GENERAL INTRODUCTION: Drug development and pharmaceutical industry

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What is Pharmacology?

- **Studies the interaction between living organisms and compounds that affect their functions (i.e. „*pharmacons*”)**
- **A discipline dealing with compounds used for *prevention*, *diagnosis* and *treatment* of diseases**

Major chapters of Pharmacology

General pharmacology

- history
- physical / chemical characteristics
- pharma industry and drug development
- absorption
- distribution
- biotransformation
- elimination

Pharmacokinetics

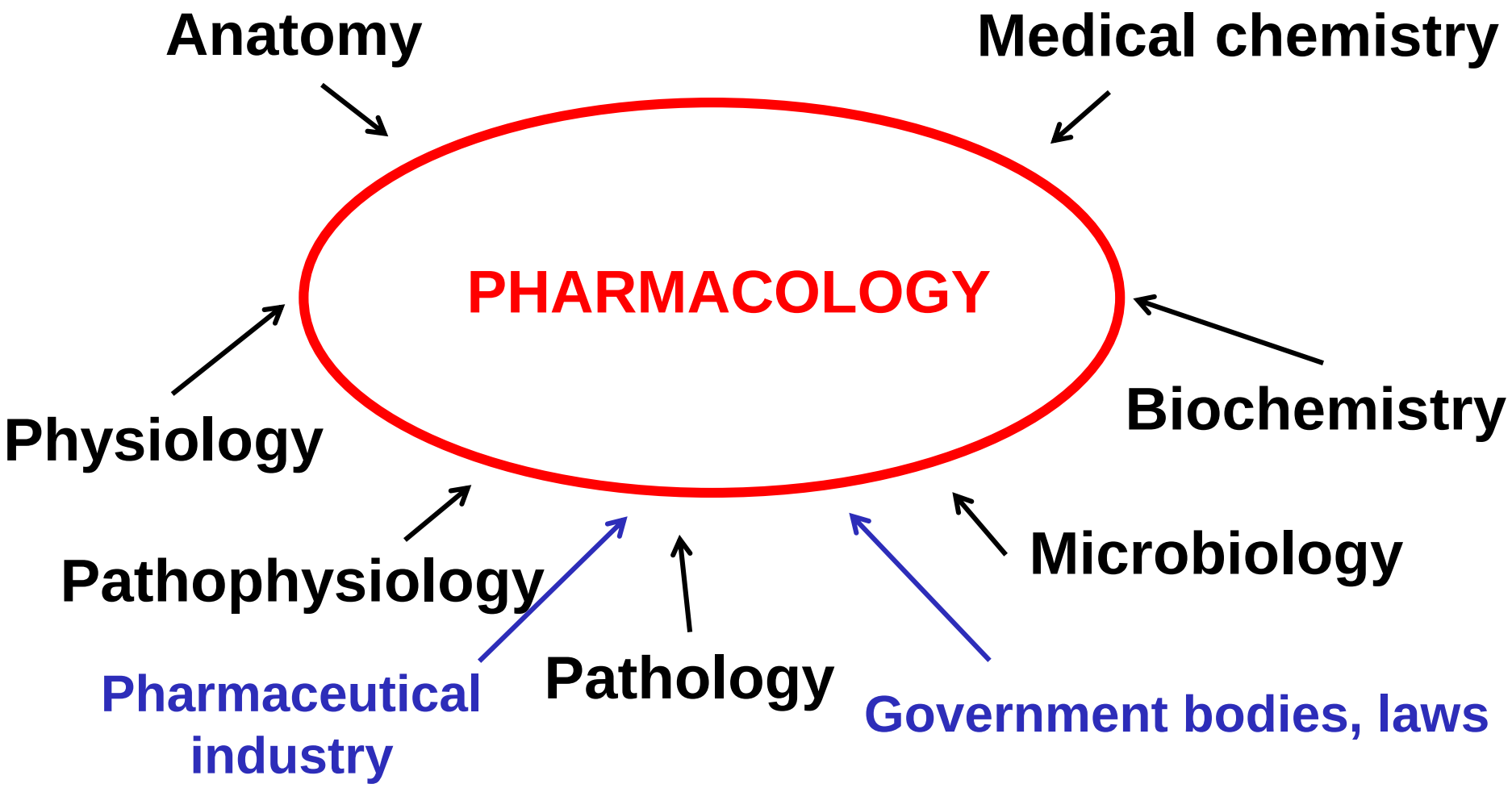
- biochemical / physiological effects
- mechanism of action

Pharmaco-dynamics

Detailed

- therapeutic (and other) use
- clinical pharmacology
- toxicology, safety, pharmacovigilance

Pharmacology is multidisciplinary, driven by the pharma/biotech industry



History of medicinal treatment

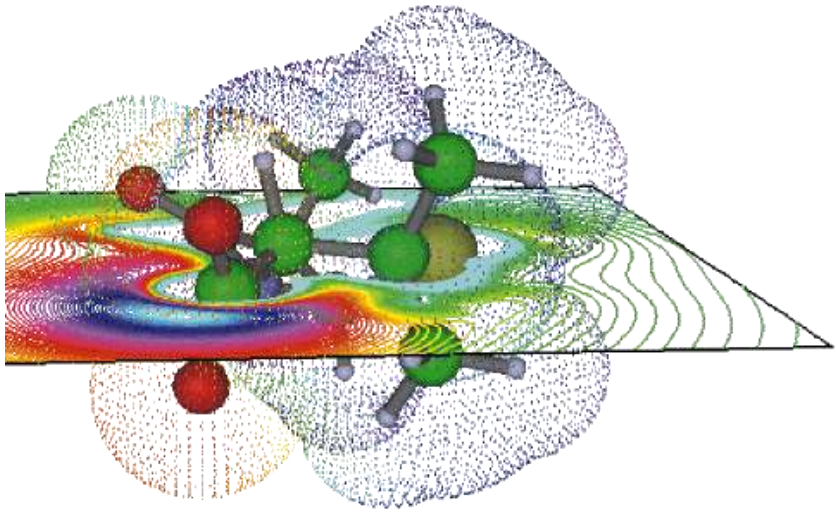
„The desire to take medicine is perhaps the greatest feature which distinguishes man from animals.”

Sir William Osler 1849-1919
(Founder of the John Hopkins Hospital)

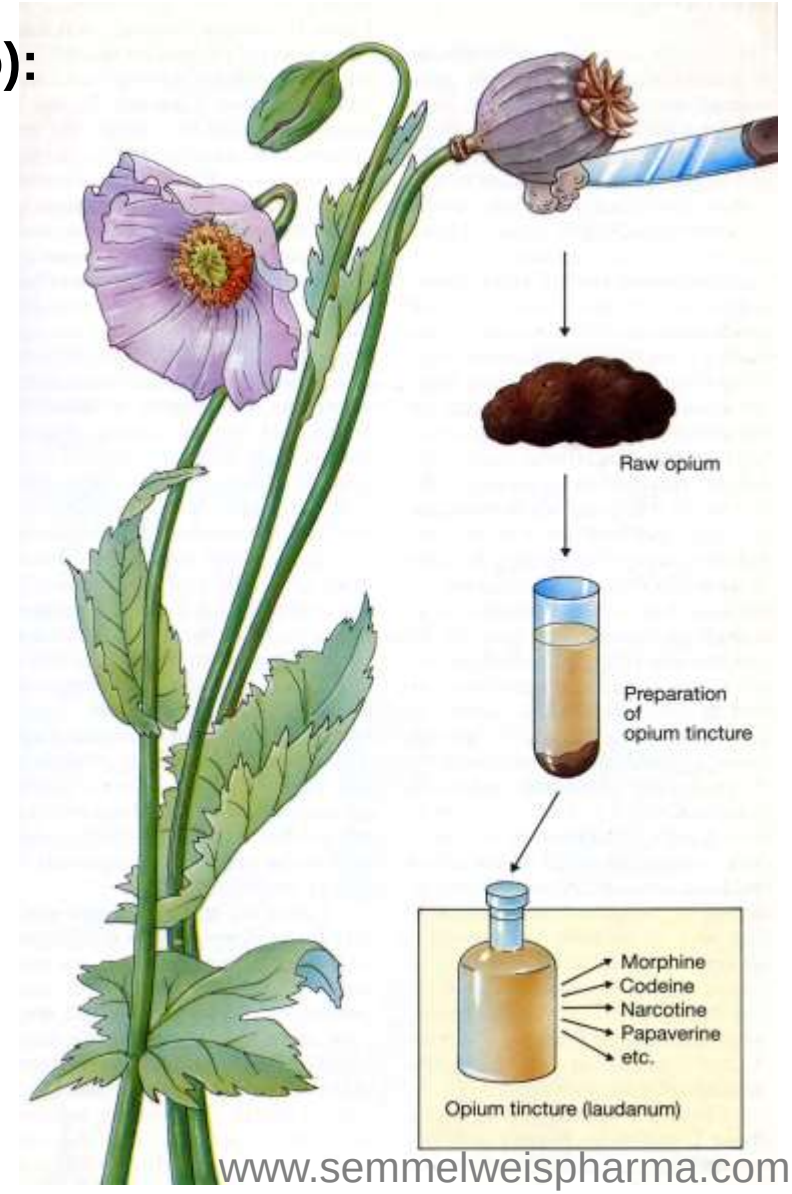
History of medicinal treatment

- **from plants (from thousands of years ago):**
  coffee, fungi, chinese medicines,
  arrow poisons

- **via computational chemistry**



to „biotechnological” processes



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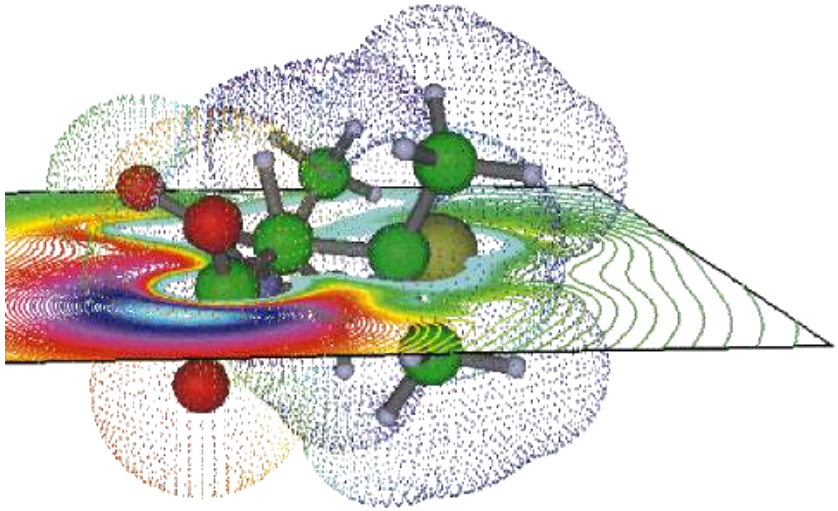


- to „biotechnological” processes (Károly Ereky, Minister of Food, Hungary, 1919)

History of medicinal treatment

- Claudius Galenus (2nd century): classification of pharmacons
- Paracelsus (1493): use of metals (arsenic, mercury) – medicinal chemistry
- **allopathy** (18th century) – to treat or supress symptoms (emetics/laxatives, phlebotomy, etc)
- **homeopathy** (Hahnemann, 19th century)

  (dilution increases efficiency - $10^{60}\times$ dilution – where is the active ingredient?)

- natural (plant-based) drugs (20th century)
- synthetic (chemical) + natural drugs
- biotechnology – gene therapy (antibodies, enzymes, hormones, cytokines, etc.)
- **evidence-based medicine: clinical trials**

History of medicinal treatment

Discovery of anesthetics

- Humphry Davy:

  1800: N_2O (nitrous oxide) inhalation: laughing, dizziness, erotic hallucinations

- Horace Wells:

  1844: discovery of the narcotic effect of N_2O, successful self test,

  1845: failure in Boston

- William Thomas Green Morton:

  1846: ether narcosis

  Queen Victoria - 1853

(Dr. Charles T. Jackson – competition)

The first public demonstration of operation under anesthesia: Boston, Oct 16, 1846

What can be a medicine?

any substance:

- synthesized in the body (e.g. hormones)
- not synthesized in the body (xenobiotics)
- poisons (e.g. arsenic)
- toxins (poisons with biological-, plant-, animal- origin)
- important features of drug molecules:

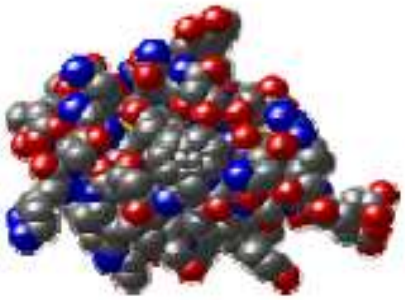
  - size 7-50000 Da
  - most drugs are **small molecules**, i.e. 100-1000 < Da)
  - macromolecules (peptides, proteins, nucleic acids)

    „biologics”
  - transportability (inactivation/elimination)
  - binding to drug receptors (enzymes, ion channels, nucleic acids, etc) „key and keyhole”

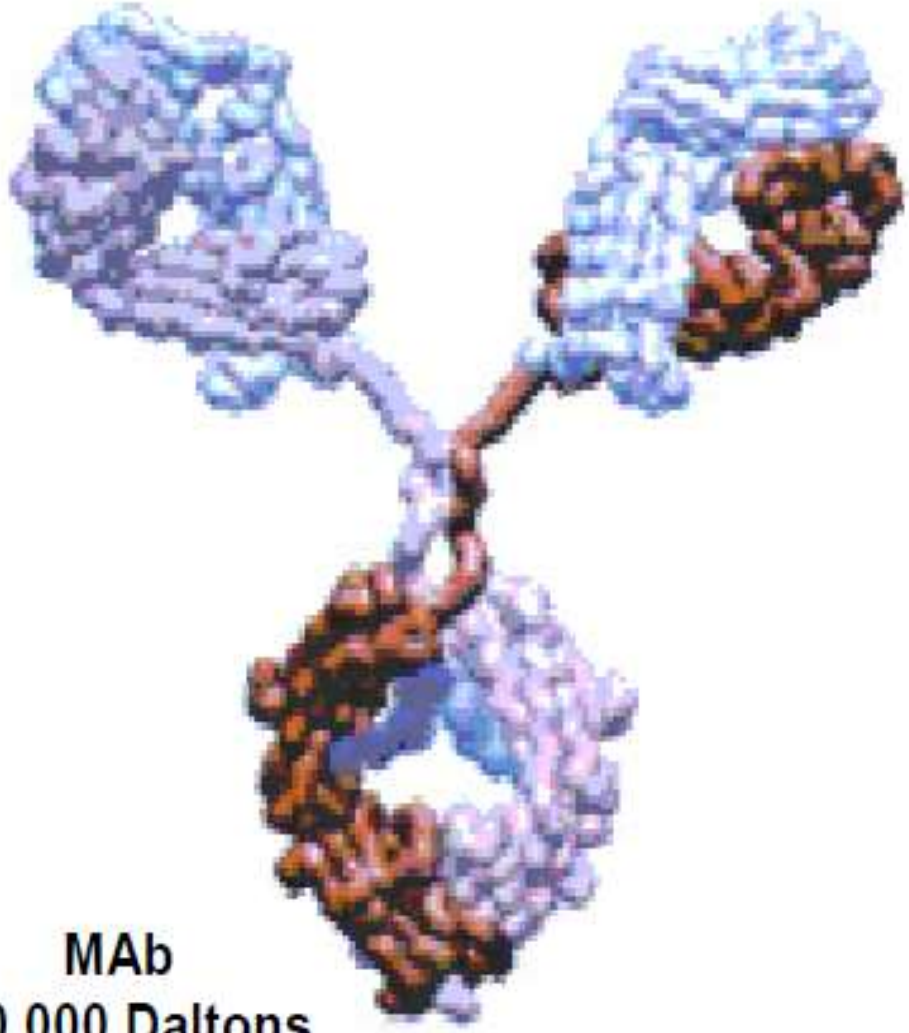
What can be a medicine?

Size and complexity of drug molecules

Aspirin
180 Daltons



Insulin
5 700 Daltons



MAb
150 000 Daltons

What can be a medicine?
Biologics / macromolecules

Medicines made **from biological sources** (extracted from plants, animals, humans, or synthesized by biotechnological techniques):

- **not possible to fully characterize (mostly proteins)**
- combination of **physical, chemical and biological methods are necessary for their production** and control of their quality
- safety problems: unexpected consequences
- pharmacokinetic problems: unusual pharmacokinetics, not fully understood
- **expensive** to develop and manufacture

- several hundred products on the market, e.g. recombinant insulin, growth hormone, antibodies, etc

What can be a medicine?
Biologics - „Advanced therapy medicinal products" ATMP

2009/120/EC Directive (Advanced Therapy Medicinal Products):

- **Gene therapy medicinal products:**

-recombinant nucleic acid for the regulation, repair, substitution, addition or delation of a specific gene sequence
- e.g. genetically modified tumorspecific GM-CSF producing herpesvirus, siRNA, miRNA, etc

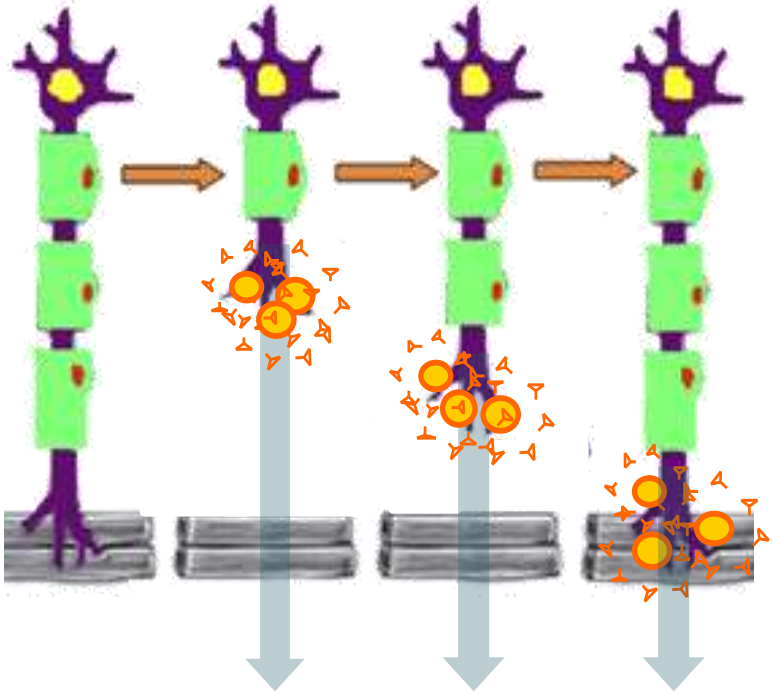
- **Cell therapy medicinal products (manipulated cells):**

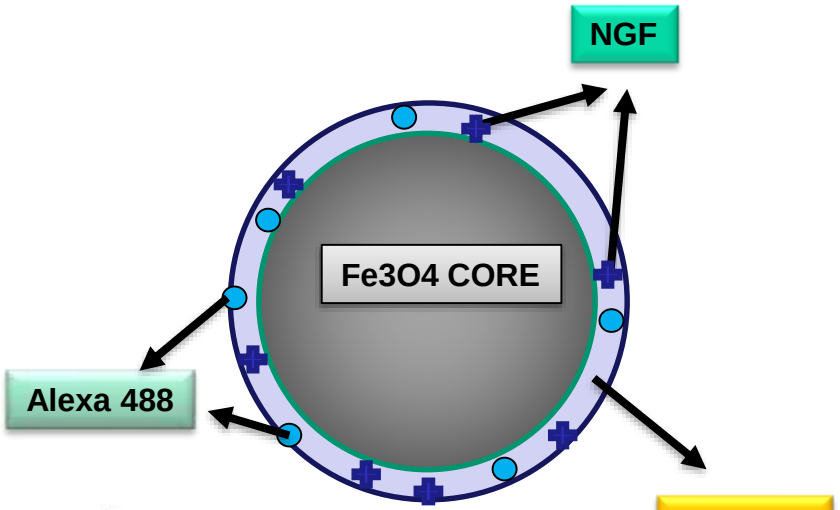
-E.g. autologus chondrocytes, corneal epithel cells

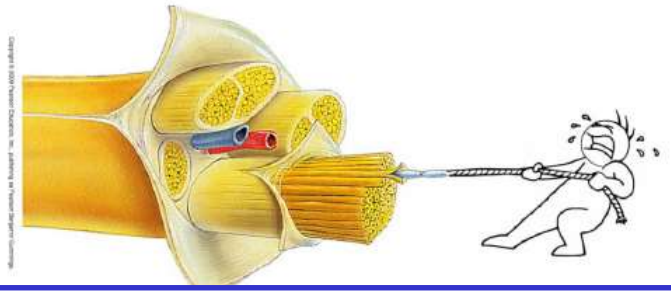
- **Tissue therapy medicinal products (manipulated tissues)**

- **Combination** of the above **with medical devices**

What can be a medicine?
An example of a drug-device combination development to speed up neuroregeneration





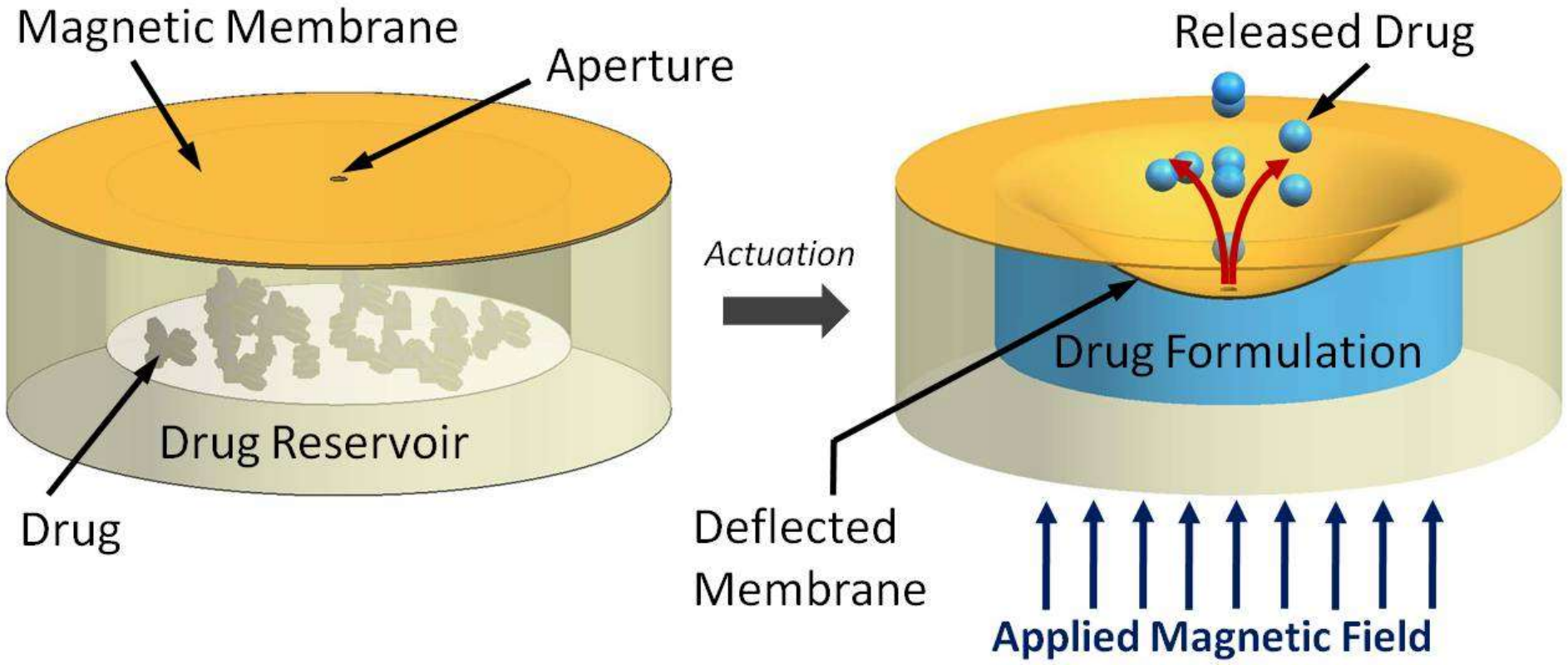


Magnetic nanoparticle

Direction of the magnetic field

Magnetic nanoparticles provide physical guidance to direct more efficient nerve regeneration (Riggio *et al*, Nanomedicine, 2014)

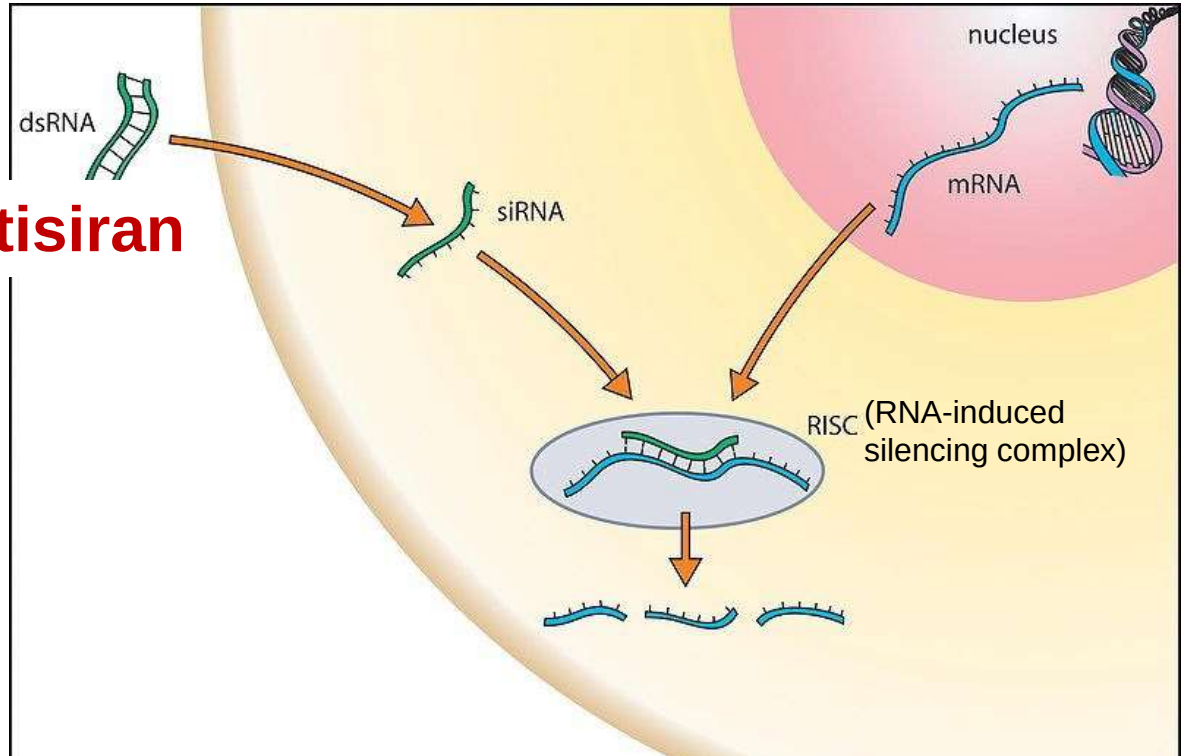
What can be a medicine?
Innovative drug-device development: drug release induced by magnetic field



What can be a medicine?
The first therapeutic siRNA „patisiran”

- **a rare disease:** hereditary transthyretin-mediated amyloidosis (hATTR) affects about 50,000 people worldwide
- **pathology:** buildup of a protein called amyloid in the peripheral nerves, heart and other organs
- **therapy:** amyloid gene silencing by the siRNA „patisiran” (FDA approval in 2018):

patisiran



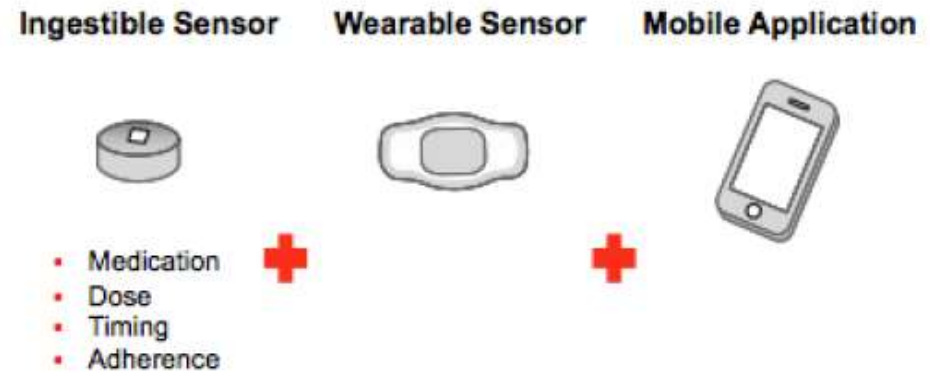
What can be a medicine? No limits of drug development technologies – the first digital drug-device combination on the market

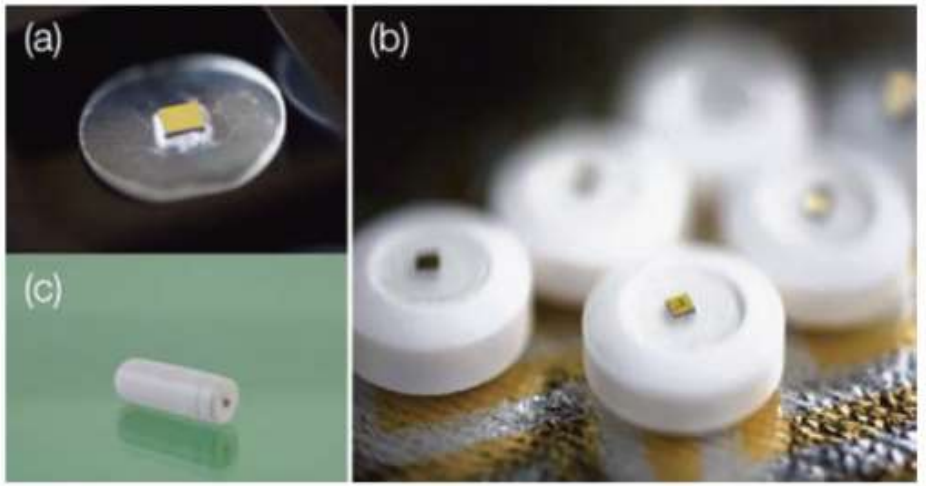
- The FDA approved a first drug–device product: a digital chip to monitor ingestion.

- atypical antipsychotic (aripiprazole) + Proteus Digital Health's tracking device

- <u>Proteus Digital Health's tracking device:</u>

- 1 mm ingestible chip
- activated by stomach acid,
- sending signals to a band-aid sized patch sensor
- sensor is paired to a smartphone





Nature Reviews Drug Discovery 2015, 2017

Drug nomenclature and „indication”

- Company code
- Chemical name
- ***INN (International Non-proprietary Name; WHO assigns)***
- Trademark name

ATC classification:

(**A**natomic, **T**herapeutic, **C**hemistry) (WHO regulates)

The ICD system: (International Statistical Classification of Diseases and Related Health Problems, WHO) – important for drug prescription

Indication of a drug: „on label” „off label” only by special permit from regulatory agencies

Drug registration categories

Authorities that release the „marketing authorization”

(Summary of Product Characteristics (SmPC), Patient’s Information Leaflet, and package labels

- National Institute of Pharmacy and Nutrition in Hungary (www.ogyei.gov.hu)

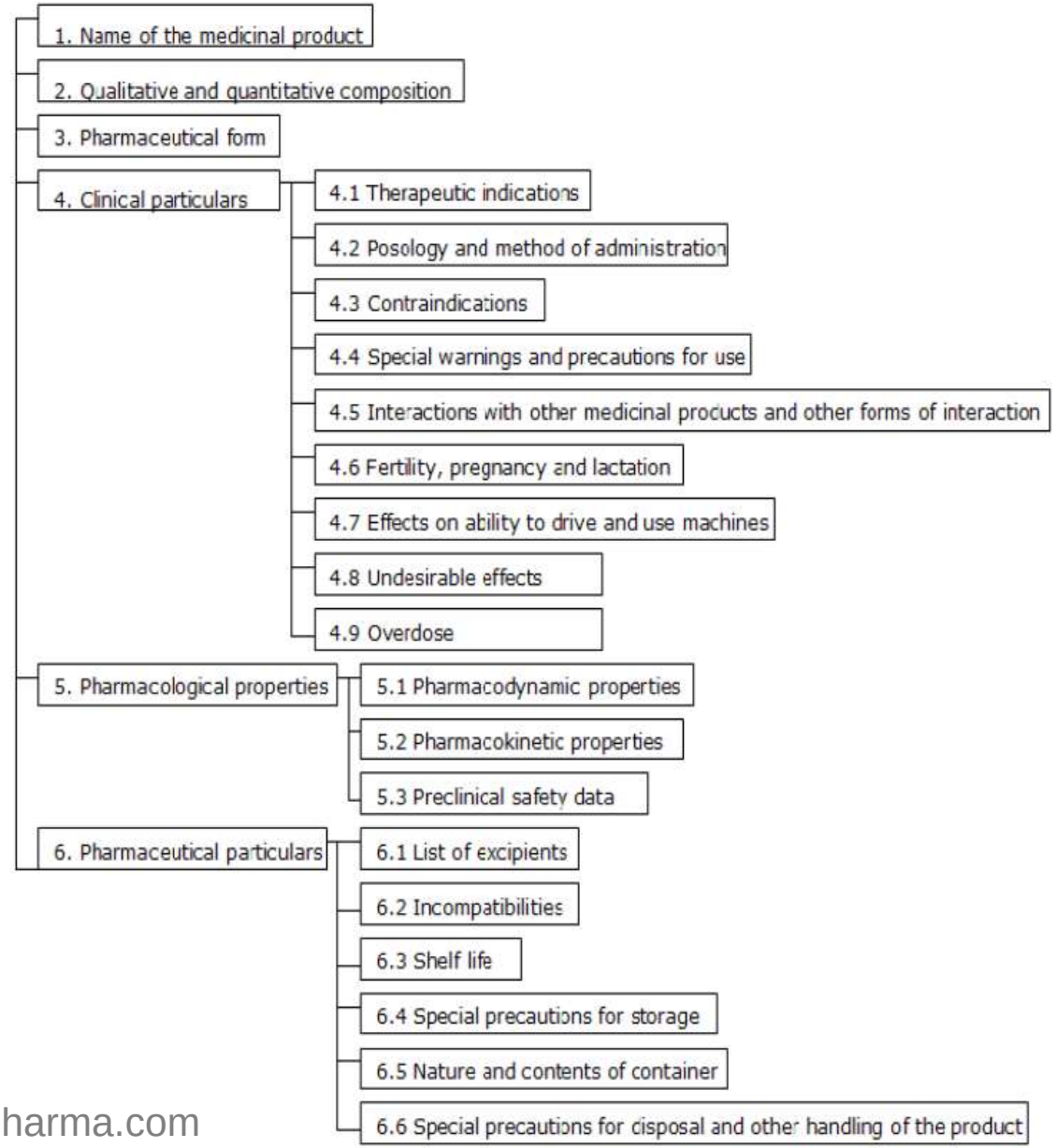
- European Medicines Agency in the EU (www.ema.europa.eu)

- **Prescription drug**
- **OTC (Over The Counter) drug**
- Paramedicinal product
- Traditional herbal medicine (used for more than 30 years)
- Homeopathic composition

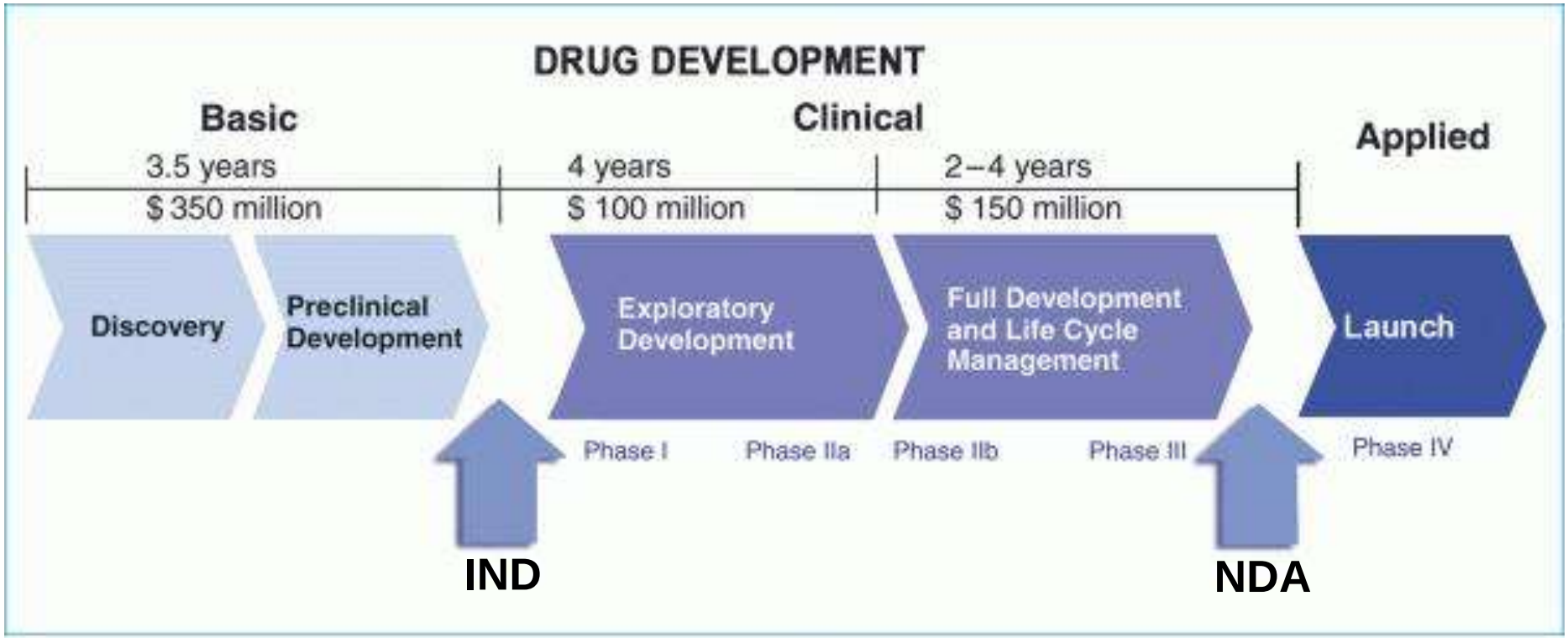
Similar or identical to drugs, but other categories

- **Food supplements** (*not a drug!*, e.g. multivitamins), regulated by e.g. European Food Safety Authority www.efsa.europa.eu)**:**
- **Special Medicinal Food** (e.g. multivitamins for diabetics)
- **Medical devices** and their combination with drugs (drug-device combinations, e.g. drug eluting stents)

„summary of product characteristics" SmPC



Major phases of drug development:



- takes 8-12 years,
- cost increasing, now $1bn up to market for a single drug
- patent protection 20+5 years

Drug development and pharma industry: total cost of drug development

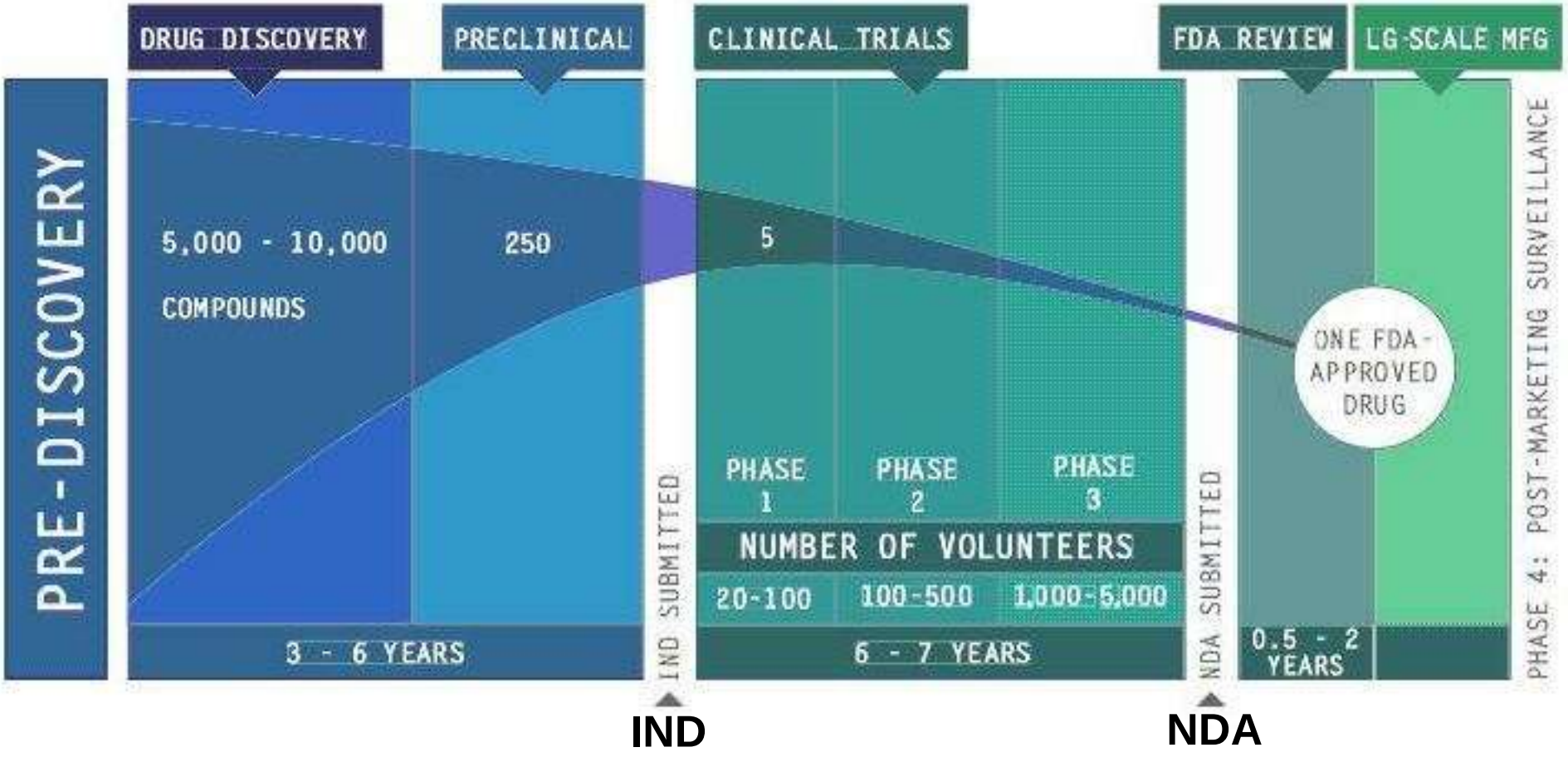
Company	drugs approved	R&D Spending/ Per Drug ($Bil)	Total R&D Spending 1997-2011 ($Bil)
AstraZeneca	5	**11,8**	58,9
GlaxoSmithKline	10	8,2	81,7
Sanofi	8	7,9	63,3
Ro			
Pfi			
Jo			
Eli			
Abbott Laboratories	8	4,5	36,0
Merck & Co Inc	16	4,2	67,4
Bristol-Myers Squib			45,7
Novartis AG	21	4,0	83,6
Amgen Inc.	9	**3,7**	33,2

Forbes 2012: „At $12 billion per drug, inventing medicines is a pretty unsustainable business"
„At $3.7 billion, you might just be able to make money"

„the main expense is failure"

Sources: Forbes; InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems, 2012

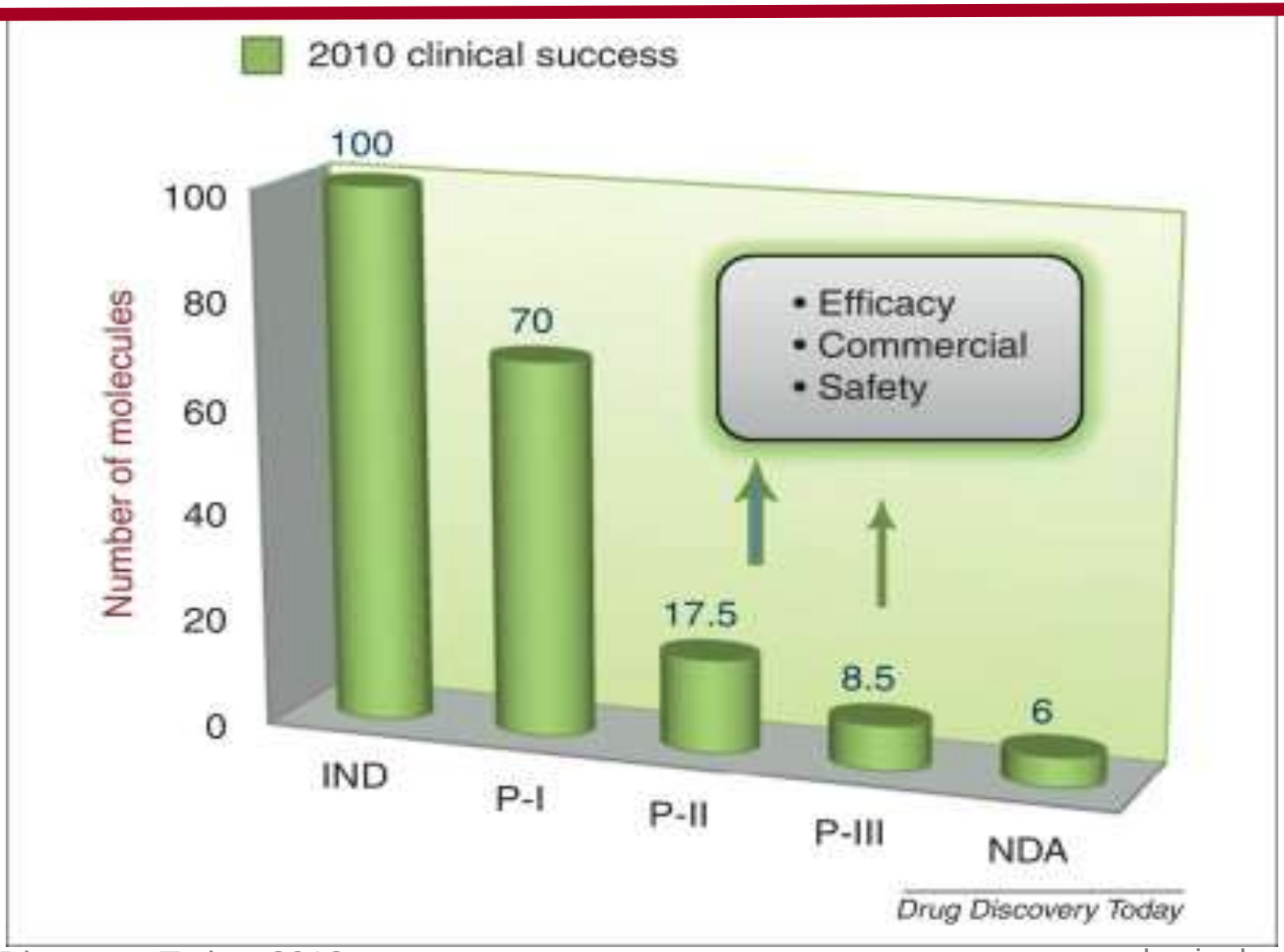
Drug development and pharma industry: risk of drug develpment is extremely high



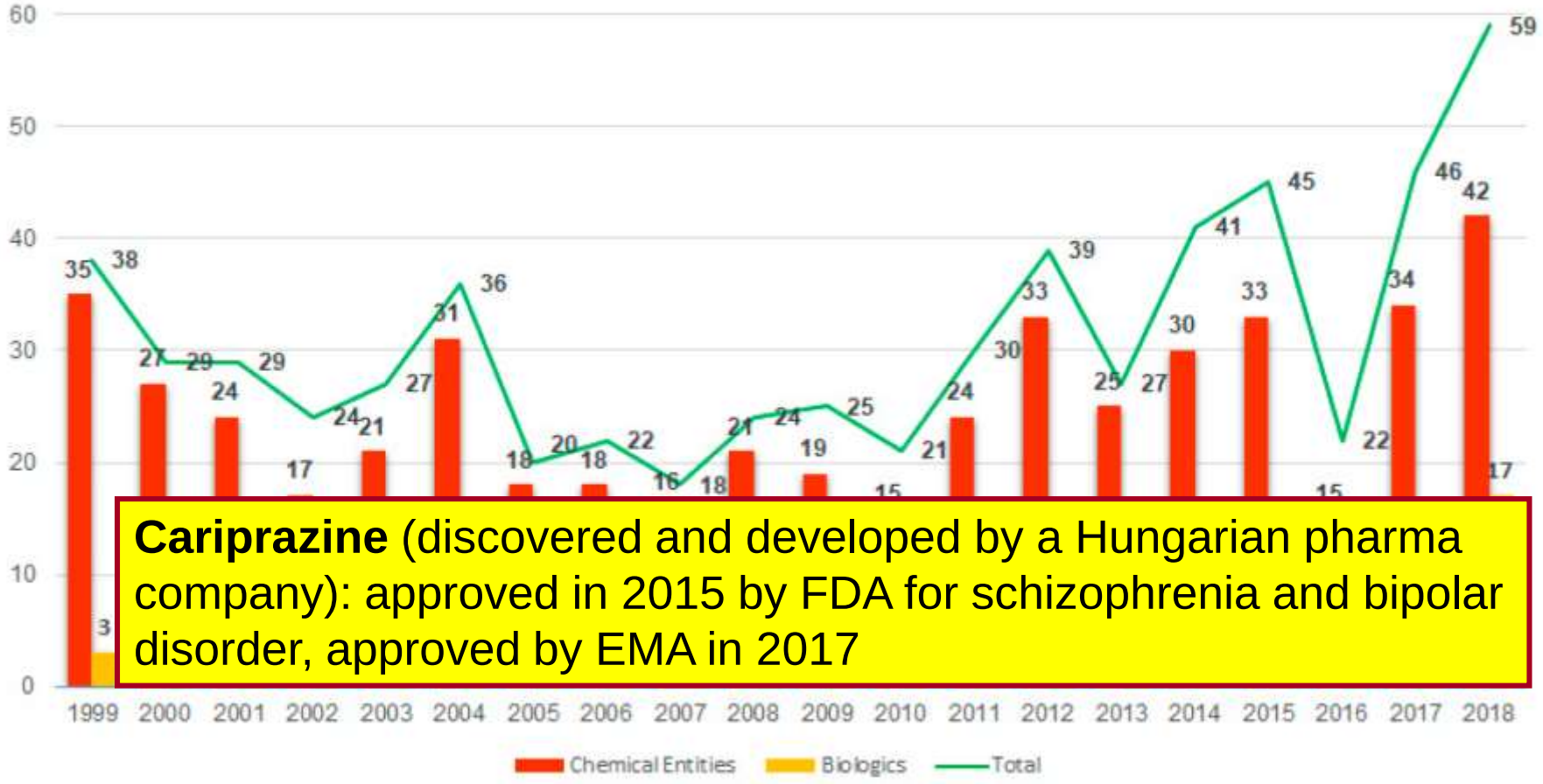
High risk of development: role of private capital, health insurance

Drug development for rare diseases (orphan disease, orphan drug) financing problems

Drug development and pharma industry: risk of drug develpment is extremely high



Number of drug approvals started to increase recently?



Cariprazine (discovered and developed by a Hungarian pharma company): approved in 2015 by FDA for schizophrenia and bipolar disorder, approved by EMA in 2017

Drug development and pharma industry:
modern drug development is a cooperative effort

- **Academic institutions:** basic science and new technologies („omics”, nanotech, in silico models, etc)
- **Small innovative R&D companies** („small biotech”)
- **Large pharma companies:** development, financing
- **Investors:** business angels, FFF, venture capitalists, investments funds
- **R&D service companies:** organizing clinical studies, patent lawyers, etc
- **Government regulatory authorities**
- **Health care insurance** (government, private)
- **Hospitals**
- **Doctors, pharmacists**

Drug development and pharma industry: research and preclinical phase

drug „target” discovery:

-Target discovery

- Target validation (genetically modified animals)

- Development of measurement of key parameters of the target

Discovery of the pharmacon:

- *in silico* molecule design

- chemical synthesis

- HTS (High throughput screening) ***hit***

Development of „Lead molecule”:

- structure-effect analysis: ***„lead optimization”***

- testing the efficacy *in vitro, ex vivo*

- *in silico* toxicology

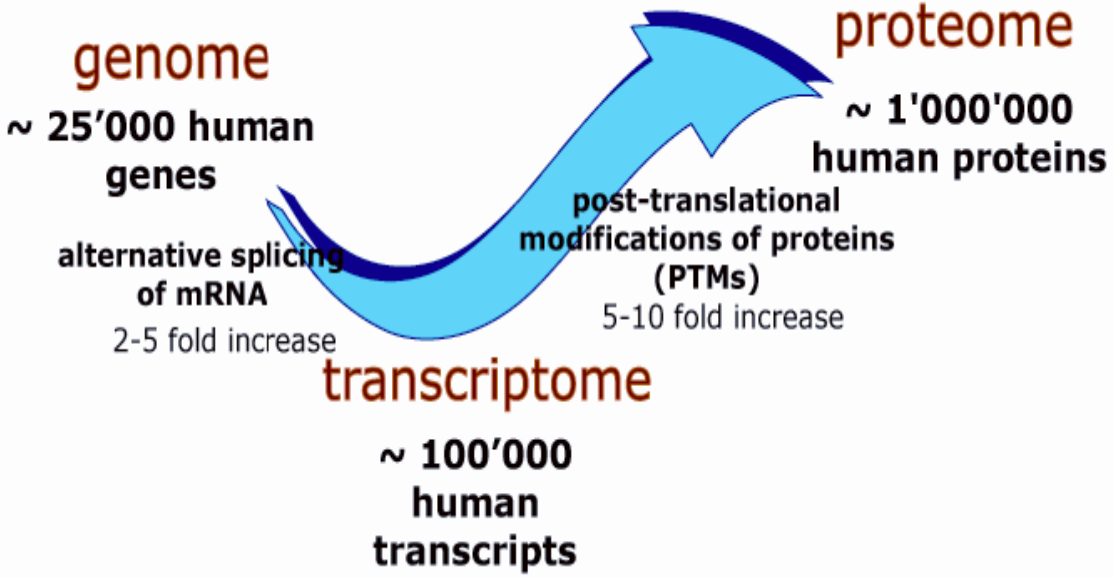
Preclinical pharmacology:

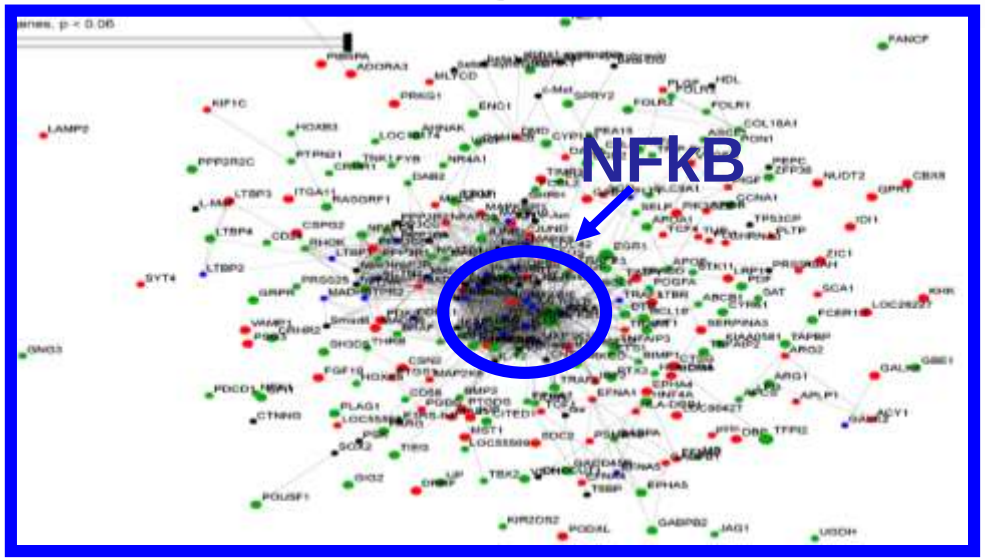
- pharmacokinetics & toxicology (ADMeTox)

- pharmacodynamics *in vivo*

- Safety pharmacology

Target discovery: „multi-omics”





Healthy-diseased comparison: **genomics, proteomics**

Bioinformatics (e.g. network analysis, **Albert-László Barabási**): **target discovery**

Target validation: „in vivo” genetically modified animals

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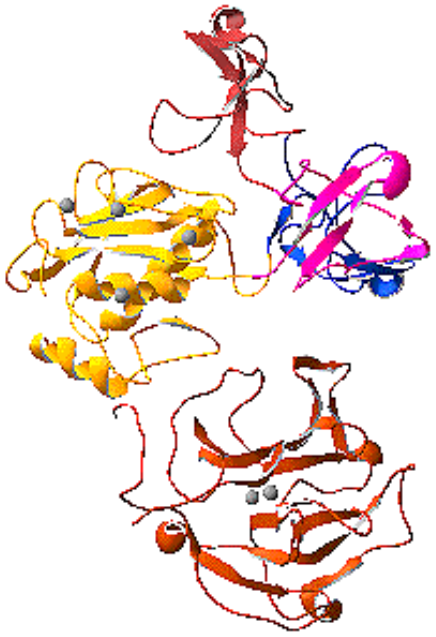
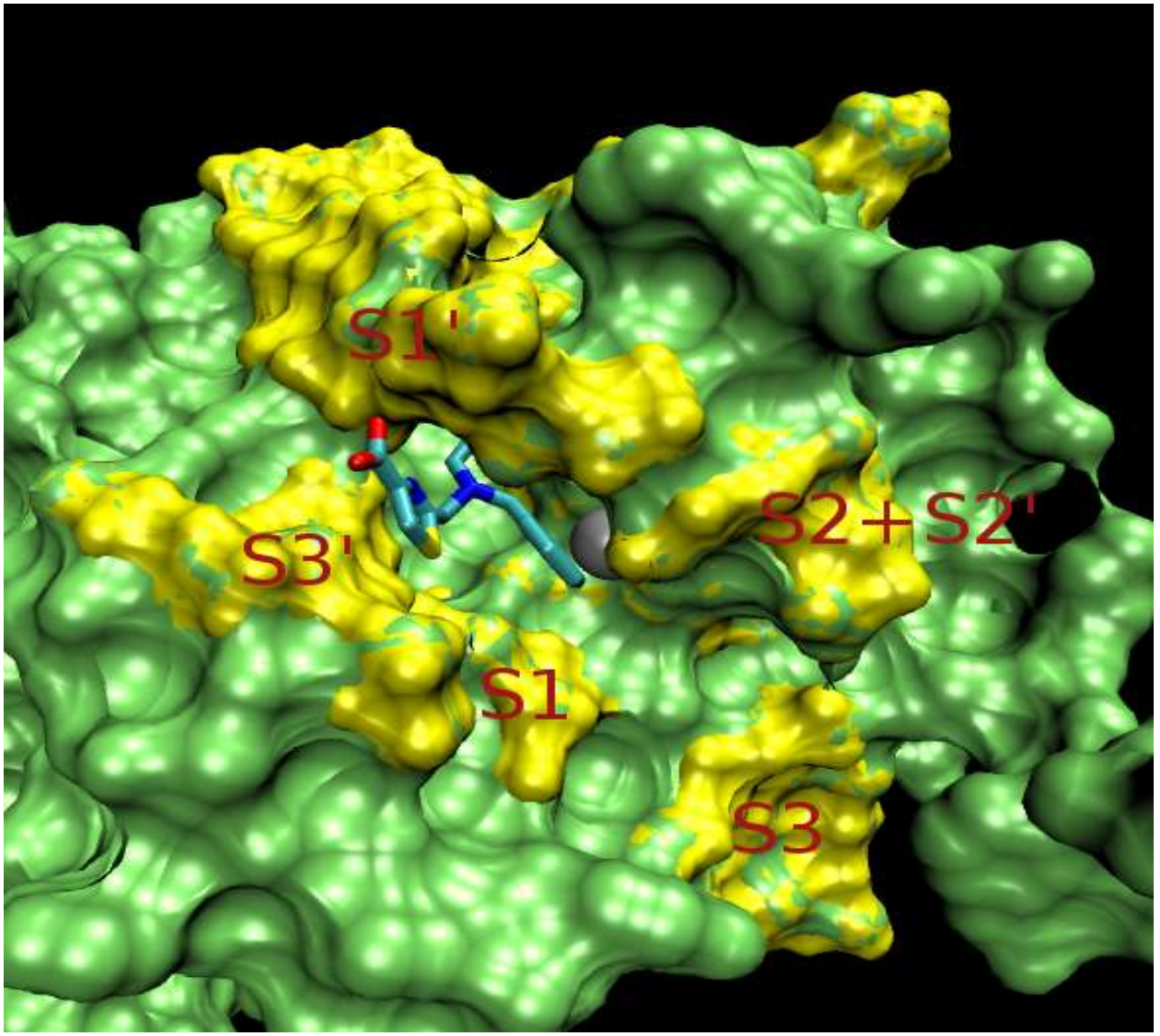
Drug development and pharma industry: structure-effect analysis: „in silico” docking



Structure of Matrix-Metalloprteinase-2

Docking of a newly designed MMP-2 inhibitor molecule



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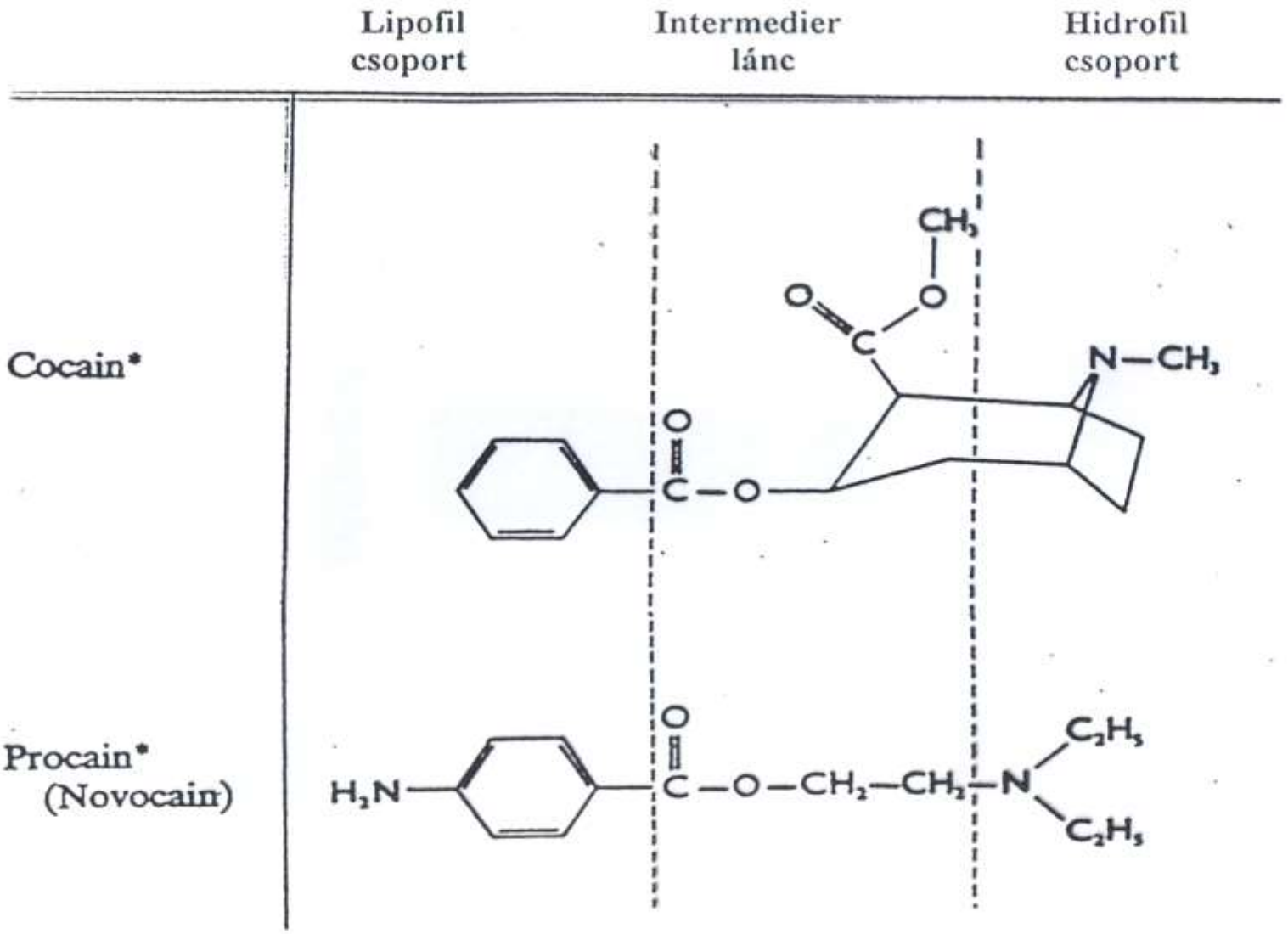
An example of structure-effect relationship, development of procaine



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Development of „Lead molecule”:

- structure-effect analysis

- testing the efficacy

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Preclinical pharmacology:

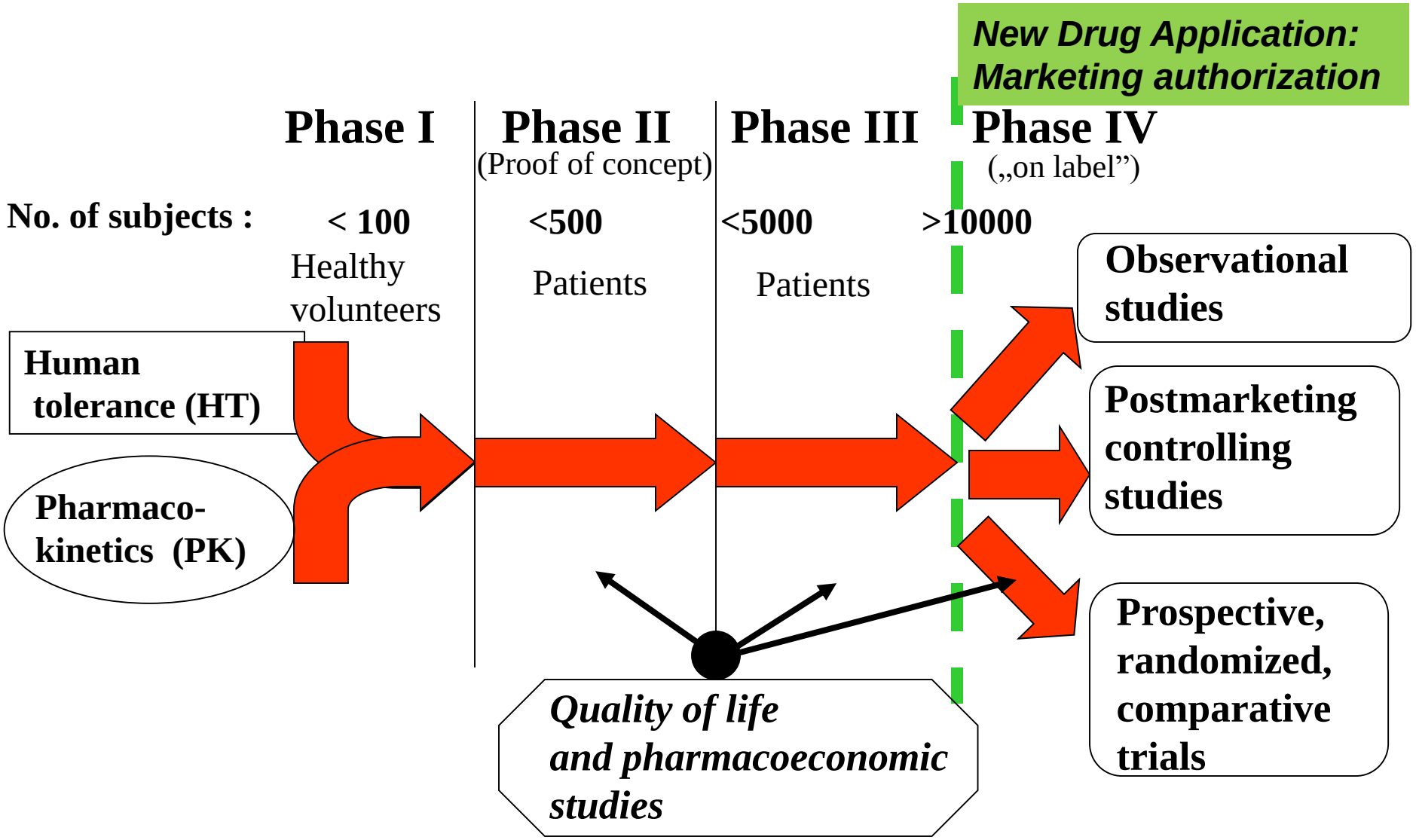
- pharmacokinetics, pharmacodynamics *in vivo*

- Toxicology

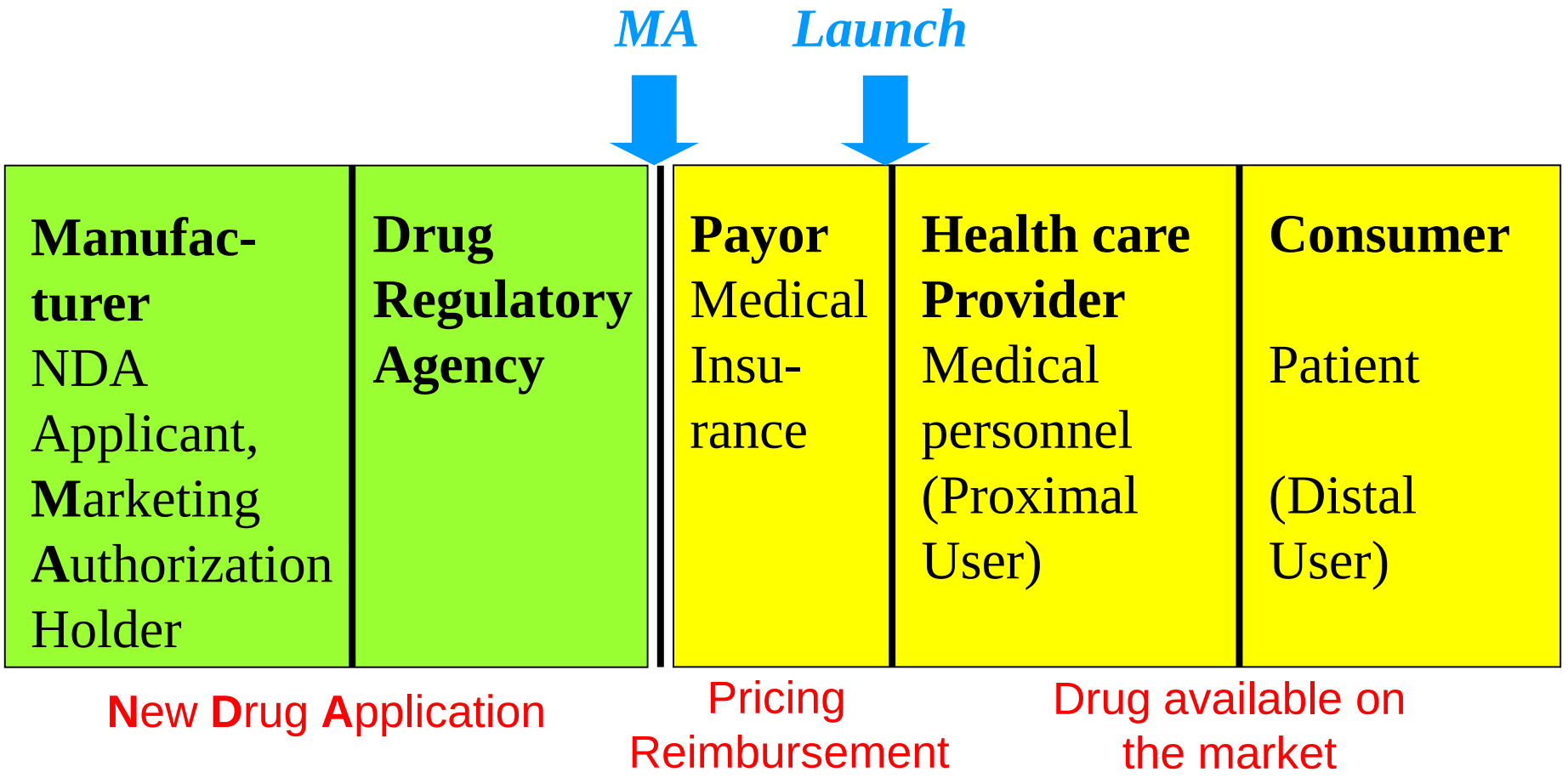
- Safety

IND application

Drug development and pharma industry: clinical phases (efficacy & safety)

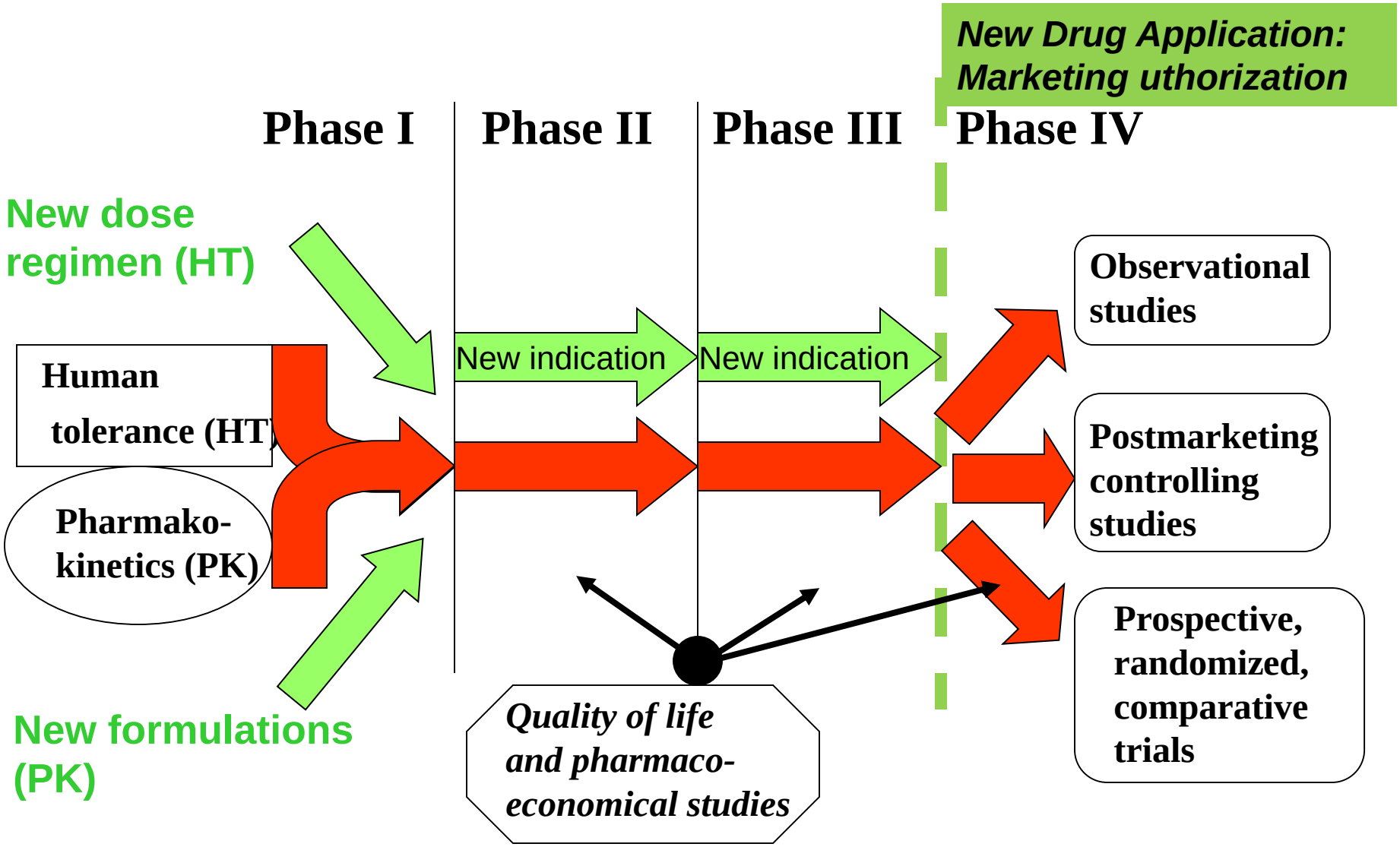


Drug development and pharma industry: Marketing Authorization after successful phase III clinical study



Drug promotion: strictly regulated in the EU and USA
- only according to marketing authorization !

Drug development and pharma industry: clinical phases: easier ways



Modern concept of drug develpment: „*translational medicine*” and „*biomarkers*”

Marketing Authorization

- Indication
- Side effect profile
- Companion biomarkers,
- Diagnostics

Predictive preclinical research

- PK/PD parameters
- Pathway analysis
- Dose selection
- Biomarker identification

Proof of concept in humans (phase 1-2)

- Mechanism of action
- Confidence in safety
- Biomarker validation

Clinical research

Confirmation (phase 3)

- Use of biomarkers for patient selection,
- Efficacy/Safety
- Benefit/Risk

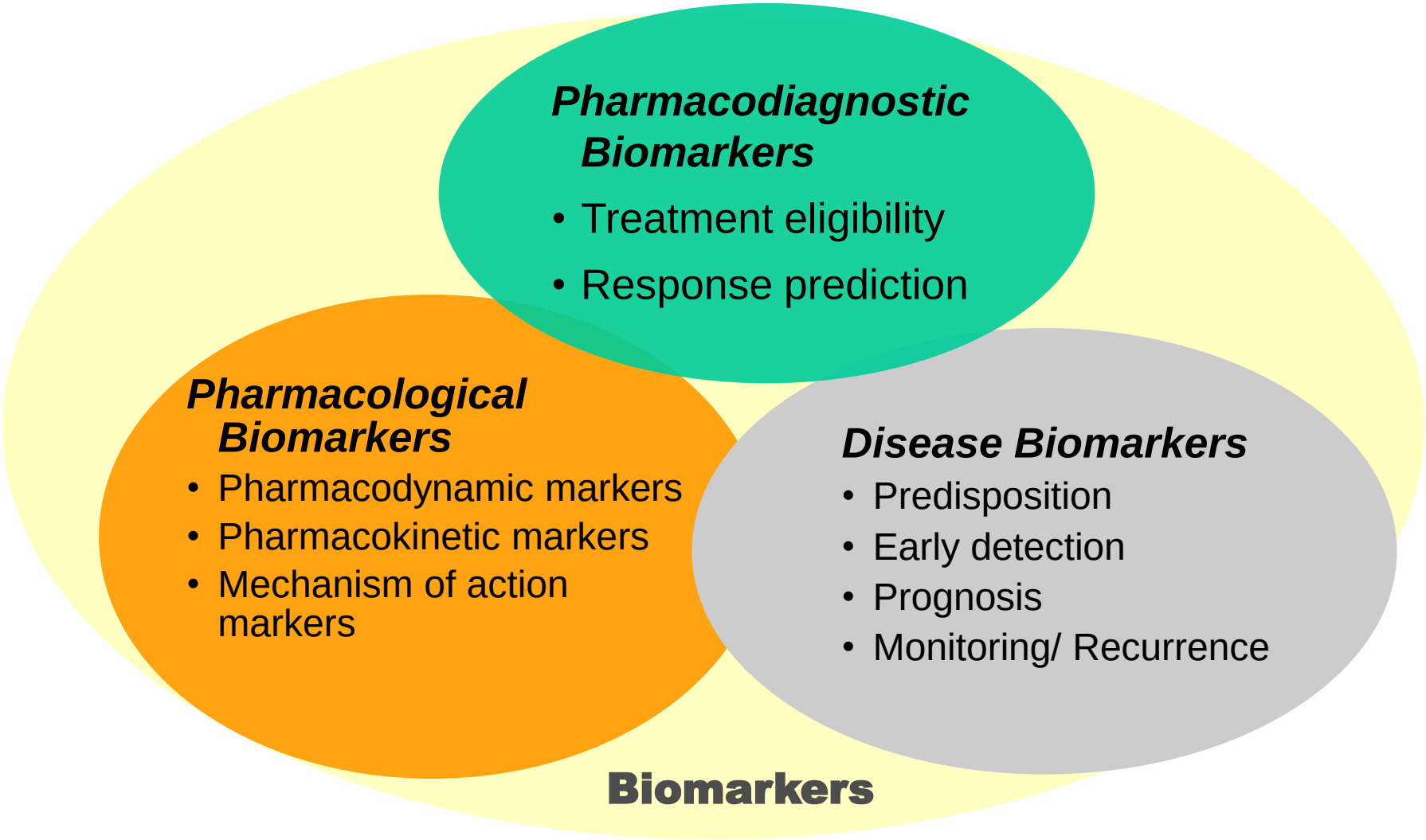
Modern concept of drug development: translational medicine and biomarkers

Translational medicine: integrated innovative pharmacology tools (biomarkers, clinical methods, clinical technologies) in order to:

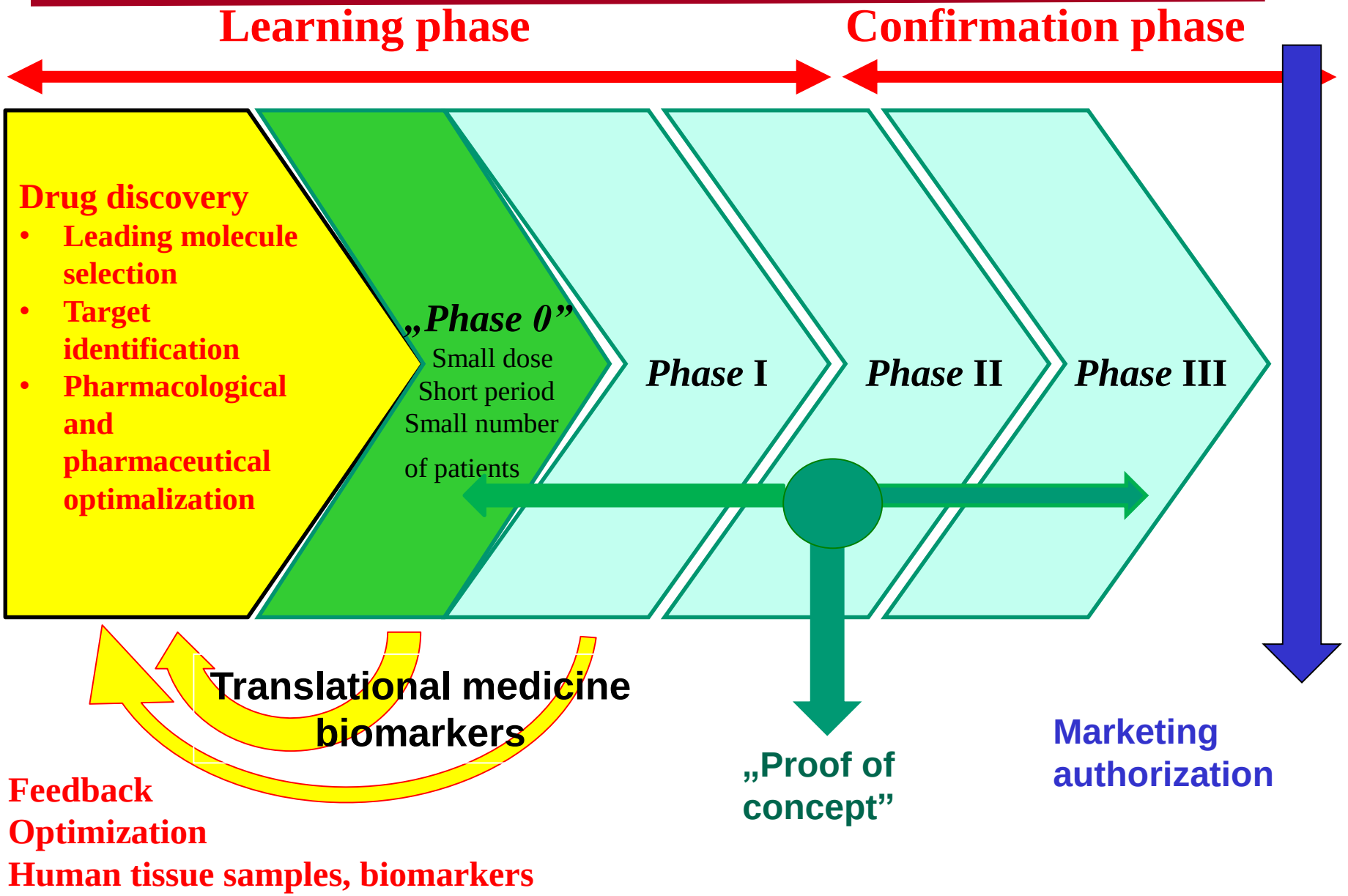
- improve **disease understanding**
- increase confidence in human **drug targets**
- increase confidence in **drug candidates**
- understand the **„therapeutic index”** in humans
- enhance **cost-effective decision** making in exploratory development
- increase **phase II clinical trial success**.

Modern concept of drug development: biomarkers

Courtesy of Bühler F, EFCPM, Basel



Modern concept of drug development: translational medicine and biomarkers



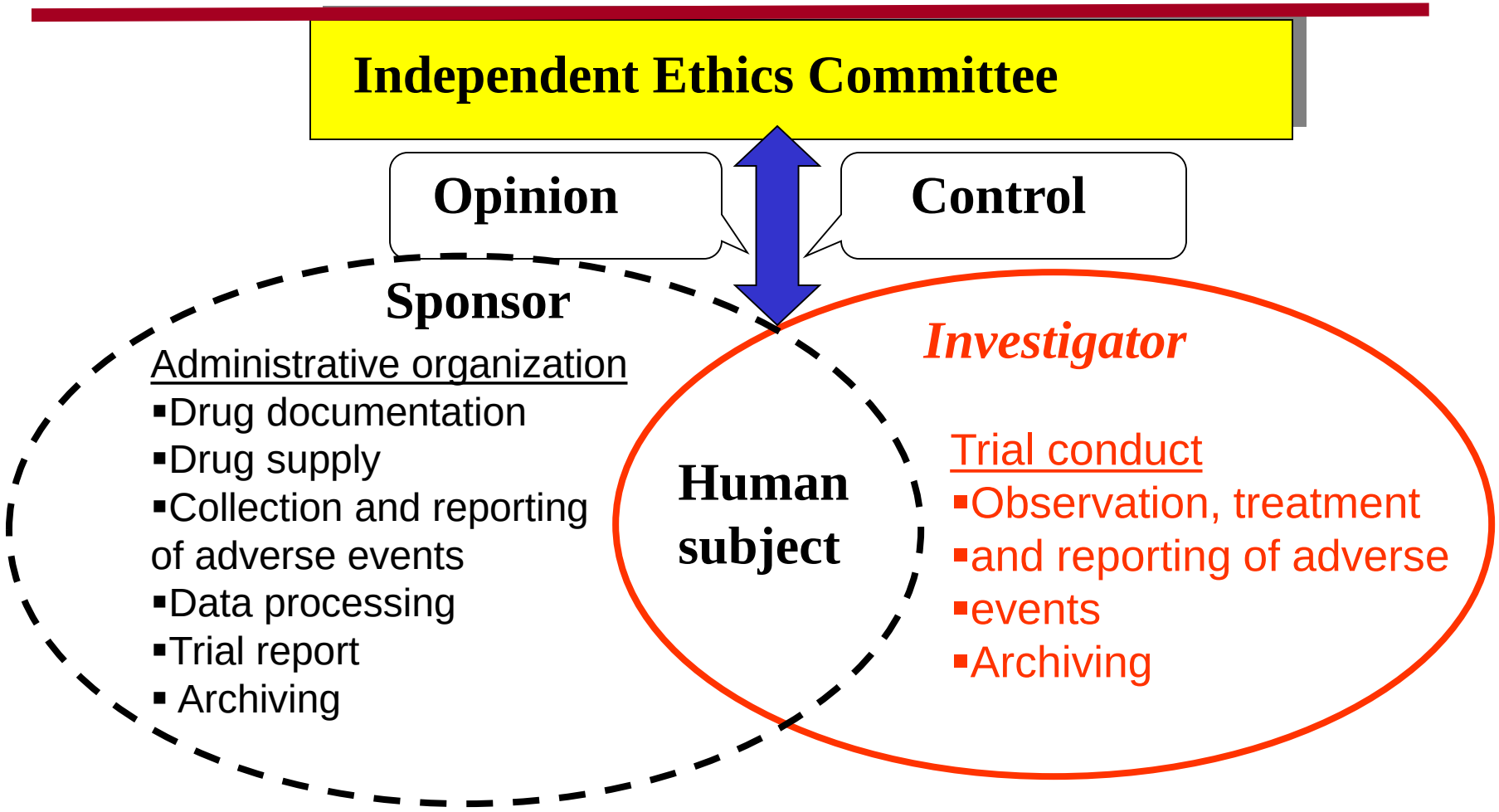
Drug development and pharma industry: *quality control* of clinical phases

„Good Clinical Practice (GCP)”

Competence of the directives:

- Investigator‘s brochure
- Trial protocol and case report form
- Monitoring: controlling of the trial conditions, measuring and data processing systems, comparison of the data base with the local data source
- Adverse effect report
- Final report of the results
- Archiving

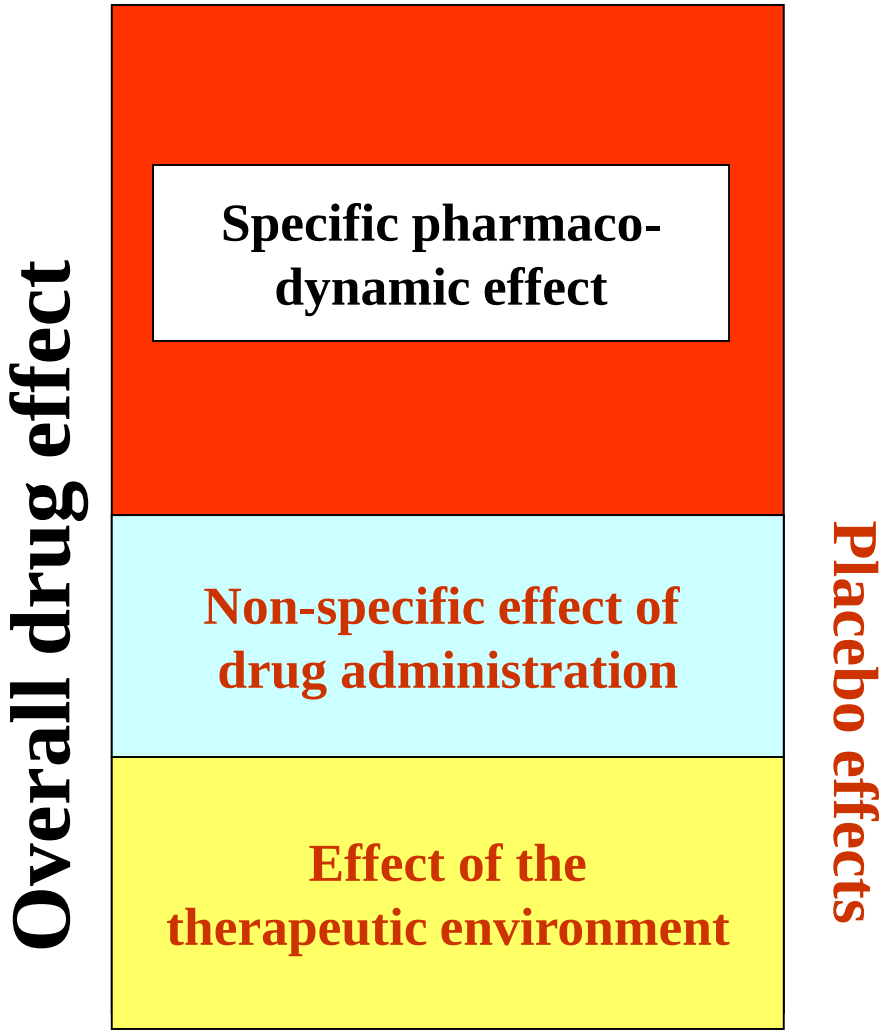
Drug development:
distribution of tasks in the clinical studies



- The clinical trial may endanger the health and social status of the subjects
- The Independent Ethics Committee determines the socially acceptable measure of the risk/benefit ratio and continuously controls its development during the trial

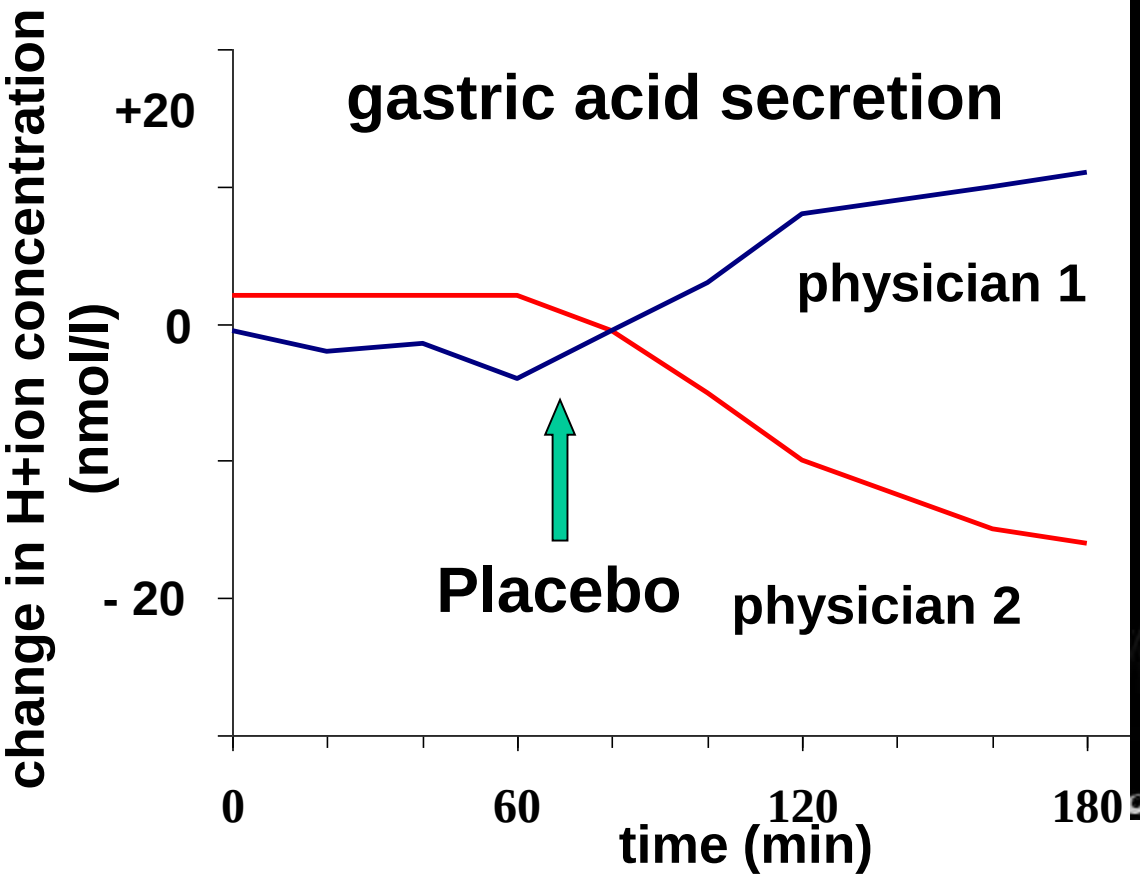
Drug development:
Use of placebo in clinical studies

- Placebo effect is due to the changes in the patient's condition which are causally connected to the patient's **personal awareness**
- It is the most specific and most sensitive method for proving pharmacodynamic effects; it requires a small number of cases (placebo and treatment groups)
- It cannot be used if withholding the active treatment would permanently damage the patient
- It may be used only in clinical trials, with the permission of an Ethics Committee



Placebo

- clinical studies prove efficacy
- prefrontal lobe plays a role in mechanism (no effect in Alzheimer's)
- ethical issues in clinical studies



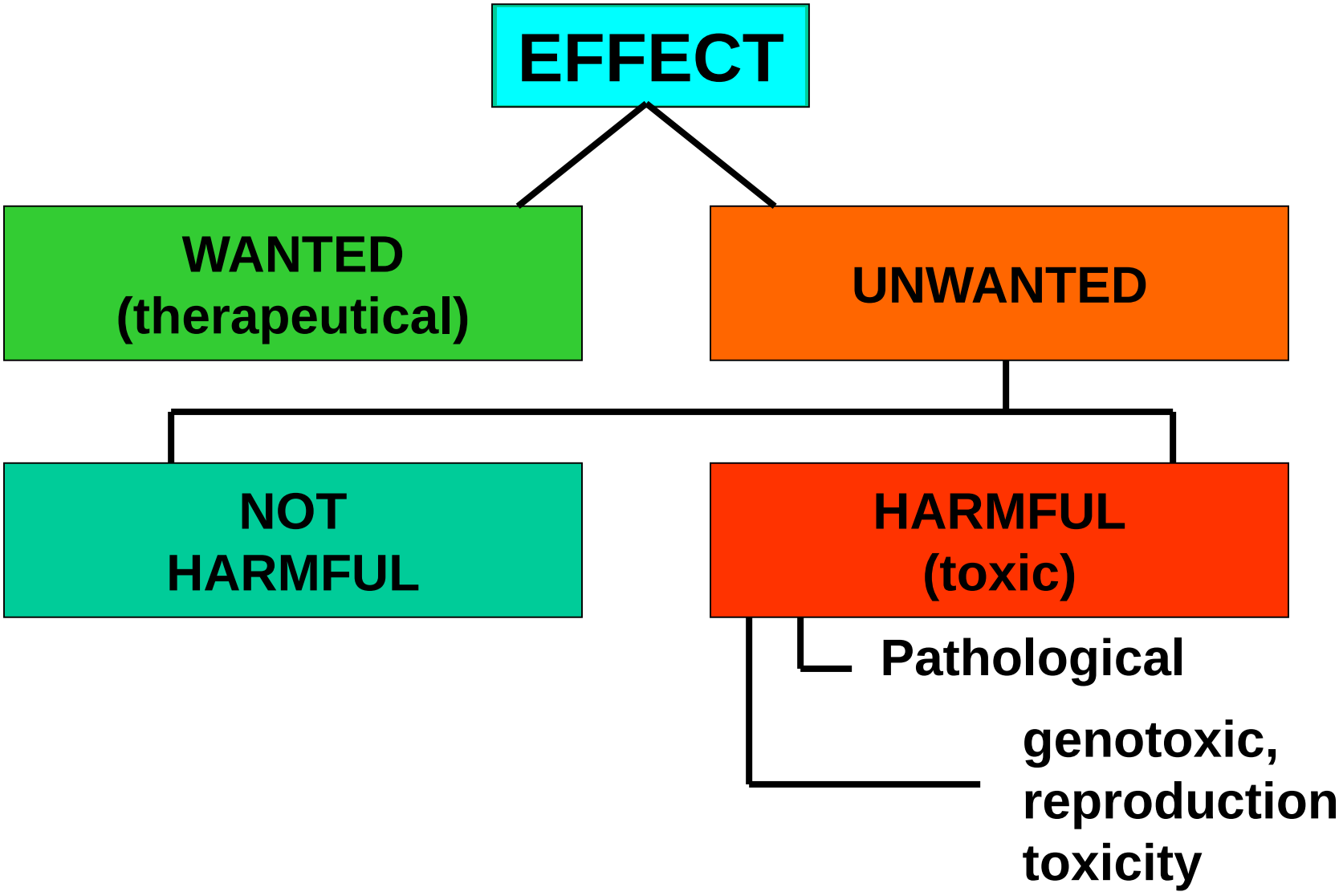
Toxicology

- A branch of pharmacology, that studies the **harmful effects** of medicinal products to the body
- Not only pharmacons, other chemicals as well
- **Prevention, diagnosis and treatment of these harmful effects**
- Studying the effects from cellular to ecosystem level

„THE DIFFERENCE BETWEEN A MEDICINE AND A POISON IS THE DOSAGE THEREOF”

(Paracelsus)

Toxicology



Toxicology: the „contergan scandal”

Thalidomide:

-sedato-hipnotic, 1957

- became OTC drug, also used against nausea and vomiting for pregnant women

- thousands of infants was born with deformities, 50% died – due to thalidomide (revealed in 1961)

- the scandal led to the development of modern drug regulations

Toxicology: drug withdrawals due to safey issues

Drugs withra
safety issues

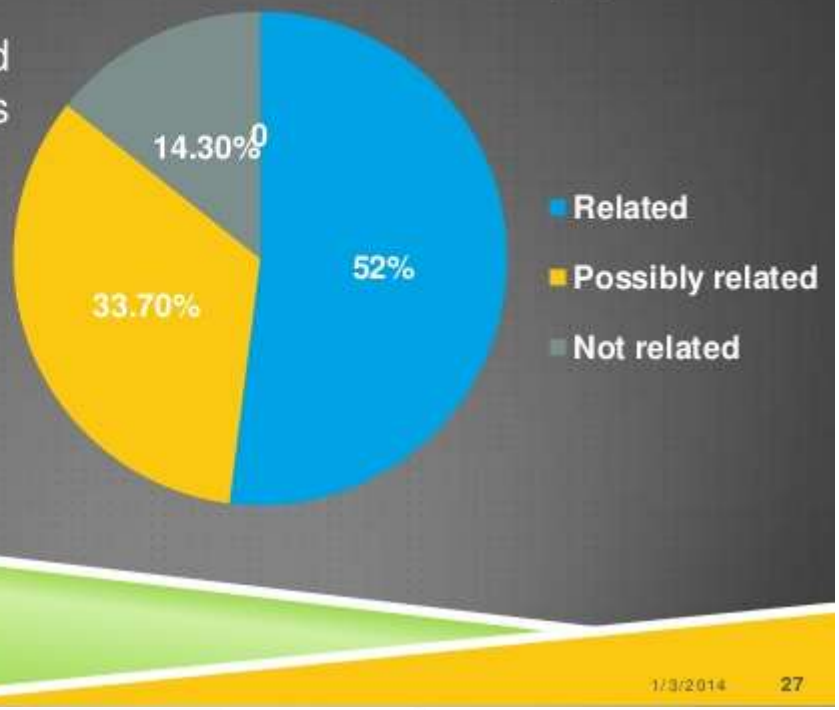
Terfenadine (Seldane)	
Mibefradil (Posicor)	
Trovafloxacin (Trovan)	19
Troglitazone (Rezulin)	
Cisapride (Propulsid)	
Cerivastatin (Baycol, Lipobay)	
Rofecoxib (Vioxx)	

Katalyst Healthcares & Life Sciences

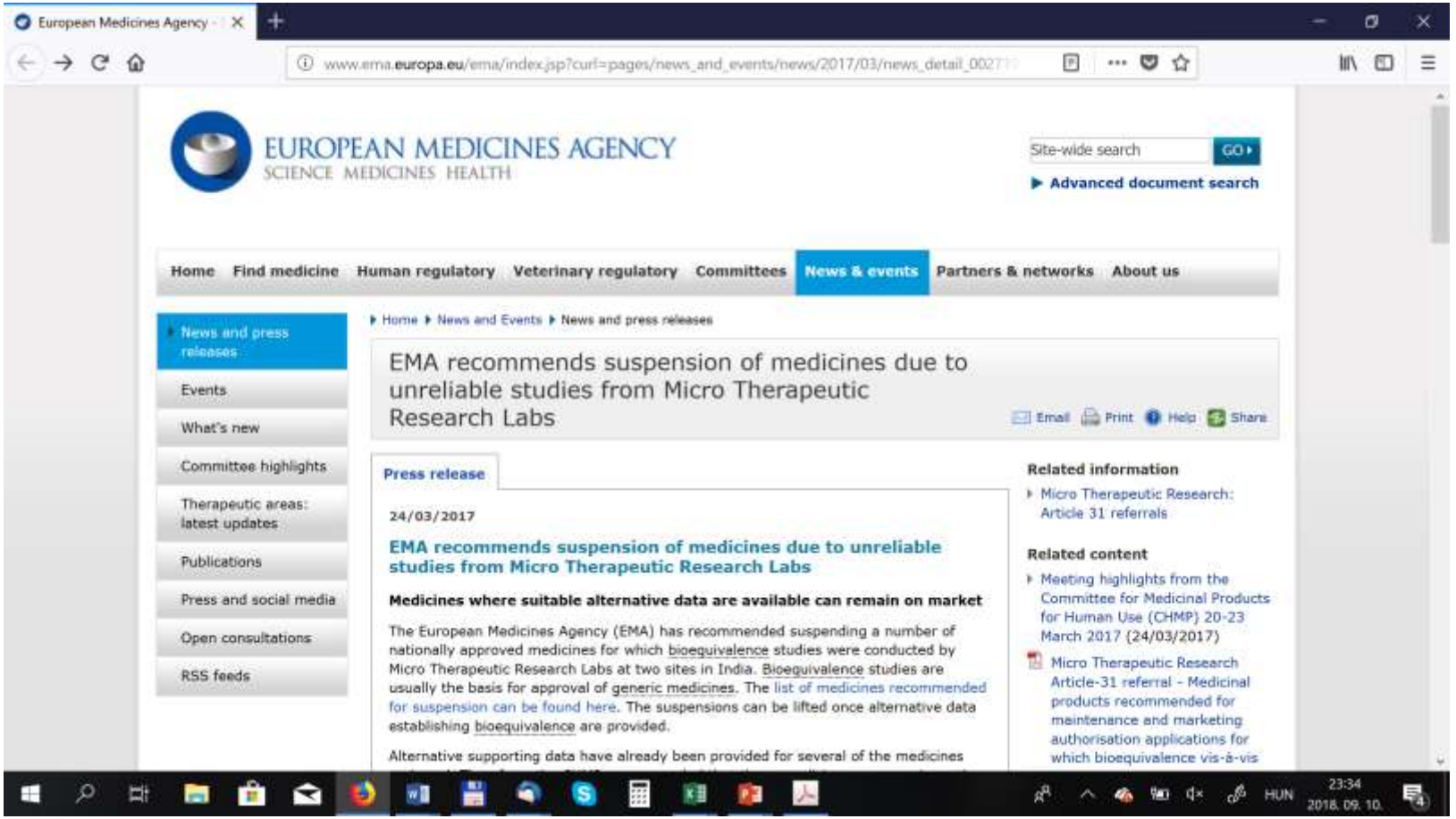
FATAL CASES

Marketing till withdrawal: Confirmed rhabdomyolysis cases had a (n=99) 7.6% fatality rate.

The majority of reported fatal cases occurred in 2001 (70.51%).



Toxicology: drug withdrawals due to unreliable research

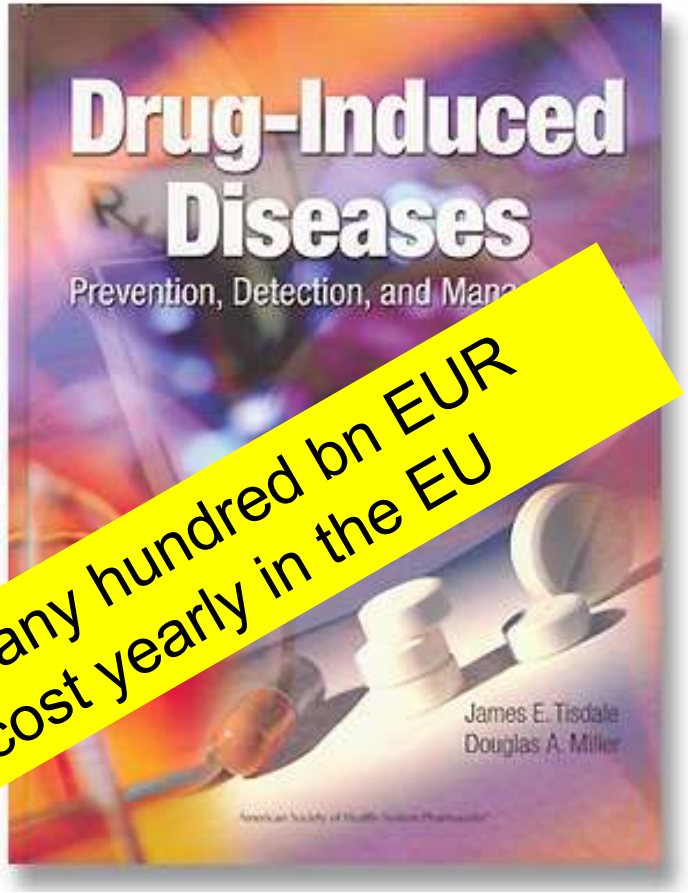


Clinical pharmacology

- **Right drug for the right patient –** at a good price (pharmaco-economy)
- **Human studies:**
  - baisis of ***evidence-based medicine***
  - efficacy and safety
  - human trials of new drugs
  - bioequivalency studies: generics, biosimilars
- **Drug level measurements, monitoring**
- **Pharmacotherapy recommendations:**
  - risk-benefit assessment, guidelines

Personalized pharmacotherapy

"Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease." **Sir William Osler 1849-1919**



Lots of *non-responders* even to well-known efficacious drugs

There are side effects even in case of well-managed therapies

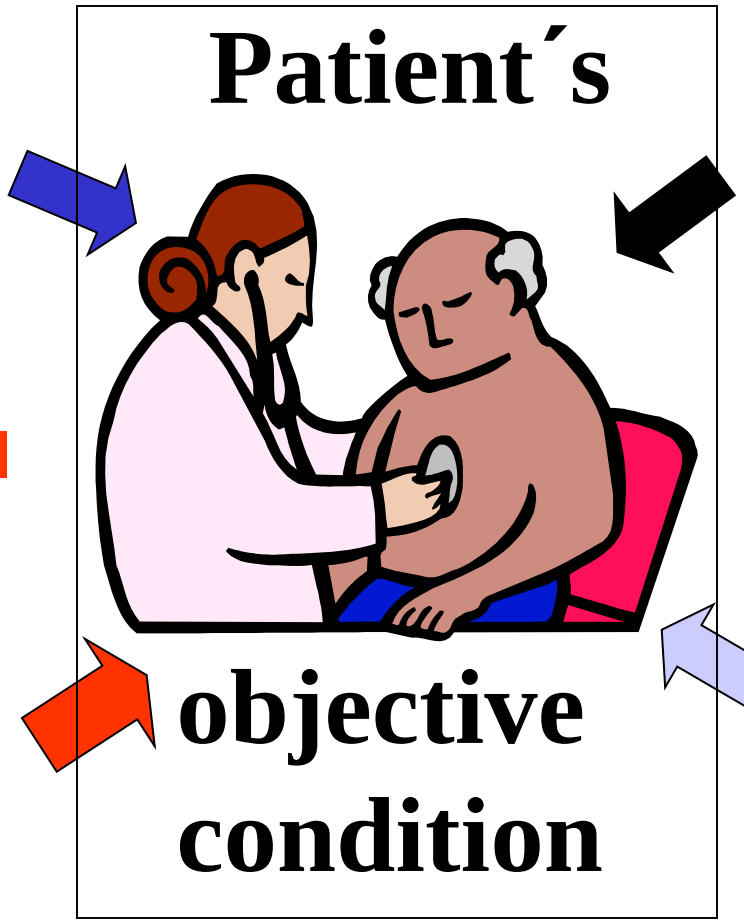
Personalized pharmacotherapy: factors influencing the physician's decision in drug therapy

Physician

- Hippocratic oath
- Professional knowledge
- experience
- Private economic interests

Pharmaceutical industry

- Development cost and pricing
- Generic preparations
- Professional information
- Advertising



Health politics

- Pharmaceutical authorities
- Health insurance companies
- Health provider
- Local rules
- Medical professional regulations

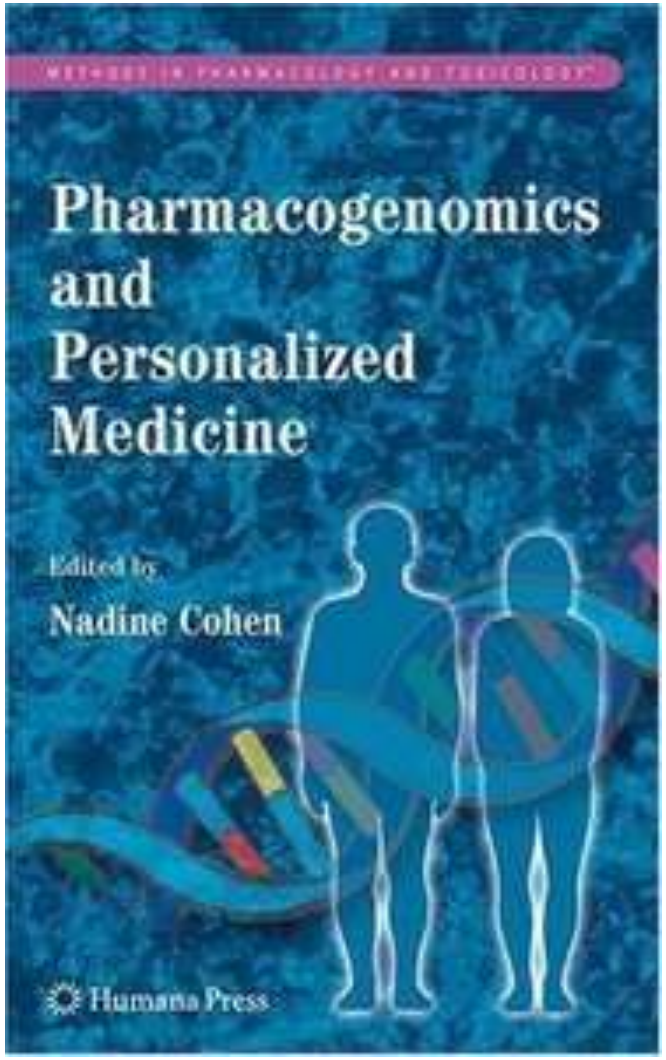
Patient´s

- subjective experience of disease,
- economic state,
- final decisions (yes, no)

Personalized pharmacotherapy

Pharmacogenomics:
• Interaction of individual genome and pharmacological treatment

To identify:
• good responders
• group of patients with high chance of side effects



Personalized medicine: Pharmacotherapy for the elderly:„5 x i”

- Intellectual decline
- Immobility
- Instabilility
- Incontinency
- Iatrogenic effect

(unwanted drug effects)

Modified drug effects in the elderly

CHANGES IN PHARMACOKINETICS

- muscle mass ↓
- body fat ↑
- liver mass/blood flow ↓
- renal function ↓

PHARMACODYNAMIC DIFFERENCES

- altered receptor binding and secondary effects
- altered homeostasis
- common diseases: glaucoma, diabetes, arthritis, coronary diseases, etc.

SOCIAL ASPECTS

- insufficient nutrition
- polypragmasy
- low compliance

Modified drug effects in the elderly

Most common drug interactions:

- Oral anticoagulants
- Oral antidiabetics
- Antibiotics
- Antiepileptics
- Antiarrhytmic agents
- Cardiac glycosides

Drugs most commonly used in the elderly:

- Oral anticoagulants
- Sedato-hypnotics
- Antibiotics
- Cardiac agents
- Antidepressants and antipsychotics
- glaucoma drugs

DO NOT BE THE *FIRST*

TO USE A NEW DRUG,

BUT DO NOT BE THE *LAST*

TO STOP USING AN OLD ONE