MUNI
MED

FACTORS INFLUENCING DRUG EFFECT.
ADVERSE EFFECTS.
DRUG-DRUG INTERACTIONS.
DRUG DEVELOPMENT.

Department of Pharmacology MU

FACTORS INFLUENCING DRUG EFFECT

- Related to the drug
- Related to the patient
- Related to both (drug and pacient)

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FACTORS RELATED TO THE DRUG

- Physics and chemical properties
  - Molecule size, chemical configuration, weak acid/base, lipophilicity…
- Drug dosage form
- Food
  - Lipids tend to slow down intestinal absorption
  - Drug+ion complex formation
  - pH changes

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FACTORS RELATED TO THE PACIENT

1. AGE
2. SEX
3. BODY WEIGHT
4. CIRCADIAN RHYTHMS
5. PATOLOGICAL CONDITION
6. GENETIC FACTORS

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1. AGE

- CHILDREN
  - DOSE ADJUSTMENT DEPENDENT ON BW OR BODY SURFACE AREA
  - NEWBORNS – INMATURE LIVER AND KIDNEY PROCESSES, LEAKY BBB
- SENIORS
  - POLYMORBIDITY, POLYPRAGMASY
  - ↑ $T_{1/2}$ OF ELIMINATION
  - PHARMACODYNAMICS – DIFFERENT TARGET SENSITIVITY – OFTEN PARADOXICAL AND HYPERERGIC REACTIONS

⇒ ↓ DOSING

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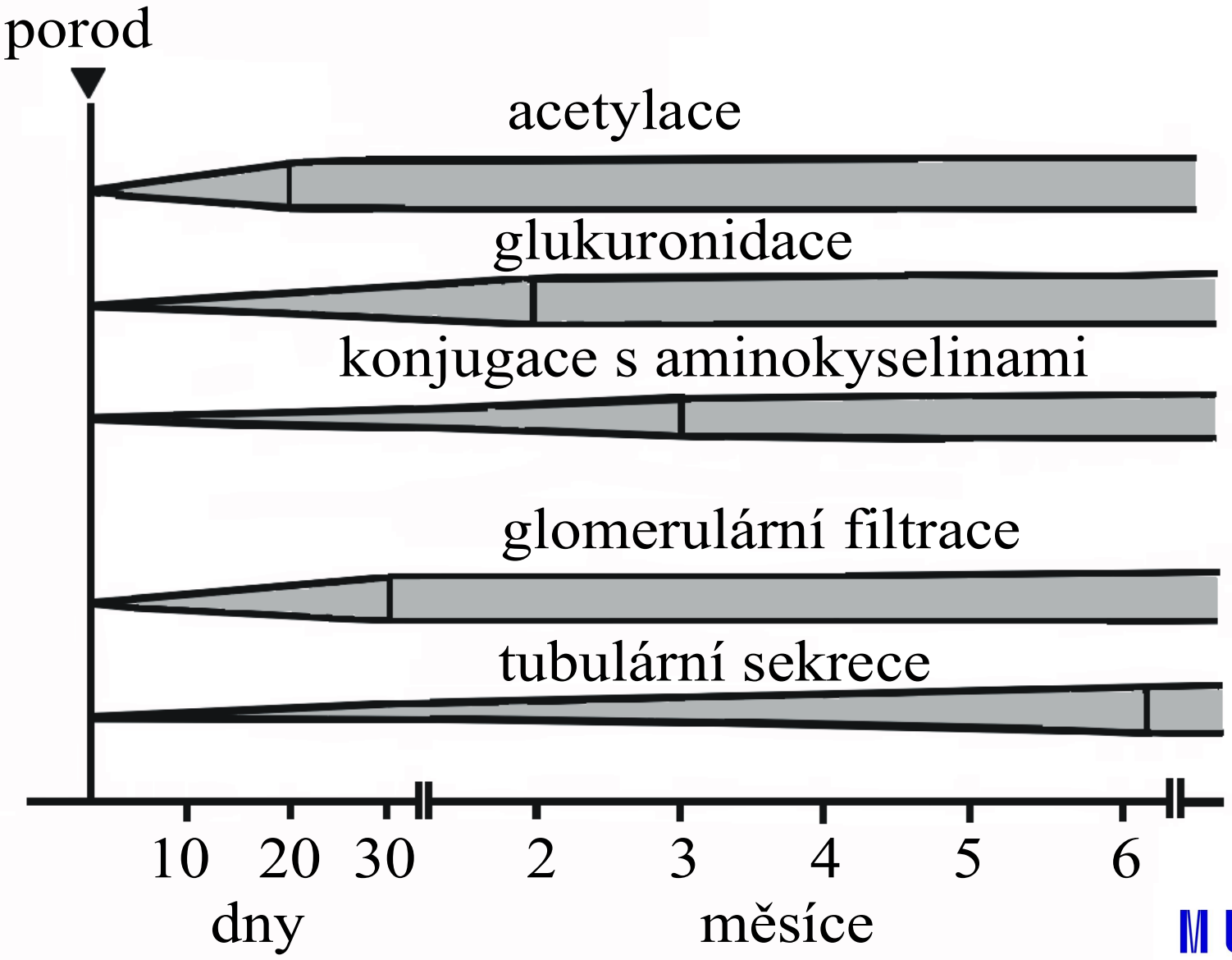
porod
acetylace
glukuronidace
konjugace s aminokyselinami
glomerulární filtrace
tubulární sekrece
10
20
30
2
3
4
5
6
dny
měsíce

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2. SEX

- Woment tend to experience stronger effects
- sensitivity to drugs acting in the brain is altered by menstual cycle / menopause
- Pregnancy and breast feeding

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3. BODY WEIGHT

- Doses are usually calculated for male pacient with 70 kg of BW
- Body composition
- Better fitting – dose per meter square or BW

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4. CIRCADIAN RHYTHMS

- BIOLOGICAL RHYTHMS OF PHYSIOLOGICAL FUNCTIONS (GLUCOCORTICOIDS, ETC.)
- CHRONOPHARMACOLOGY, CHRONOTHERAPY

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5. PATHOLOGICAL CONDITION

- IMPAIRMENT OF ORGANS RESPONSIBLE FOR METABOLISM OR EXCRETION (LIVER, KIDNEY)

  ⇒ DOSE ADJUSTMENT

- SOMETIMES THE PATHOLOGY IS NECESSARY TO OBSERVE THE EFFECT
  - ANTIPYRETICS, INHLALATION GLUCOCORTICOIDS IN ASTHMA…

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6. GENETIC FACTORS

- FARMAKOGENETICS
  - GENETIC POLYMORPHISMS OF CYP450
  - SLOW VS. EXTENSIVE METABOLISERS

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FACTORS RELATED TO BOTH, DRUG AND PACIENT

1. DOSE
2. REPEATED DRUG ADMINISTRATION
3. COMBINATION OF DRUGS
4. LATE EFFECTS

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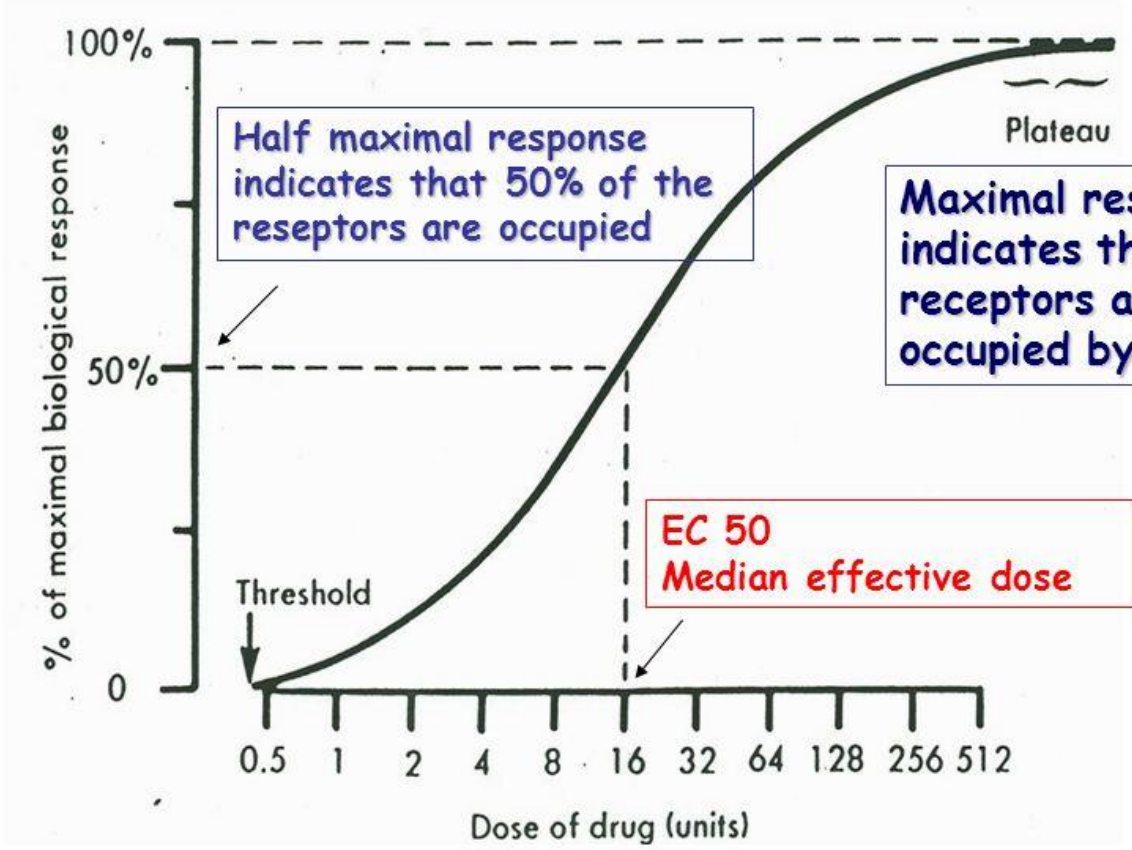
1. DOSE

Dose-response (dose-effect) curve



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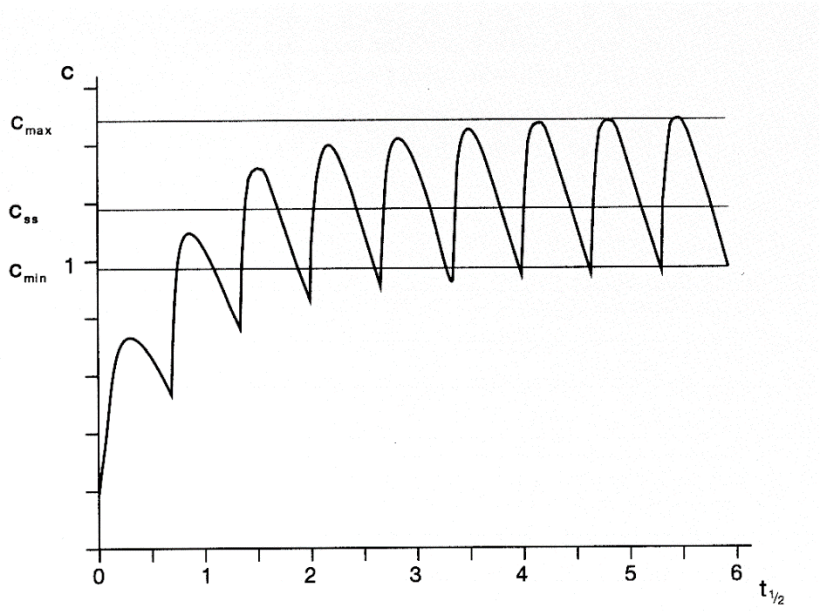
2. REPEATED DRUG ADMINISTRATION

- MAY LEAD TO STRONGER EFFECT
  - CUMULATION
  - RECEPTOR SENZITIZATION
- MAY LEAD TO WEAKER EFFECT
  - TOLERANCE
  - TACHYPHYLAXIS



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3. COMBINATIONS OF DRUGS

- See interactions later

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4. LATER EFFECTS

- THERE IS A LONG INTERVAL BETWEEN THE DOSE AND THE EFFECT

- TERATOGENICITY
- MUTAGENICITY
- CANCEROGENICITY

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ADVERSE EFFECTS OF DRUGS

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ADVERSE EFFECTS (AE) OF DRUGS

= ANY UNINTENDED ADVERSE REACTION TO ANY DOSE ADMINISTRATION

- ADVERSE EFFECTS OF DRUGS ARE THE CAUSE OF UP TO 6 % OF ALL HOSPITALISATIONS

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AE FREQUENCY - SPC

- VERY COMMON (WITH OCCURRENCE FREQUENCY ≥10 %)
- COMMON (1 %- 10 %)
- UNCOMMON (0.1 % - 1 %)
- RARE (0.01 %- 0.1 %)
- VERY RARE (< 0,01 %)

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ADVERSE EFFECTS

1. Type A (augmented) - dose-dependent, predictable
2. Type B (bizarre) - do not follow from the mechanism of action
3. Type C (continuing, continuous, chronic) - consequence of long-term drug use
4. Type D (delayed) - manifested after a longer interval from the drug administration
5. Type E (end of use) - manifested after the drug discontinuation

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TYPE A - AUGMENTED

intensified “normal”, or natural drug effects observed for usual therapeutic doses

Predictable

breathing attenuation by opioids, bleeding after Warfarin administration, etc.

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TYPE B - BIZARRE

UNEXPECTED DRUG RESPONSES

DO NOT FOLLOW FROM THE MECHANISM OF ACTION

OCCURRENCE IS RARE

INCLUDE **ALLERGIC REACTIONS** OR **IDIOSYNCRASY** - ABNORMAL DRUG RESPONSE DUE TO A GENETIC DEVIATION

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TYPE C – CHRONIC ADMINISTRATION

CONSEQUENCE OF LONG-TERM DRUG USE

MAY BE ADDITIVE BY NATURE (CUMULATIVE EFFECT OF LONG-TERM USE OF EVEN LOW THERAPEUTIC DOSES)

NEPHROTOXICITY OF CERTAIN NON-STEROIDAL ANTIPHLOGISTICS (MAINLY PHENACETIN) OR OSTEONECROSIS OF THE JAWBONE AFTER ADMINISTRATION OF BISPHOSPHONATES

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TYPE D - DELAYED

MANIFESTED AFTER A LONGER INTERVAL FROM THE DRUG ADMINISTRATION

THEIR CAUSALITY IS DIFFICULT TO PROVE

LEUCOPENIA FOLLOWING ADMINISTRATION OF CYTOSTATIC LOMUSTINE OR LATE PRO-CARCINOGENIC AND TERATOGENIC EFFECTS OF SOME CYTOSTATICS OR HORMONES

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TYPE E – END OF USE

REBOUND PHENOMENON - CAUSED BY ADAPTATION MECHANISMS ON THE RECEPTOR SIDE AFTER LONG-TERM ADMINISTRATION OF RECEPTOR ANTAGONISTS (CAUSING UP-REGULATION, OR RECEPTOR NUMBER INCREASE).

INSOMNIA AND ANXIETY AFTER DISCONTINUATION OF BENZODIAZEPINES OR HYPERTENSION AFTER DISCONTINUATION OF BETA BLOCKERS

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DRUG-DRUG INTERACTIONS

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DRUG-DRUG INTERACTIONS

EFFECT OF A CONCURRENTLY ADMINISTERED DRUG ON ANOTHER DRUG

ALSO INCLUDES INTERACTIONS BETWEEN DRUGS AND FOOD SUPPLEMENTS OR BETWEEN DRUGS AND FOOD

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DRUG INTERACTIONS

- ADITIVE: 1+1=2
- SYNERGISTIC: 1+1=3
- POTENCIATION OF EFFECT: 1+0=2
- ANTAGONISTIC: 1+1=0

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DRUG-DRUG INTERACTIONS

INTERACTIONS CAN BE DIVIDED TO

PHARMACEUTICAL,

PHARMACOKINETIC AND

PHARMACODYNAMIC

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PHARMACEUTICAL DRUG-DRUG INTERACTIONS

- Occur also outside of the body
- E.g. In an infusion bag

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PHARMACODYNAMIC DRUG-DRUG INTERACTIONS

- Opposite mechanism of action
- E.g. Sympatomimetic and parasympatomimetic drug together

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PHARMACOKINETIC DRUG-DRUG INTERACTIONS

- Most common
- On level of:
  - Absorption (inhibition of enterohepatal recirculation)
  - Distribution (binding to plasma proteins)
  - Metabolism (CYP)
  - Excretion (competition on tubular transporters)

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INTERACTIONS ON CYP

Inducers of CYP 450

- dexamethasone
- phenobarbital
- rifampicine
- phenytoine
- St. Johns wort *(Hypericum perforatum)*

Inhibitors of CYP 450

- antidepressants (fluoxetine)
- chinine, chinidine
- chloramphenicol, erytromycine
- ketokonazole, itrakonazole
- Grapefruit juice

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DRUG DEVELOPMENT

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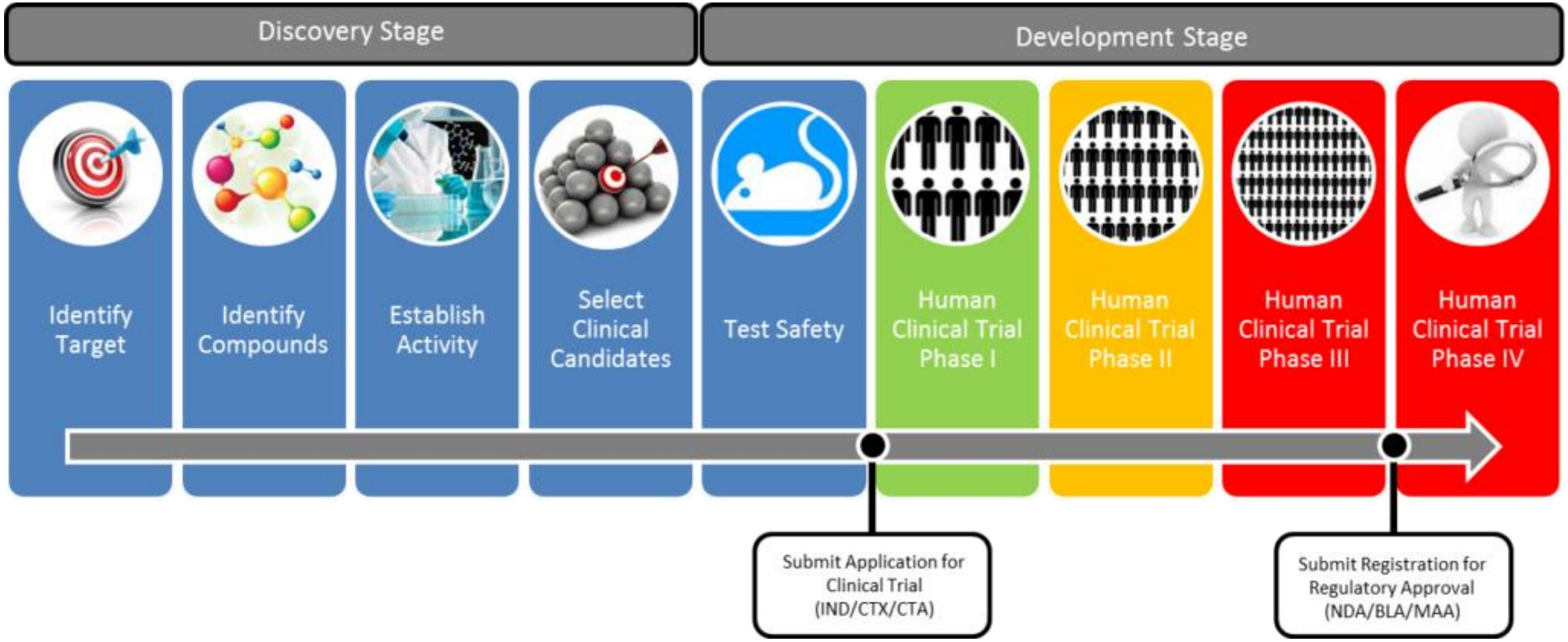
DRUG DEVELOPMENT



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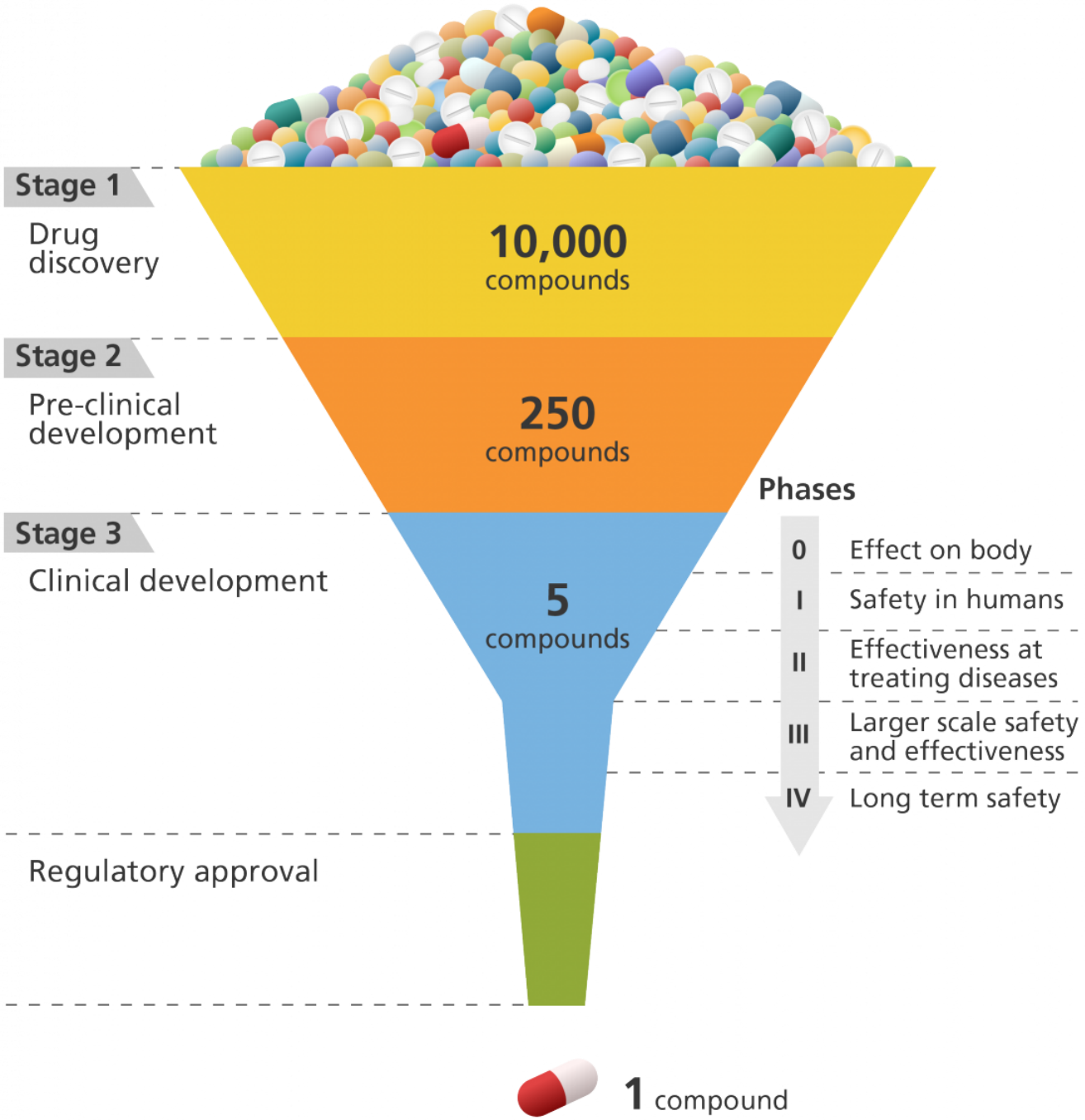
Stage 1
Drug discovery
10,000 compounds
Stage 2
Pre-clinical development
250 compounds
Stage 3
Clinical development
5 compounds
Regulatory approval
Phases
0 Effect on body
I Safety in humans
II Effectiveness at treating diseases
III Larger scale safety and effectiveness
IV Long term safety
1 compound

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1. SYNTHESIS

- Natural resources
  - herbs
  - Animal tissues (heparin)
  - Microorganisms (penicilin)
  - Human cells
  - biotechnology (insulin)
- Drug design = based on structure – effect relationship

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2. PRECLINICAL TESTING

- CELL CULTURES
- ISOLATED ORGANS
- ANIMALS

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3. CLINICAL TRIALS

- Phase 1 – healthy volunteers
- Phase 2 – small group of patients
- Phase 3 – big trials
- Phase 4 – after marketing (when the drug reached market)

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PHASE 1 – HEALTHY VOLUNTEERS

- Establishing the effecxt of the drug on bodily functions
- Pharmacokinetic details
- Safety!
- Dose selection
- Acute dose only
- Participants may receive money

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PHASE 2 – PILOT STUDY

- First administration to real patients
  - Assessment of drug efficacy, adverse reactions, pharmacokinetics in patientsm repeated administration
  - Definition of indications, contraindications
- No finantial reward

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PHASE 3 – EXTENSIVE CLINICAL TRIAL

- Hundreds to thousands of patients
- Assessment of efficacy and safety compared to active treatment or placebo

= controlled clinical trial

  - randomized
  - single x double blind or open label
- multicentric
- Required for SPC redaction and marketing authorization

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PHASE 4 – POSTMARKETING STUDY

- At least 5 yeard from registration
  - Verification of efficacy
  - Detailed assessment of adverse effects in many different pacient populations
- Comparison to standard treatment
- Possibility of market withdrawal

- Field of pharmacology: pharmacovigilance

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