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

required for all new 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).

Subacute and Chronic Toxicity

required for most agents, especially those intended for chronic use.
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
teratogenic
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.

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.

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)
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

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

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

GUIDELINES TO FILL SERIOUS ADVERSE EVENT REPORT FORM

An adverse event is "Serious", if it

- 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
- Intercurrent disease

- Coincidental accident
- Drug associated effect
- Concomitant medication

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.

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 by storage in room temperature & for two weeks by storage in refrigerator.

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 after opening

Tablets & capsules: remain stable in the package but after removal expiry date wi ll be changed.