

INTRODUCTION TO THE STUDY OF PHARMACOLOGY

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Pharmacology, definition, aims



„pharmakon“ + „logos“ / „logia“

Scientific discipline dealing with

INTERACTIONS BETWEEN SUBSTANCES..

introduced into the organism from the environment

..AND THE LIVING ORGANISM

on all levels of complexity:

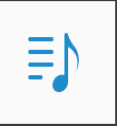
molecular

cellular

organ

organism as a whole

DRUG



„substance or mixture of substances, supposed to be administered to the humans or animals for prevention, treatment or diagnosis of diseases or its symptoms or for physiological function adjustment“

Drugs are administered for

- Prevention,
- Diagnosis,
- Treatment of diseases

Pharmacon/um - drug



classical WHO definition:

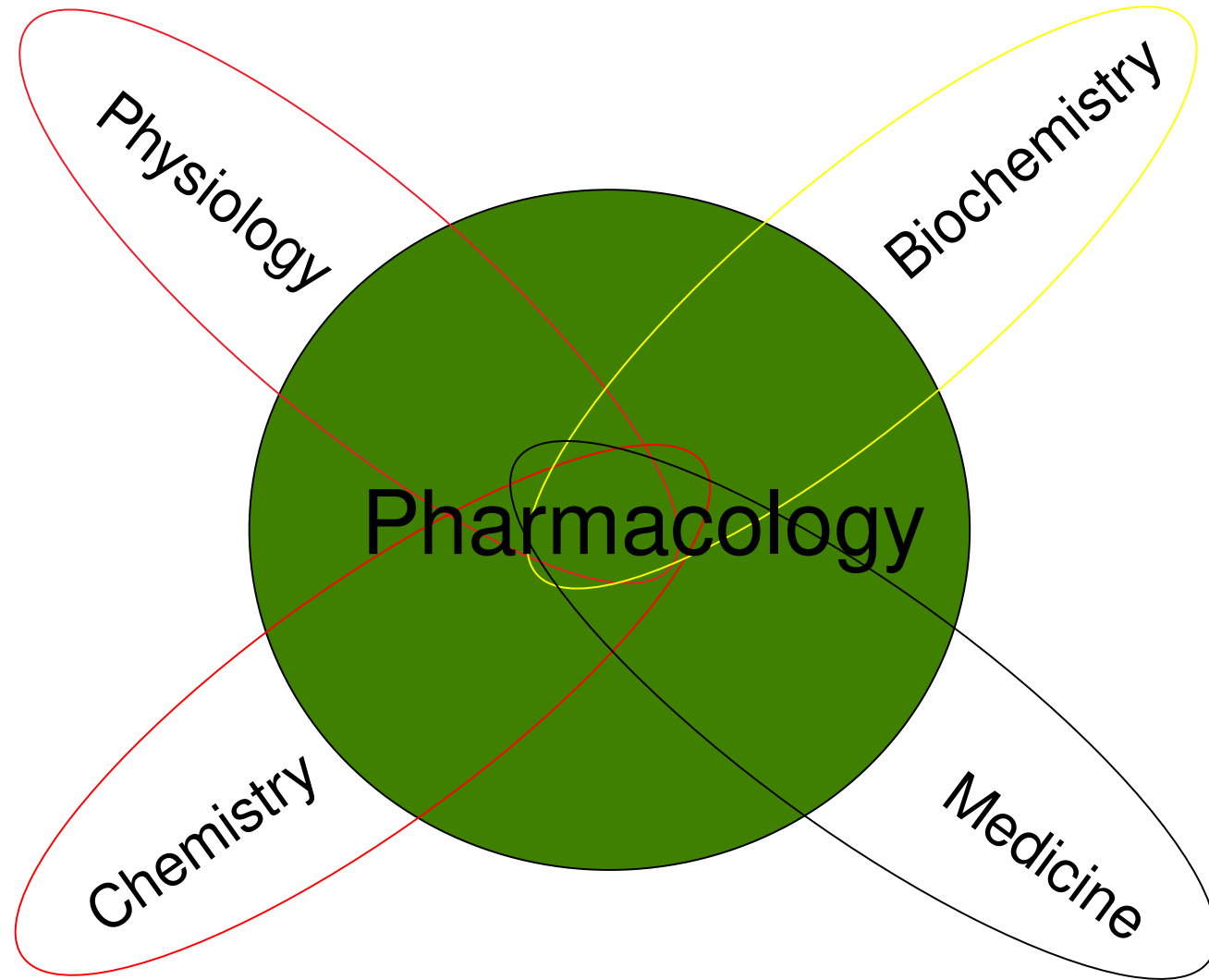
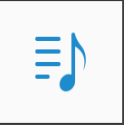
„Any substance (other than normal body components or substances necessary for normal body functions (food, water, oxygen), that, after administration into the organism evokes a change of a body function“

More precise definition according to Ph.Eur.:

Substances or their mixtures designed to the administration in humans or animals with a purpose of treatment, mitigation, prevention or diagnose of a disease or its symptoms and also to modulation of physiological substances.

*European Pharmacopoea (Ph. Eur. 6th Ed.)
Pharmacopoea Bohemica 2009 (Ph. B. 2009)*

A synthesis of several biomedical sciences....

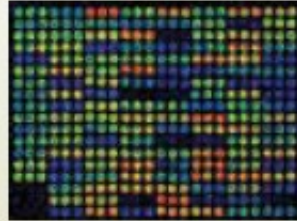


...but unique in its own right

Pharmacologists study science at every level

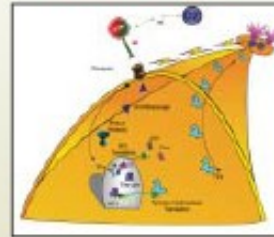


Genetic



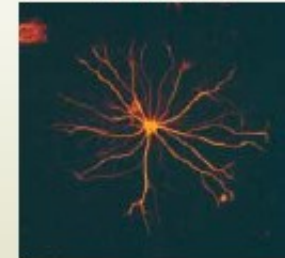
*Gene Chip Microarray.
Courtesy of Aronette Thelen, MSU Genomics Structure Facility.*

Molecular



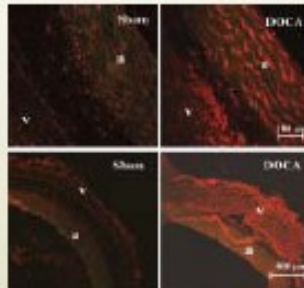
*Interaction of the dopamine (D2) and dynorphin system in regulation of tuberoinfundibular neuronal function.
Courtesy of Y. Will-Murphy and K. Lookingland*

Cellular



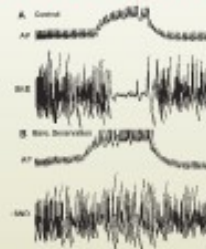
*Astrocyte, labelled with Glial Fibrillary Acidic Protein
Courtesy of J. Edwards and B. Achison*

Tissue



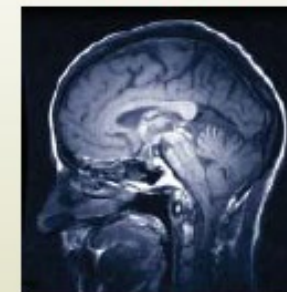
*Superoxide measurement through dihydroethidium in artery (a) and vein (v) of normotensive (sham) and hypertensive (DOCA) rats.
Courtesy of H. Xu and J. Galligan*

Whole Animal



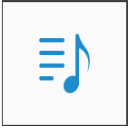
*Effect of sectioning baroreceptor nerves (denervation) on the inhibition of sympathetic nerve discharge during a rise in arterial pressure in an anesthetized cat.
AP - arterial pressure, SND - sympathetic nerve discharge.
Courtesy of S. Barman and G. Gebber.*

Human



*MRI of Human Head
Courtesy of Kevin Henley and James Petchen of the Radiology Department, MSU*

What Pharmacology is NOT...



❖ Pharmacy

This is a separate profession responsible for the preparation and dispensation of medication.

❖ Pharmaceutical Science

Basic Pharmacology



General principles

Systems Pharmacology



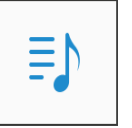
General principles



Principles which predestinate the interactions of the drug and body

Two important and interrelated areas:

- General Pharmacokinetics
- General Pharmacodynamics



Pharmacokinetics (PK)

Deals with the fate of the drug in the body
– processes of

Absorption,
Distribution
Metabolism
Excretion

„What the body makes with the drug“

...“ADME“

Pharmacodynamics (PD)

deals with the mechanism of action (e.g.
receptor sites, molecular level of action..)

„How does it work“

Systems Pharmacology



Is focused on individual organ systems and its pharmacotherapy

e.g.

Autonomic drugs

Psychoactive drugs

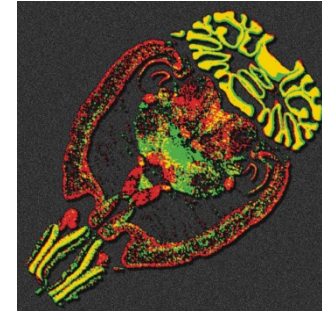
Drugs used in cardiovascular diseases....

Systems Pharmacology



❖ **Neuropharmacology:** study of the effect of drugs on components of the nervous system (brain, spinal cord, nerves)

Example: treatment of Alzheimer's disease



❖ **Cardiovascular Pharmacology:** study of the effects of drugs on heart, vasculature, kidney, nervous and endocrine systems that participate in cardiovascular function.

Example: treatment of high blood pressure (hypertension)



Branches of Pharmacology



Clinical pharmacology

- deals with different drugs and their varied clinical usage
- interdisciplinary branch, which integrates basic and experimental Pharmacology with the clinical and complementary branches

AIM: to study and evaluate the effect of the drug using objective methods (EBM)

Sub-branches of clinical pharmacology:

Clinical Pharmacokinetics, clin. Pharmacodynamics,
Rational prescribing, Clinical toxicology

Toxicology



the study of the toxic effects of chemicals on living organisms

study of symptoms, mechanisms, treatments and detection of poisoning

experimental (in vitro, in vivo)

clinical - poisoning prophylaxis, diagnosis, treatment

forensic toxicology...



Pharmacogenetics

deals with the influence of genetic variation on Pharmacokinetics and Pharmacodynamics

study of the drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity

consequences can be either quantitative or qualitative

Pharmacogenetics



- 1959 Friedrich Vogel used first time term „pharmacogenetics“
- 1997 First time used term “**Pharmacogenomics**“

Pharmacogenetics considers one or at most a few genes of interest, while pharmacogenomics considers the entire genome.

Biochemical and molecular pharmacology



detail study of the mechanism of action at molecular level

Chronopharmacology

Study of the action of the drugs with respect to the biorhythm

(antiasthmatics, glukocorticoids, statins, etc.)

Pharmacoepidemiology



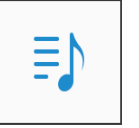
- study of the effect of drugs on populations; questions dealing with the influence of genetics are particularly important

risks and benefits of the therapy using epidemiological methods

Approach of the health specialists (GP, pharmacist)

patient (compliance)

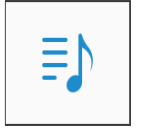
society (drug abuse, marketing, financial resources...)



Pharmacoeconomy

- rationalize the use of sources in health care
- Compares the costs of therapeutic approaches by the pharmacoeconomical analyses

The goal is not „to decrease total money spent in health care“ , but to use the sources effectively



Pharmacovigilance

Pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects

collecting, monitoring, researching and evaluating information from healthcare providers and patients on the adverse effects of medication

Drug safety monitoring

AIM: to minimize the risk of adverse effects

Experimental pharmacology

Biological experiment



in vitro – isolated structures or organs,
cell cultures, microorganisms

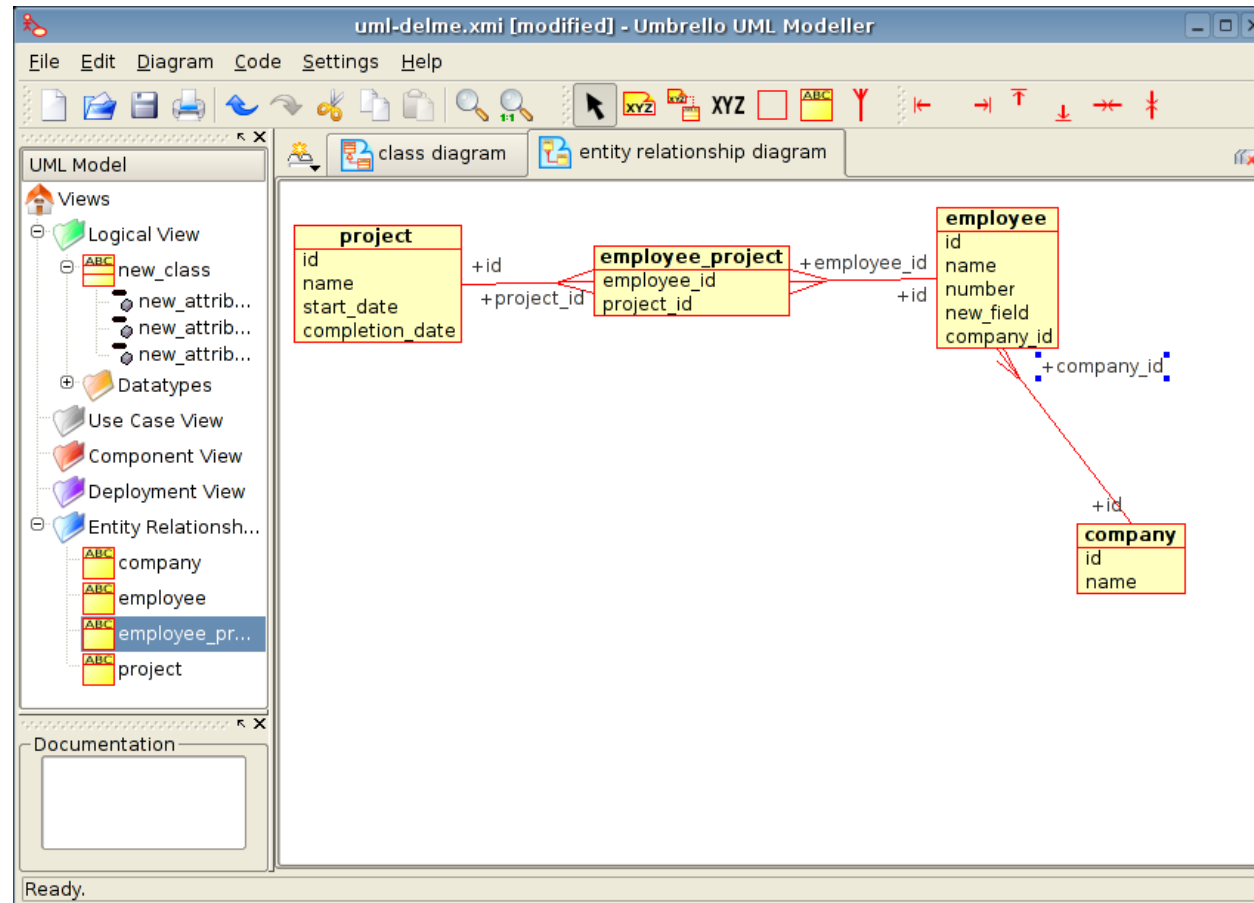
- regulatory factors we have to satisfy:

- ethical (replacement, refinement, reduction)
- small amounts of drugs
- use of human cells
- elimination of systemic reaction of the whole body

Biological experiment



in silico – use of IT, especially computer modelling (f-kinetics), databases



Biological experiment



in vivo – whole animal

- systemic effects
- we record toxicity, possible adverse and allergic effects
- impact on memory and other cognitive faculties, learning abilities, depression

Experimental animal



Experimental animal (is born, bred and maintained for experimental purposes)

Defined genetic features:

- **randombred** – natural breeding - heterozygots
- **inbred** – breeding of brothers and sisters, approx. 20 generations

homozygots

diabetic mice, hypercholesterolemic mice, hypertonic mice...

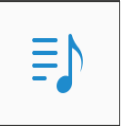
Experimental animal



Defined microbial settlement:

- **SPF** – have 4-5 saprophyte pathogens
- **Gnotobiotic animals** – are born by hysterectomy, pathogens free
- **Conventional breeding** – not defined settlement

Experimental animal



Mammals

RODENTS: mouse, hamster, rat, guinea-pig

NON-RODENTS (e.g. Lagomorpha): rabbit

Experimental animal



Mammals

carnivores: dog, cat, ferret

Mammals

monkeys: macaque (*Macacus* sp.), green monkey (*Erythrocebus* sp.)

Birds

common quail, hen, duck

Amphibians

Xenopus sp.

Fish

guppy (*Poecilia reticulata*), carp, trout

Crustaceans

Cladocera, *Cyclops strenuus*

Laws



EU

1986 Council of Europe – rules of protection for vertebrates used for experimental purposes in Europe

Principle 3R: replacement

reduction

refinement

Laws



Czech Republic

Law no. 149/2004 „*na ochranu zvířat proti týrání*“ - about animal protection against cruelty

Notice no. 207/2004 „*o ochraně, chovu a využití pokusných zvířat*“ - about protection, breeding and use of laboratory animals

Authorities encharged of animal protection:

Ministry of agriculture, Comission for animal protection, veterinary authorities, ethical comitties

Drug names



Chemical name

according to the IUPAC nomenclature rules

e.g.: **N-acetyl-para aminophenol**

Generic name (non-proprietary)

INN (International Non-proprietary Name)

not registered, supposed to be used internationally

has to be printed on the packing of the drug (under the registered trade name)

for the universal terminological identification of the medicines

formed from the chemical name (shortness) accordingly with the rules (WHO)

each drug has its own CAS No (Chemical Abstracts Service Number)

e.g. **paracetamol**

Drug names



Trade name (proprietary)

registered, patent-protected[®]
has to be accompanied with the INN

e.g. **Panadol, Coldrex, Paralen**

Official name

latin name in Pharmacopoeia (e.g. Paracetamolum)

usually very similar to INN

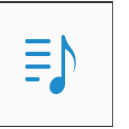
has to be prescribed on Rx formulary in case of individually prescribed medicines

established name for a drug substance is usually found in the originating country's Pharmacopoeia

Paracetamolum

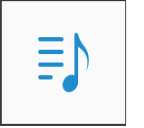
...

Some drug-family names



- olol betareceptor antagonists
- caine local anaesthetics
- tidine histamine receptor antagonists
- dipine calcium channel blockers of
dihydropyridine type
- statin inhibitors of HMG CoA transferase

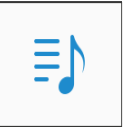
DOSE



A specified quantity of a therapeutic agent, prescribed to be taken at one time or at stated intervals.

If administered in the body, desintegrates, solutes, and distribute across the barriers in the body compartments. Than it is measured like „concentration“

DOSE



DOSIS SINGULA - single dose

on Rx !

DOSIS PRO DIE - daily dose

- for 24 h !!

DOSIS CHRONICA

- (adjusted) dose in the chronic treatment (long-term)

DOSE



DOSIS CURATIVA

- total dose of the drug needed for whole period of treatment

DOSE (from effect point of view)



Sub-threshold - cause no observed biological effect

Threshold - minimally effective dose; dose, after which can be observed any effect

Therapeutic dose - produces mostly beneficial effects;

▶ MAXIMAL

- does not produce harmful effects

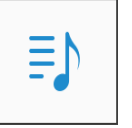
▶▶ DOSIS MAXIMA SINGULA

▶▶ DOSIS MAXIMA PRO DIE

TOXIC – mostly harmful effects (RISK > BENEFIT)

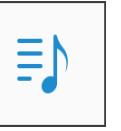
LETHAL – cause death

ORIGIN OF DRUGS



Modification of the chemical structure of the already known drug
Searching for natural substances
Investigation (screening) of already known chemical compounds
Targeted synthesis of substances with a structure designed by
computer modeling

Origin of drugs – synthesis/isolation



Medicinal Plants (cardiac glycosides)

Animal tissues (heparin)

Microorganisms (penicillin)

Human cells (autologue vaccines)

Biotechnology (insulin, MAb)

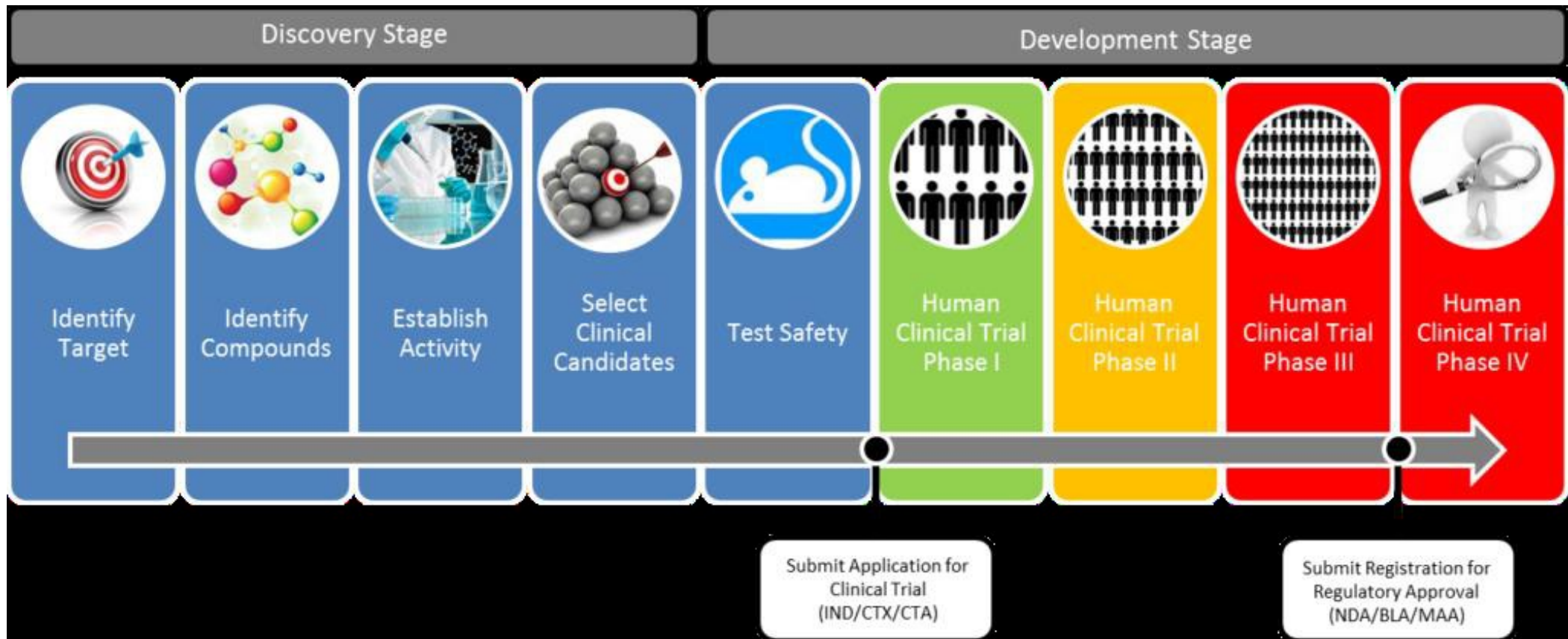


Thalidomide crisis



Thalidomide - Contergan ©
1950 - 1960
hypnosedative used by
pregnant women
It gave birth to 12,000
children with disabilities







- Evaluation of effect in vitro
- Evaluation of effect + toxicity in animal models (2 animal species at least)

In situ

- Influencing organ systems that can not be studied in isolation (KVS , DS , GIT)

Living animals

- overall effects (convulsions , sedation , anesthesia, temperature)
- affecting cognitive function (learning, attention, memory)
- influence on the specialized function (immune system)

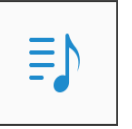


- Evaluation of acute and short term toxicity in animals. It Involves :
 - Lethal dose determination
 - Effect of dose at normal level for short/Long term
- Assess how the drug is absorbed/distributed/metabolized and excreted in animals.



- All CTs has to be approved by SUKL
(State institute for drug control)/EMA
- Drug given to 10-100 healthy volunteers
 - Duration could vary from 1 month to 1 year.
- Following is studied here :
 - Drug absorption/Metabolism in human.
 - Effect on organs and tissues
 - Side affect of different dosages.

Proceed to next Stage



○ 1st administration to the patient

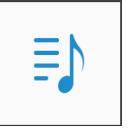
○ randomized clinical trial tested the drug x = standard therapy x

placebo

- Often called „Blinding“ – blinding also in multicentric manner

○ It monitors the effect of the disease, dose , pharmacokinetics in patients

○ Informed consent , with no financial reward



- Drug given to 100 - 300 patients - volunteers

- Duration could vary from 1 year to 2 years

- Cost could vary from \$10 - \$100 million.

- Following is studied :

- Drug effectiveness in treating the disease.

- acute side effects in patients

- Less than 1/3rd of New Chemical Entities (NCE) enter phase 2



- Phase 3 - Extended trial
- Patients 100-1000
- Comparison of the therapeutic efficacy and safety to standard therapy
- In the Czech Republic a year to 300 proposals involving 30,000 patients
- Coordinates the SUKL/EMA/FDA
- Approval for new substances to launch the market issued by the State Institute for Drug Control (SUKL)/EMA (European Medicines Agency)

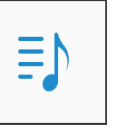
- FDA consulted before beginning phase 3

- Drug given to 1000-3000 patient volunteers
- Duration could vary from 3 years to 4 years.
- Cost could vary from \$10 - \$500 million

- Following is studied here :

- Safety of Drug [Benefits v/s risk analysis] –
- Long term side effects in patients

- Proceed to next Stage - registration

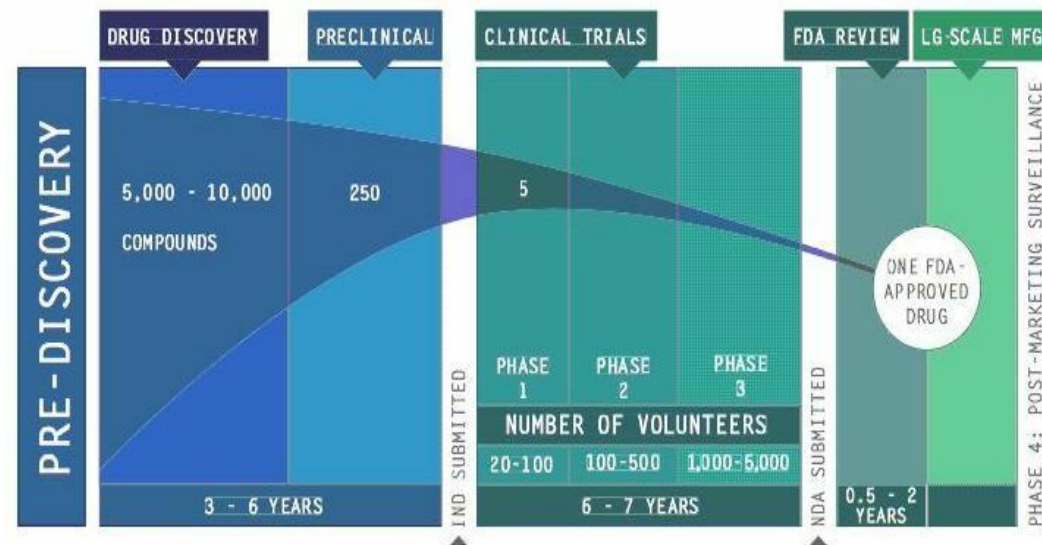


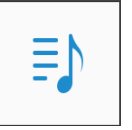
Market Launch/Phase 4 :

- 4th phase - post-registration
- post-marketing evaluation
- verification of effects in broad clinical practice
- An average of 5 years
- Data on the incidence of adverse effects, interactions , differences in the age groups etc.
- Comparison with standard therapy
- The possibility of drug withdrawal

Market Launch/Phase 4 :

- Additional post marketing testing of patients to
 - Support the use of the approved indication
 - Finding new therapeutic opportunities
 - Extending use of the drug to different classes of patients like children





Examples of drug withdrawals

rofecoxib (HVLP Vioxx)

CVS AE, - AMI

clobutinol (HVLP *Silomat*)

Heart dysrhythmias

rosiglitazon

CVS risk

Reasons for drug withdrawal

