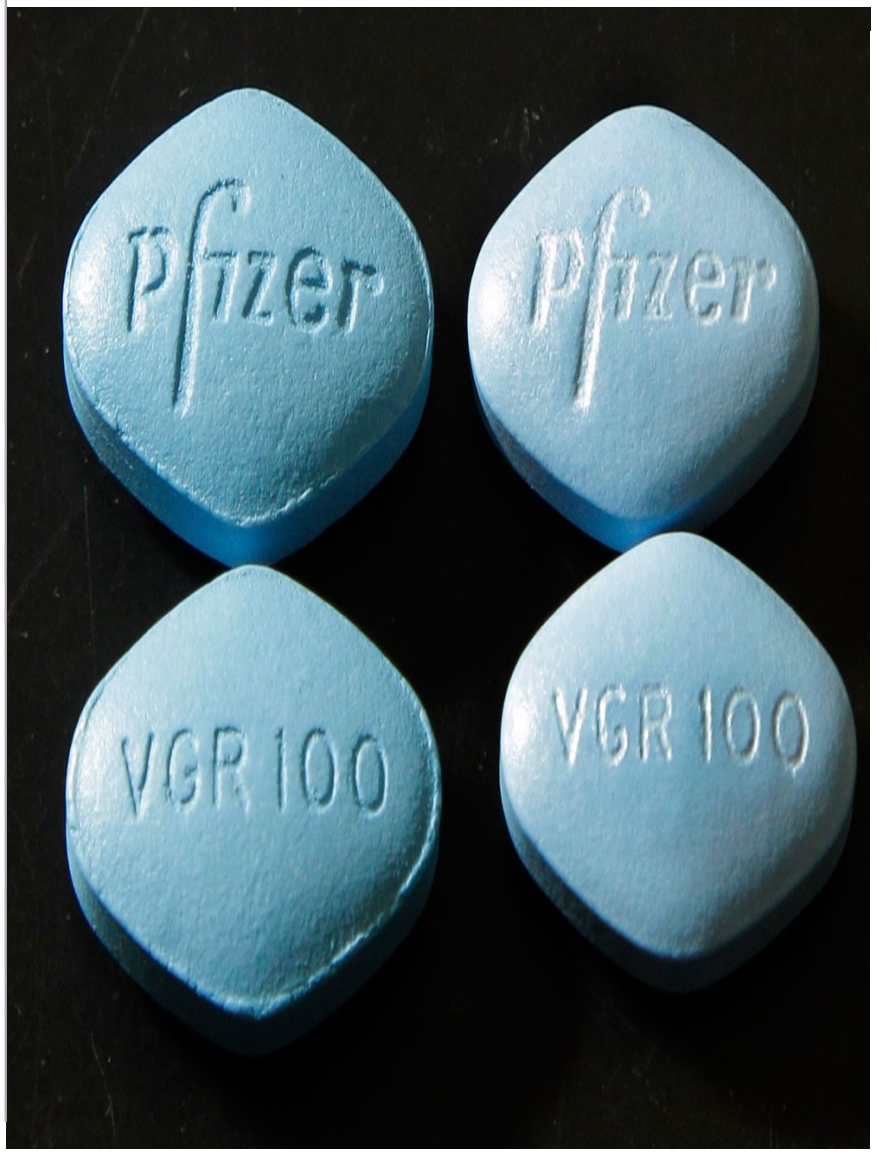
- ***Drug*** is a substance or a mixture of substances that is manufactured, sold, stored, offered for sale or represented for internal or external use in the treatment, mitigation, prevention or diagnosis of disease in human beings or animals.
- Surgical ligatures, sutures, bandages, absorbent cotton, disinfectants, adhesive plasters, gelatin capsules and antiseptic solutions are also included amongst drugs for the purpose of Drugs Act 1976.

Counterfeit Drug

- **Not genuine**; imitating something superior
- Make a **copy** of with the intent **to deceive**
- **A copy that is represented as the original**
- A drug the label or outer packing of which is an imitation of, or resembles or so nearly resembles as to be calculated to deceive the label or outer packing of a drug of another manufacturer.




Panadol
Panadol
Original
19.03.2012 17:14
Counterfeit


pfizer
pfizer
VGR 100
VGR 100


Counterfeit medicines seized in France
1,354,705
2,580,793
2013
2014

Hidden Poisons in Counterfeit medication

There are a lot of shady ingredients that go into counterfeit medications that consumers can be exposed to by buying directly from unlicensed drug sellers on the internet, or when medical professionals purchase medications from outside the secured supply chain.

Investigators have found these dangerous ingredients in fake medicine:

heavy metals

mercury
aluminum
lead
cadmium
arsenic
chrome
uranium
strontium
selenium

ARSENIC has been found by researchers

actual poisons

PCBs
benzopyrenes
rat poison
boric acid
antifreeze

ANTIFREEZE was substituted for glycerine in cough syrup and other common medications, killing 365 people in Panama, 88 children in Haiti, 84 children in Nigeria, and 18 people in Guangzhou. Lethal in doses as small as 1/3 of a teaspoon, it causes kidney damage and failure.

common household items

road paint
wall paint
brick dust
floor wax
sheet rock
paint thinner

Used by counterfeiters to provide color to pills, WALL PAINT can contain heavy metals for pigment, as well as hydrocarbons which are poisonous and can cause coma, blurred vision, rapid heartbeat, nausea, vomiting, and diarrhea.

drugs you didn't ask for

aminotadalafil
holosildenafil
xanthoanthrafil
psuedovadenafil
hongdenafil
sibutramine
haloperidol

Consumers who wanted to purchase safe FDA-approved sleep medication instead received foreign versions of HALOPERIDOL, an anti-psychotic drug when they

no drugs at all

dextrose
dextrin
lactose
starch
saline
salt

Over the Internet a Canadian man sold STARCH, DEXTRIN, DEXTROSE, and LACTOSE to cancer patients seeking an experimental cancer drug called dichloroacetate (DCA). They paid over $100 a shipment for something with no therapeutic value, like glorified guilty in US

Adulterated Drug – Mixed with impurities

- Corrupt, make impure by adding a foreign or inferior substance; often by **replacing valuable ingredients with inferior ones**
- A drug which consists in whole or in part of any filthy, putrid or decomposed substance or any foreign matter

or

- which has been manufactured, packed or held under unsanitary condition whereby it may have been contaminated with dirt, filth or any other foreign matter

or

- whereby it may have been rendered injurious to health, or it has been mixed with any substance so as to reduce its quality or strength.

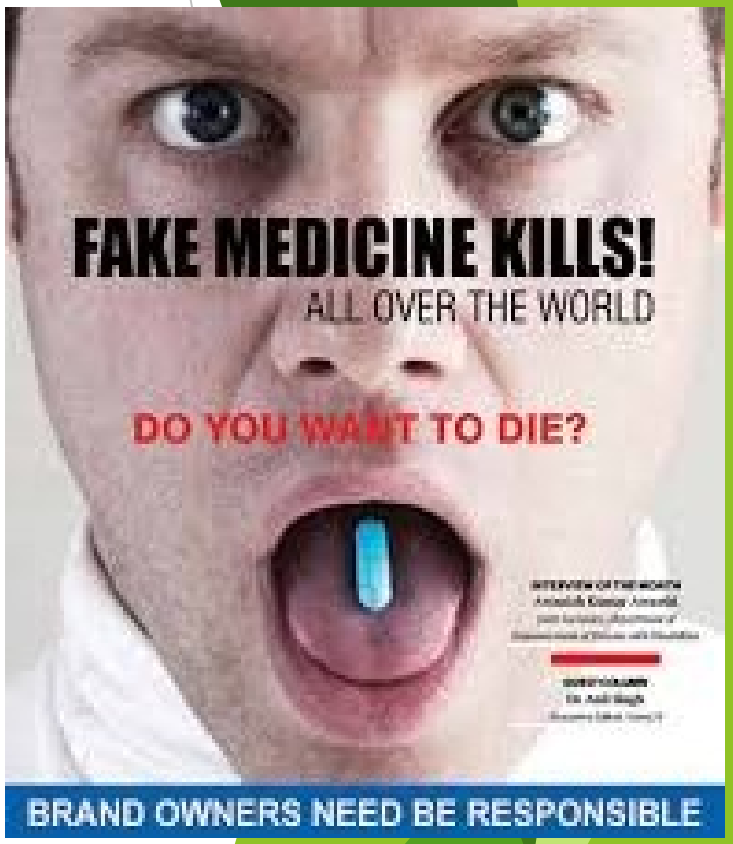
Misbranded drug

- **Branded or labeled falsely** and in violation of statutory requirements

- *A* drug which is **not labeled in the prescribed manner** or the label or container of which bears any statement, design or device which **makes any false claim** for the drug.

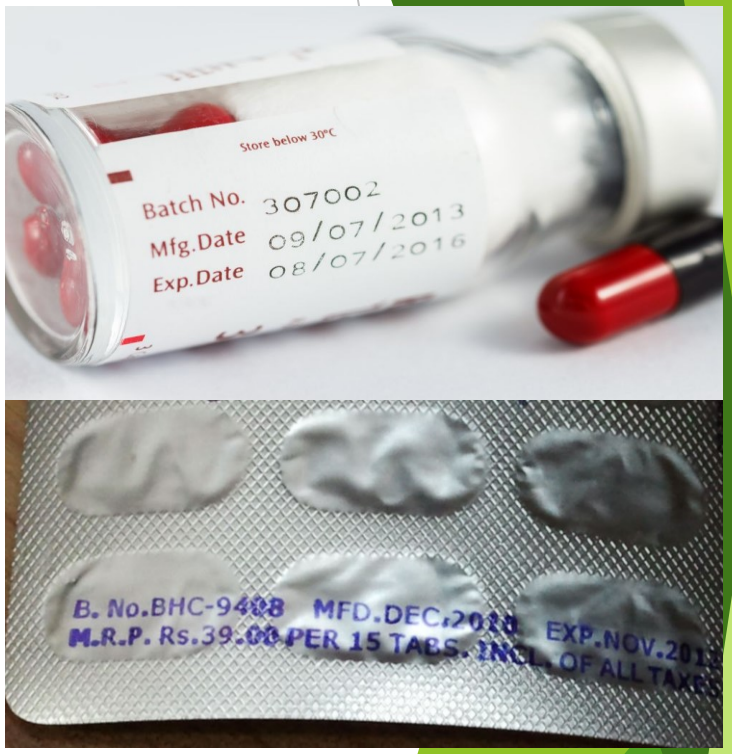
Spurious Drug

- Drug which **does not contain the active ingredient of the drug** which it claims to be or claims to be the product of a manufacturer, place or country whereas it is not truly such product or bears the name of a company but that company is factious or does not exist.
- **Intended to deceive**



Expiry Date of Drug

The date stated on the label of a drug after which the drug is not expected to retain its claimed efficacy, safety, quality, potency or **after which it is not permissible to sell the drug.**



The expiry date will be shorter in case of

- Eye drops: can be used for one month after opening the droppers.
- Antibiotic syrups & suspensions: generally can be used for one week b y storage in room temperature & for two weeks by storage in refriger ator.
- Ampoules: must be used immediately but the vials (multi-dose) are stable for 24 h in the presence of preservatives.
- Nebulizer solution: can be used for one month after opening.
- Insulin: once punctured, it must be used within 28 days.
- Syrup/Suspension (except antibiotics): can be used for one month aft er opening
- Tablets & capsules: remain stable in the package but after removal e xpiry date will be changed.