Original drugs, generic drugs, biosimilars, drugs for modern therapy, orphans

Fundamental Terms

The Czech Act on Pharmaceuticals (AP) defines the following terms:

- Substance
- Medicinal Product

What is a substance?

Any matter irrespective of origin, which may be

- human (e.g. human blood or its constituents);
- animal (e.g. microorganisms, toxins, parts of organs, animal secretions, extracts);
- vegetable;
- chemical.

What is considered a substance?

- **Active substances** (form part of MPs; initiate the MP's effect; this effect is usually pharmacological, immunological or modifies the metabolism)

- **Excipients** (form a part of MPs; have no therapeutic effect in the quantities applied and are vital for the manufacture, preparation, storage or application of MPs)

What is a medicinal product?

- a substance or combination of substances presented as having therapeutic or preventive properties or as having influence over physiological functions, or administered to set the medical diagnosis.

The PA fails to define “pharmaceuticals” and “drugs”

…nevertheless, the terms

“pharmaceutical” and “active substance”
“drug” and “medicinal product”

can be considered equivalents.

Names of drugs/MPs

- systemic names, chemical names
- code names
- generic names
- national and international non-proprietary names (INN)
- Pharmacopoeia names
- Trade names, manufacturer names

Code Names

- working names of medicinal products during research
- often alphanumeric combinations
- used until an INN-compliant name is allocated

- Example: GSK-184072 (manufacturer: GSK), originally SRT-501 (manufacturer: Sirtris)
- Example: RU-486

Generic Names

- Internationally used name first used by the inventor or manufacturer to designate the substance, adjusted to local language standards
- Working designation of potential medicinal products

- Must not be confused with “generics”!

INN – National and International Non-Proprietary Names

- Easy, short and unique names recognised globally as public domain
- Established in 1950, in use since 1953
- Used only to designate accurately defined substances that can be clearly characterised with a chemical name or formula
- Not allocated to combinations, herbal drugs or homeopathic preparations
- INN names incorporate a system prefixes, infixes and suffices
- Example: simvastatin, metoprolol, trastuzumab, sunitinib

Trade/Manufacturer Names

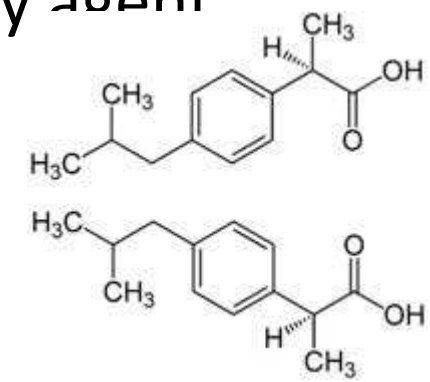
- Protected names used by the manufacturer

Code name	Generic name	INN name	Trade name
VUFB 10615	dosulepin	dosulepin	PROTHIADEN
GSK-184072	resveratrol	resveratrol	Stage III KH
T-20, DP 178	pentafusid	enfuvirtid	FUZEON
LY640315	Not known	prasugrel	EFFIENT

Ibuprofen…

- The history of this drug starts with Dr. Stewart Adams, the scientific research manager of Boots Pure Drug Company in the 1950s. It was patented in 1961 (BRUFEN)

- Analgesic, antipyretic, anti-inflammatory agent
- Generic name: ibuprofen
- INN: ibuprofen
- Systemic name: (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid
- Trade name: more than twenty…



Ibuprofen…

Generics vs. Original MPs

- **Original MPs** – originally conceived MPs

- **Generic MPs** – equivalents to original MPs that may enter the market:

  - once the patent protection of the original MPs expires
  - once the principle of fundamental similarity with the original MP is met
  - the price of generic MPs is usually lower than the price of original MPs

Generics vs. Original MPs

- Medicinal products that have equivalent qualitative and quantitative composition in terms of active substances and the same pharmaceutical form with the reference medicinal product, and that have been proved to be bioequivalent to the reference medicinal product by relevant bioavailability studies;

- Various salts, esters, ethers, isomers, isomer combinations, complexes or derivatives of active substances are deemed the same active substance, unless they have substantial different features in terms of safety or effect;

Types of Bioequivalence Studies

A/ Pharmacokinetic Studies

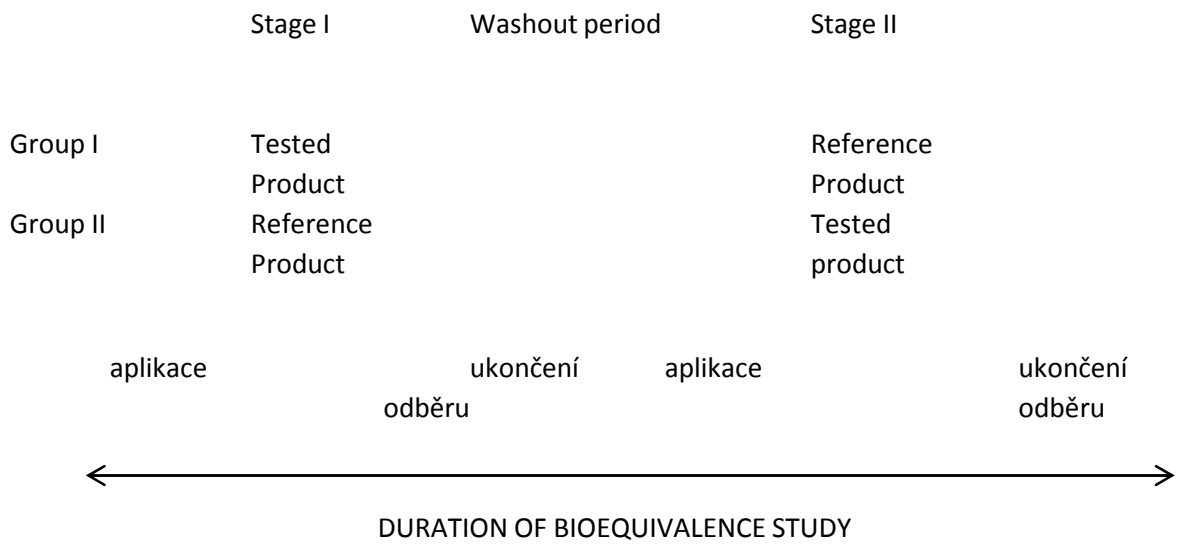
- Pharmacokinetic studies are carried out when the pharmaceutical creates measurable concentrations in various biological liquids (e.g. plasma).
- The approach is based on the fact that the pharmaceutical's concentration in the place of its effect cannot be generally measures and that there is a relation between the safety, effectiveness and concentration of a pharmaceutical or active metabolite in systemic circulation.

Types of Bioequivalence Studies

A/ Pharmacokinetic Studies

- Cross-sectional structure, healthy volunteers
- Basic parameter = pharmacokinetic parameters (AUC, C_{max} and t_{max}, $t_{1/2}$); generics must achieve 80-125% of the original MP's values so that both products may be declared bioequivalent.

Example of a cross-sectional study



Types of Bioequivalence Studies

A/ Pharmacokinetic Studies

- **WHO recommends n = 18 to 24 subjects**
- **Drugs are bioequivalent if their pharmacokinetic parameters are <u>essentially similar</u>**
- **…90% reliability interval for the given FK parameters to be found between 80 and 125% of the corresponding FK parameters of the compared product (original MP)**

- “Bioequivalence” does not necessarily mean “therapeutic equivalence”
- Antiepileptic drugs? Antibiotics?

Proving Bioequivalence

B/ Pharmacodynamic Studies

- when FK studies are not suitable (products where systemic absorption is not assumed)
- suitable for topical or inhalation pharmaceutical forms

Proving Bioequivalence

- **In vivo** bioequivalence studies are always required in the Czech Republic if the submitted application for a generic drug registration includes reference to the original product.
- In vitro **bioequivalence studies (dissolution tests)** can be used solely in the registration of multiple dosages of the same product or in certain changes after the approval of both the original and generic products, and in other cases.
- The position of the regulator (EMA, SUKL) is the decisive factor.

Biosimilars

- …”generic approach” is not fitting and justifiable by science in this case…

Definition of “biosimilars”

“copies” of biotechnological pharmaceuticals

- after the patent protection of the original biotechnological pharmaceutical expires
- Called Follow-on-Biologics, or FOBs for short, overseas.
- Another similar term, sometimes used e.g. in the terminology of oncology, is biological treatment (affecting angiogenesis, differentiation etc.)

In general terms, biological pharmaceuticals are pharmaceuticals based on the products of micro- or macro-organisms (toxins, treatment serums, blood products etc.)

“Biotechnological pharmaceuticals”

- manufacture is based on the use of recombinant DNA, produced via prokaryotic or eukaryotic cells in artificial cultures.
- Very complex structure and molecular weight by two and more orders higher than common synthetic pharmaceuticals.
- Effect and safety is based not only on the primary but also secondary, tertiary and possibly quarterly structure.
- This extreme complexity means that these substances, or rather their safety profile and effect, are very susceptible to change with even the slightest variation in the manufacturing process – they are DE FACTO ORIGINALS

“Biosimilars”

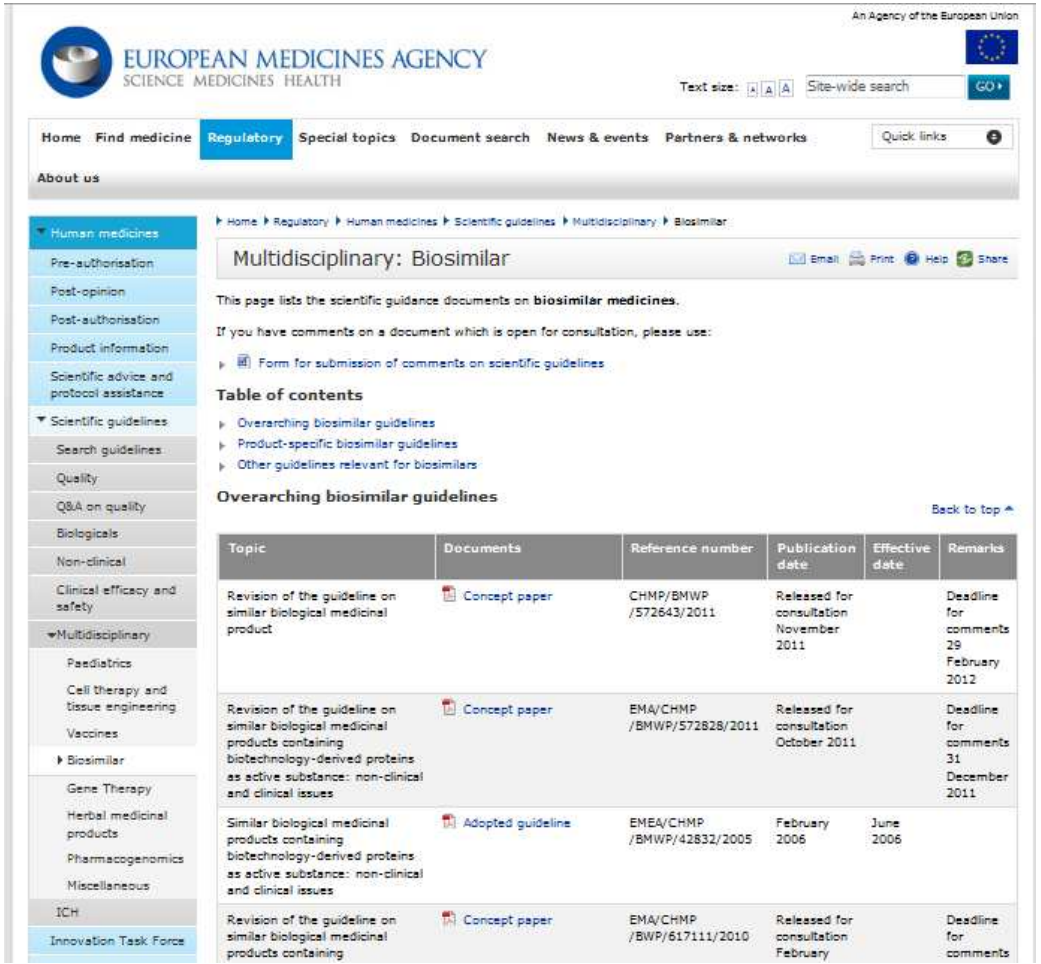
- protein nature
- immunogenicity
- sensitivity to chemical, physical and biological agents
- inability to freely exchange equivalent medicinal products with their content.

“Biologic Treatment” – Historical overview

- 1972: recombinant deoxyribonucleic acid (rDNA) acquired
- 1975: the first monoclonal antibody (MAb)
- First biotechnological pharmaceutical companies founded in the follow-up, incl. Genentech in the USA and Biotech in Europe.
- 1982: recombinant insulin becomes the very first biotechnological product (Genentech, marketed by Eli Lilly)
- 1986: products with significantly more complex structure enter the market: monoclonal OKT3 antibody (OrthoClode®) or recombinant interferon

European Regulation…

- EMEA/CHMP/437/2004 - Guideline on Similar Biological Medicinal Products - overarching guideline – Being revised
- EMEA/CHMP/BWP/49348/2005 - Quality Issues
- EMEA/CHMP/3097/2002 - Guidance on Comparability - Non-clinical and clinical issues
- EMEA/CHMP/89249/2004 - Clinical Investigation on the Pharmacokinetics of Therapeutic Proteins
- EMEA/CHMP/BMWP/42832/2005 - Non-clinical and Clinical Issues - Being revised
- EMEA/CHMP/BMWP/101695/2006 - Non/clinical and Clinical Issues After a Change in the Manufacturing Process
- EMEA/CHMP/BMWP/14327/2006 - Immunogenicity assessment



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- Human medicines
  - Pre-authorisation
  - Post-opinion
  - Post-authorisation
  - Product information
  - Scientific advice and protocol assistance
  - Scientific guidelines
    - Search guidelines
    - Quality
    - Q&A on quality
    - Biologicals
    - Non-clinical
    - Clinical efficacy and safety
    - Multidisciplinary
      - Paediatrics
      - Cell therapy and tissue engineering
      - Vaccines
      - Biosimilar
      - Gene Therapy
      - Herbal medicinal products
      - Pharmacogenomics
      - Miscellaneous
    - ICH
  - Innovation Task Force

Home › Regulatory › Human medicines › Scientific guidelines › Multidisciplinary › Biosimilar

Multidisciplinary: Biosimilar

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This page lists the scientific guidance documents on **biosimilar medicines**.

If you have comments on a document which is open for consultation, please use:

- Form for submission of comments on scientific guidelines

Table of contents

Overarching biosimilar guidelines

Back to top

Topic	Documents	Reference number	Publication date	Effective date	Remarks
Revision of the guideline on similar biological medicinal product	Concept paper	CHMP/BMWP /572643/2011	Released for consultation November 2011		Deadline for comments 29 February 2012
Revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues	Concept paper	EMA/CHMP /BMWP/572828/2011	Released for consultation October 2011		Deadline for comments 31 December 2011
Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues	Adopted guideline	EMEA/CHMP /BMWP/42832/2005	February 2006	June 2006	
Revision of the guideline on similar biological medicinal products containing	Concept paper	EMA/CHMP /BWP/617111/2010	Released for consultation February		Deadline for comments

Compassionate use
Pharmacovigilance
Advanced therapies
Inspections
Product defects and recalls
Parallel distribution
Pandemic influenza
Non-pharmaceutical products
New countries/EFTA
Fees
Veterinary medicines

Product-specific biosimilar guidelines

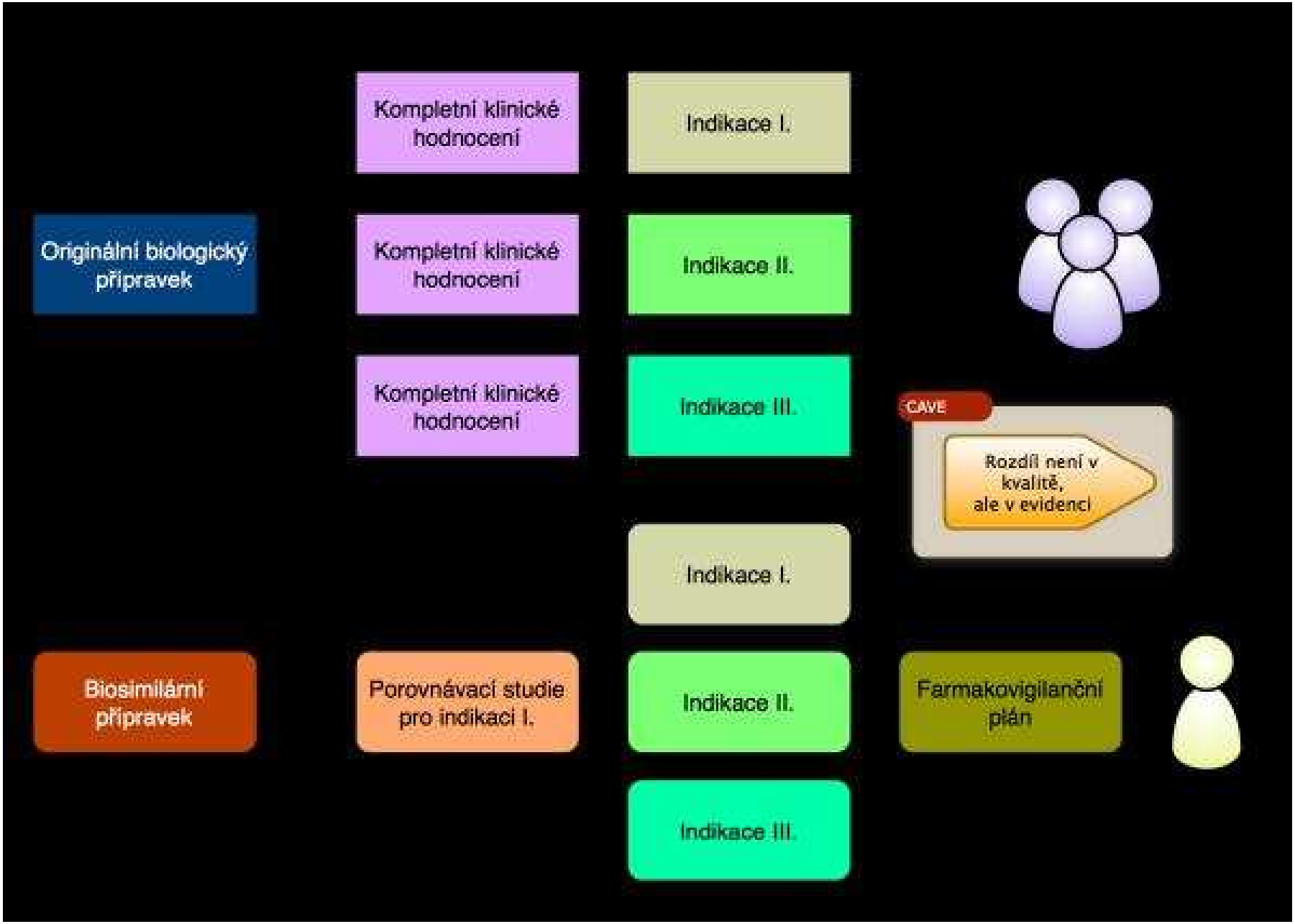
Back to top

Topic	Documents	Reference number	Publication date	Effective date	Remarks
Similar biological medicinal products containing interferon beta	Draft guideline	CHMP/BMWP /652000/2010	Released for consultation December 2011		Deadline for comments 31 May 2012
Similar biological medicinal products containing recombinant follicle stimulation hormone	Draft guideline Concept paper	CHMP/BMWP /671292/2010	Released for consultation November 2011		Deadline for comments 31 May 2012
Similar biological medicinal product containing recombinant interferon beta	Concept paper	EMA/CHMP /BMWP/86572/2010	Released for consultation Mar 2010		Deadline for comments 11 June 2010
Similar biological medicinal products containing monoclonal antibodies	Draft guideline Concept paper	EMA/CHMP /BMWP/403543/2010	Released for consultation November 2010		Deadline for comments 31 May 2011
Similar biological medicinal products containing recombinant erythropoietins	Overview of comments Adopted guideline Draft guideline Concept paper	EMEA/CHMP /BMWP/301636/08	April 2010	30 September 2010	
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Guidance on similar medicinal products containing recombinant erythropoietins	Submission of comments Adopted guideline	EMEA/CHMP /945626/2005	March 2006	July 2006	Superseded by EMEA/CHMP /BMWP/301636/08
Revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins	Concept paper	EMA/CHMP /BMWP/522386/2011	Released for consultation July 2011		Deadline for comments 30 September 2011
Similar biological medicinal products containing low-molecular-weight-heparins	Overview of comments Adopted guideline Draft guideline Concept paper	EMEA/CHMP /BMWP/118264/2007	April 2009	October 2009	
Non-clinical and clinical	Adopted guideline	EMEA/CHMP	June 2009	April 2009	

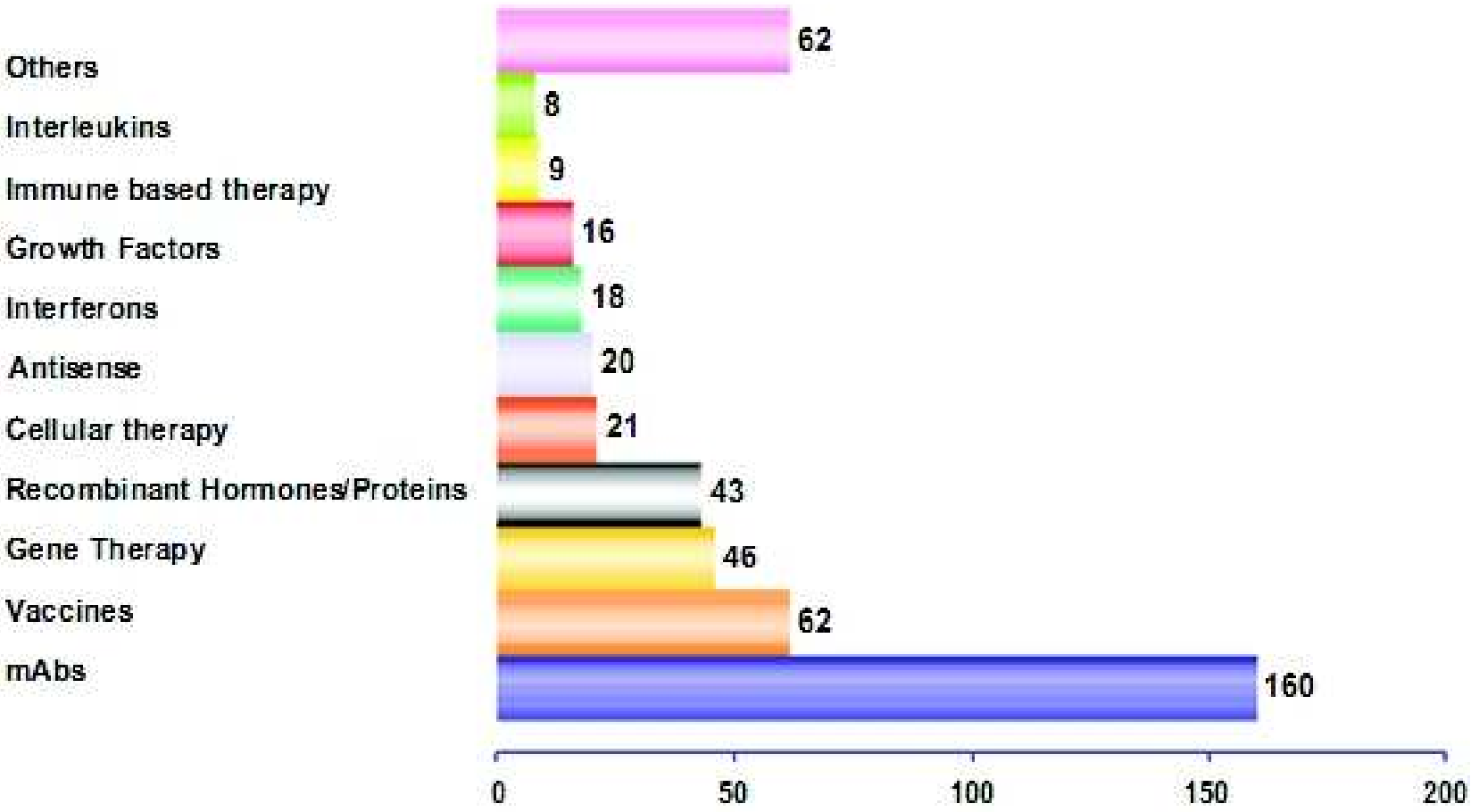
Definition and Regulation in the PA

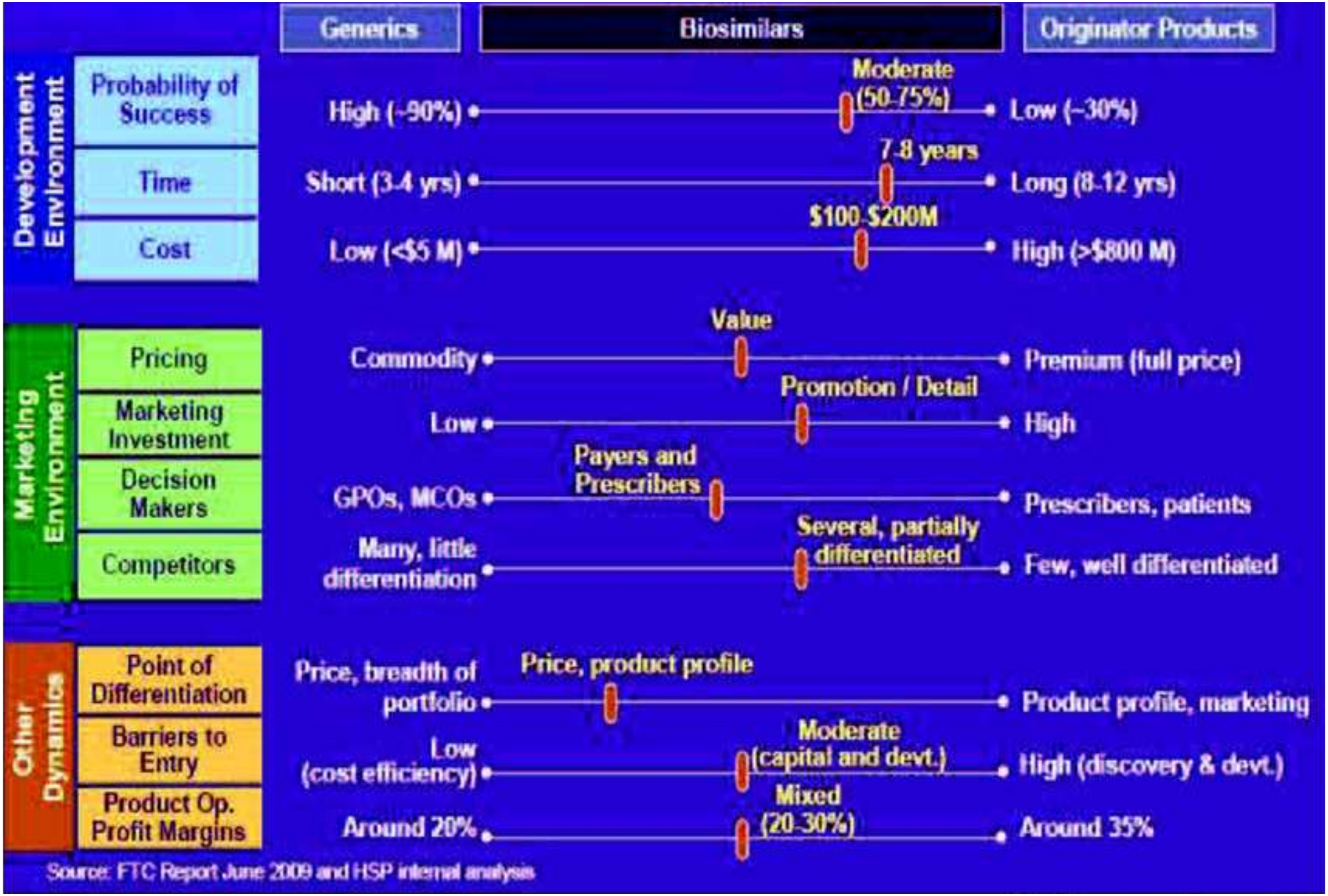
Biological medicinal product similar to the reference biological product.

- Safety and effect is assessed against a benchmark, i.e. the original product.
- Safety and affect can be assessed solely for a single indication and the results for others can be extrapolated if the effect in the given indications is based on the same mechanism
- Data on the product's immunogenicity must be submitted.
- A pharmacovigilance plan must be compiled and submitted for approval, with emphasis on:
  - expressions of immunigenicity;
  - rare adverse effects.


Originální biologický přípravek
Kompletní klinické hodnocení
Kompletní klinické hodnocení
Kompletní klinické hodnocení
Indikace I.
Indikace II.
Indikace III.
CAVE
Rozdíl není v kvalitě, ale v evidenci
Biosimilární přípravek
Porovnávací studie pro indikaci I.
Indikace I.
Indikace II.
Indikace III.
Farmakovigilanční plán

Biosimilars in development…




Generics
Biosimilars
Originator Products
Development Environment
Probability of Success
Time
Cost
Moderate (50-75%)
High (~90%)
Low (~30%)
7-8 years
Short (3-4 yrs)
Long (8-12 yrs)
$100-$200M
Low (<$5 M)
High (>$800 M)
Marketing Environment
Pricing
Marketing Investment
Decision Makers
Competitors
Value
Commodity
Premium (full price)
Promotion / Detail
Low
High
Payers and Prescribers
GPOs, MCOs
Prescribers, patients
Several, partially differentiated
Many, little differentiation
Few, well differentiated
Other Dynamics
Point of Differentiation
Barriers to Entry
Product Op. Profit Margins
Price, breadth of portfolio
Price, product profile
Product profile, marketing
Low (cost efficiency)
Moderate (capital and devt.)
High (discovery & devt.)
Around 20%
Mixed (20-30%)
Around 35%
Source: FTC Report June 2009 and HSP internal analysis

Biosimilars registered in the Czech Republic

- 12 products at the moment

- substances:
  - Epoetin alfa – EPREX original MP (generics ABSEAMED, BINOCRIT, EPOETIN ALFA HEXAL)
  - Epoetin zeta (RETACRIT, SILAPO)
  - Filgrastim – NEUPOGEN (BIOGRASTIM, FILGRASTIM HEXAL, RATIOGRASTIM, ZARZIO)
  - Somatotropin (GENOTROPIN, HUMATROPE, ZOMACTON)

But in the outlook…

- Patents for more than 30 original MPs to expire between 2012 and 2015
- This represents about USD 64 bn by 2015

Trade name	INN of active substance	Clinical use (examples)
Mabthera/Rituxan®	Rituximab	B-cell non-Hodgkin's lymphoma Rheumatoid arthritis
Avastin®	Bevacizumab	Colorectal cancer, lung cancer
Erbitux®	Cetuximab	Colorectal cancer, head and neck cancer
Vectibix®	Panitumumab	Colorectal cancer
Campath®	Alemtuzumab	B-cell chronic lymphocytic leukaemia (B-CLL)
Herceptin®	Trastuzumab	Breast cancer
Humira®	Adalimumab	Rheumatoid arthritis, Crohn's disease
Remicade®	Infliximab	Rheumatoid arthritis, Crohn's disease, psoriasis
Simulect®	Basiliximab	Transplant rejection
Zenapax®	Daclizumab	Transplant rejection
Xolair®	Omalizumab	Asthma
Tysabri®	Natalizumab	Multiple sclerosis
Lucentis®	Ranibizumab	Macular degeneration
Synagis®	Palivizumab	Respiratory syncytial virus infection

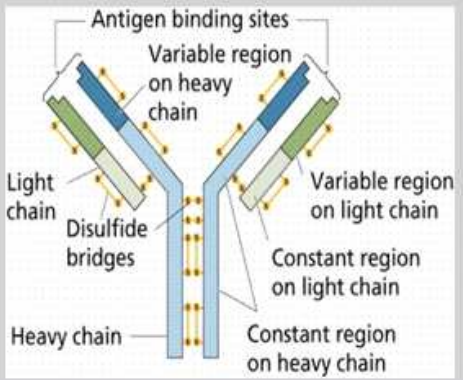
Monoclonal antibodies

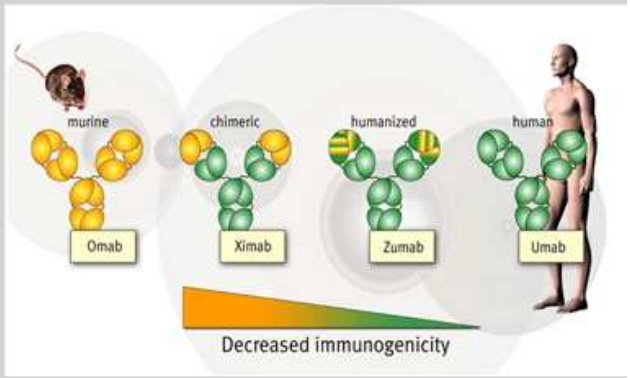
belimumab

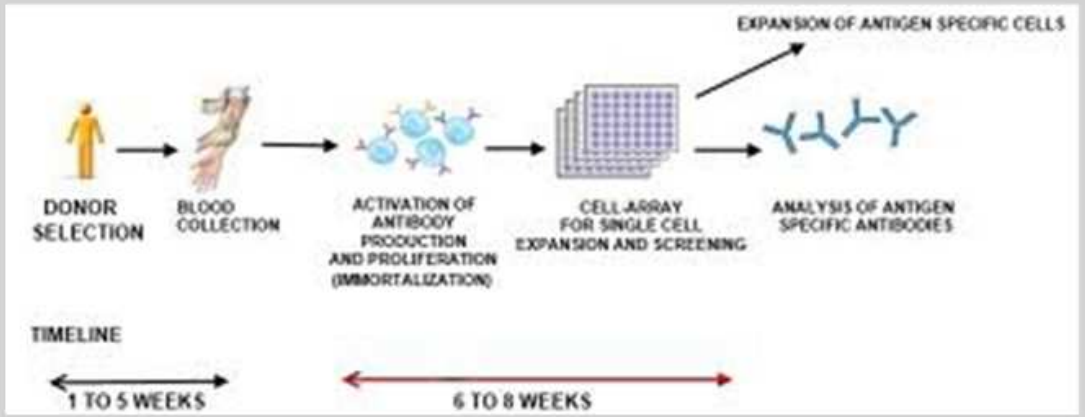
ipilimumab

brentuximab vedontin

denosumab



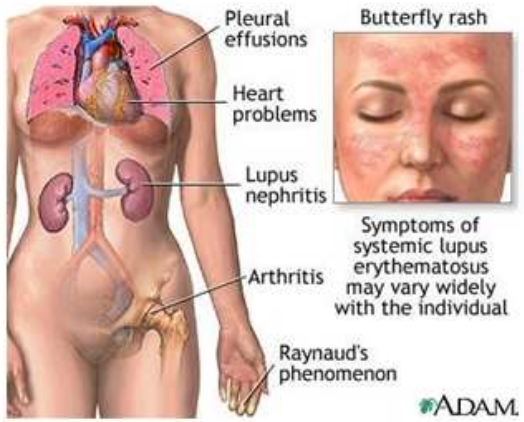


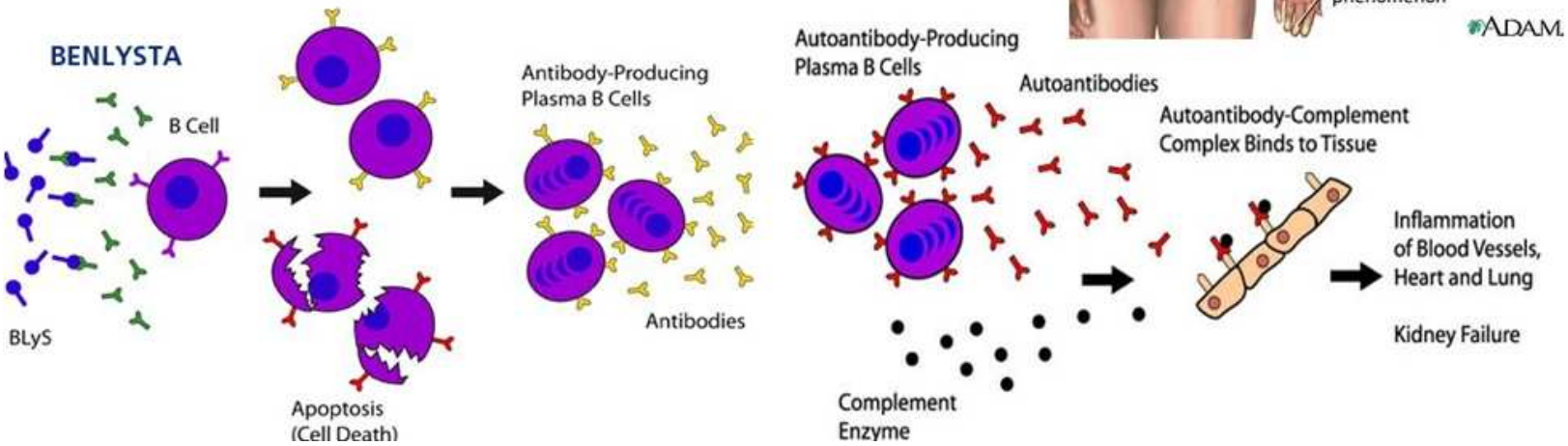


Belimumab

The first inhibitor targeted at a protein stimulating B-lymphocytes (BLyS), which reduces the number of abnormal B lymphocytes causing the

Systemic Lupus Erythmatosis (SLE)



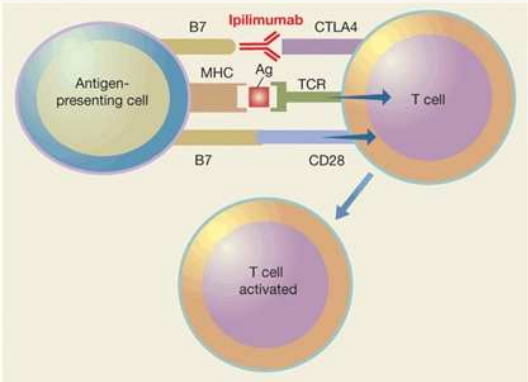


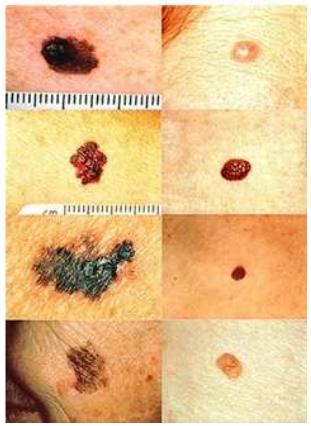
Ipilimumab

Inhibitor of CTLA-4 T lymphocytes receptor

By blocking this receptor, the T lymphocyte remains active against cancerous cells as melanoma

Stage III clinical trial for treatment of non-small cell lung carcinoma (NSCLC), small cell lung cancer (SCLC), and stage II trial for treatment of the metastatic hormone-refractory prostate cancer.

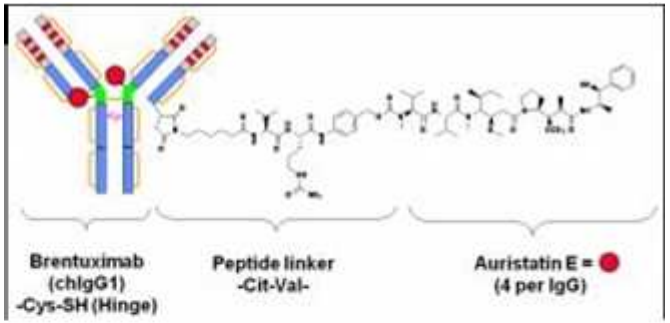


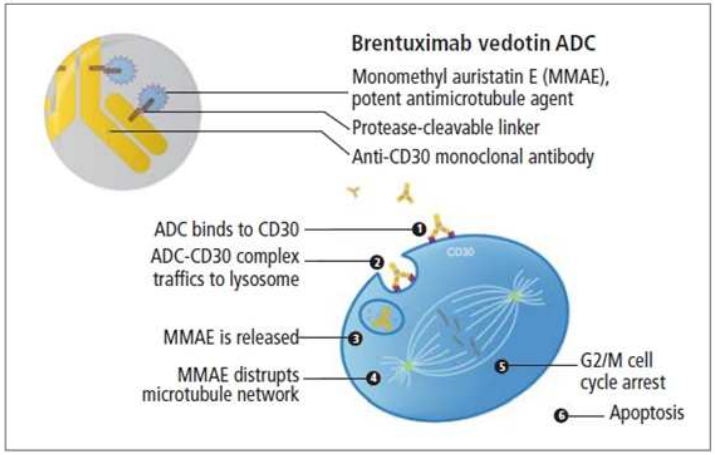


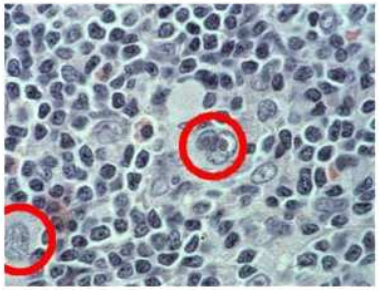
Brentuximab vedontin

An antibody-drug conjugate (ADC) targeted at CD-30

Used to treat the Hodgkin lymphoma after the autologous stem cell transplant (ASCT) fails or after the failure of two prior multi-agent chemotherapy in patients who are not suitable candidates for the ASCT



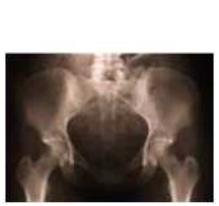


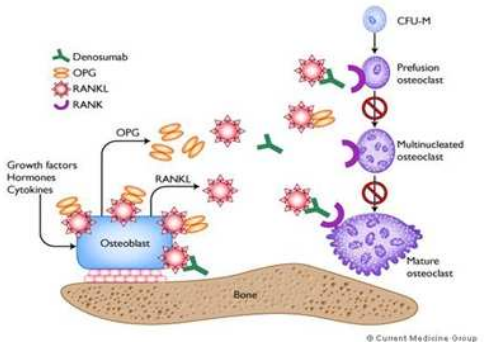


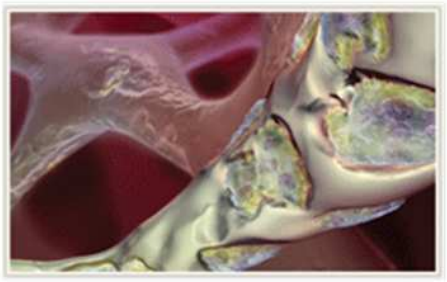
Denosumab

Receptor activator of nuclear factor kappa-B ligand (RANK ligand, RANKL), which is the key mediator of the function, formation and survival of osteoclasts

Prevention of bone loss in patients with bone metastases from solid tumours.





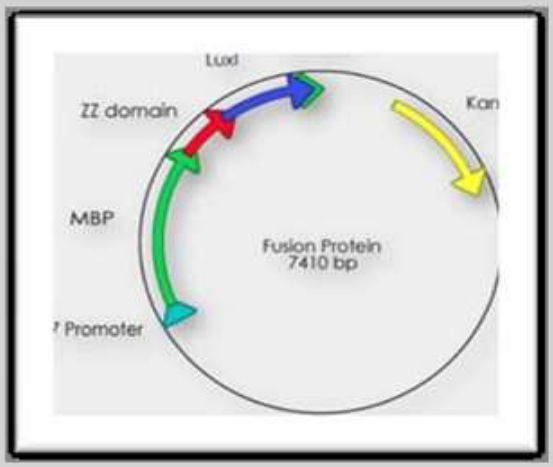


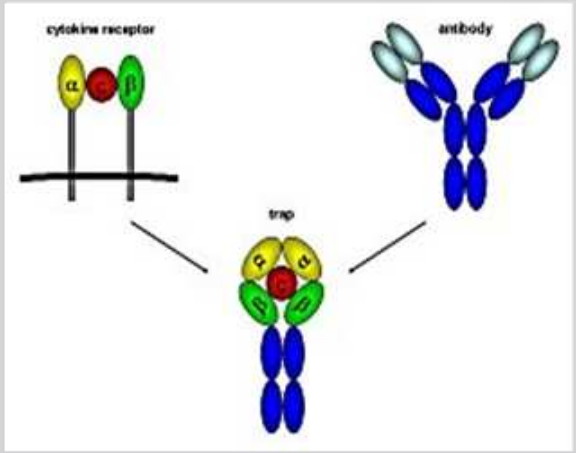
Fusion Proteins

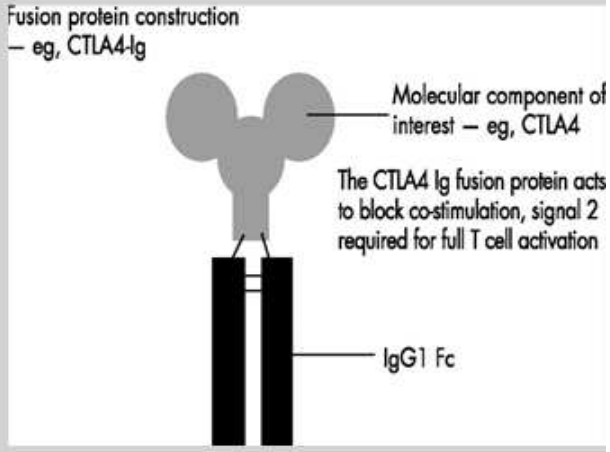
Aflibercept

Belatacept

Contain molecules of cytokine receptors or adhesive molecules and a part of the Fc fragment of immunoglobulins that increases molecular stability



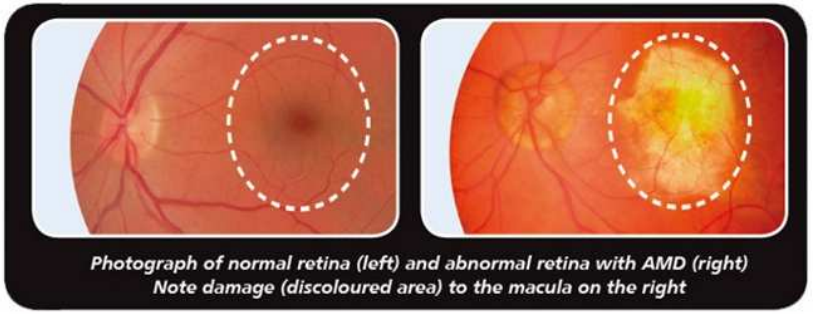




Aflibercept

- Recombinant fusion protein

- Dimetric glycoprotein contains a vascular endothelial growth factor VEGFR-1 receptor.
-
- Neovascular (wet) ag degeneration (AMD).



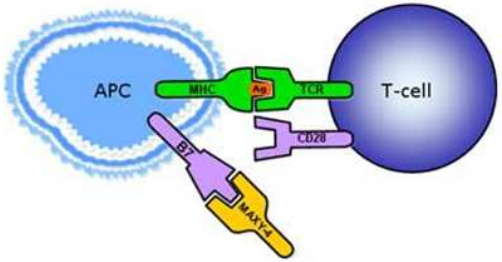
Photograph of normal retina (left) and abnormal retina with AMD (right)
Note damage (discoloured area) to the macula on the right

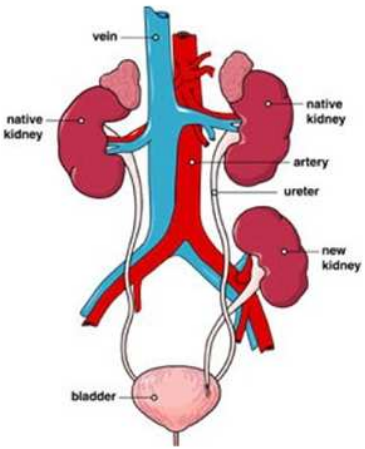
Belatacept

- Fusion protein composed of the Fc fragment of a human IgG1 immunoglobin linked to the extracellular domain of CTLA-4

- Selective blocks co-stimulation of T-lymphocytes indicated for prophylaxis of organ rejection in adults after liver transplants

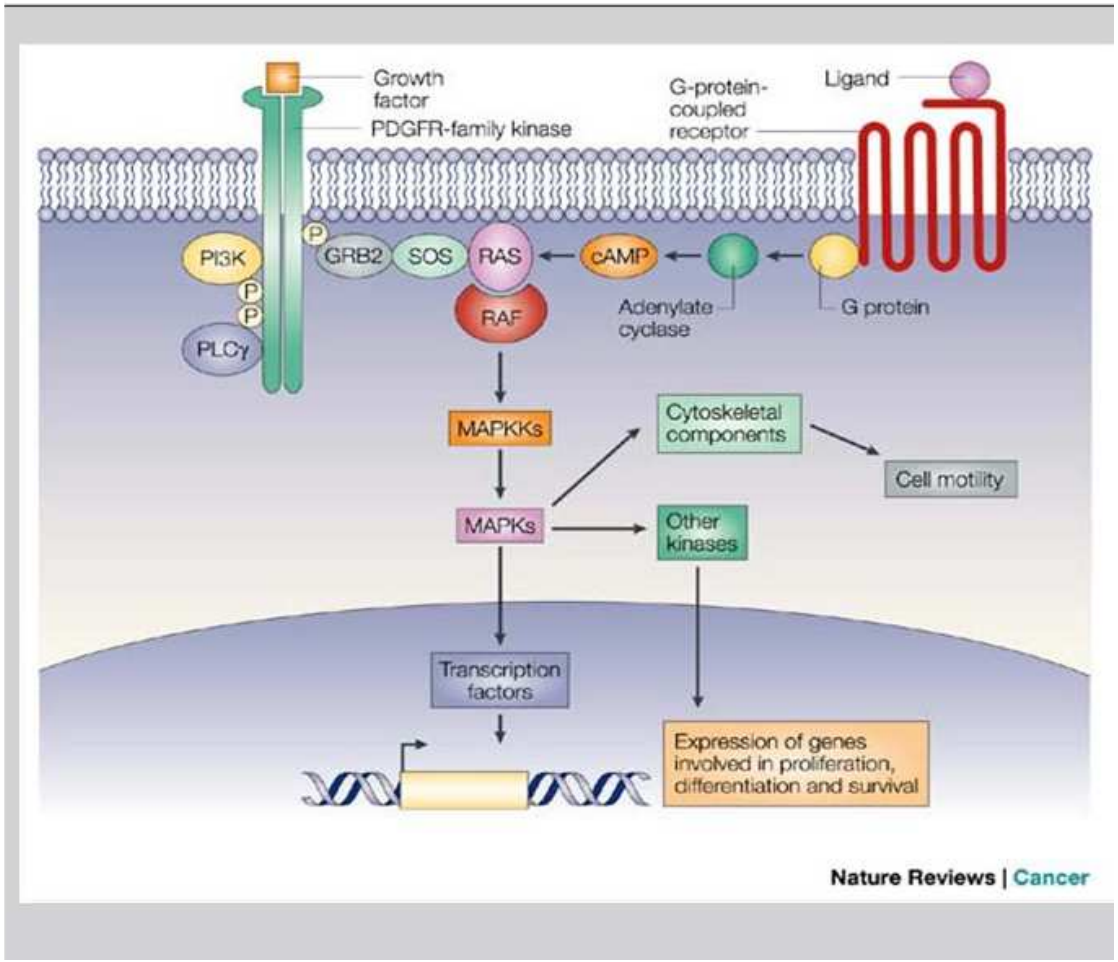
- Approved in combination with immunosuppresive agents basiliximab, mycophenolate mofetil, corticosteroids





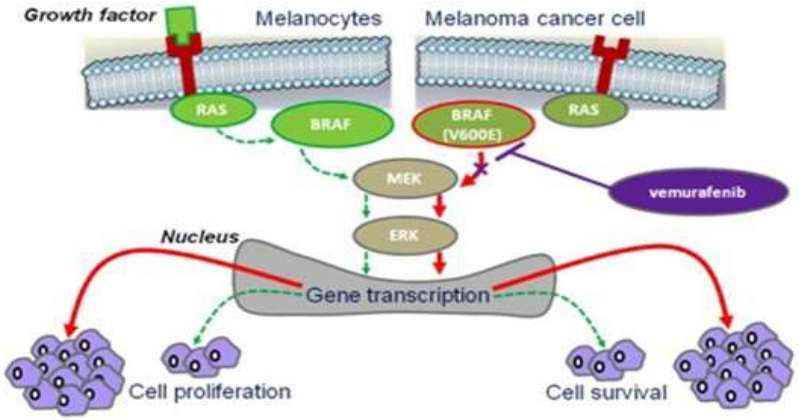
Kinase Inhibitors

Vemurafenib



Vemurafenib

- Competitive small molecule of serine-threonine (B-RAF) kinase
- Selective ATP inhibitor of the B-RAF kinase pathway
- BRAF gene mutations in half of melanoma, known as V600E



Advanced-Therapy Medicinal Products

Advanced-therapy medicinal products (ATMPs)

Medicinal products of biological/biotechnological origin that include

- MPs for **gene therapy**, as defined in Section IV of Annex I to Directive 2001/83/EC
- MPs for **somatic cell therapy**, as defined in Section IV of Annex I to Directive 2001/83/EC
- MPs for **tissue engineering**, as defined under letter (b) of Regulation EC 1394/2007

Committee for Advanced Therapies

- CAT (Committee for Advanced Therapies), established by the EMA
- Prepares draft statement on the quality, safety and effect of each advanced-therapy medicinal product for final approval by the CHMP (Committee for Human Medicinal Products)
- Established under EC Regulation 1394/2007

National Legislation

- Section 2(a) and (q) of Act No. 378/2007 Coll. ("Act on Pharmaceuticals") that define medicinal products for gene therapy and medicinal products for somatic cell therapy
- Decree No. 228/2008 Coll., on MP Registration (Annex 1, Section IV directly provides for ATMPs)

National Legislation

Legislation that further provides for donations, acquisition, examination and release of tissues and cells for use in the manufacture of MPs:

- Act No. 296/2008 Coll. (“Act on Human Tissues and Cells”)
- Decree No. 422/2008 Coll., on Detailed Requirements to Ensure Quality and Safety of Human Tissues and Cells for Human Use

European Legislation

- Directive 2001/83/EX on the community code relating to medicinal products for human use
- Regulation No. 1394/2007 on advanced therapy medicinal products (effective from 30 December 2008)
- Directive of the Commission No. 2009/120/EC amending Directive 2001/83/EC on the community code relating to medicinal products for human use as regards advanced therapy medicinal products

Gene Therapy

- Includes any procedure aimed to treat a disease through genetic modification of the patient's cells.

- Genes, parts of genes, or oligonucleotides are transferred into cells.

Gene Therapy

- *The objective* is to transfer genes or parts of genes to suitable target cells to achieve the optimum expression of the transferred genes with the aim to:

- 1. ensure production of a missing substance

- 2. activate immunity system cells so that the organism may initiate its own immunity response

Gene Therapies

- If the excision of a “bad” allele and its replacement with a “correct” one was successful, the doors for “genetic surgery” would open
- Gene therapy: effective treatment would change the very genetic essence of the disease, not only its symptoms

- Fears of “genetic doping” already present at the Turin Winter Olympics
- Questions of “plastic genetics”

Genetic Transfer

- In vivo
  - ✓ Transfer directly into the patient's tissue using lyposomes or viral vectors (adenoviruses or retroviruses)

- Ex vivo
  - ✓ Transfer of cloned genes into cells in a culture (transplantation of autologous genetically modified cells)

In vivo and Ex vivo gene therapy

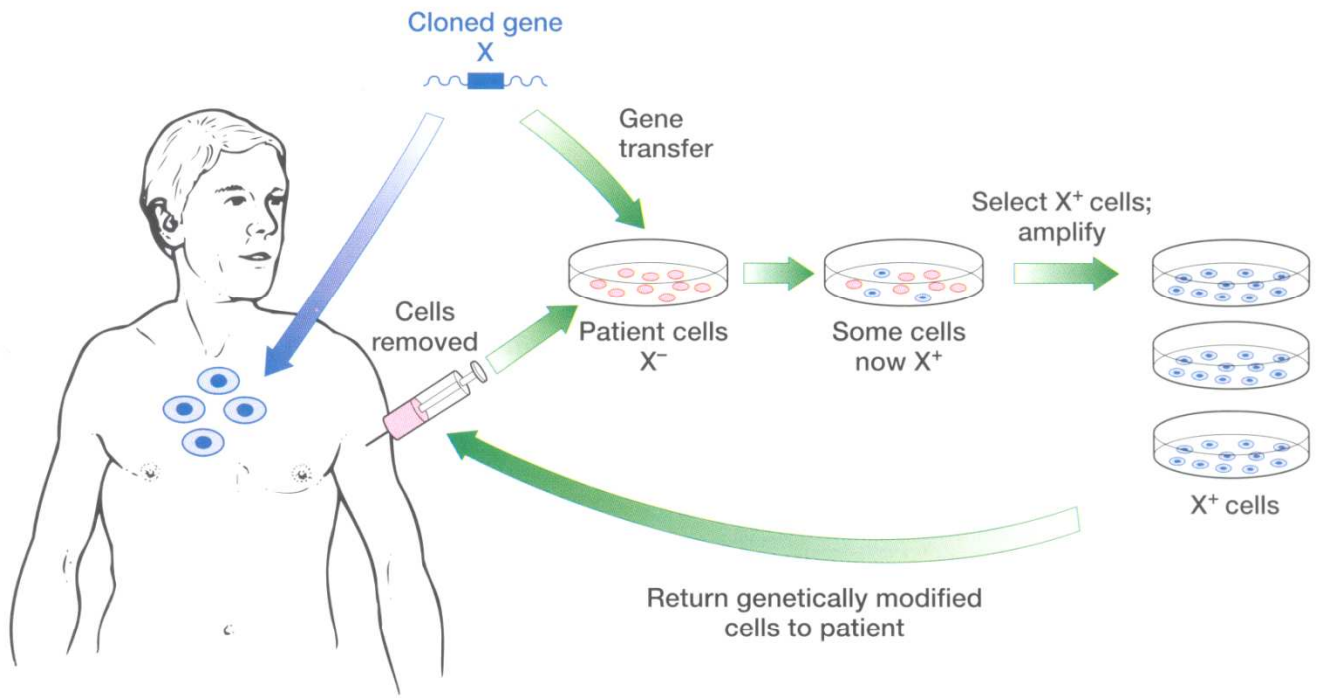


Figure 21.6: *In vivo* and *ex vivo* gene therapy.

Where possible, cells are removed from the patient, modified in the laboratory and returned to the patient (*ex vivo* gene therapy; green arrows). This allows just the appropriate cells to be treated, and the cells can be checked before they are replaced to make sure that the desired change has been achieved. For many tissues this is not possible and the cells must be modified within the patient's body (*in vivo* gene therapy; blue arrow).

Gene Therapies

- Somatic-cell gene therapy (= changes of genetic information in somatic cells only)
- Germ-line gene therapy (also in stem cell lines)

Gene Therapy

- of somatic cells
  - applicable to single patients
- of stem cells
  - applicable to multiple patients

- Germ-line therapy will always be unethical on principle, since informed consent will always be missing.
- The subsequent generations will be formed by unwanted results of our experiments.
- We will never be able to foresee all the consequences of our experiments in the next generations.

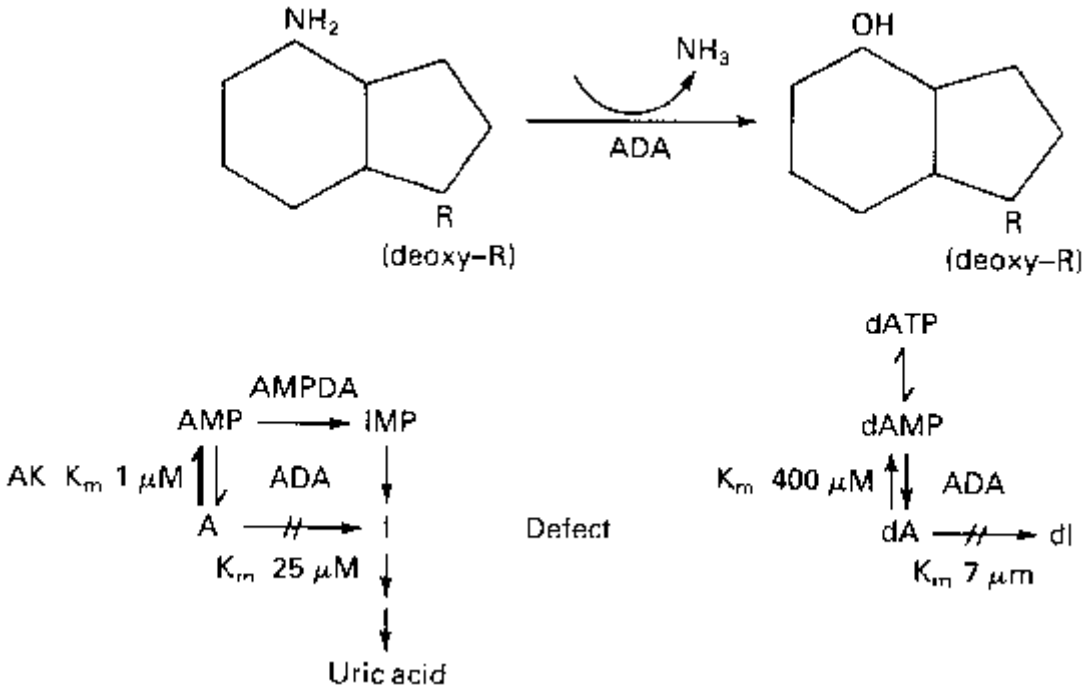
Non-Therapeutic Genetic Modifications - Ethical Problems

- Can the same approach be applied to the genetic modification of human features that are not directly related to disease?

- Certain human features have a genetic component
  - height
  - colour of skin
  - intelligence

Gene Therapy

First successful gene therapy performed on 24 September 1990 in NIH, Maryland, USA



ADA (adenosindeaminosis) deficiency

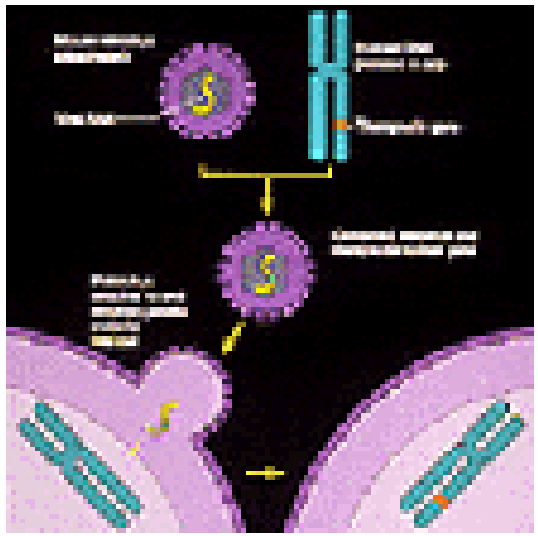
A four-year old girl suffers from ADA deficiency

Congenital primary combined immunodeficiency caused by ADA deficiency due to a point gene mutation for this enzyme (20q13-ter).

Accumulation of adenosine and deoxyadenosine in tissues has a direct and indirect toxic effect on T and B cells.

ADA

- **In the treatment, the girl's own immunity system cells (primarily T-lymphocytes), modified by having a normal ADA gene copy inserted <u>ex vivo</u>, were injected in her**



- Several weeks into the gene therapy, the immunity system's performance improved, and after several months, the patient began to live a "relatively normal life"

- The 1990 case received a lot of publicity
- The therapy was repeated with other patients (10 to 12 treatments per patient)
- The gene therapy witnessed its first clear and undisputed success by treating a related disease, namely X-linked SCID

First Clear Success of the Gene Therapy: X-SCID

X-SCID (X-linked severe combined immunodeficiency) – tied to the X-chromosome, AR

Patients are boys who lack T-cells and NK, number of B-cells is standard but unable to produce Ab

- Mutation on the gene for IL-2 (in 2/3 of patients)

First Clear Success of the Gene Therapy: X-SCID

- the treatment was again ex vivo treatment
- a retrovirus containing the IL2R gene that codes the yc cytokine receptor was used
- marrow bone stem cells exprimating CD34 (=only done by haematopoietic marrow bone cells) were incubated for three days in the presence of a retroviral vector
  - in that time, the cells divided five to eight times
- these cells were later returned to the patients
- 9 of 11 patients experienced dramatic improvements with the ability to lead normal lives

First Clear Success of the Gene Therapy: X-SCID

- however, two of the treated boys later suffered from leukaemia, almost certainly due to the activation of the LMO2 oncogene
- this oncogene was activated by the insertion of the retrovirus in its vicinity
- this fact has lead to the suspension of retroviral lymphocytes transduction studies in some countries
- http://blisty.cz/art/11770.html

Jesse Gelsinger

- born 18/06/1981
- first symptoms at 2 years and eight months of age
  - erratic behaviour; the condition deteriorates dramatically and the patient enters coma after a protein-rich diet
- diagnosed with OTC (ornithine transcarbamylase deficiency syndrome), a rare metabolic disease – 50% of children with this disease die within 1 month of birth
  - however, JG's disease is mild and treatable by medication and correct diet
  - if the nutrition contains more proteins, more ammoniac is found in the blood

OTC Syndrome

- the patient does not create the OTC protein whose task is to remove excessive nitrogen within the urea cycle
- the nitrogen from proteins accumulates in the blood and brain as urea
- this may lead to permanent brain damage
- treatment: low-protein diet and, for instance, phenylbiturate (conjugation with AMK and exclusion of nitrogen in other form than urea)
- half of the patients die before reaching five years of age

Jesse Gelsigner

- waits for his 18th birthday to give an informed consent to treatment
- receives genetic therapy on 13 September 1999; gets sick in the evening, enters a coma the next afternoon
- dies on 17 September
  - Within hours after doctors shot the normal OTC gene attached to a therapeutic virus into his liver, Jesse developed a high fever. His immune system began raging out of control, his blood began clotting, ammonia levels climbed, his liver haemorrhaged and a flood of white blood cells shut down his lungs.
- the therapy is the evident and clear cause of the death
- the case causes horror in the scientific community and makes the media headlines
- the case has lead to many questions concerning the quality of informed consent
  - much of the important information was subject to various business secrets. Paul Gelsinger (the father) now blames the hospital of concealing important information and of intentionally putting his son's life in jeopardy

The entire memoir of JG, written by his father, is available at http://www.jesse-gelsinger.com

Possible candidates for gene therapy

- diseases caused by defects in a single gene: ADA deficiency, cystic fibrosis, haemophilia, familial hypercholesterolemy, alpha-1 antitrypsin deficiency

- diseases caused by defective interaction of several genes: diabetes, hypertension

A. Gene Therapy Medicinal Products

- contain or consists of **recombinant nucleus acid** used in humans or administered to humans to regulate, repair, exchange, add or remove genetic sequences ;

- their therapeutic, prophylactic or diagnostic **effect applies directly to the sequence of the contained recombinant nucleus acid, or to the product of the sequence's genetic expression**.

A1. Medicinal Products Containing GMOs

- GMO – Genetically modified organism
- Organisms (not human) capable of reproduction whose hereditary material was changed by genetic modification carried out by a technical procedure set out by the law.
- Gene therapy ATMPs may contains GMOs (e.g. viral vectors)

GMOs – Legislation

- Regulated by the Ministry of Environment in the Czech Republic
- GMOs and genetic products may be handled solely under a license issued under the applicable legislation
- All the decisions of the Ministry issued under Act No. 78/2004 Coll., on Handling Genetically Modified Organisms and Genetic Products, are published in the Approved GMOs Registry and the GMO Users Registry

B. Medicinal Products for Somatic Cell Therapy

- contain or consist of cells or tissues that were subjected to **substantial manipulation <u>or</u>** cells or tissues that **are not designed** for use **for the same fundamental function** in the recipient and donor;

- are used for **treatment, prevention or diagnostics** of diseases based on the pharmacologic, immunologic or metabolic effect of their cells or tissues, or are used in or administered to humans for this purpose

Non-substantial Manipulations

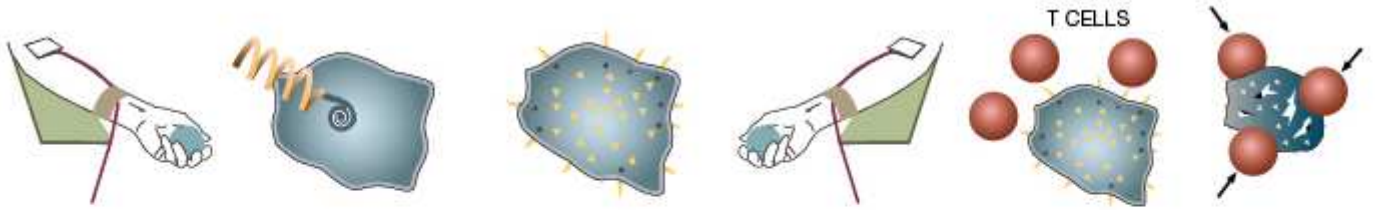
- listed in Annex I to Regulation (EC) No. 1394/2007
- cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilisation, irradiation, cell separation, concentration or purification, filtering, lyophilisation, freezing, cryopreservation, vitrification.

Somatic Cell Therapy Medicinal Products

Example:

- **Provenge** – prepared by in vitro cultivation of Dendritic cells and with prostatic acid phosphatase to treat prostate cancer resisted to hormonal therapy. Registered in the USA.
- Substantial manipulation (cultivation) + immunologic mechanism-based effect

Provenge



1. White blood cells are drawn from the patient. Certain immune system cells are isolated.

2. The immune system cells are exposed to a protein often found in prostate cancer cells.

3. These immune system cells display part of the protein on their surface, alerting the immune system.

4. Days after the white cells are drawn, these immune system cells are put back in the patient.

5. The body's T cells are stimu-lated...

6. ...multiply-ing in the body and attacking cancer cells bearing the protein.

Source: Dendreon Corporation

The New York Times

C. Tissue Engineered Medicinal Products

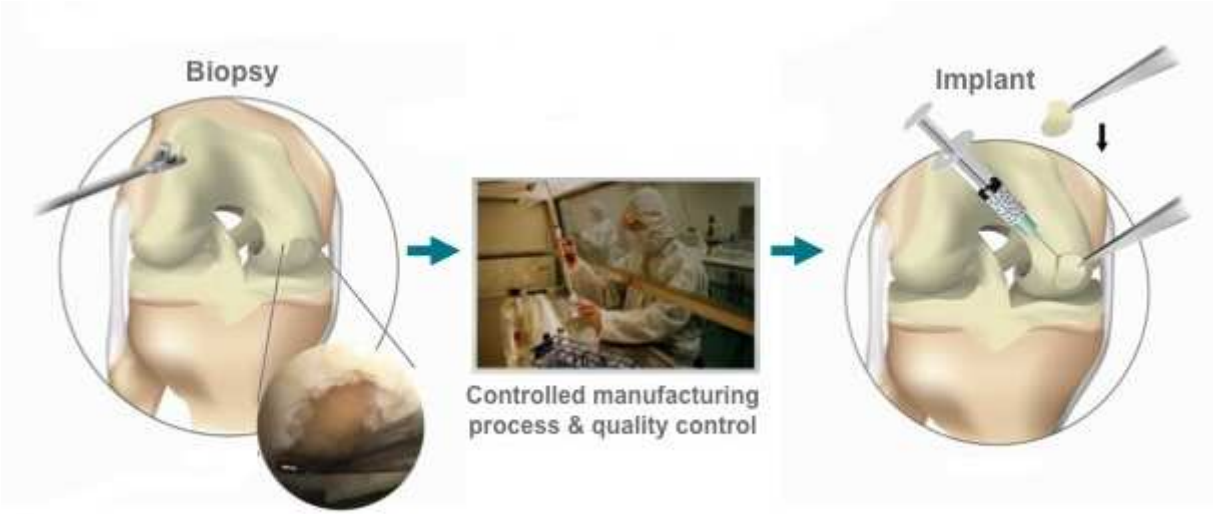
- serve to recover, repair or replace human tissue, or is used in or administered to humans for this purpose
- cells or tissues were subjected to **substantial manipulation <u>or</u>** cells or tissues that **are not designed** for use **for the same fundamental function(s)** in the recipient equivalent to the fundamental function(s) in the donor

Tissue Engineered Medicinal Products

Example:

- **Chondreocelect** – viable autologous cartilage cells that are expanded ex vivo, exprimate specific protein markers to treat cartilage lesions. Registered in the EU.
- Substantial manipulation (cultivation) + designed for tissue reparation

Chondrocelect



Source: http://www.tigenix.com

“Orphan Drugs”

Rare Disease

- Rare disease: **prevalence of < 5:10000** [Orphan Drug Regulation 141/2000] = 27 – 36 million in the EU
- 5,000 to 8,000 diagnoses with this definition are estimated
- Corresponds to about 5% of population (Germany: 4 million; Czech Republic: 0,5 million)
- Predominantly chronic, progressive, degenerative, life-threatening diseases or diseases deteriorating the quality of life
- 50% is found in children, and 80% is of genetic origin

Rare Disease Medicinal Products (Orphans)

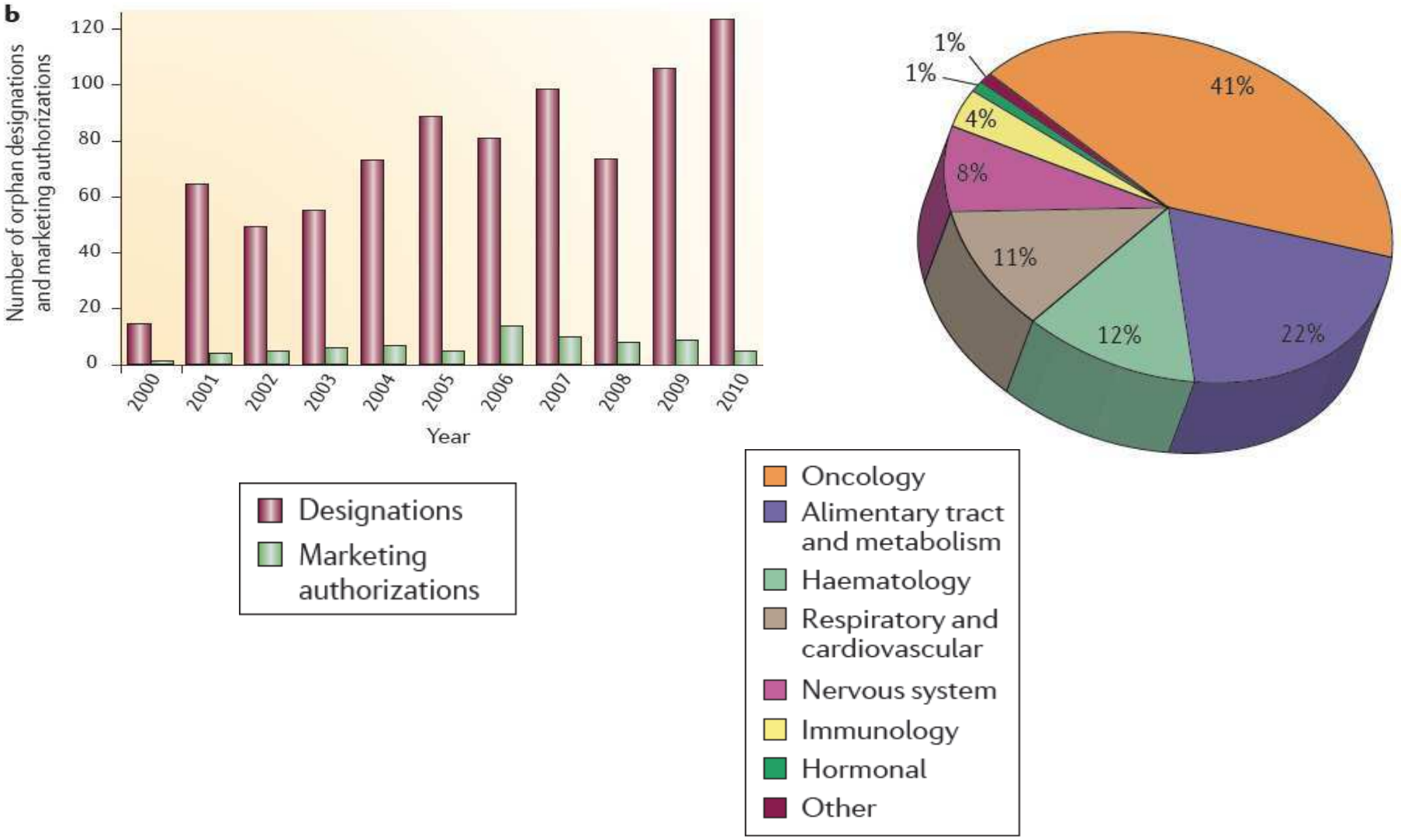
- 2000: EC Regulation No. 847/2000
- Diseases with prevalence ≤ 5/10,000; diagnosis/prevention/treatment of life-threatening or chronically incapacitating diseases
- Incentives for research and manufacturers

COMP (Committee for Orphan Medicinal Products) of EMA

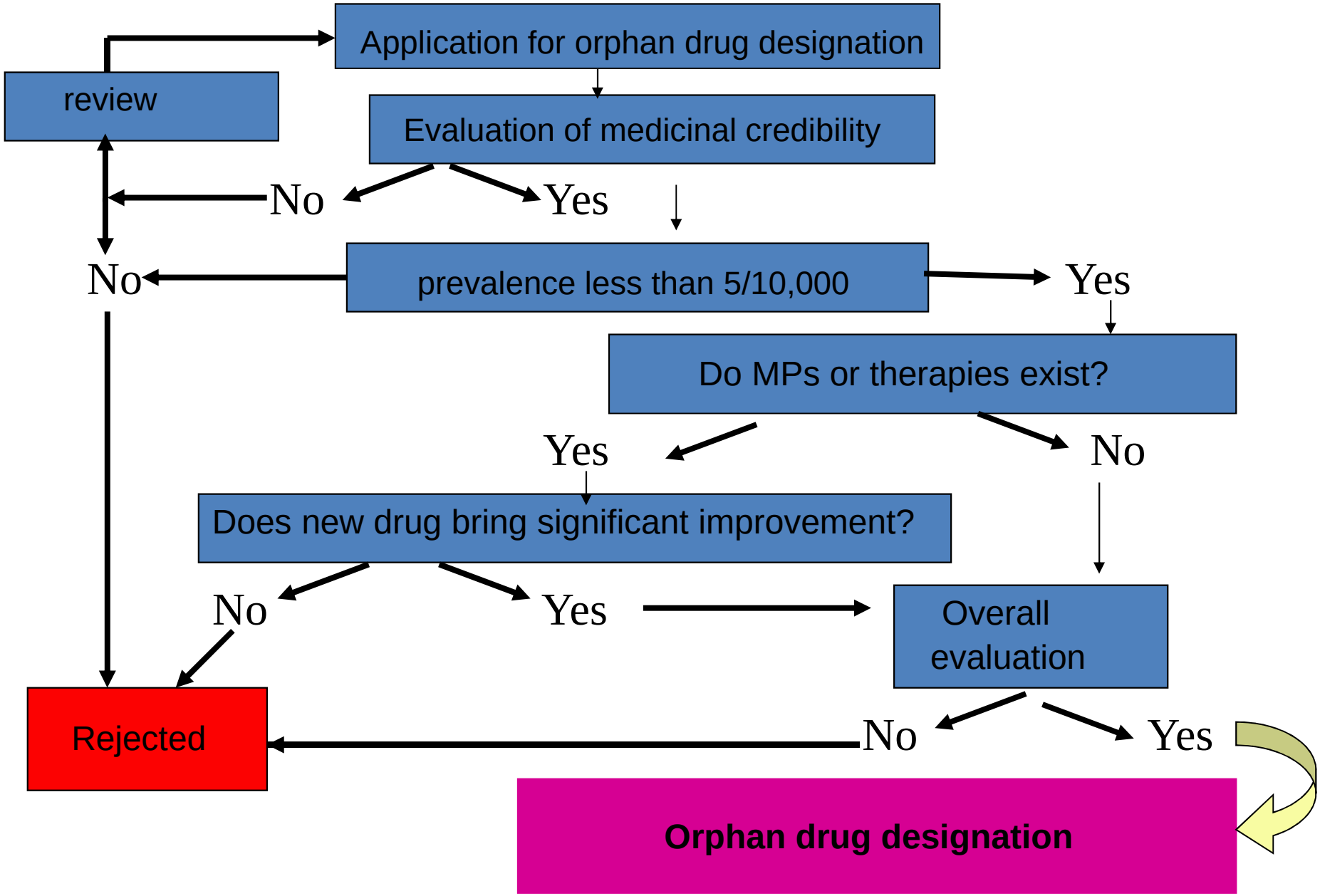
Incentives for Research, Development and Marketing

- Assistance in the administrative registration process
  - significant for small and medium enterprises
- Access to centralised procedure
  - registration in the entire EU
- Waiver of or discount from the registration fees
- Exclusive right on the market
  - 10 years
- Access to other EU incentives
  - framework programs of support to public health research

COMP regulation – EU

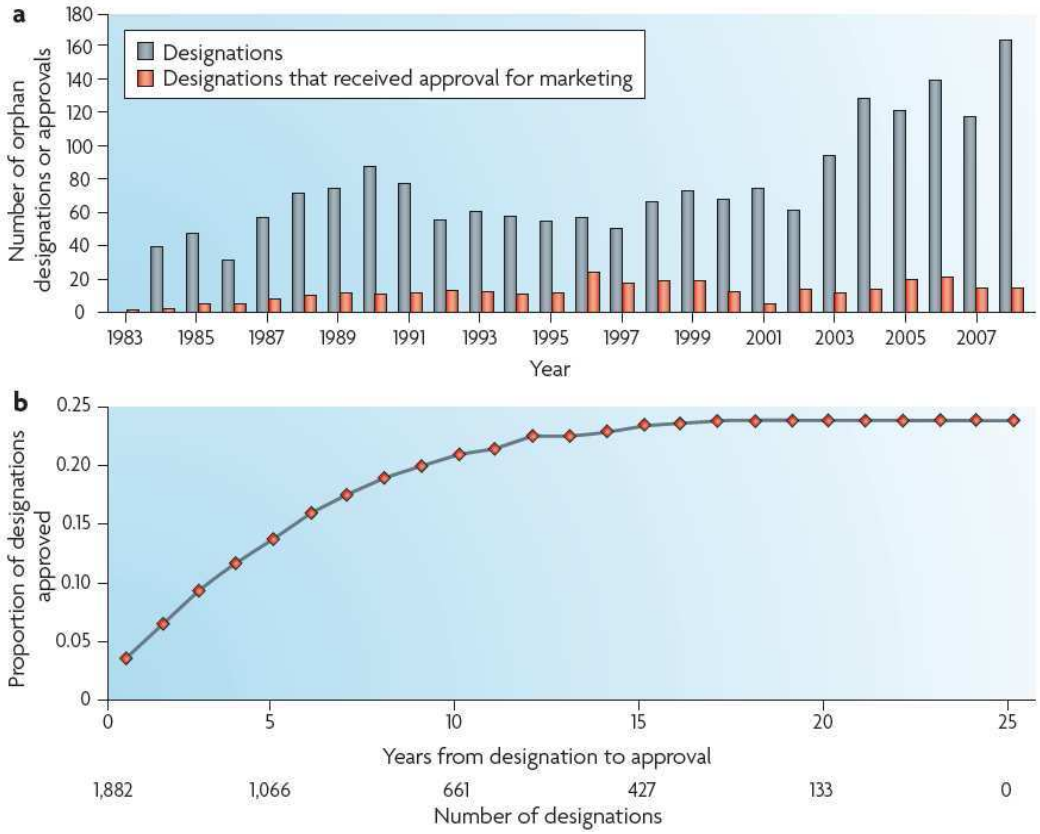


Designation of “Orphan Drugs” in the EU



US Orphan Drug Act – 1983 (FDA)

- 1983-2008:
- - 1,892 designations
- - 326 registrations
- - 200 diagnoses
- - predominantly oncology



Orphans Regulation in the Czech Republic – Reimbursement of Highly Innovative MPs (VILP)

- Section 39d: temporary reimbursement from health insurance
- 1. product has no alternatives;
- 2. product may be used to treat diseases that so far could not be treated by existing therapy with sufficient success, and the existing data indicate clinically significant improvement of effect;
- 3. the products signal an entirely new concept of treatment compared to the existing therapy when the existing therapy is not sufficiently suitable for a significant group of patients, and there clinically significant improvement of effect and safety is reasonably assumed.

- **The S symbol (expensive treatment in centres)**

Register of designated Orphan Medicinal Products (alphabetical)

- http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm