# Drug development and bioequvivalence

Institute of Pharmaceutical Technology and Biopharmacy
University of Pécs

# Drug Development

## Pre-discovery

**Goal:** Understand the disease and choose a target molecule.

**How:** Scientists in pharmaceutical research companies, government, academic and for-profit research institutions contribute to basic research.

## Discovery

**Goal:** Find a drug candidate.

**How:** Create a new molecule or select an existing molecule as the starting point. Perform tests on that molecule and then optimize (change its structure) it to make it work better.

## Preclinical

**Goal:** Test extensively to determine if the drug is safe enough for human testing.

**How:** Researchers test the safety and effectiveness in the lab and in animal models.

# Drug Development

## Clinical Trials

**Goal:** Test in humans to determine if the drug is safe and effective.

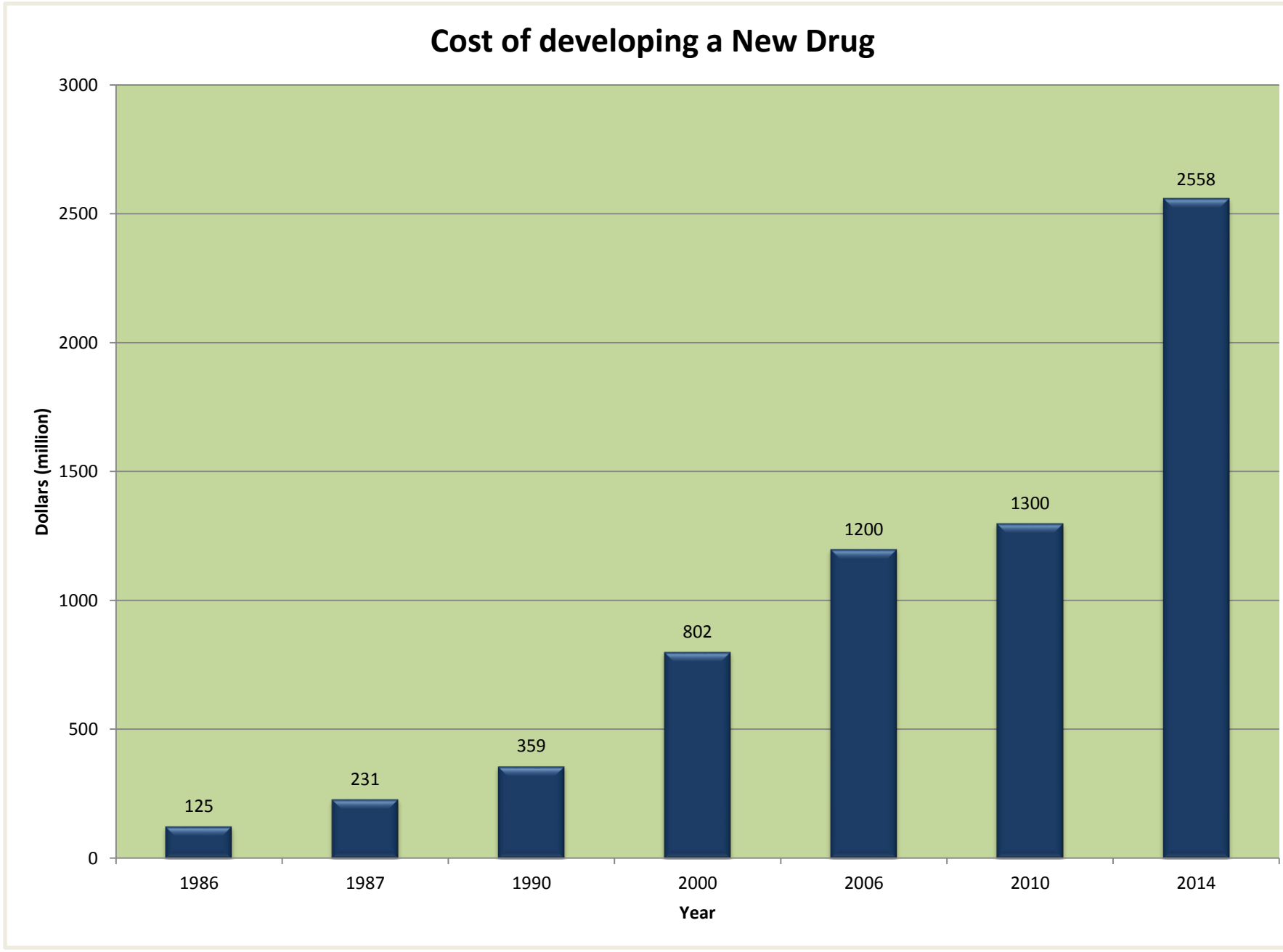
**How:** Candidate drug is tested in clinical setting in three phases of trials, beginning with tests in a small group of healthy volunteers and moving into larger groups of patients.

## Manufacturing

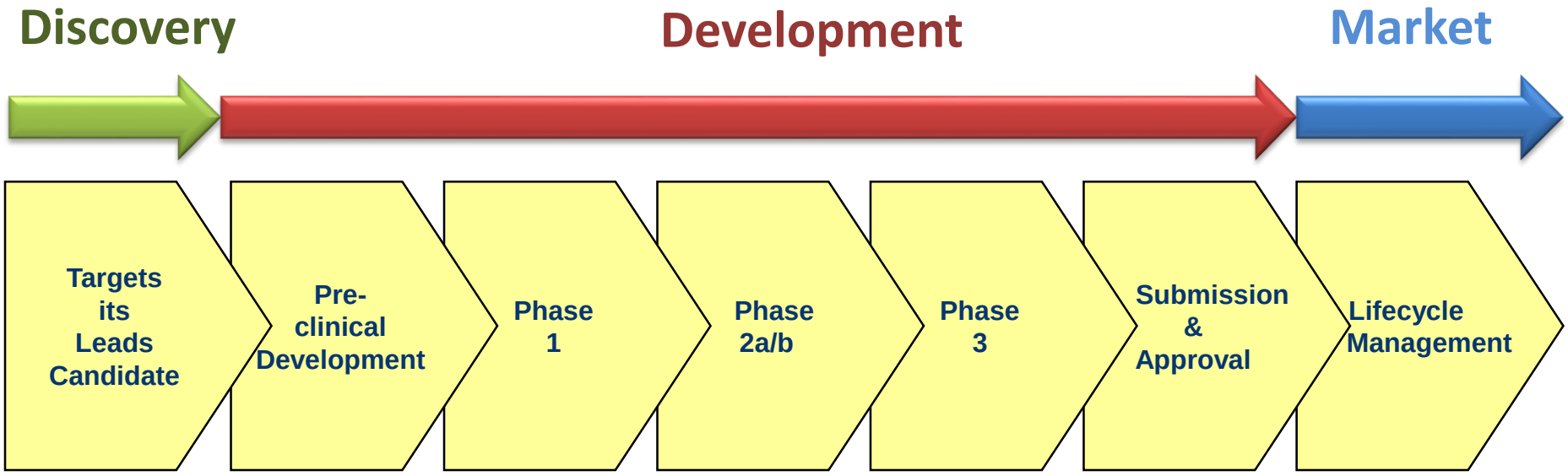
**Goal:** Formulation, scale up and production of the new medicine.

## Ongoing Studies

**Goal:** Monitor the drug as it is used in the larger population to catch any unexpected serious side effects.


Cost of developing a New Drug
3000
2500
2000
1500
1000
500
0
Dollars (million)
125
231
359
802
1200
1300
2558
1986
1987
1990
2000
2006
2010
2014
Year

# Drug Development




2-5 yrs

0.5 - 2 yrs

1 - 2 yrs

1.5 - 3.5 yrs

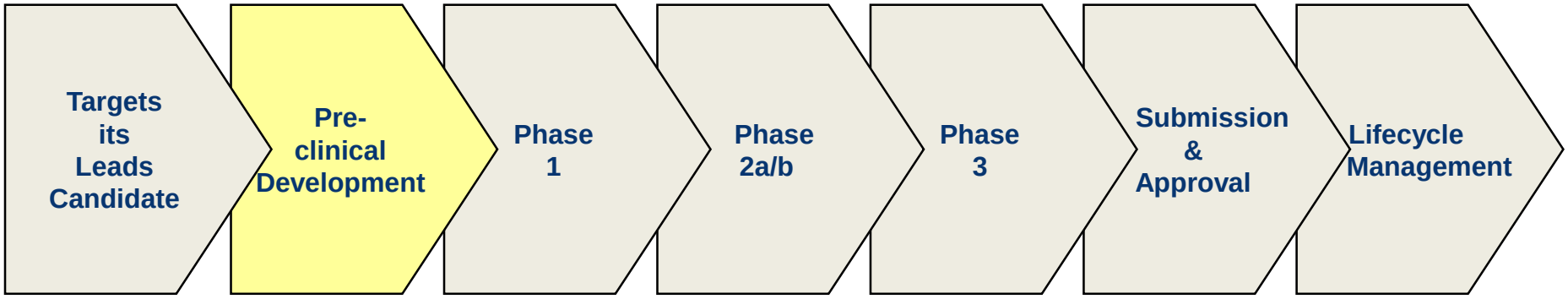
2.5 - 4 yrs

0.5-2 yrs

10-20 yrs

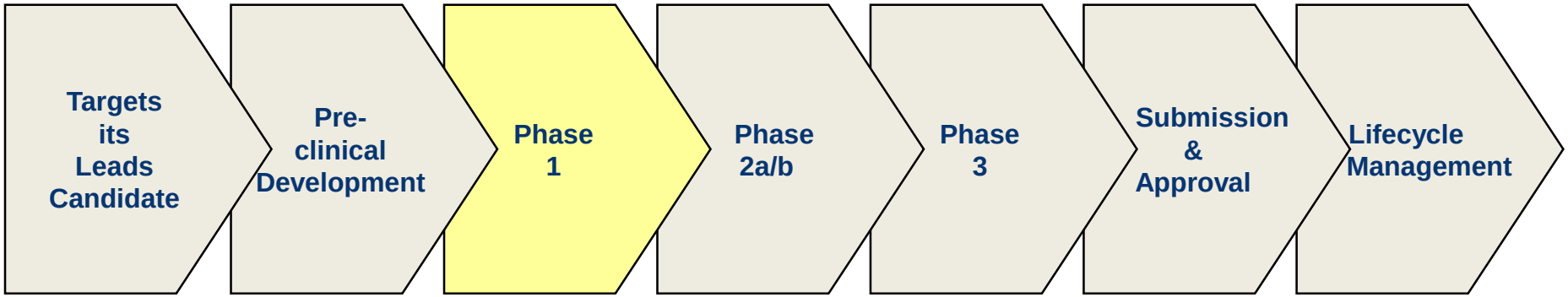
**Challenges: - Find safe and effective drugs**
**- Speed to market**

# Drug Development




- Animal tests of toxicity and efficacy of therapy
  - Rodents (mice and rats)
  - Mammals (pigs)
  - Primates (monkeys and chimpanzees)
  - Mouse Lemurs (*Microcebus*)

# Drug Development




Small group of healthy volunteers (10's) to determine

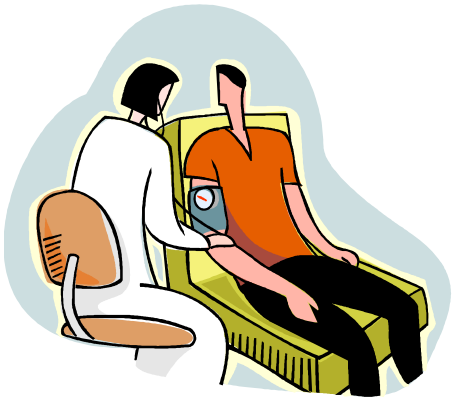
- safety and
- toxicity.

Maybe some members of target group

# Clinical Trials

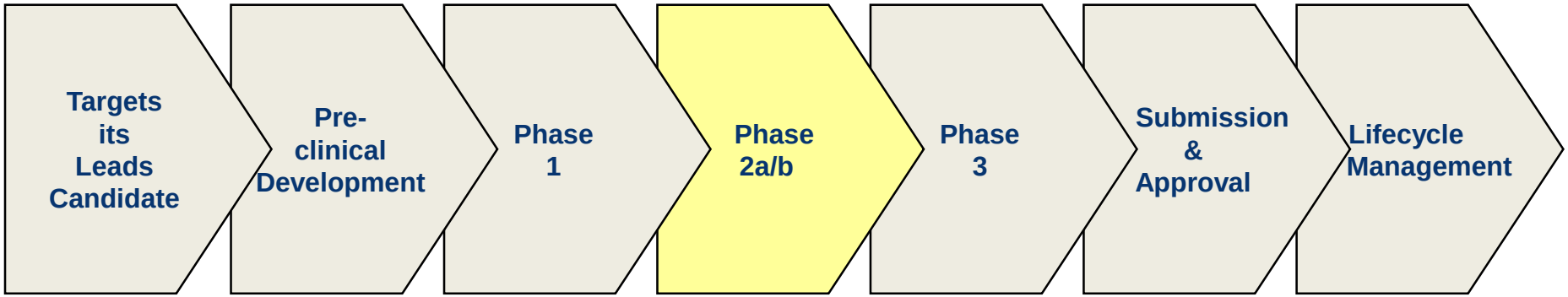
## Phase 1

- Drug is tested for its interaction with the human system.
  - How is the drug absorbed
  - How is the drug distributed in the body
  - How is the drug metabolized by the body



- *Trials usually involve normal, healthy volunteers and take about a year to complete.*

# Drug Development



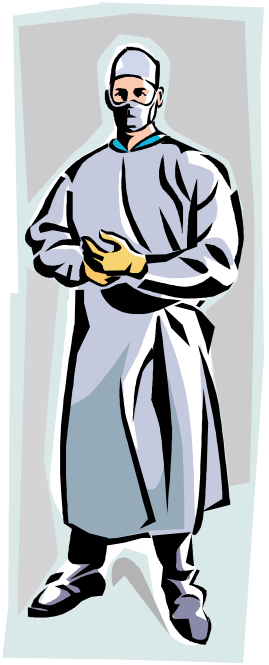

100's of patient population to determine

- efficacy,
- dosage,
- safety

# Clinical Trials

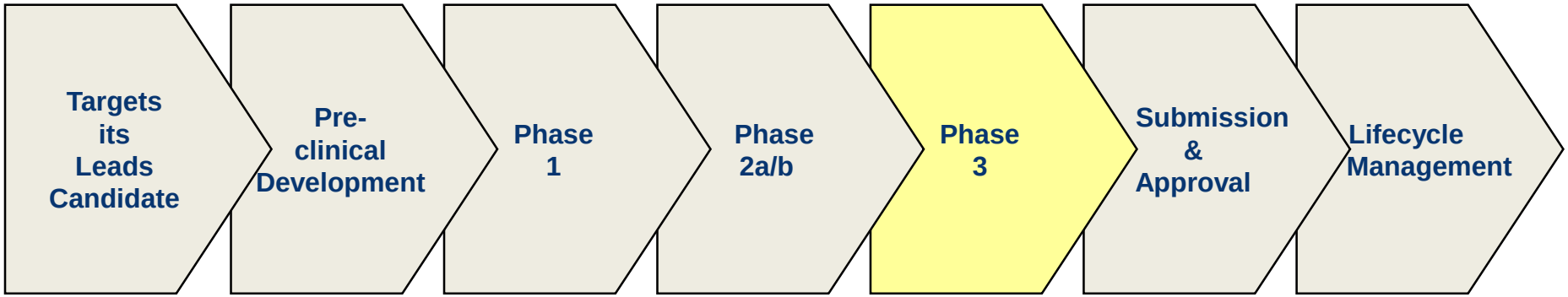
## Phase 2

- Pilot studies to begin to define the effectiveness and safety of the drug in patients with the disease or condition to be treated, diagnosed or prevented.



*Testing the various doses of the drug and dosing regimens*

# Drug Development



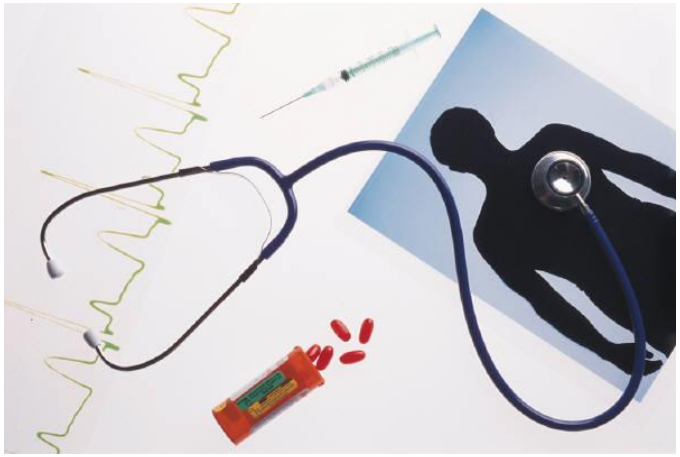

1000's of patients and controls (normals) to determine

- efficacy,
- dosage,
- safety,
- side effects, and
- interactions.

Each prospective patient group (men, women, children, elderly and ethnic groups)

# Clinical Trials

## Phase 3

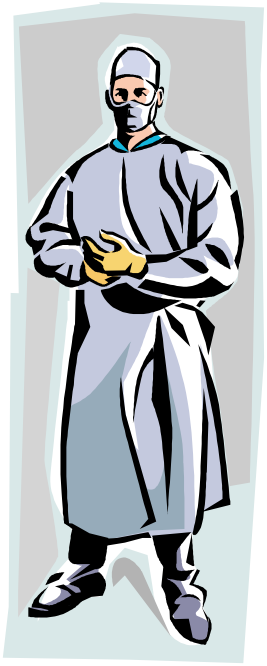


- Expanded clinical trials
- Designed to …
  - Gather additional evidence of effectiveness for specific interactions
  - Better understand safety and drug-related adverse effects

# Clinical Trials

## Phase 4

- Studies that occur after a drug has received approval from the U.S. Food and Drug Administration to be marketed
  - Performed to determine the incidence of adverse reactions
  - Determine the long-term effect of the drug
  - To study a patient population not previously studied
  - For marketing comparisons against other products and users

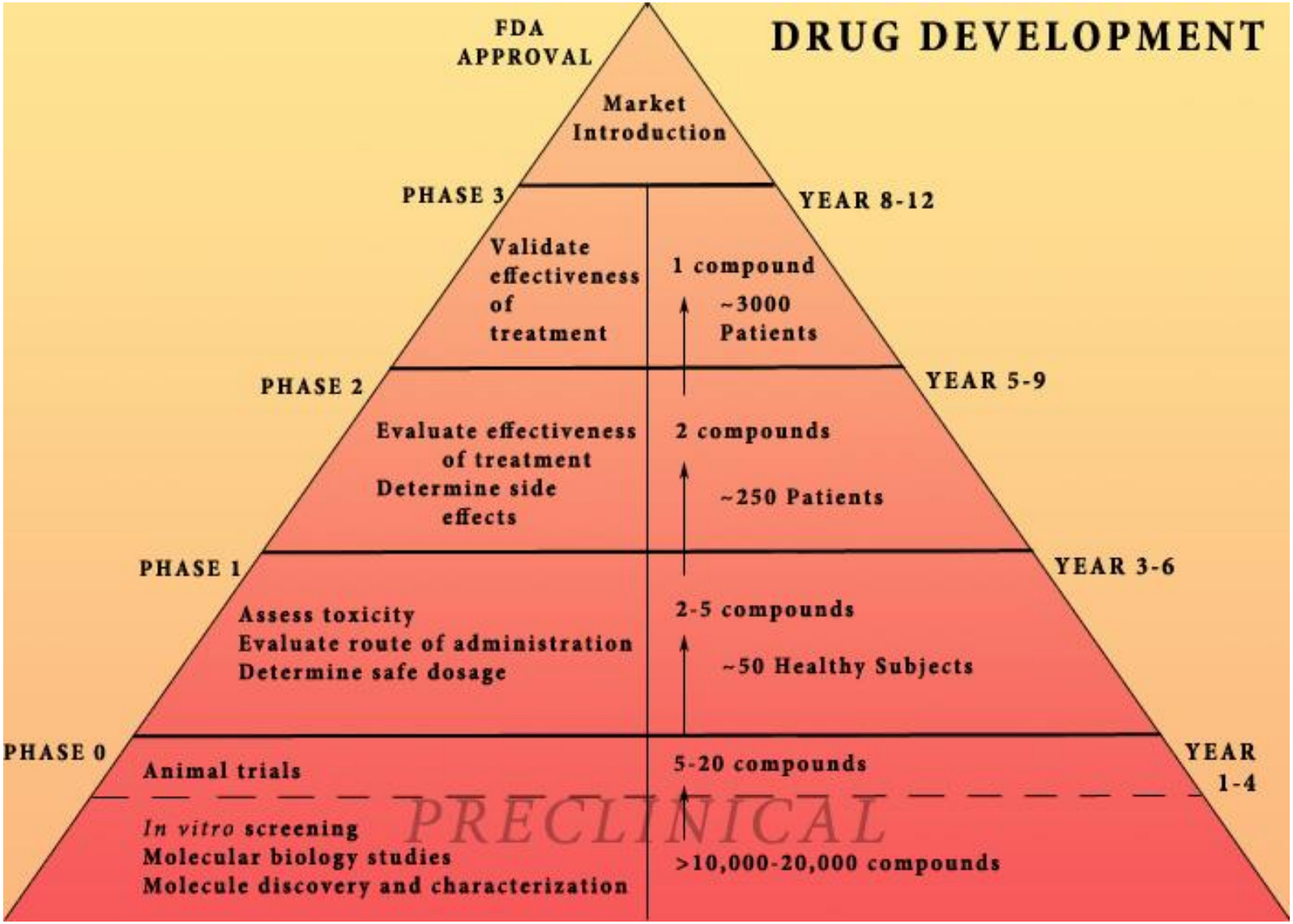


# Clinical Trials

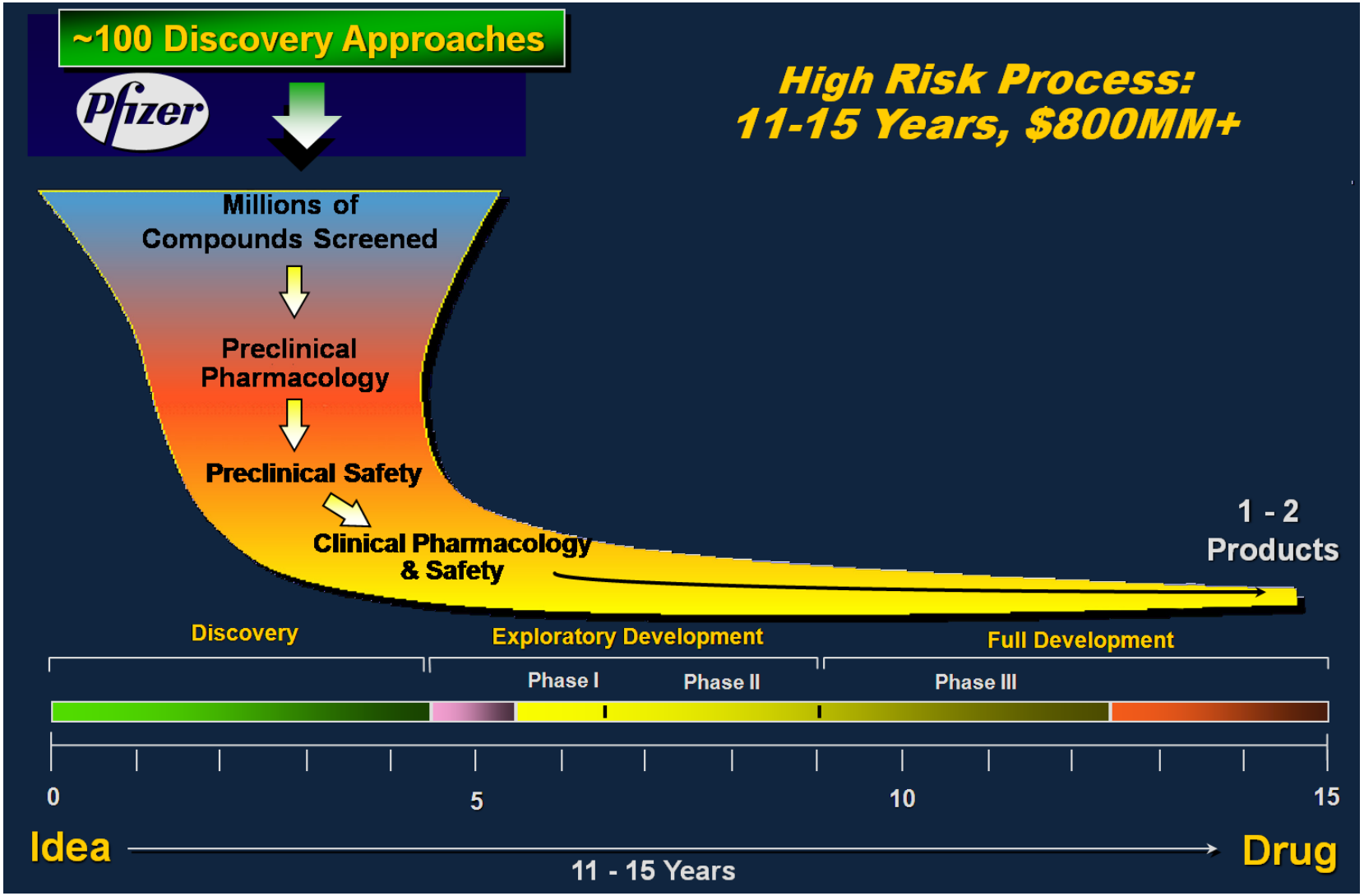
## Post-marketing surveillance

- Monitor the ongoing safety of marketed drugs by reassessing drug risk based on …
  - New data collected after the drug is marketed
  - By recommending ways of trying to most appropriately manage that risk
    - Includes adverse reaction reporting by the medical community of the pharmaceutical company that markets the drugs
    - Periodic sampling and testing of the drug
    - Periodic inspections of the manufacturing and distribution process

# Drug Development



# Drug Development



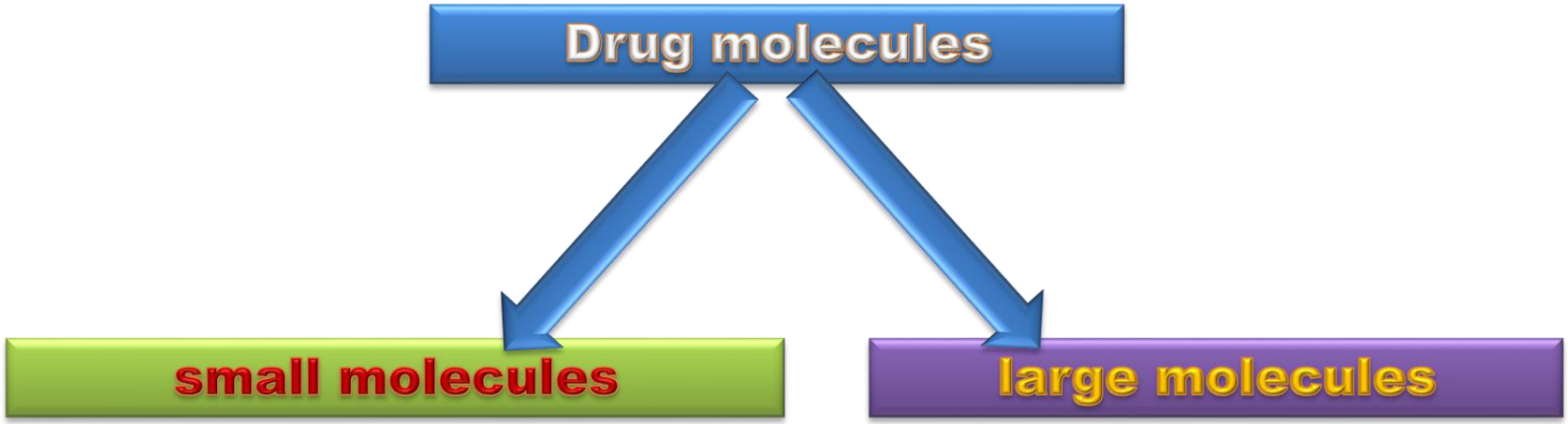
# Pharmaceutical Research and Development

SUMMARIZING:

A drug to approve as a medicine **you need**

- 0.8-1 billion$,
- 10-15 years
- 10 000 test preparation
- 6000 animals,
- 5000 human subjects.

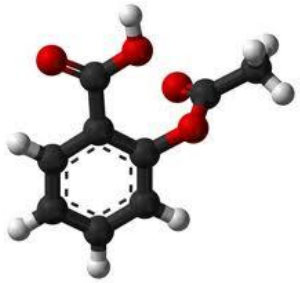
# Medicines



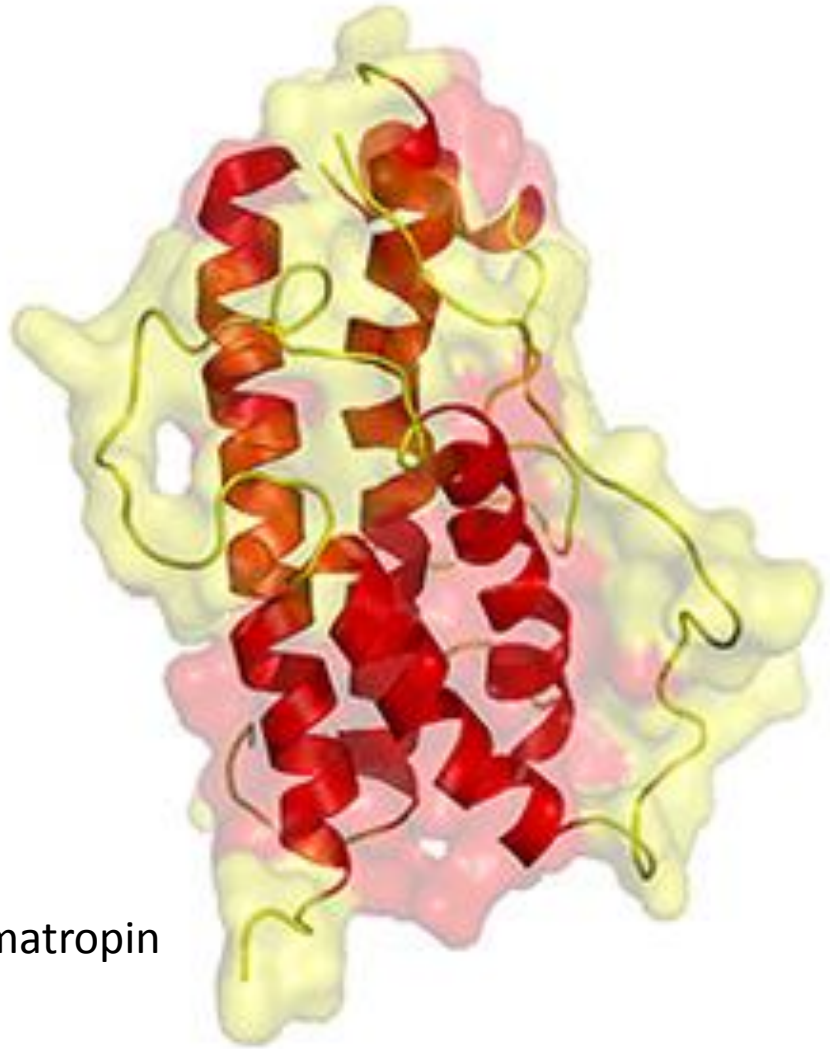

**MW ≤ 800 Daltons**

**MW > 800 Daltons**

# Medicines



aspirin



somatropin

# Medicines

**Tradidional drugs:**

- manufactured through **chemical synthesis**, which means that it is made by combining specific chemical ingredients in an ordered process
- **small molecules**
- **well-defined chemical structures**, and a finished drug can usually be analyzed to determine all its various components.

**Biologicals:**

- manufactured in a **living system** such as a **microorganism**, or **plant** or **animal** cells.
- very **large, complex molecules** or mixtures of molecules produced using recombinant DNA technology
- **difficult**, and sometimes impossible, **to characterize** a complex biologic by testing methods available in the laboratory, and some of the components of a finished biologic may be unknown

# Medicines

| Traditional | Biologicals |
|---|---|
| **Physico-chemical properties** | |
| small molecules<br>stable | large molecules<br>instable (heatsensitive) |
| **Pharmacological properties** | |
| short acting<br>non-immunogenic<br>species independent | long acting<br>immunogenic<br>species dependent |
| **Biopharmaceutical properties** | |
| oral administation<br>general practice | parenteral administation<br>hospital |

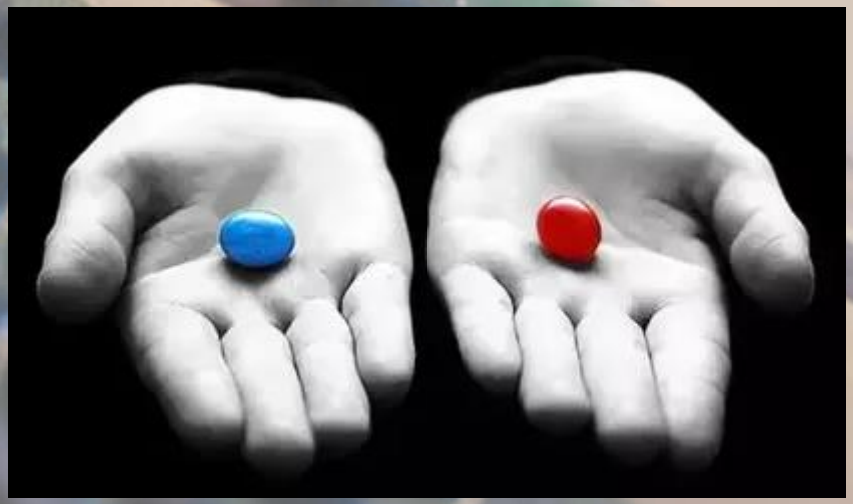
## Pharma Market Trends 2009-2014

**Table I: Combined global prescription sales for the top 50 pharmaceutical companies (excluding generic-drug companies) by molecule type (2009–2014).**

| | Sales ($ billion) | | | | | | |
|---|---|---|---|---|---|---|---|
| Molecule type | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | Difference in sales between 2009 and 2014 |
| Small molecule | 411 | 414 | 415 | 405 | 394 | 394 | –4% |
| Therapeutic protein | 65 | 68 | 70 | 72 | 74 | 76 | 17% |
| Monoclonal antibody | 38 | 43 | 48 | 53 | 58 | 62 | 63% |
| Vaccine | 21 | 22 | 24 | 25 | 27 | 28 | 33% |

Sources: Datamonitor, PharmaVitae Explorer, January 2010, and company-reported information.

# Original and generic medicines



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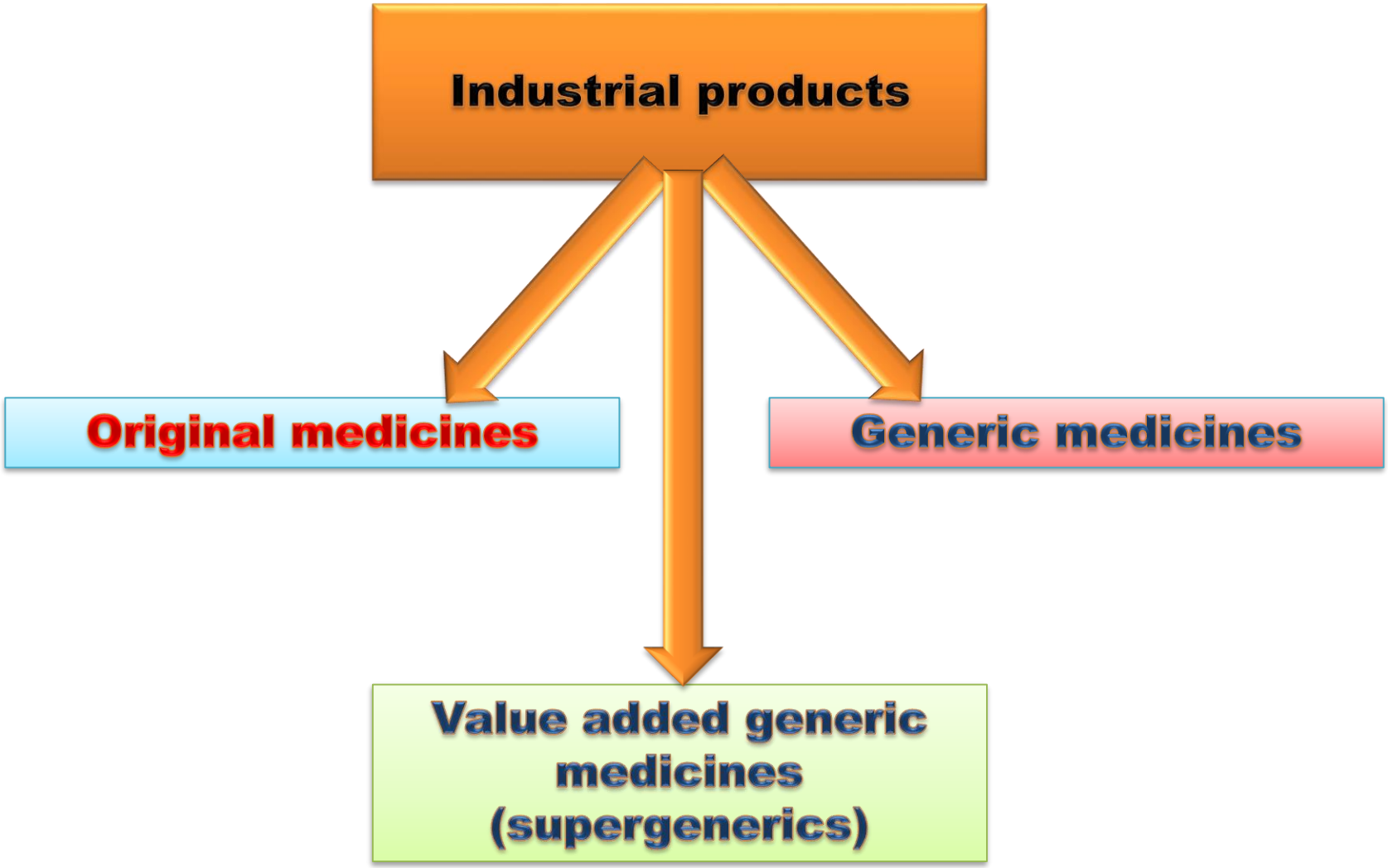
2014.

# Original and generic medicines



# Original and generic medicines

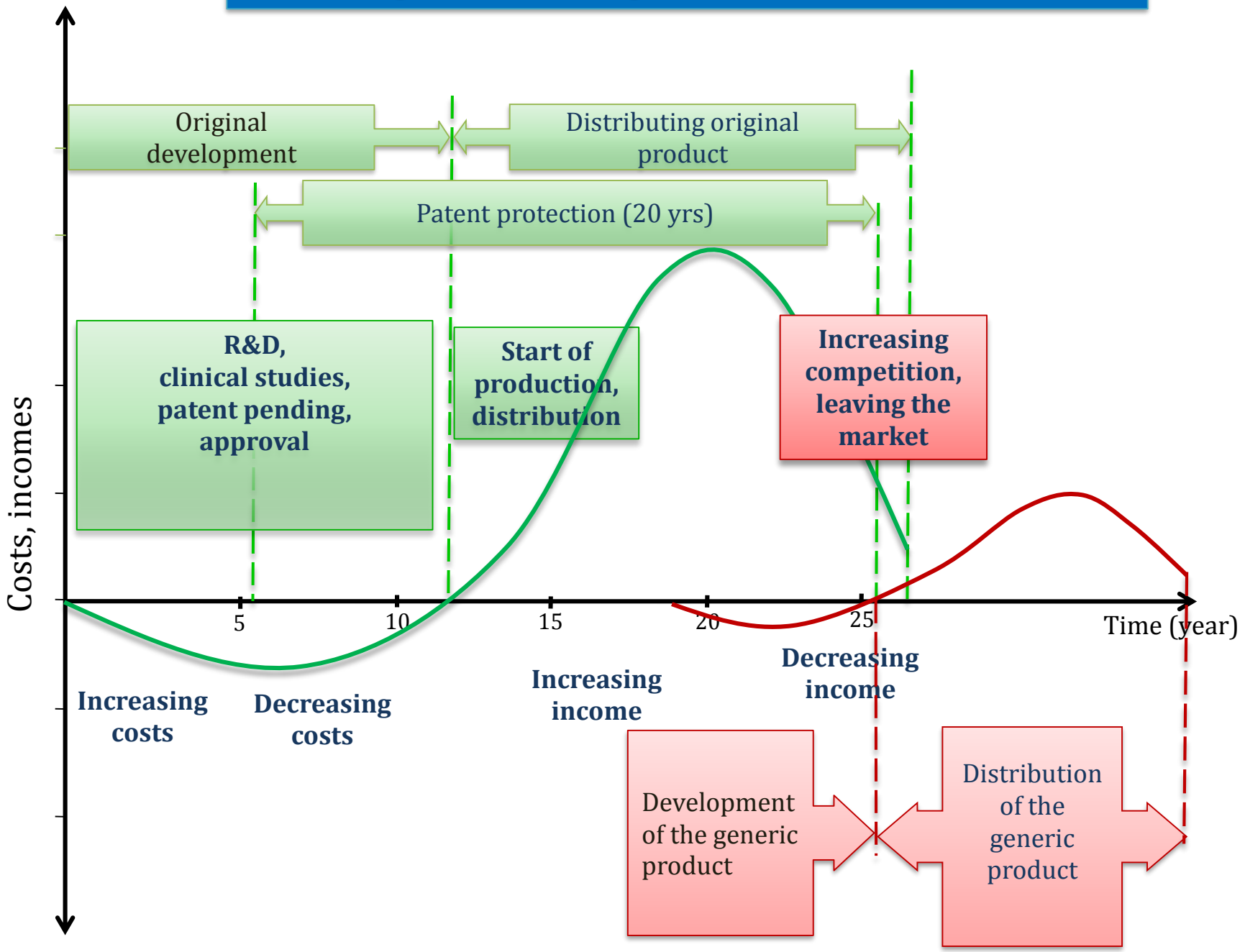
## Original

- 10-15 years of research and testing in animals and people
- During this testing, the company making the drug must prove that it is safe and effective for people to use.
- All of this testing can cost over $1 billion.
- Once the new drug is approved, the company that made and tested it receives a patent

## Generic

- copy of a brand name drug
- same as the original brand name drug in the following ways:
  - ✓dosage form (tablet, capsule, liquid, etc.)
  - ✓strength (same amount of drug in both)
  - ✓ safety
  - ✓ how it is taken (by mouth, injection, etc.)
  - ✓quality
  - ✓how the medicine gets into the bloodstream and works in the body
- Generic drug companies do not have to spend as much time and money because they do not have to test the drug for safety and get FDA-approval.
- This is why generic drugs cost less

# Original and generic medicines



# Original medicines

API of **original medicines** is a **result** of a **new research/development** which **did not exist before** or it was **not used in the therapy**.

These medicines are **original ones** which contain **new API**'s with **new therapeutic possibilities**.

# Original medicines

Newly developed medicine (API) is **under the protection** of **patent for 20 years** *(or 25 years)* **from the discovery** (production of the medicine).

The **discoverer** is **the only manufacturer** which can produce and distribute the medicine during this period.

# Original and generic medicines

Development for the **generic** manufacturer is much more easy, because there is **no need to spend huge money on experiments**, there is no research lasting for 12-13 years.

It is enough to **buy the API** from the original manufacturer and develop, then distribute its generic medicine.

Generic manufacturer has to exhibit a detailed documentation regarding the medicine, since the API is re-formulated and a **bioequivalence examination** has to be carried out.

# Original and generic medicines

A generic drug should be **80%-125% "bioequivalent"** to the original brand name drug.

For example:

- A **brand** name drug is taken and 100 mg of medicine reaches the person's bloodstream.
- For a **generic** version of the drug to be considered safe and effective, the active drug must release between 80 mg and 125 mg reach the bloodstream (80-125%).

**This difference isn't a problem in most drugs.** There are a few drugs, however, in which this can be an issue.

# Original and generic medicines

Some drugs are only safe and effective when the amount of medicine is within a small range in the bloodstream (**narrow therapeutic index**).

***Example:***

*A person is taking one of these drugs with a narrow therapeutic window. They have been taking a generic version of the drug that is 80% bioequivalent to the original brand name drug. After a few months, their pharmacy orders a generic version of the same drug which is 125% bioequivalent to the original brand name drug.*

This means that the new version of the drug could contain as much as **45% more active drug** than the old version!

# Original and generic medicines

Drugs that have narrow therapeutic indices:

- **Warfarin** (used to prevent blood clots)
- **Theophylline** (used to improve breathing in people with asthma and other lung diseases)
- **Phenytoin** (used to prevent and treat seizures)
- **Clonidine** (used to treat high blood pressure)
- **Quinidine** (used to keep your heartbeat normal)
- **Levothyroxine** (used to treat low thyroid activity)

# Generic medicines

If the **patent protection is over**, the company reveals its knowledge regarding the API, thus it will be reproducible and new **generic** products will appear.

**Generic medicines only appear after a patent protection is over**. Their prices are usually much more **lower** than the original product's one.

Since the same API can be produced by several manufacturer, the same medicine is available under different brand names - **multisource (generic) pharmaceutical products.**

# Generic medicines

**Generic medicines or generics** are pharmaceutical preparations containing APIs with expired patent protection.

These products **do not contain new API(s)** and they are proved to be **equal with the original** (**reference**) product.

Active ingredient(s) are present in the **same amount** and in the **same dosage form**, as the original product, but the **excipients may be different.**

# Generic medicines

Not all medicines with expired patent protection have a generic version;

sometimes it is **very hard to make a copy** of an original preparation

or

the **market of the medicine is so poor**, that it has no worth to develop its generic version.

# Bioequivalence and biosimilarity

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**University of Pécs**
**2014.**

# Bioequivalence

## Pharmaceutical equivalence


- same API
- same amount
- same, equal dosage form

# Bioequivalence

## Pharmaceutical alternatives

*contain the same API, but can differ in the:*

- **chemical form of the API** (i.e.: salt, esther, isomer, isomer mixture, ether, complex, etc.)
- **dosage form** (i.e.: tablet, capsule) with the same route of administration
- **amount of API** (10 mg, 20 mg, 30 mg)



# Bioequivalence

**Generic product is essentially similar to the original one, if:**

- API(s) quality and quantity is the same,
- dosage form is the same,
- biologically equal,
- there is no difference in toxicity and efficiency.

# Bioequivalence

## Supergeneric or generic plus medicine

The term "**supergeneric**" has been given to the development process for small molecule drugs which **offer a therapeutic advantage.**

**Generic drugs** = **copycat version of the parent drug**,
**Supergenerics** = **new therapeutic entities** that demonstrate improvements in product delivery, design or the manufacturing process.

**Supergenerics** may **offer a low-risk, low-cost alternative to the traditional pharmaceutical development** of new medicines, due to their shorter development timeline. New Chemical Entities (NCEs) take a long time to develop, often at a cost of over $1billion. Conversely, the development of a supergeneric is more comparable to that of a generic compound, as it has a known mechanism of action and an established safety and efficacy profile.

# Bioequivalence

## Supergeneric or generic plus medicine

The supergeneric approval pathway offers a less complex clinical development process.
Temporary market exclusivity is guaranteed (a three-year period of market exclusivity) providing some degree of product protection.

Since 2004,
over 245 drugs have been approved via this pathway:

- 70% were novel formulations
- 18% were new combinations

There are currently **more than 60 novel supergeneric** formulations of approved **oncology, CNS, pain and respiratory products** undergoing development.

# Bioequivalence

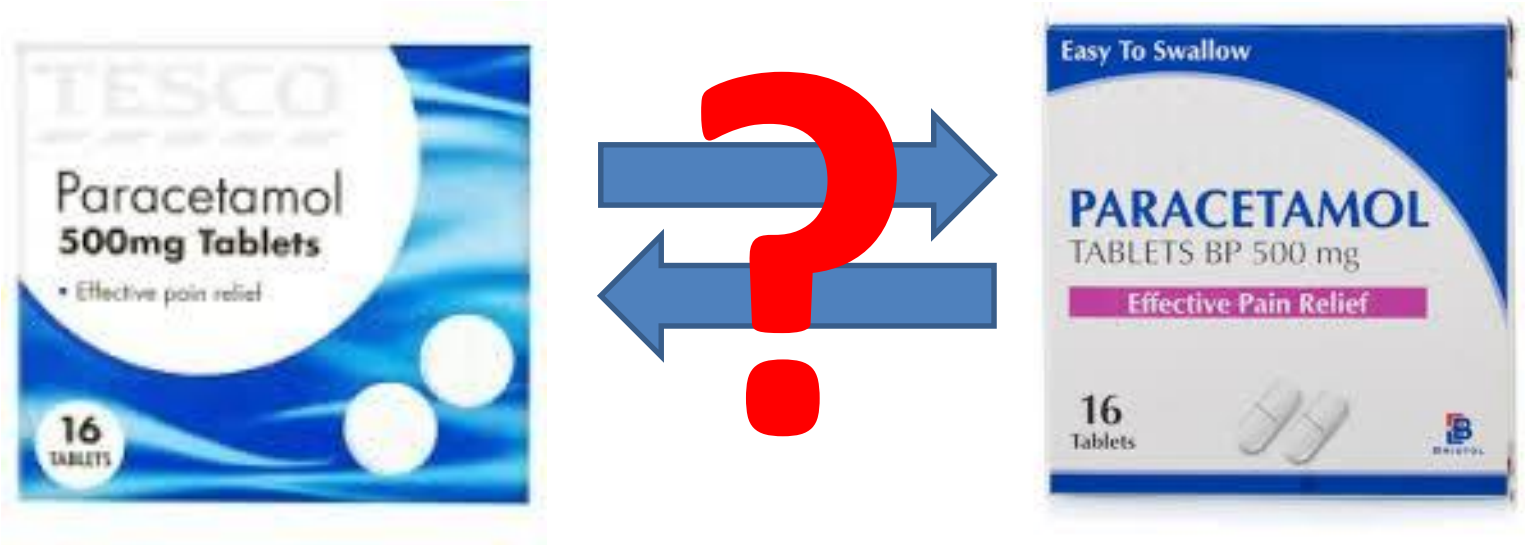
What kind of files should a **generic manufacturer** exhibit for the approval?

- pharmaceutical documentation,
- non-clinical examinations,
- clinical trials regarding the bioequivalence can be substituted with a simple bioequivalence test.

**The time and cost consuming animal and human trials can be skipped.**

# Bioequivalence

The generic manufacturer has to examine the **bioequivalence** with the original product, so these two medicines has to be compared concerning their effect in the human organism.



# Bioequivalence

## Bioequivalence studies

Bioequivalence studies point to

- the amount of the API absorbed into the systemic circulation (**AUC**),
- the speed of absorption ($\mathbf{t_{max}}$) and
- the peak concentration ($\mathbf{c_{max}}$),

which **should be equal to the original** product's experimental data.

# Bioequivalence

The authority (**FDA** in the USA, **OGYÉI** in Hungary) makes an evaluation from all geric products.

**The generic medicines is only approved if the examinations prove the bioequivalence with the original medicine.**

The authority also has to examine the amount of the API and the evaluate the manufacturing procedures (according to the Good Manufacturing Practice, GMP).

# Bioequivalence

## Documentation for the generic products

If the original and the generic medicine **differs in the chemical form** (salt, esther or other derivative), but the **biological effect is the same**, the generic manufacturer has to prove the **equivalence** of the **pharmacokinetic** and **pharmacodynamic** profile as well as the **effect** and the **toxicity**.

# Bioequivalence

The bioequivalence must be proved for each new „**dosage form**”.

The „new dosage form” may be the new form of an existing form, strength of this or a modified administration form of the existing preparation or a new generic medication.

# Bioequivalence

## Essentiality list

The National Institute of Pharmaceutics (OGYÉI) publishes the list of bioequivalent preparations in the proper media (journal and ministry's webpage).

These preparations are substituted with each other during the therapy.

This list contains the name, dosage form and strength of the substituting preparations.

# Bioequivalence

## Bioequivalence

Two preparations are **equivalent**, if there is:

- the same API,
- the same amount,
- in the same dosage form,
- the dissolution of API is the same,
- the concentration of the API in the blood and in the tissues is the same

If these conditions are observed in case of two medicines, we can be sure, that these two preparations result the **same therapeutic effect.**

# Bioequivalence

## In vitro investigations

**Fit factors** ($f_1$ , $f_2$)

This method can compare the values (%) of the given points of the curves.
These factors can characterise the **diversity** or **similarity** of the curves.

***$f_1$ = diversity factor***

$$f_1 = \frac{\sum_{i=1}^{n}(R_i - T_i)}{\sum_{i=1}^{n} R_i} \times 100$$

***$f_2$ = similarity factor***

$$f_2 = 50 \lg \left\{ \left[ 1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i) \right]^{-0,5} * 100 \right\}$$

$n$ the number of samples

$R_i$ the API concentration (expressed in %) of the **reference** preparation at the given sampling time

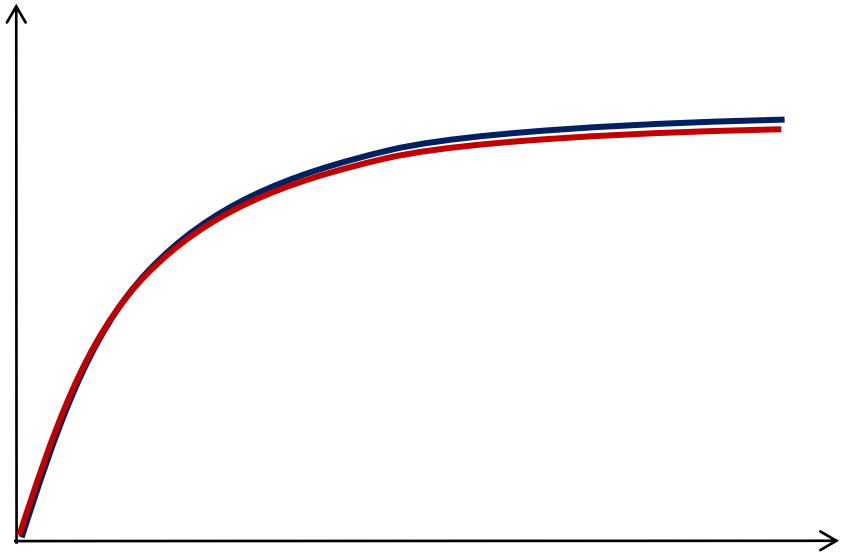
$T_i$ the API concentration (expressed in %) of the **examined** preparation at the given sampling time

# Bioequivalence

In vitro investigations

**Fit factors** $(f_1 , f_2)$

**If the *diversity ($f_1$) factor* is 0, than the dissolution profile of the preparations is the same.**



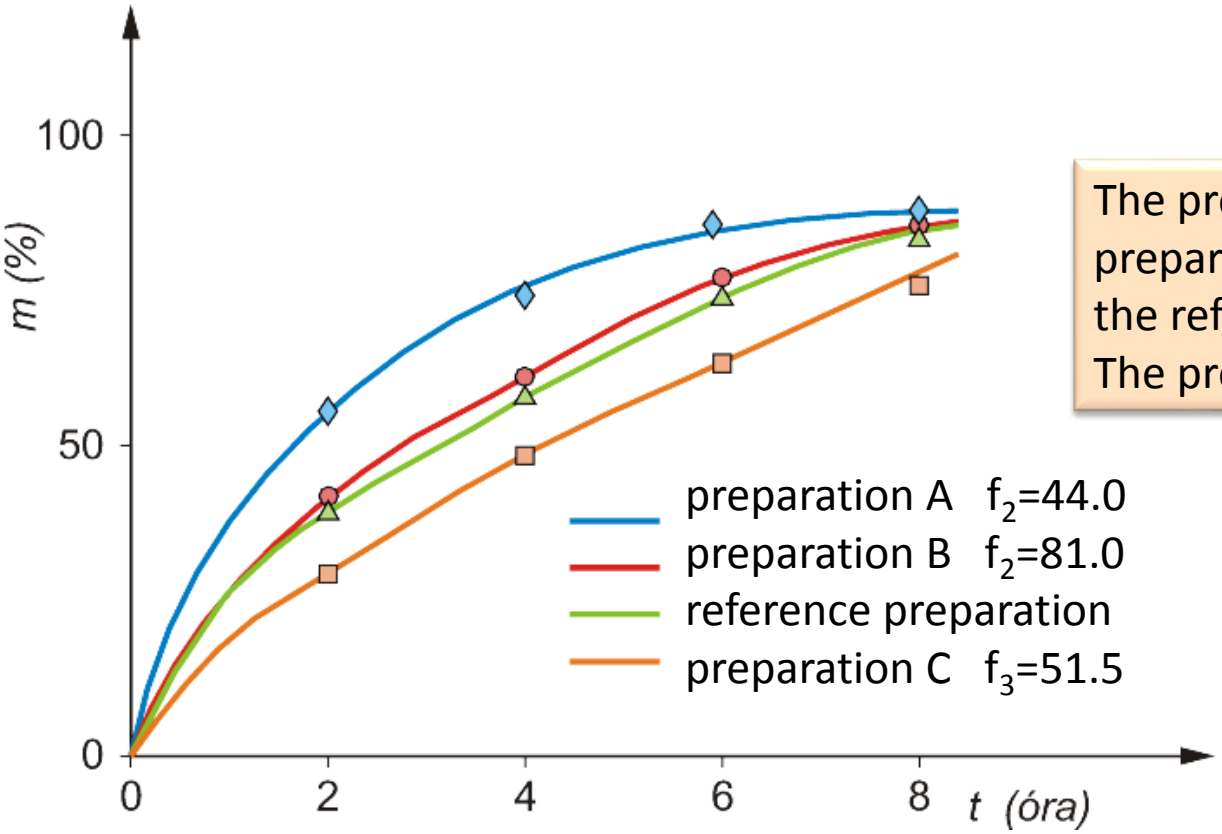
# Bioequivalence

## In vitro investigations

**Fit factors** $(f_1, f_2)$

The **similarity *($f_2$) factor*** is a **dimensionless number** which value is between 0 and 100.

**If $f_2 > 50$, than the two curves are similar.**




The preparation B (51,5) and preparation C (81) show similarities to the reference preparation.
The preparation A (44) is different.

# Bioequivalence

## In vivo investigations

The examinations are made on a few (24-36) healthy volunteers.

The volunteers take the investigated preparations for a few weeks. (washout period, dosing rate and doses)

In contrast, studies of new drugs for developing are more complex, requiring a large number of participants (therefore much more expensive). These tests could prove the safety and efficacy of drugs.

# Bioequivalence

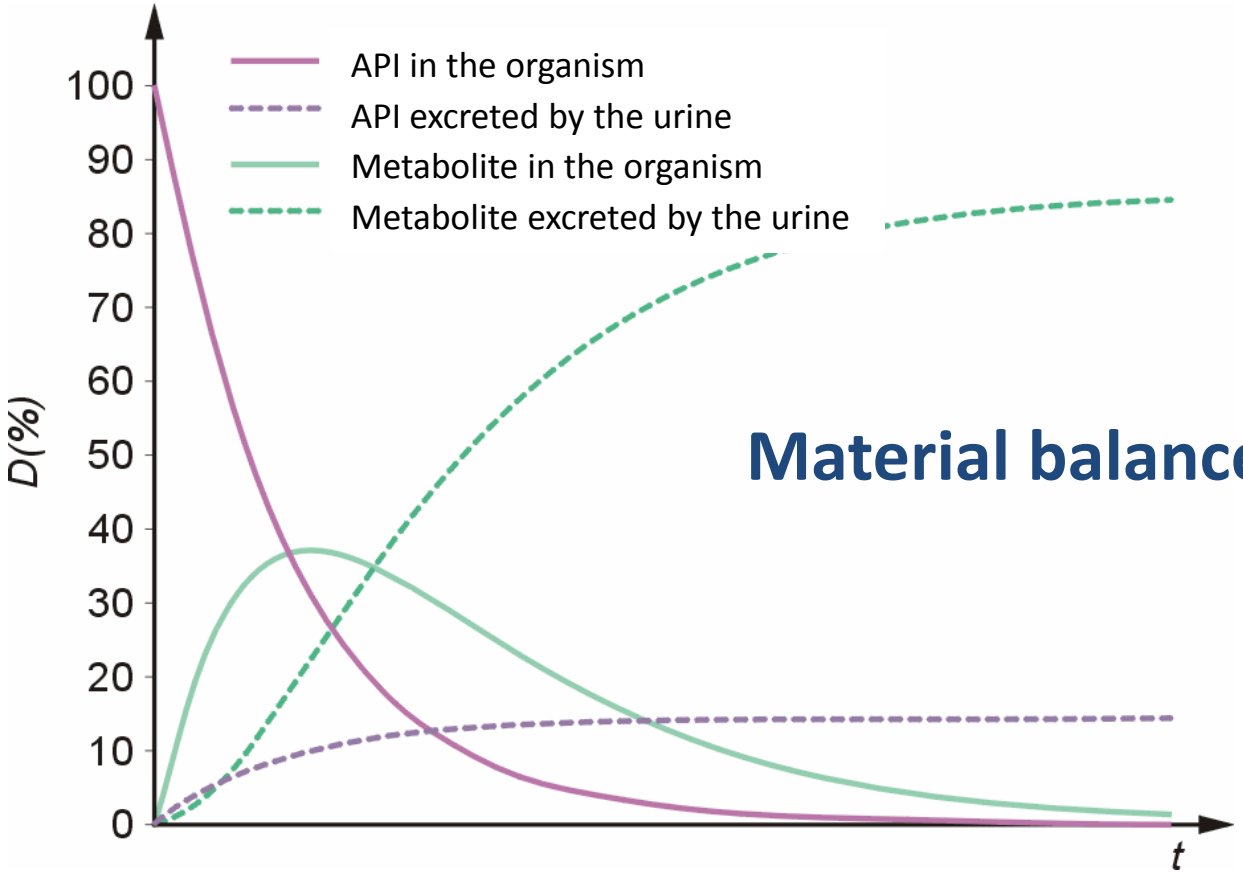
## In vivo investigations

The blood plasma level of API is a commonly measured parameter.
The scientist comparise the plasma concentration-time curves of APIs to can gain pharmacokinetic parameters.
These parameters may differ 20% in both direction.

The real difference between the original and generic preparations is less than 20%.
The real difference is about 3.5% and it can be rarely more than 10%.

# In vivo investigations

Amount of API and metabolites in different compartments of the organism




**Material balance**

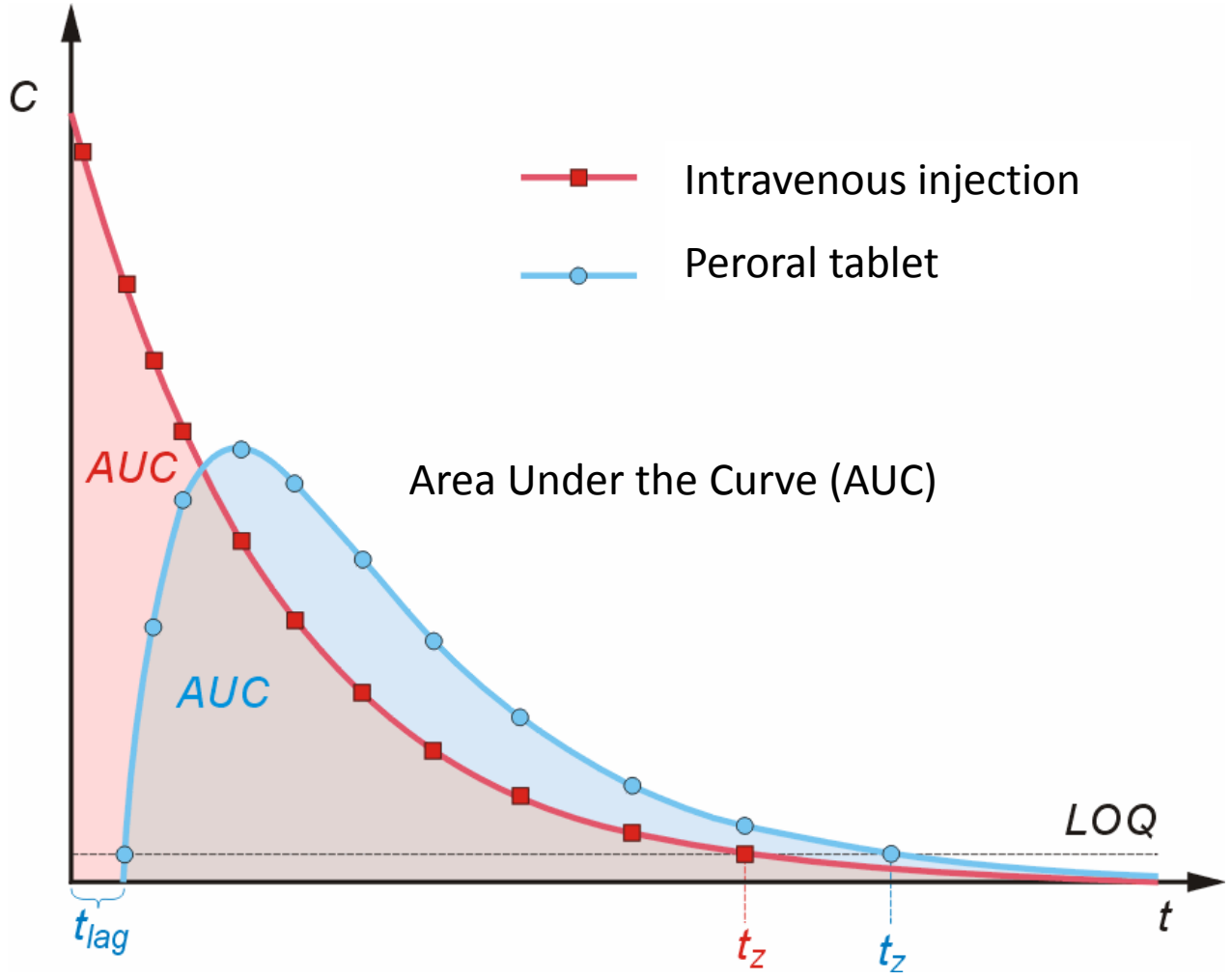
**Absorbed API fraction (F)** = $M_a$ / D

$M_a$= amount of absorbed API

D=dose

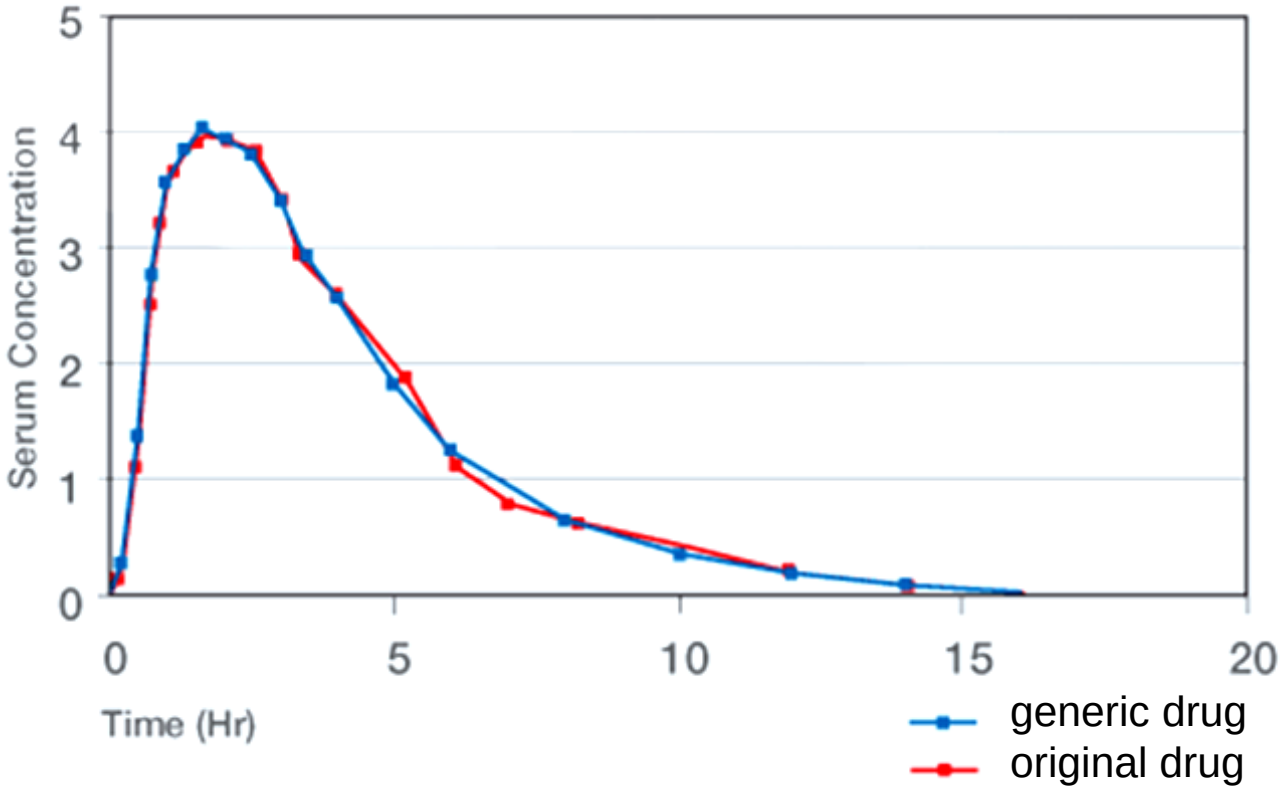
# Modeling and analysis of pharmacokinetics

## In vivo investigations



# Bioequivalence

## In vivo investigations




Parameters what are defined under the bioequivalence examinations:

1. $C_{max}$
2. $t_{max}$
3. MEC
4. AUC
5. $t_{therapeutic}$

# Biosimilarity

## In vivo investigations

The biosimilar products may be cheaper than the original preparation but not more than 20-30%.

# Biosimilarity

Bioequivalence of biological products is not be definable.

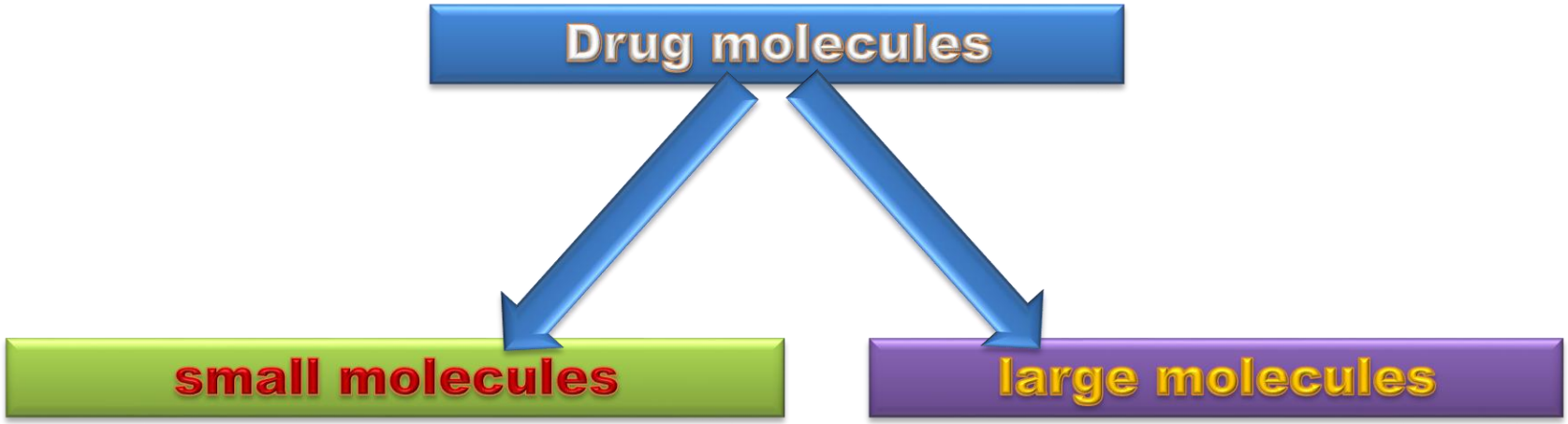
The similarity should be proven by toxicological and clinical data.

# Biosimilarity

The bioequivalence of biological products (biological medicinal product) are called ‘biosimilarity’, and

the generics of these medications are called ‘**similar biological medicinal product**’.

# Medicines




**MW ≤ 800 Daltons**

**MW > 800 Daltons**

**bioequivalence** → **biosimilarity**

**generic product** → ***similar biological medicinal product***

# Thank you for your attention!