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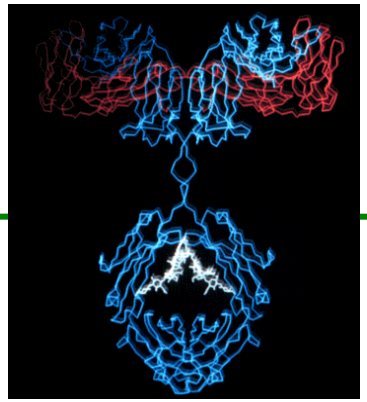

Biologicals in clinical practice

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What is a biological?

A biopharmaceutical, also known as a biologic(al) medical product, biological, or biologic, is any pharmaceutical drug product produced by or extracted from a biological source.

- Products produced by recombinant DNA technology
- Products extracted from a biological source

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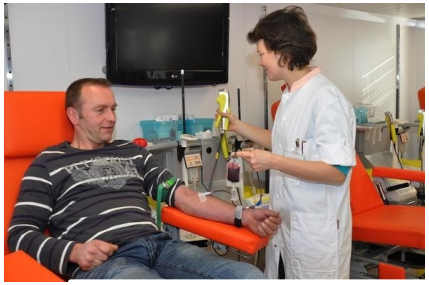
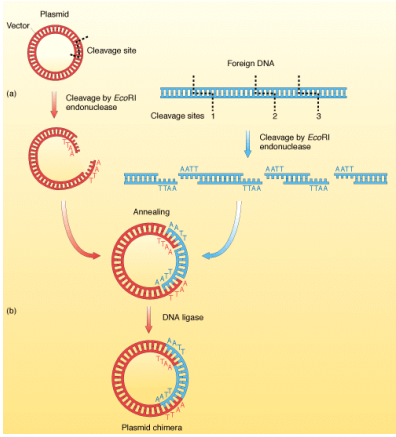
Biologicals

Banting & Best



Sanquin



Recombinant DNA technology

1900s Salvaran

1931 Sulfonamide

2000s Biosimilars

1897 Aspirin

1920s Insulin

1980s Recombinant DNA technology

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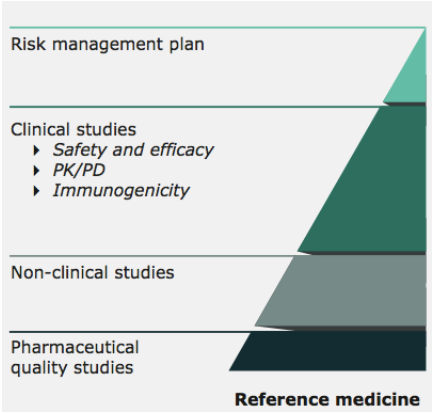
Biologicals in clinical practice

- Antibodies:
  - Auto-immune diseases: infliximab, etanercept
  - Oncology: trastuzumab, pembrolizumab, rituximab
- Enzymes: enzyme replacement therapy
- Hormones: growth hormones, insulins
- Vaccines



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Characteristics of biologicals

Biopharmaceuticals vs small molecules	Examples of safety-related problems
Large complicated molecules and often mixtures of different isoforms	
Relatively unstable	Formation of aggregates can influence the immunogenic potential
Complex production and purification process/(small) changes in manufacturing process can influence safety	Pure red cell aplasia in patients treated with epoetin alfa following manufacturing changes
Manufactured in living cells	The host cell used and contamination with host cell DNA and host cell material can influence the immunogenic potential, e.g. natural interleukin (IL)-2 was reported to be less immunogenic than IL-2 produced by *Escherichia coli*
Potential for immunogenicity	Thrombocytopenia after treatment with recombinant thrombopoietin due to neutralizing antibodies blocking endogenous thrombopoietin
Limited predictability of preclinical to clinical data due to species-specific action and immunogenicity of human proteins in animals	Cytokine storm in TeGenero phase I trial Human interferon has a different pharmacological effect to mouse interferon in mice
Adverse events often related to exaggerated pharmacology	Tuberculosis with the use of the tumour necrosis factor-α inhibitor infliximab

Drug Saf 2009; 32 (10): 811-817

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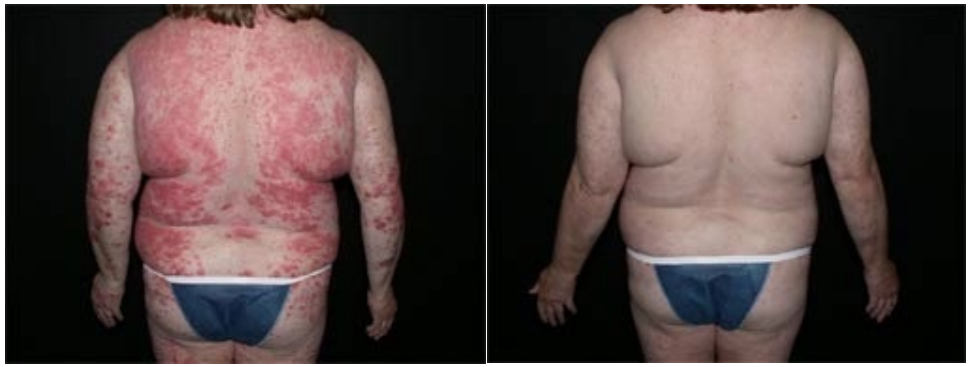
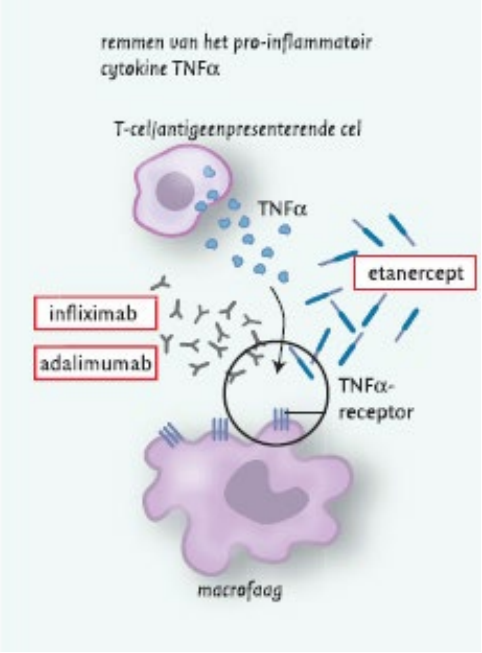
Biologicals are highly effective



Before treatment After treatment



NTVG 2006; 150: 1065-70

Summary of PASI response and PGA score at Weeks 10, 24 and 50. EXPRESS.

	Placebo → Infliximab 5 mg/kg (at week 24)	Infliximab 5 mg/kg
Week 10		
n	77	301
≥ 90% improvement	1 (1.3%)	172 (57.1%)[a]
≥ 75% improvement	2 (2.6%)	242 (80.4%)[a]
≥ 50% improvement	6 (7.8%)	274 (91.0%)
PGA of cleared (0) or minimal (1)	3 (3.9%)	242 (82.9%)[ab]
PGA of cleared (0), minimal (1), or mild (2)	14 (18.2%)	275 (94.2%)[ab]

Source: EMA Homepage, European Public Assessment Report (EPAR)

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Safety of biologicals: a classification

- **Exaggerated pharmacology*:***
  - TB with TNF-alfa inhibitors
  - PML with natalizumab
  - High HB with epoetines
  - Stimulation of immune system
- **Immunological reactions:**
  - Neutralizing antibodies
  - Hypersensitivity reactions
  - Anaphylactic reactions

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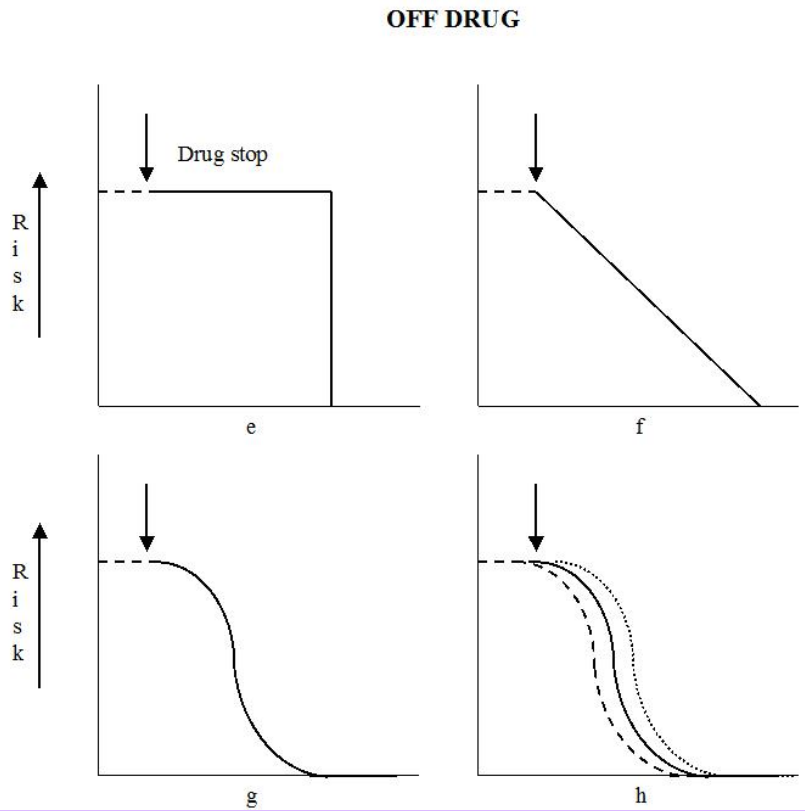
Immunosuppression

- Be aware: immunosuppression still present after drug is already eliminated from the body
  - e.g. rituximab and B-cell depletion

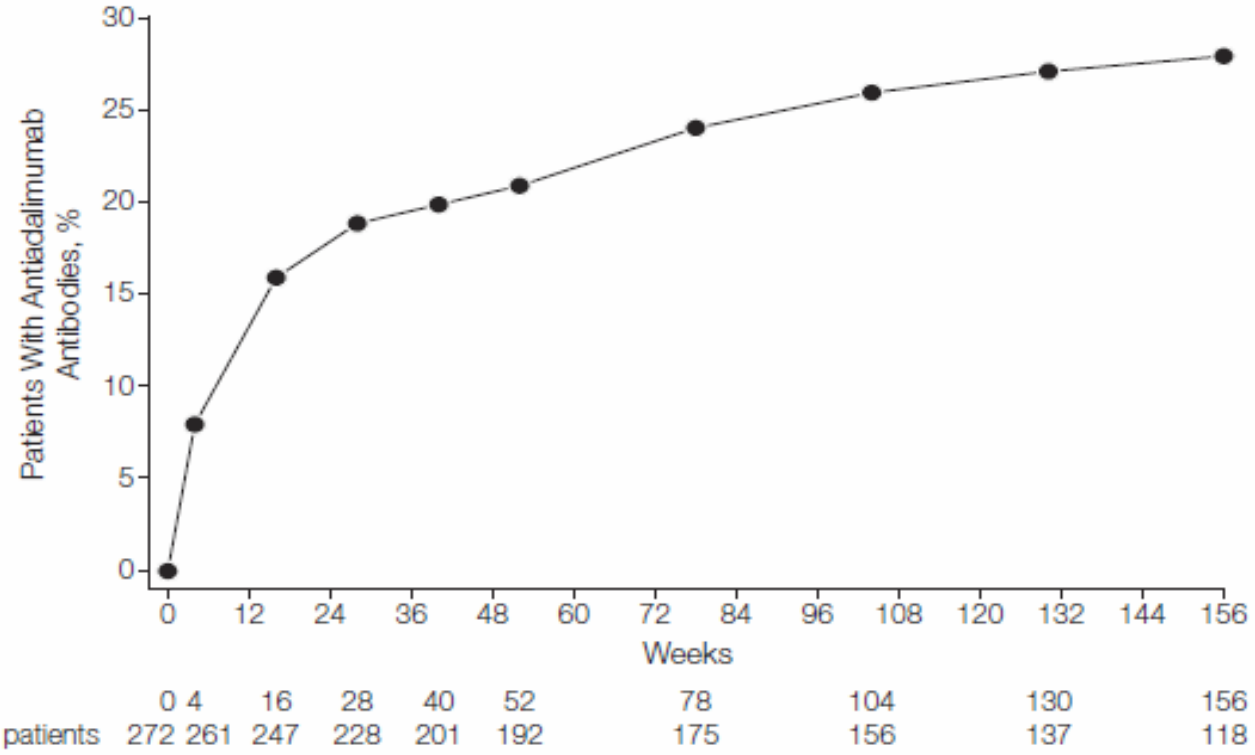


Arthritis Rheum 2007; 56(9): 2896-904

Antibodies

- Often not clinically relevant
- Neutralizing antibodies → direct effect on efficacy and/ or safety
- Clearing antibodies → direct effect on efficacy
- Serious reactions → e.g. PRCA with epoetin alfa

Figure 1. Percentage of Antiadalimumab Development Over Time



Number of patients with available serum samples are shown.

JAMA 2011; 305: 1460-68

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Biosimilars

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What is a biosimilar?

a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established

Guideline on Similar Biological Medicinal Products
(www.ema.europa.eu)

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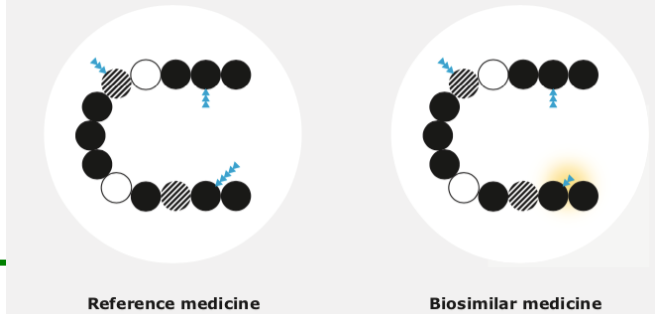
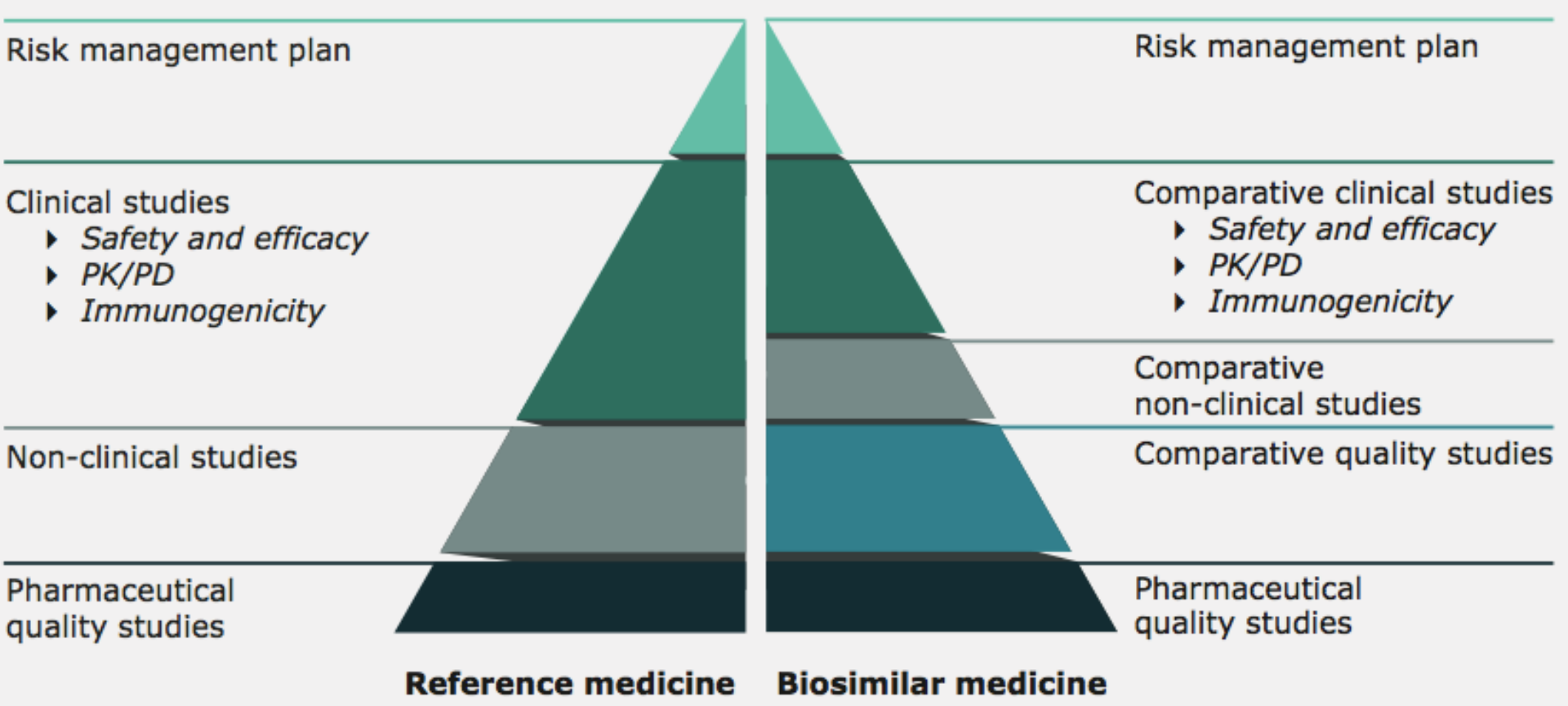


Development of a biosimilar



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CBG MEB College ter Beoordeling van Geneesmiddelen

Position of the MEB

- New patients can be treated with a biosimilar right away.
- Uncontrolled exchange between biological medicines must be avoided. In other words, a patient must receive adequate
  clinical monitoring and
  clear instructions.
- Traceability is important

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Summary

- Biologicals are important treatment options
- Biologicals have specific characteristics
- Biosimilars are as safe and efficacious as the reference product
- Switching from reference product to biosimilar is safe