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

Doc. MUDr. Regina Demlová, PhD.

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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.

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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)

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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.

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

…nevertheless, the terms

“pharmaceutical” and “active substance”

“drug” and “medicinal product”

can be considered equivalents.

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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

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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

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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”!

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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

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Trade/Manufacturer Names

- Protected names used by the manufacturer

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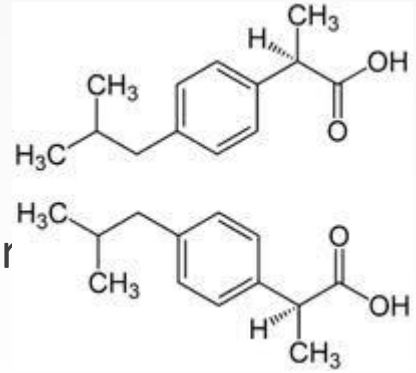
Code name	Generic name	INN name	Trade name
VUFB 10615	dosulepin	dosulepin	PROTHIADEN
GSK-184072	resveratrol	resveratrol	Stage III KH
T-20, DP 178	pentafusid	enfuvirtid	FUZEON
LY640315	Not known	prasugrel	EFFIENT

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)pr
- Trade name: more than twenty…



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Ibuprofen…

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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

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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

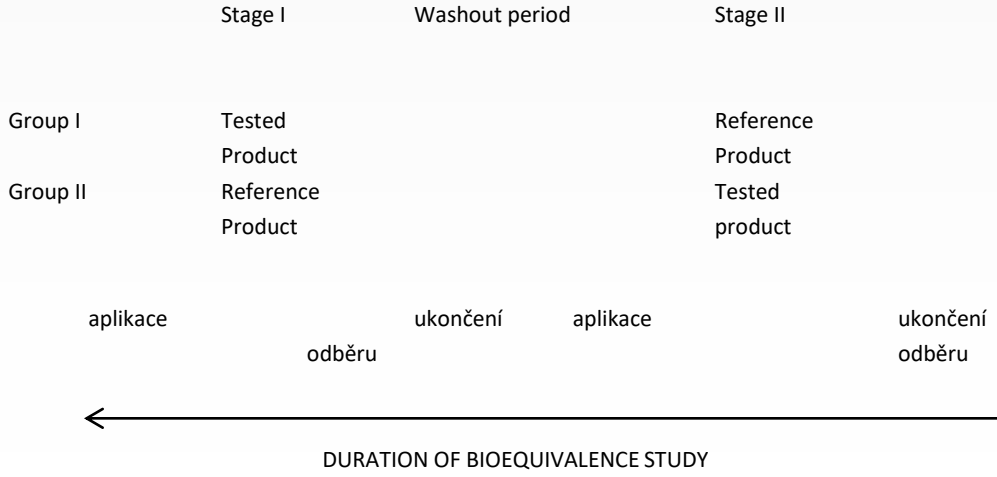
- Pharmacokinetic studies are carried out when the pharmaceutical creates measurable concentrations in various biological liquids (e.g. plasma).
- The approach is based on the fact that the pharmaceutical's concentration in the place of its effect cannot be generally measures and that there is a relation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

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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…

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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.)

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“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

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“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

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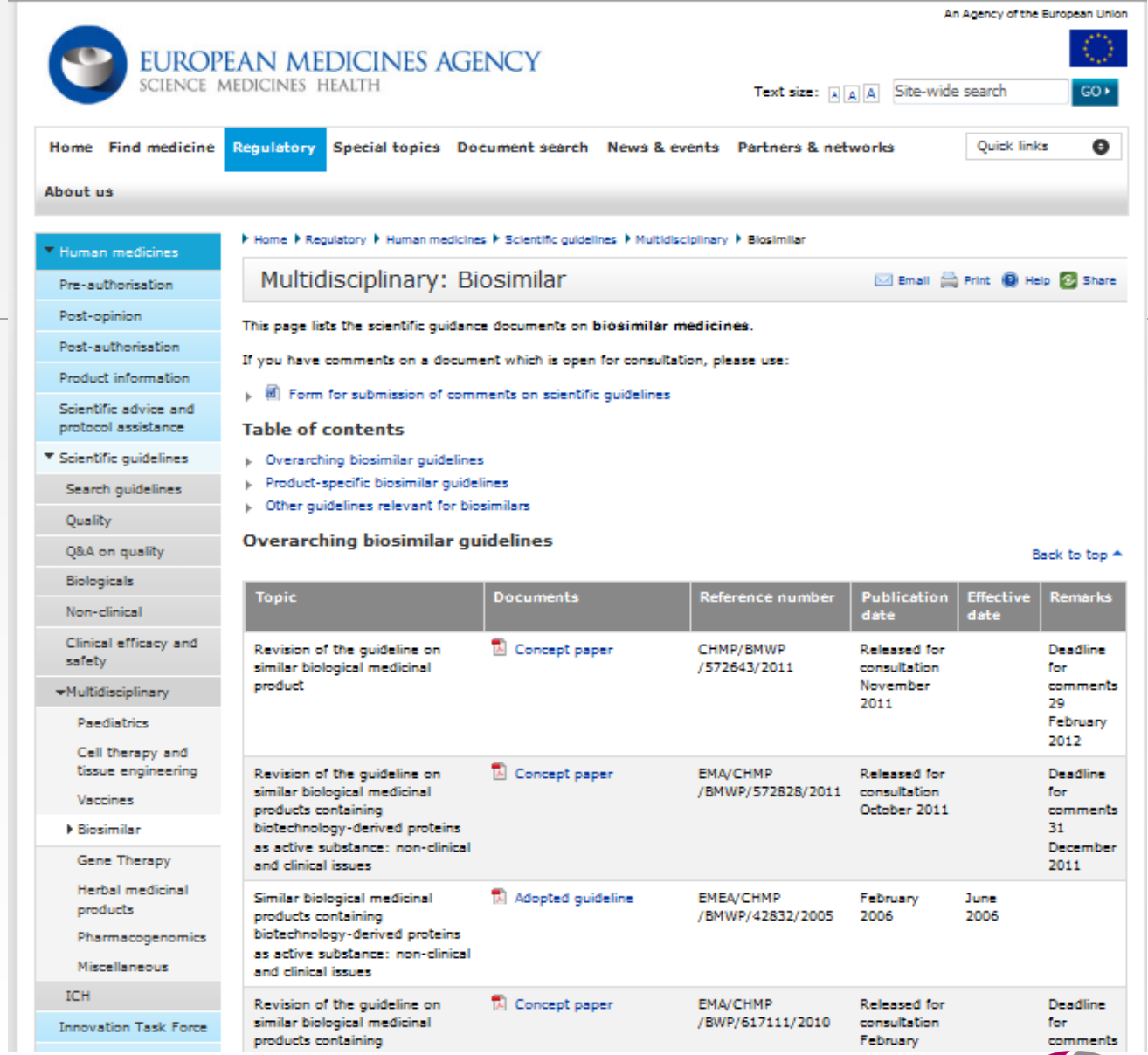
European Regulation…

- 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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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

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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

Product-specific biosimilar guidelines

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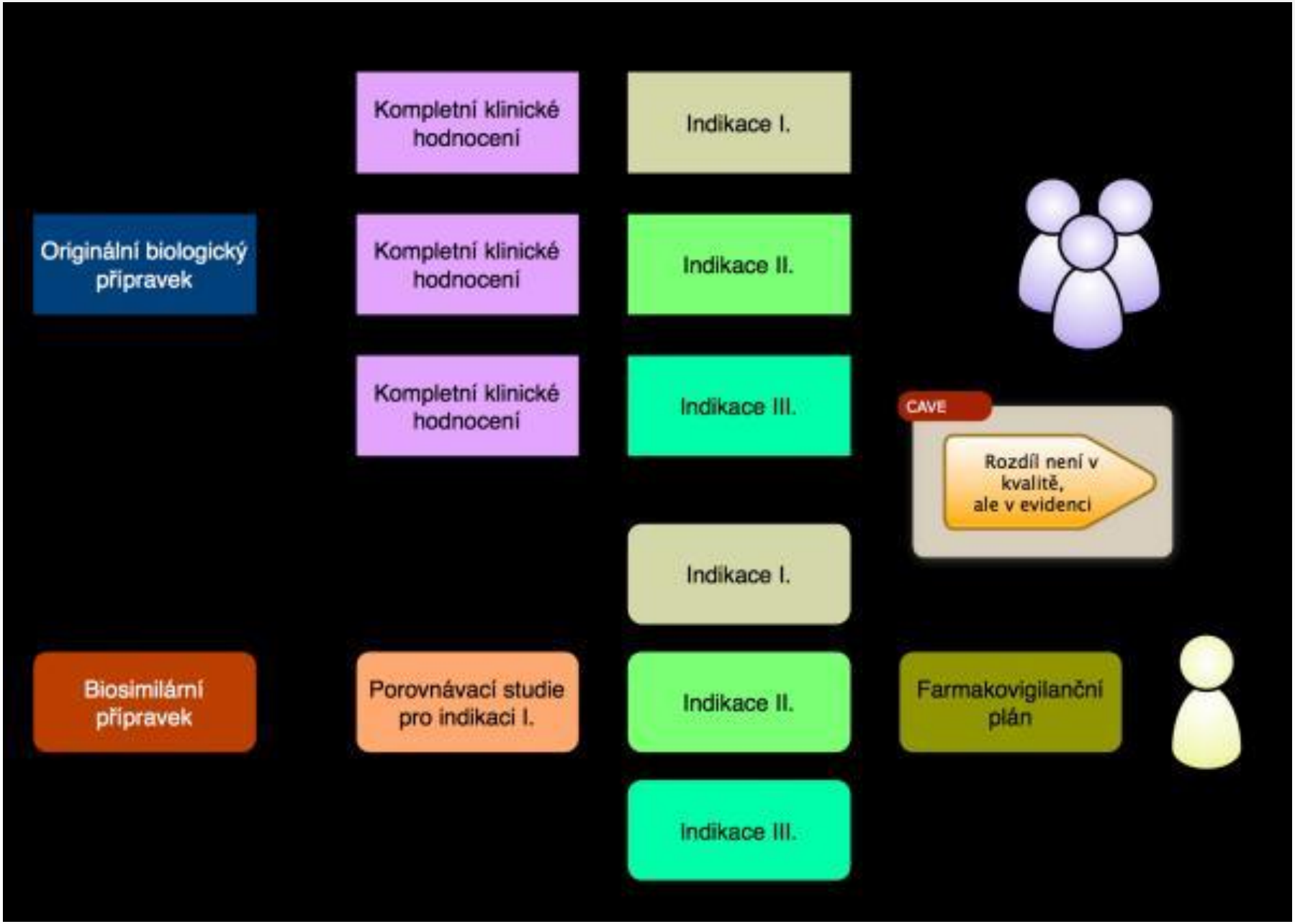
Topic	Documents	Reference number	Publication date	Effective date	Remarks
Similar biological medicinal products containing interferon beta	Draft guideline	CHMP/BMWP /652000/2010	Released for consultation December 2011		Deadline for comments 31 May 2012
Similar biological medicinal products containing 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	

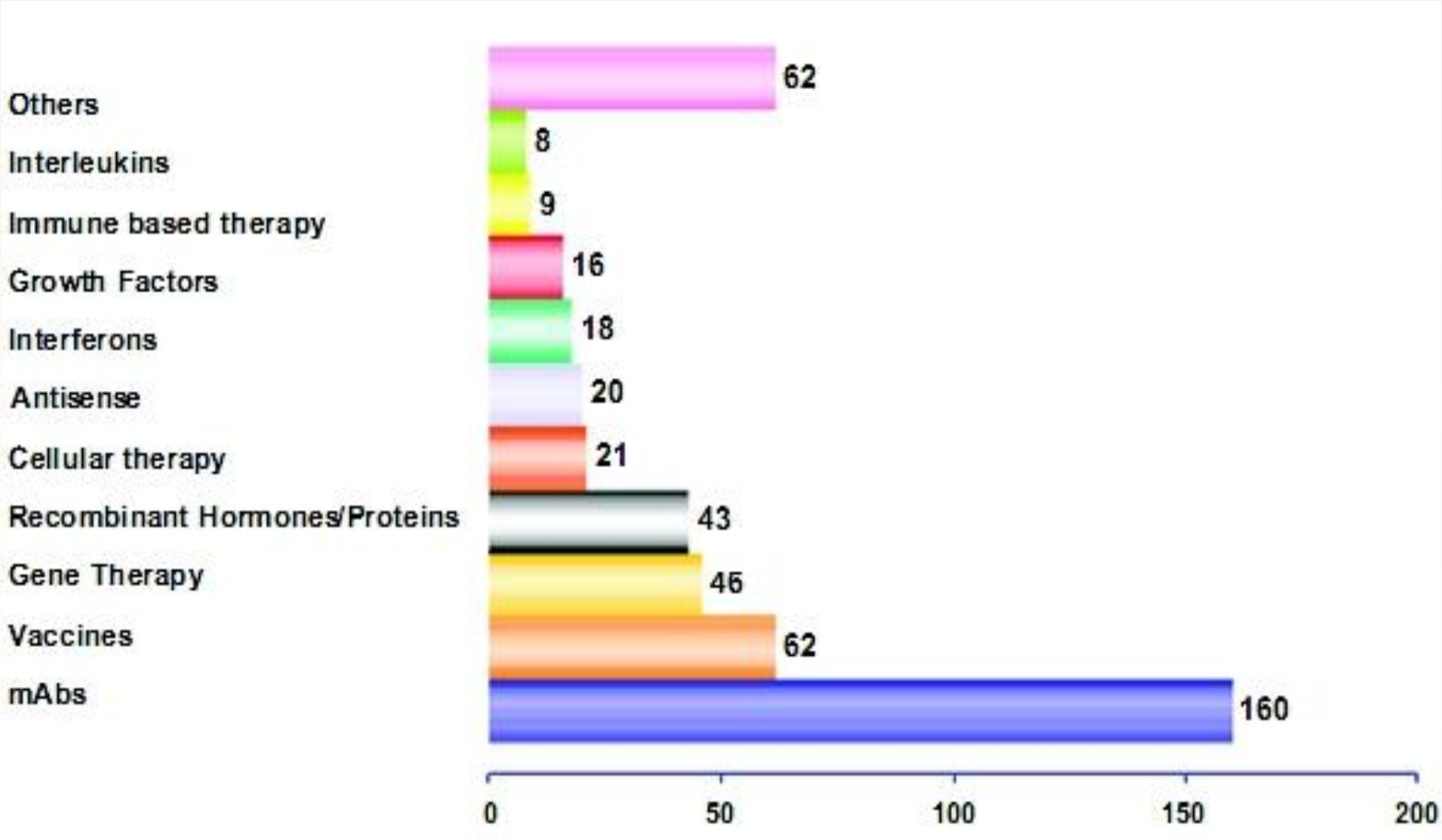
Definition and Regulation in the PA

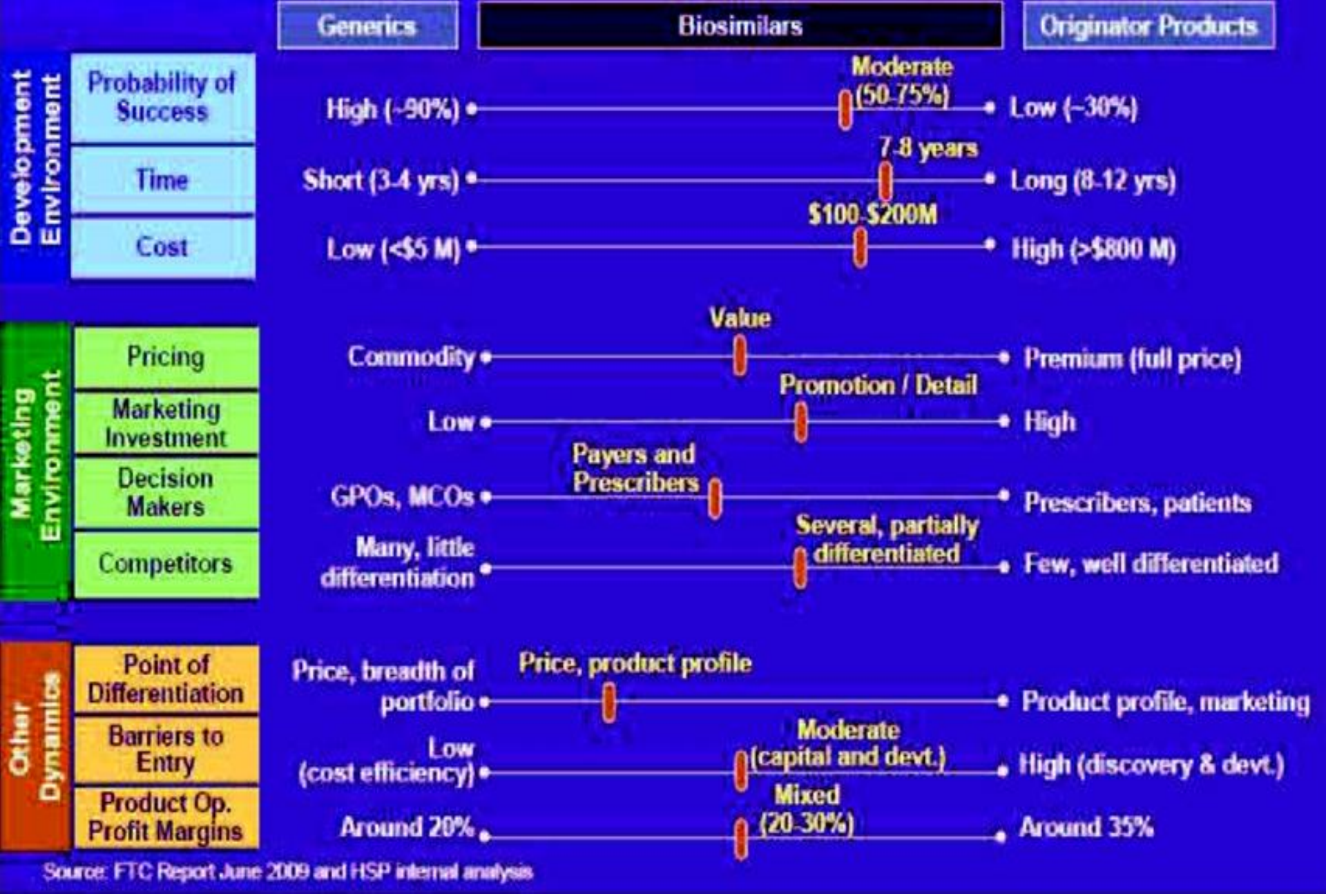
Biological medicinal product similar to the reference biological product.

- 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

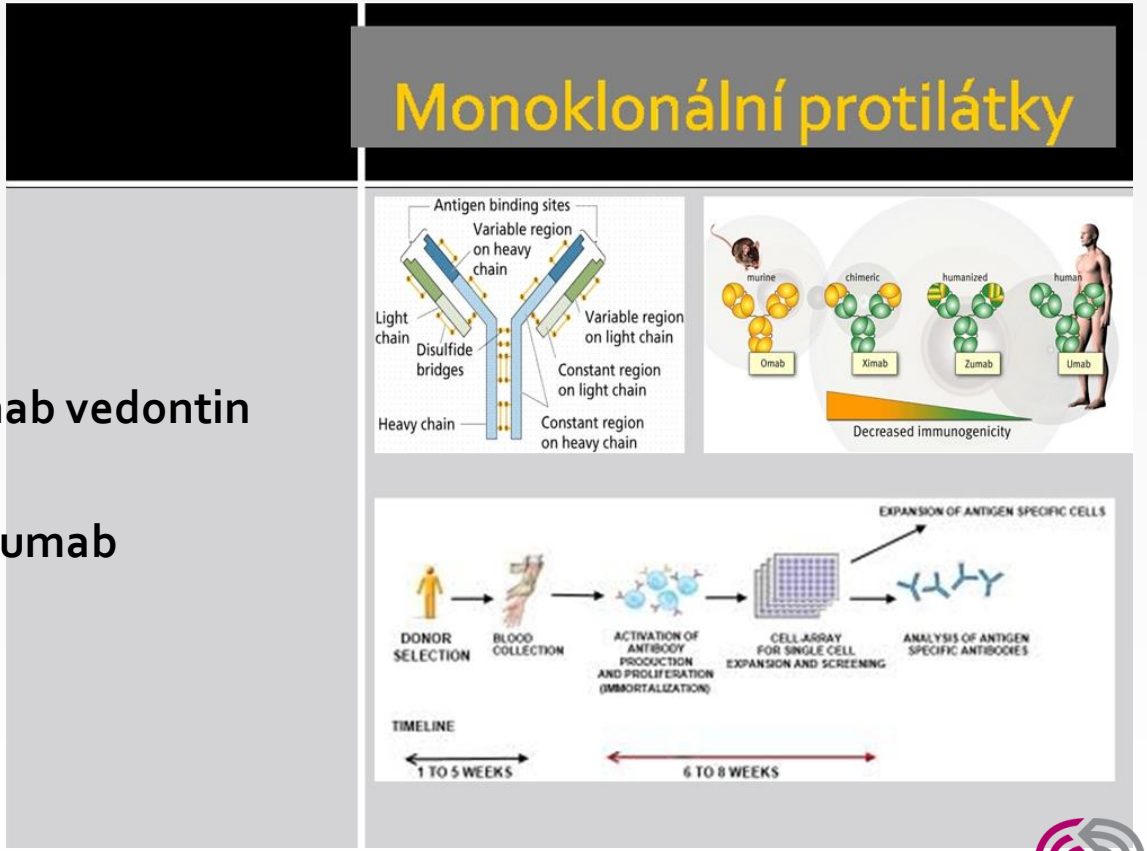
Monoclonal antibodies

belimumab

ipilimumab

brentuximab vedontin

denosumab



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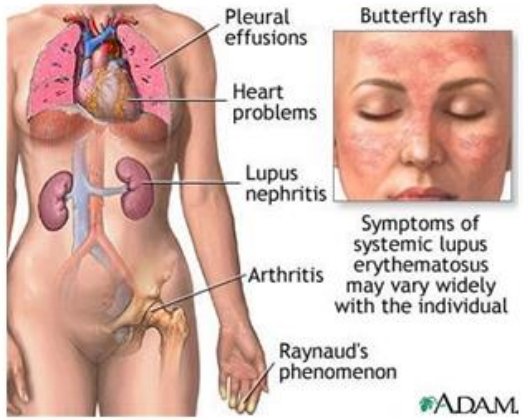
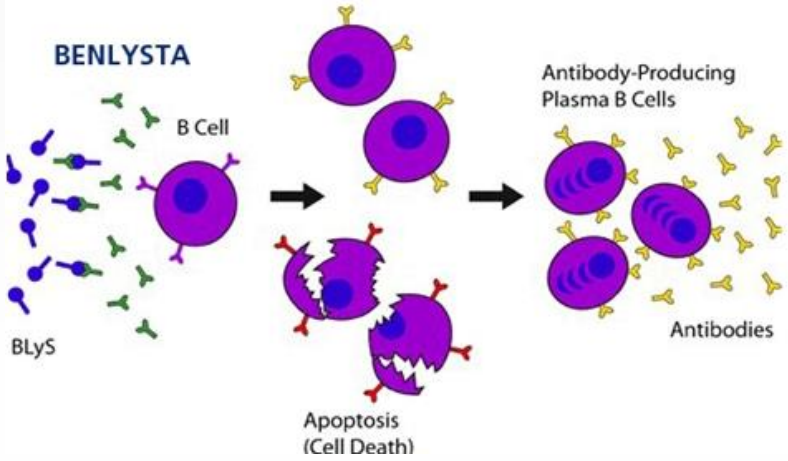
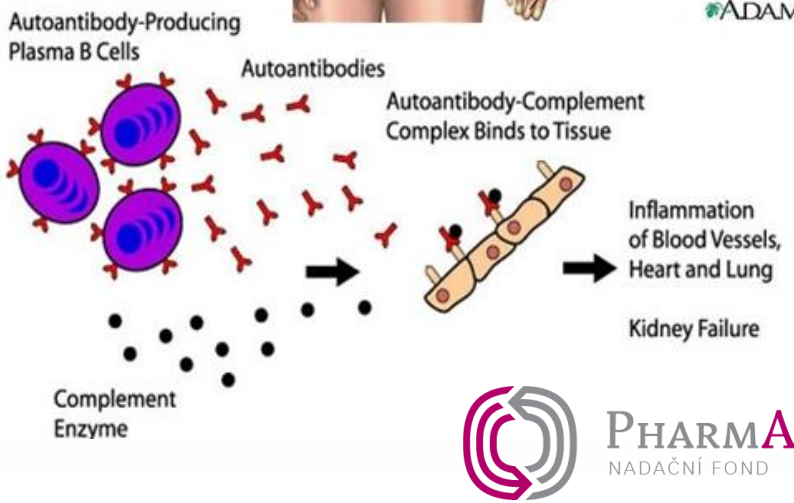
Belimumab

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)







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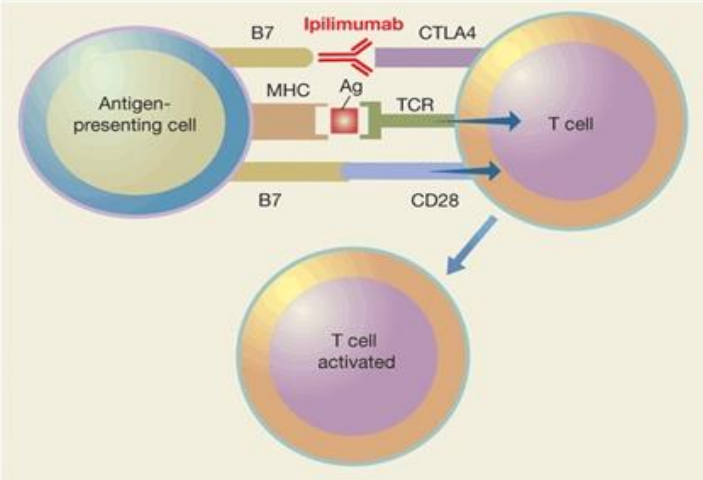
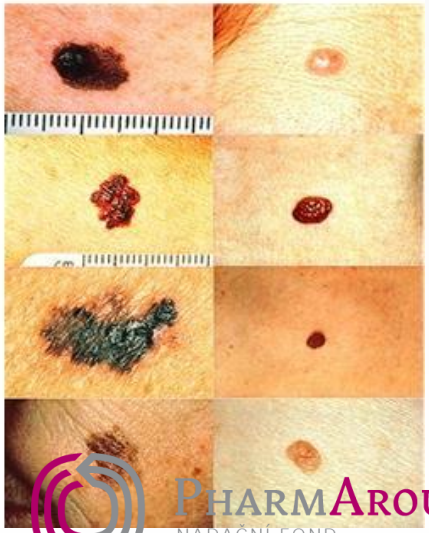
Ipilimumab

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.

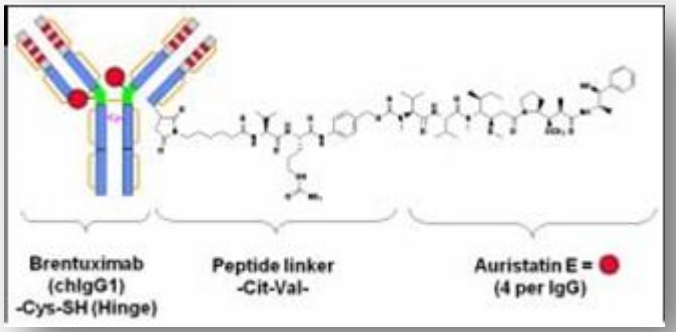


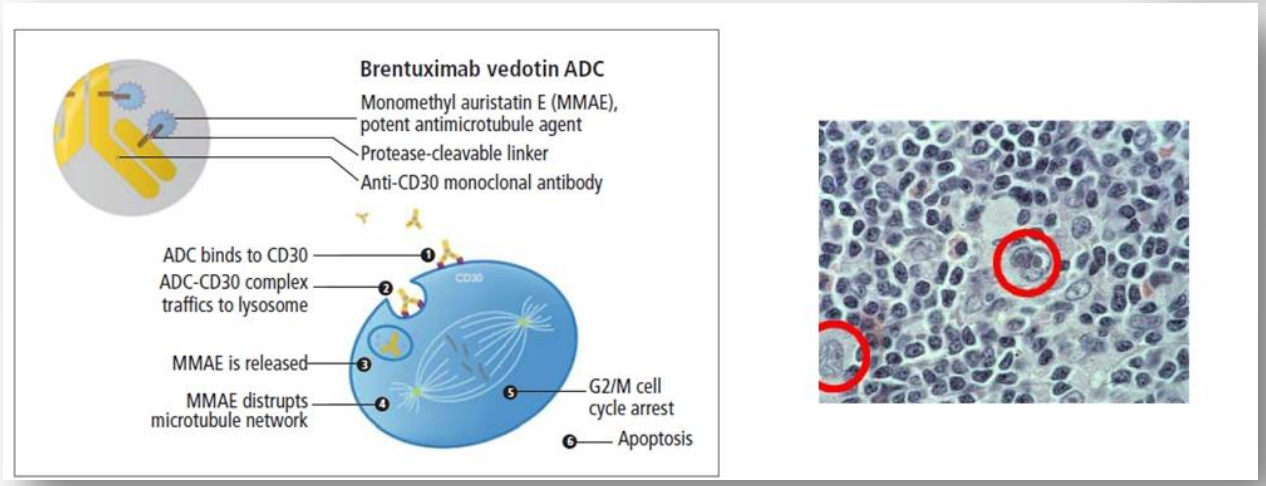


Brentuximab vedontin

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





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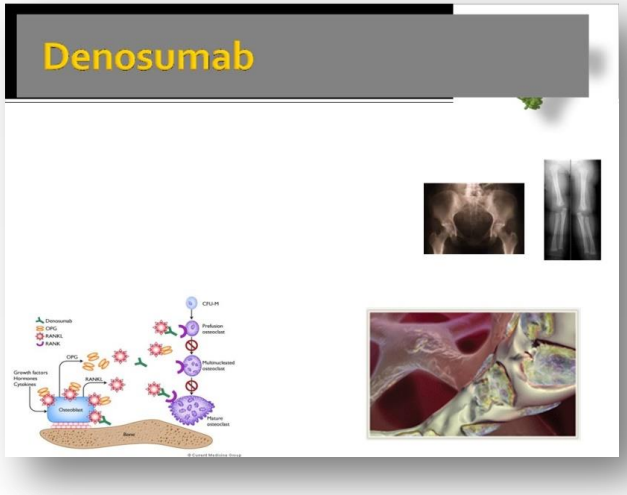
Denosumab

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.



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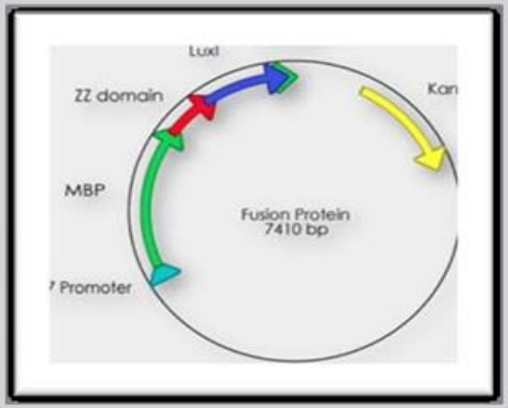
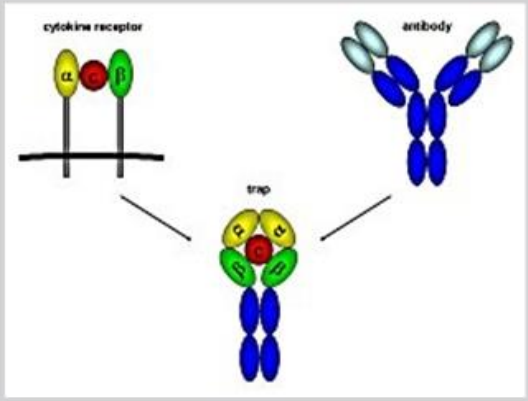
Fusion Proteins

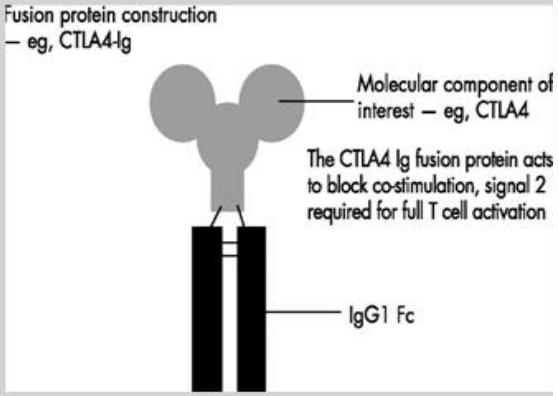
Aflibercept

Belatacept

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





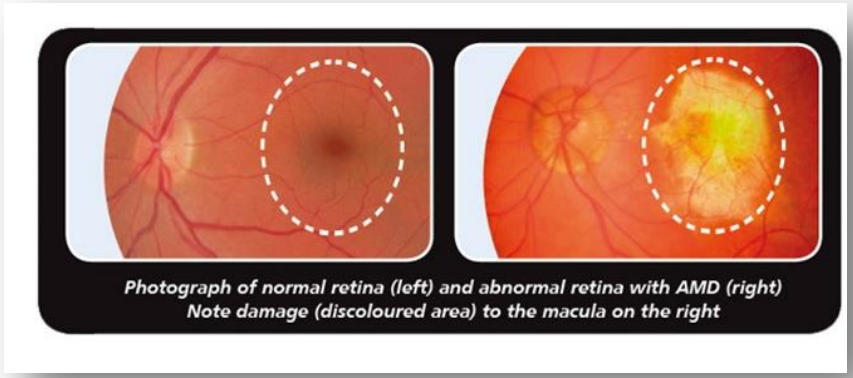


Aflibercept

Recombinant fusion protein

Dimetric glycoprotein contains a vascular endothelial growth factor VEGFR-1 receptor.

Neovascular (wet) age-related macular degeneration (AMD).



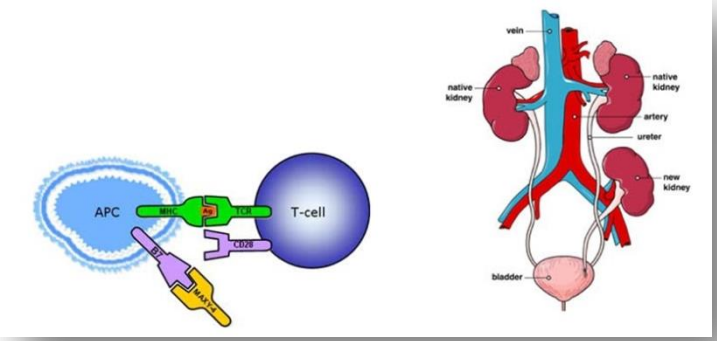
Photograph of normal retina (left) and abnormal retina with AMD (right)
Note damage (discoloured area) to the macula on the right

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



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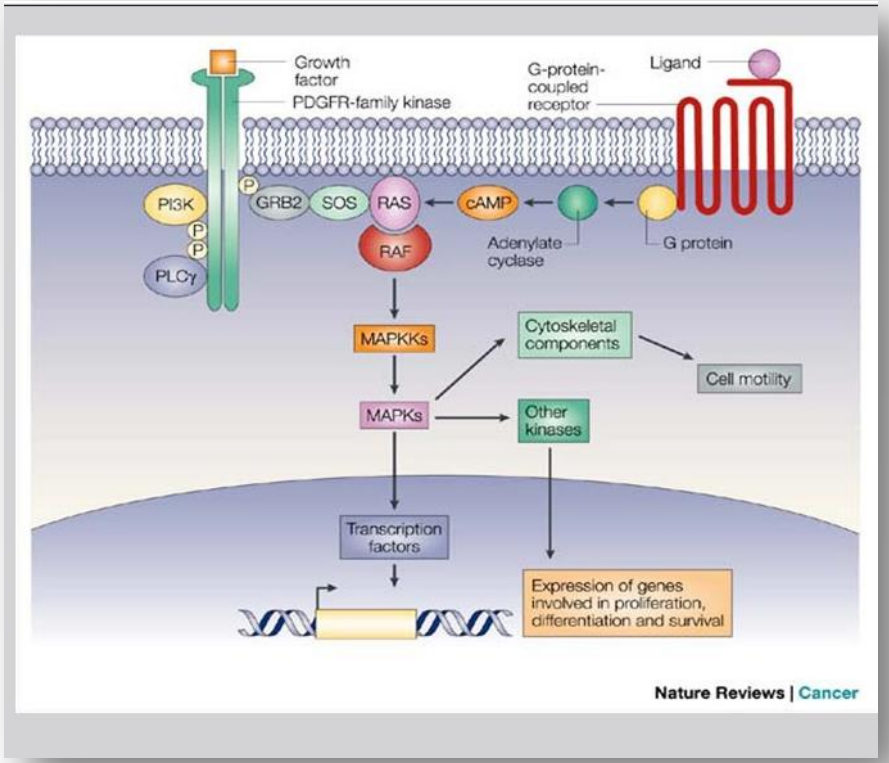
Kinase Inhibitors

Vemurafenib



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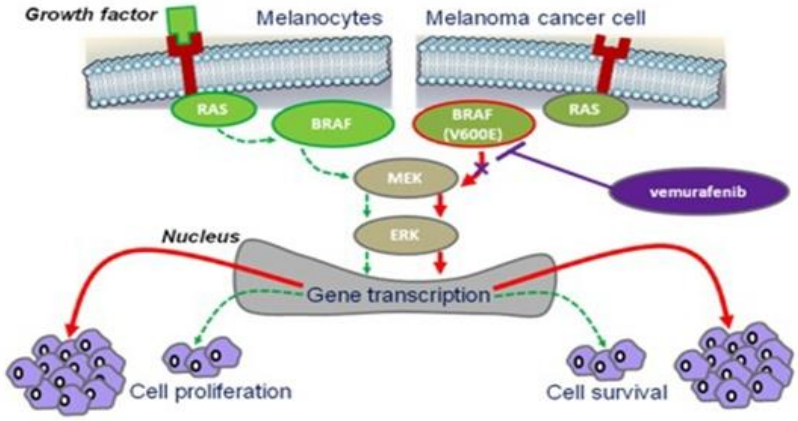
Vemurafenib

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



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