BIOSIMILARS
view from Slovak Medicine Regulatory Agency on topic

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What is a " biosimilar " ?

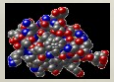
- copy version of an already authorised biological medicinal product

  with demonstrated similarity in terms of
  - quality characteristics
  - biological activity
  - safety and efficacy

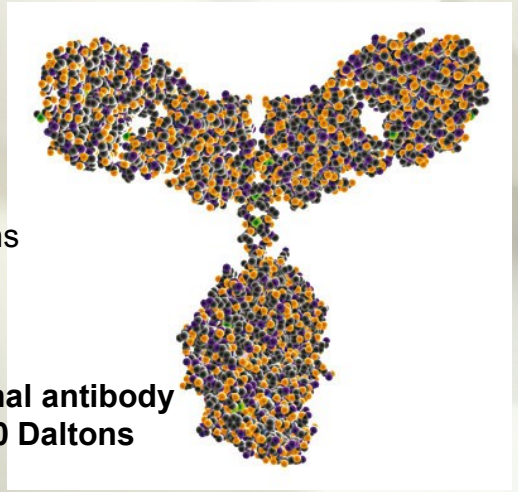
- aim is to generate a molecule as similar to reference product as possible

Biologicals are complex

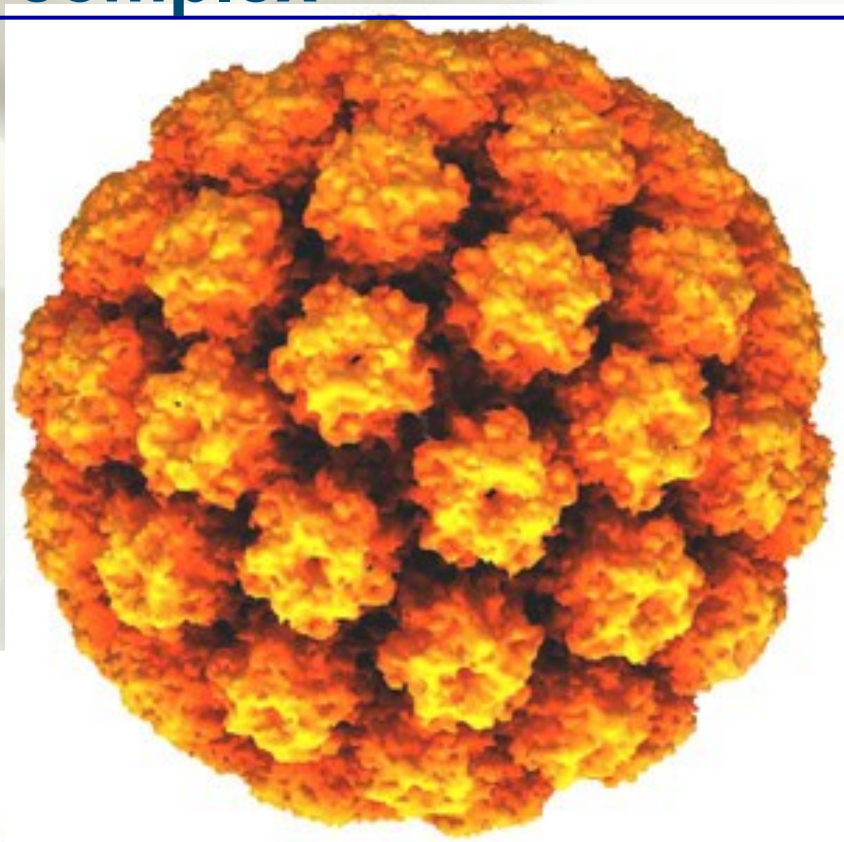
Aspirin
180 Daltons



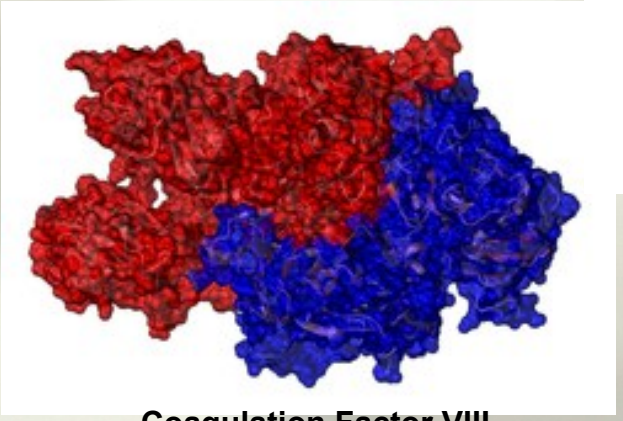
Insulin
5 700 Daltons



Monoclonal antibody
150 000 Daltons



Virus-like particle



Coagulation Factor VIII
280 000 Daltons

www.laborjournal.de, www.wikipedia.org, www.microbiologybites.com

Can more complex biologicals be biosimilars?

In principle, the concept of “similar biological medicinal products” applies to any biological medicine.

Guideline CPMP/BWP/437/04

How much do we need to know?

What is a „biosimilar“?

- Article 10: „Generics“ and legal basis for „biosimilars“
  - **Article 10(2a):** ***„Generic medicinal product” shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, (…).”***
  - **Article 10(4):** ***„Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.”***

	Generics	Biosimilars
	Identical to reference product	Similar to reference product
Active substance	Chemical origin	Biological origin
Data exclusivity	10 years	10 years
Therapeutic equivalence	In vitro data, (non)clinical studies	Bioequivalence study
Registration procedure	CP, NP, MRP, DCP	CP (biotechnologies)

Biosimilars

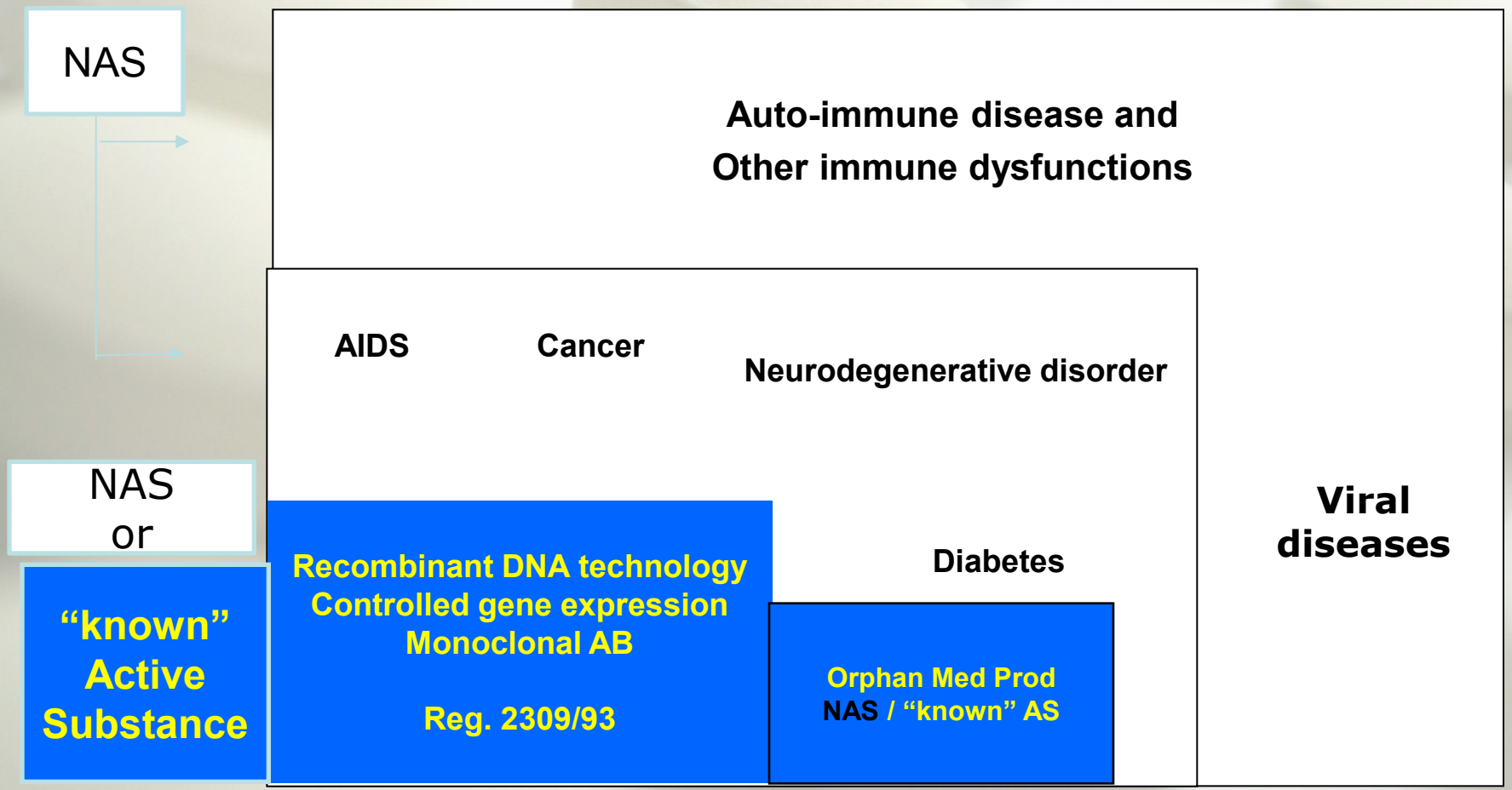
- Complex field

- There is no single unified definition (EMA, WHO, BMWP)

A biosimilar medicine is a biological medicine that is developed to be similar to an authorised medicine (the „reference medicine“). The active substance of a biosimilar medicine is essentially the same biological substance as the reference medicine’s, though there may be slight diffences due to the complex nature of biological products. Any differences will have been demonstrated not to impact on safety or effectiveness.

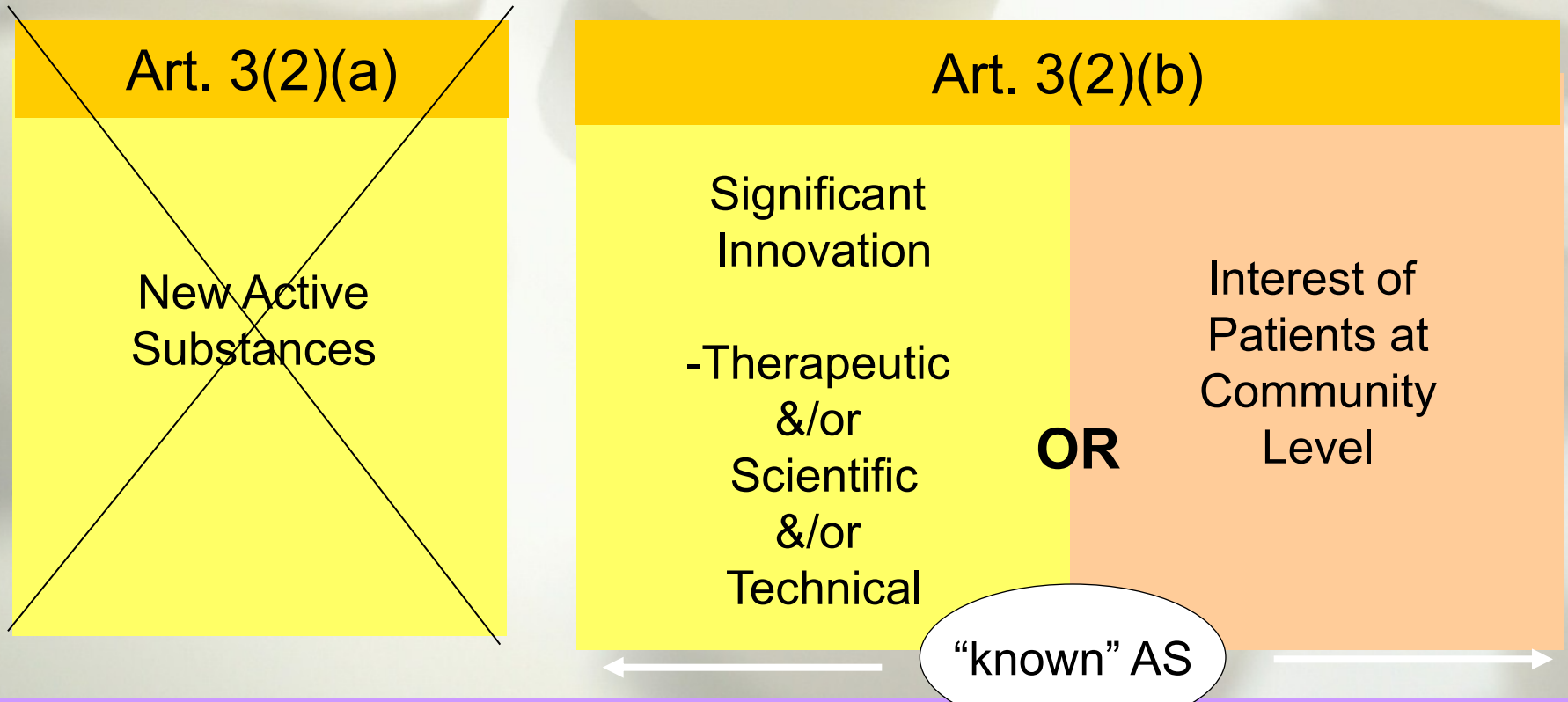
An authorized biosimilar medicine is therefore comparable to its reference medicine. The biosimilar and its reference medicine are generally used at the same dose to treat the same conditions. If there are specific precautions to be considered when taking the reference medicine, the same will generally apply to the biosimilar medicine.

Eligibility – Mandatory Scope

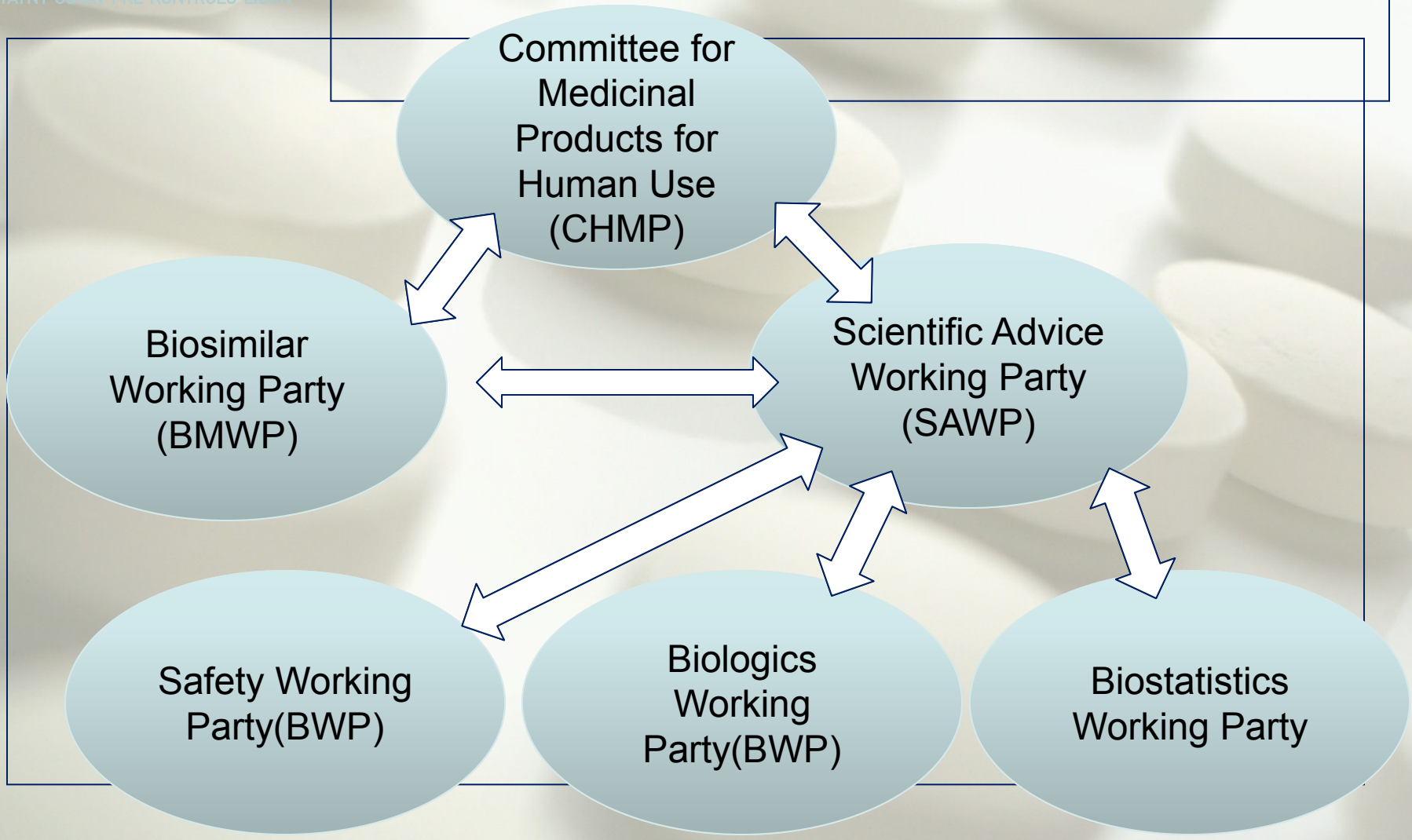


Reg. 726/2004

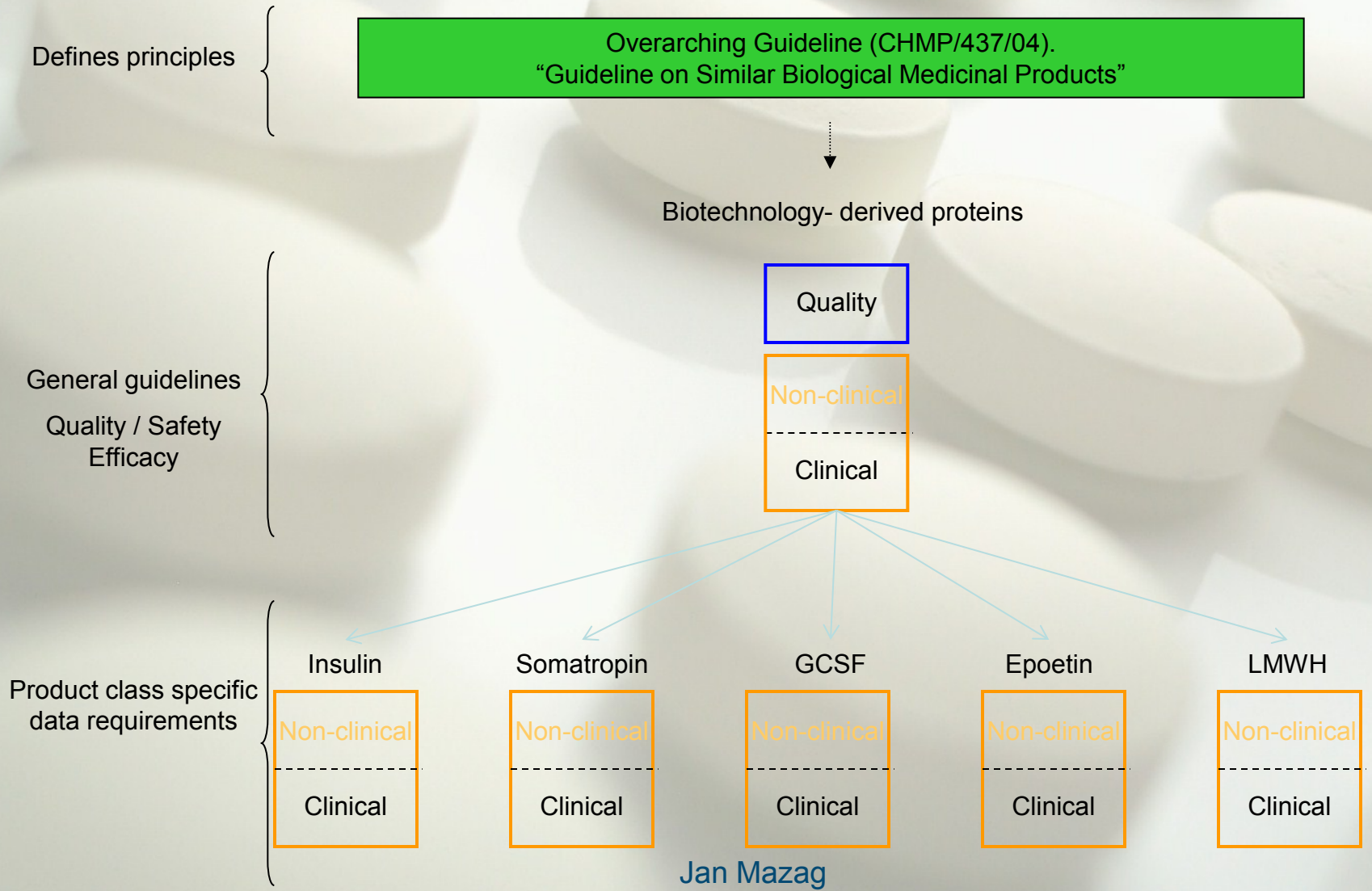
Eligibility – Optional Scope



Art. 3(3) of Regulation (EC) No 726/2004 – Biosimilars of CAPs


Committee for Medicinal Products for Human Use (CHMP)
Biosimilar Working Party (BMWP)
Scientific Advice Working Party (SAWP)
Safety Working Party(BWP)
Biologics Working Party(BWP)
Biostatistics Working Party

Regulatory framework for biosimilars



Source: Falk Ehmann, EMA, modified

Basic principles

- The aim of a biosimilar development programme is not to establish benefit of a treatment for the patient
  (this had been done before for the reference product!)

- The aim is to establish biosimilarity!

- This means:
  - The clinical study follows the idea that patients are „models“
  - The clinical study is selected to represent the most sensitive model to study differences
  - Thus, trial design might be (entirely) different from the normal guideline principles!

Dossier requirements for biosimilars

Module 1 - Normal Requirements	
Module 2 - Normal Requirements	
Quality, Module 3 - FULL	+ CE
Non-clinical, Module 4 - Reduced	= CE
Clinical, Module 5 - Reduced	= CE

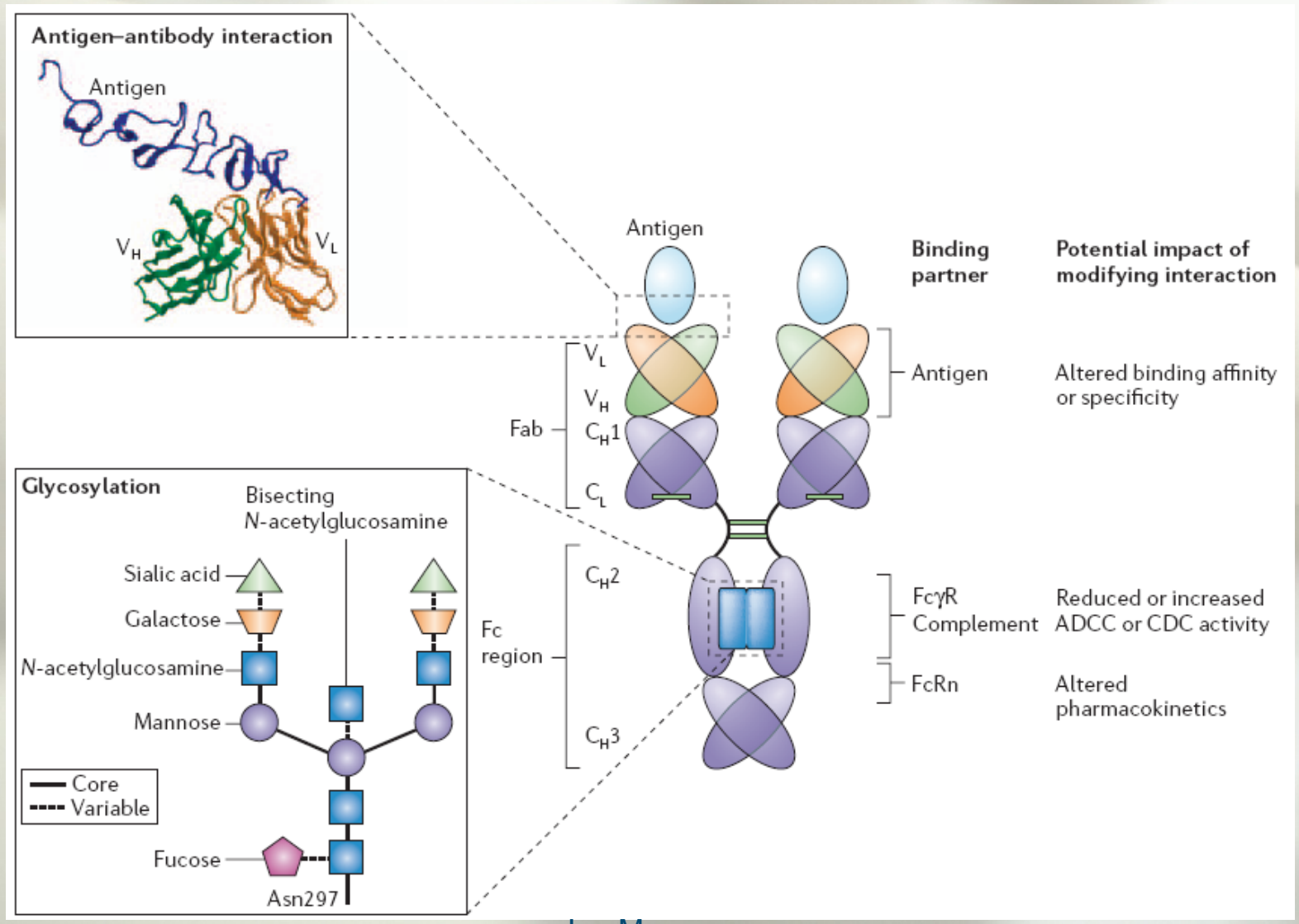
Integrated CE
(Comparability Exercise)

Source: Falk Ehmann, EMA

Analytical considerations

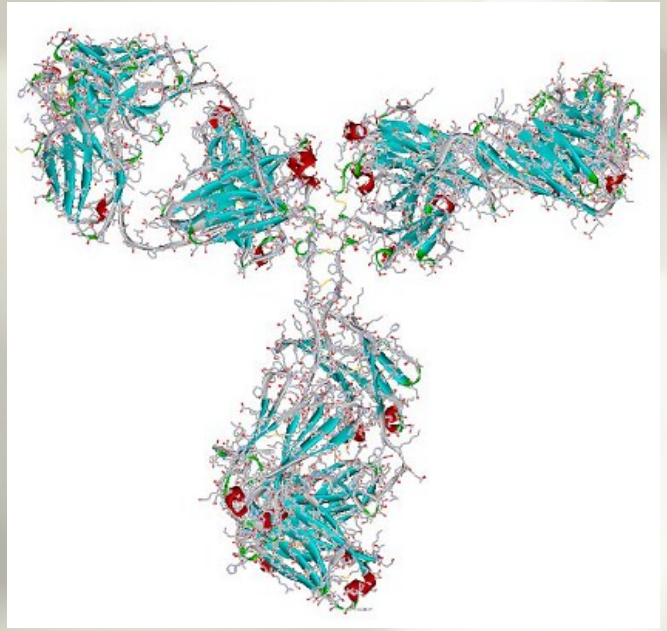
- Quality guidance introduces concept of **fingerprint-like similarity**
- Additional efforts at the analytical level = reward (less clinical data)
- Currently no clear position on what would be required to achieve fingerprint-like similarity, but expected to include:
- high number of lots of both reference product and biosimilar
- study combinations of quality attributes
- statistical analysis
- Statistical evaluation of analytical data is
- generally encouraged

Complexity of monoclonal antibodies



Carter PJ: Potent antibody therapeutics by design, Nature Rev Immunol 6, 343 (2006)

Heterogenity at quality level



- product-intrinsic heterogeneity
  - amino acid modifications (terminal cleavage, modification, oxidation, deamidation)
  - glycosylation
- product-related impurities
  - dimers, aggregates
  - fragments
- process-related impurities
  - host cell DNA, proteins
  - column leachables

Current methodology: Increasing sensitivity

- Physicochemical characterisation, e.g.
  - Capillary electrophoresis with laser-induced fluorescence detection (CE-LIF)
  - Mass spectrometry techniques (e.g., MALDI-TOF)
  - Nuclear magnetic resonance
- Antigen-antibody interaction, e.g.
  - Surface plasmon resonance
- Secondary structure detection, e.g.
  - Circular dichroism in near- and far-UV spectra

No specific guideline for quality considered necessary

Multifunctionality of monoclonal antibodies

- Binding to antigen
  - Inhibition of binding of ligand to receptor
- Binding to cellular receptors
  - Fc-gamma-RI
  - Fc-gamma-RII
  - Fc-gamma-RIII
  - FcRn
- Complement binding
- Relative contribution of effector functions mostly unknown

Non-clinical testing: A question of relevance

Central aspect: biotechnological products are species-specific.

A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies)*.

Relevant species for licensed mAbs described

Non-clinical: stepwise approach

- Step 1: non-clinical *in vitro* studies
  - Comparative
  - Evaluate the different functionalities of the molecule
    - Target binding
    - Fc receptor binding
    - Complement binding
    - Fab function
    - Fc function (ADCC, complement activation)

- Even if functionality is thought of not being involved in mode of action/efficacy a comprehensive investigation is advised

Non-clinical: stepwise approach

- Step 2: determination of need for non-clinical *in vivo* studies
  - Not needed if step 1 gives sufficient evidence

- Step 3: non-clinical *in vivo* studies
  - Toxicity studies in non-human primates and non-relevant species not recommended
  - Maximise gain of information
  - General limitations of comparative pre-clincical *in vivo* studies are acknowledged
    - *Large numbers for statistically powered studies needed*
    - *Often non-human primates*

- Important role for dose/concentration sensitive functional assay

- It is unlikely that a clear difference in function demonstrated in a non-clinical assay can be compensated by the demonstration of clinical efficacy

Potency assays are available

Product	Specificity	Potency assay	Comments
Avastin (Bevacizumab)	Anti-VEGF	**anti-proliferation bioassay** (inhibition of rhVEGF-induced proliferation of Human Umbilical Vein Endotheliae Cells HUVEC). (relative number of viable cells, quantified by fluorescence)	Assay chosen as drug substance release test based on its sensitivity (ability to detect significant changes in the activity), robustness, precision (RSD<10%) and accuracy (98-102%)
Simulect (Basiliximab)	Anti-CD25	**Inhibition of binding** of radiolabelled IL-2 to IL-2 receptor expressed on T-lymphocytes (and thus inhibition of lymphocyte proliferation)	
Synagis (Palivizumab)	Anti-RSV	**In vitro:** RSV Microneutralisation Assay, RSV Fusion Inhibition Assay, BIAcore Analysis **In vivo potency:** Reduction of RSV titre in the lungs of infected cotton rats	Comparison of different predecessor products with palivizumab during development
Tysabri (Natalizumab)	Anti-α4-integrin	**In vitro assay:** Ability to bind α4-integrins and block its interaction with its co-receptor.	
Xolair (Omalizumab)	Anti-IgE	**Inhibition of binding:** Ability of omalizumab to inhibit binding of IgE to its receptor	Shown to correlate to the inhibition of release of histamine

http://www.emea.europa.eu/htms/human/epar/eparintro.htm

Controversies: extrapolation

	infliximab	adalimumab	golimumab	certolizumab pegol	etanercept
Rheumatoid arthritis					
Psoriasis					
Psoriatric arthritis					
Crohn‘s disease				EU:  US: 	
Ulcerative colitis					
Ankylosing spondylitis					
Juvenile RA					

Wrap-up remark

Biological reference medicinal product vs. biosimilars

- Biological medicines – large and complex character, complex production processes – degree of natural variability in molecules of the same active substance

- The same variability applies for biosimilars

- variability and any differences between biosimilars and its reference medicine is shown not to affect safety or effectiveness

- biosimilar - generally used at the same dose to treat the same conditions

- information that the medicine is biosimilar is included in part 5.1 of SmPC

Evaluation of biosimilars in the proces of registration

- Comparison with reference biological product – to show that there are no significant differences between them
- Quality assessment – comprehensive comparisons of the structure and biological activity of the active substances
- Safety and efficacy assessment – show that there are no significant differences in their benefits and risks, including the risk of immune reactions

Interchangeability evaluation

- EMA's evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. This is considered to by a national issue. For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist

Biosimilar development program

Development program – stepwise approach – comparability excercise - comparison of biosimilar vs. reference biological product in terms of quality, efficacy and safety:

1) comprehensive physicochemical and biological characterisation
2) non- clinical in-vivo studies
3) clinical studies

Point 2+3 – the extend and nature based depends on the level of evidence obtained in the previous step(s)

Goal: to exclude any relevant differences between the biosimilar and the reference medicinal product - studies should be sensitive enough with regard to design, population, endpoints and conduct to detect such differences

CHMP/437/04 Rev. 1

Epoetin Alfa

- Biosimilars Abseamed, Binocrit, Epoetin Alpha Hexal
- Reference biological product – Eprex
- Treatment of anaemia in patients with chronic kidney failure, in patients recieving chemotherapy, to increase the amount of blood

Epoetin Zeta

- Retacrit, Silapo – biosimilars
- Eprex (epoetin alfa) – reference biological product
- Treatment of anaemia in patients with chronic kidney failure, in patients recieving chemotherapy, to increase the amount of blood

Somatropin

- biosimilars Omnitrope
- reference biological product – Genotropin
- Same indication:

  - Growth disturbance due to insufficient secretion of growth hormone in children, associated with Turner syndrome or with chronic renal insufficiency
  - Growth disturbance in short children born small for gestational age
  - Prader-Willi syndrome
  - Replacement therapy in adults with pronounced growth hormone deficiency

Filgrastim

- Biograstim, Filgrastim Hexal, Nivestim, Ratiograstim, Tevagrastim, Zarzio – biosimilars

- Indication:
  - neutropenia (duration and occurence shortening in patients with chemotherapy
  - mobilisation of peripheral blood progenitor cells (PBPC)
  - severe congenital, cyclic, or idiopathic neutropenia
  - persistent neutropenia (ANC less than or equal to 1.0 x 109/l) in patients with advanced HIV infection

Case study – Nivestim

- Reference biological medicine – Neupogen

- Quality – biosimilarity was shown between biosimilar and reference biological medicine

- Nonclinical studies – pharmacodynamic and toxicology studies – in vivo pharmacodynamic study with neutropenic rats, local sensitivity in rabbits, chronic toxicity

  (missing studies: single dose toxicity, genotoxicity, carcinogenity, reproduction toxicity)

- Efficacy – clinical studies – 2 phase I studies to compare pharmacodynamic, pharmacokinetic and safety in single dose and multiple dose administration
- 1 phase III study – double-blind randomised – therapeutic equivalence was shown between Nivestim and Neupogen in prophylaxis of neutropenia in patients with myelosupressive chemotherapy

(missing studies: dose dependance study, studies for other indications)

- Safety – assessed during phase III study – comparable with reference biological medicine.

Interchangeability/Substitution

- The assessment of interchangeability and substitution are outside the remit of the EMA
- These concepts are not part of the scientific evaluation performed by the CHMP
- The decisions on Interchangeability and/or Substitution rely on National Competent Authorities

Interchangeability

- Substitution without the intervention of the prescriber

- The applicant must, in addition to demonstration of biosimilarity, demonstrate that
  - the product can be expected to produce the same clinical result as the reference product in any given patient
  - there is no increased risk related to switching between the products.

- Possibly two step approach (i.e. interchangeability based on post-approval data for biosimilar)

- Future guideline developments will include a guideline on interchangeability (not yet initiated)

- Unclear how to handle drifts in quality profile

Interchengeability in Slovakia

- No interchengeability on pharmacy level (patient should be followed under supervision of physician)
- Interchengeability on physician level – yes, there is knowledge of efficacy, safety and indication based on regulatory requirements respecting current level of science
- Vigilance – the same as reference product, incl PSURs, in some cases can be on top Post Authorisation Trials part of licensing decision

- Thank you

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