

Biosimilars – Chance oder Risiko?

Pharmazeutische Gesellschaft Zürich

Donnerstag 15. Dezember 2011

Dr. Kurt Pfister
PFC Pharma Focus Ltd.



Biological Medicinal Product

- **Break-through in medical therapy in the last decades**
- **2009: 17% of all pharmaceutical products were biopharmaceuticals**

Biological Medicinal Product

➤ The top ten

Generic Name	Brands ®	Companies	Indications	Sales \$ billion		
				2006	2007	2008
Etanercept	Enbrel	Amgen, Wyeth Takeda	RA, JRA, Ps, PsA, AS	4.4	5.2	7.66
Infliximab	Remicade	J&J, MSD, Mitsubishi	RA, UC, CD, Ps, PsA, AS	4.2	5.04	6.2
Rituximab	Rituxan	Roche	NHL, RA	4.7	5.01	5.5
Bevacizumab	Avastin	Roche	Colon cancer	2.4	3.93	4.8
Trastuzumab	Herceptin	Roche	Breast Cancer	3.14	4.4	4.7
Adalimumab	Humira	Abbott	RA, Ps, JIA, PsA, AS, CD	2.04	3.06	4.5
Enoxaparin	Lovenox	Sanofi Aventis	Anticoagulant DVT	3.06	3.65	4
Insulin	Lantus	Sanofi Aventis	Diabetes	2.2	2.8	3.6
Darbepoetin	Aranesp	Amgen	Anemia	4.1	4.2	3.1
Human Papilloma Virus Vaccine	Gardasil	Merck	Cervical cancer	1.4	2.8	
TOTAL			Sales \$ billion	31.64	40.09	44.06

Biological Medicinal Product – off-patent and now?

- **2005: Biopharmaceuticals coming off-patent
appox. 12 billion USD**
- **USA 45%**
EU 30%
Japan 20%
- **Assumption Biosimilar-Penetration 10 bis 15%:
2 billion USD**

2005: Biological Medicinal Product – off-patent and now?



Biosimilars – Chance oder Risiko?

AGENDA

Der Weg vom Generikum zum Biogenerikum zum Biosimilar

Wie geht die Behörde damit um?

Beispiele Erythropoetin, Somatotropin und Filgrastim

Offene Fragen

Biosimilars – Evolutionary Development of a New Term

from Generic

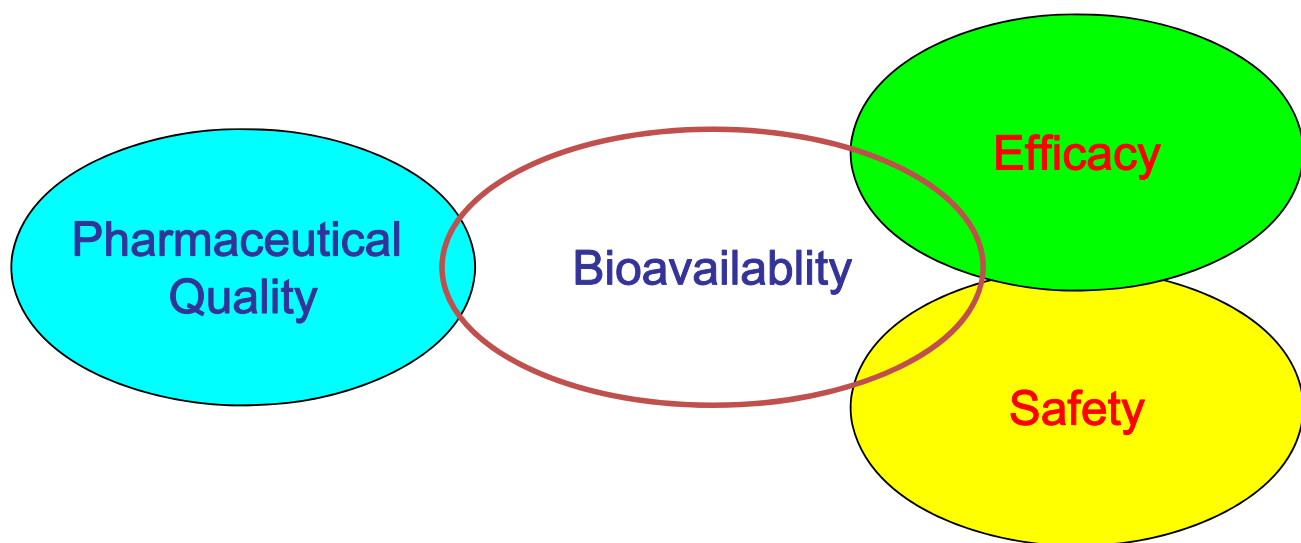
to Biogeneric

to Biosimilar (Follow-on Protein)

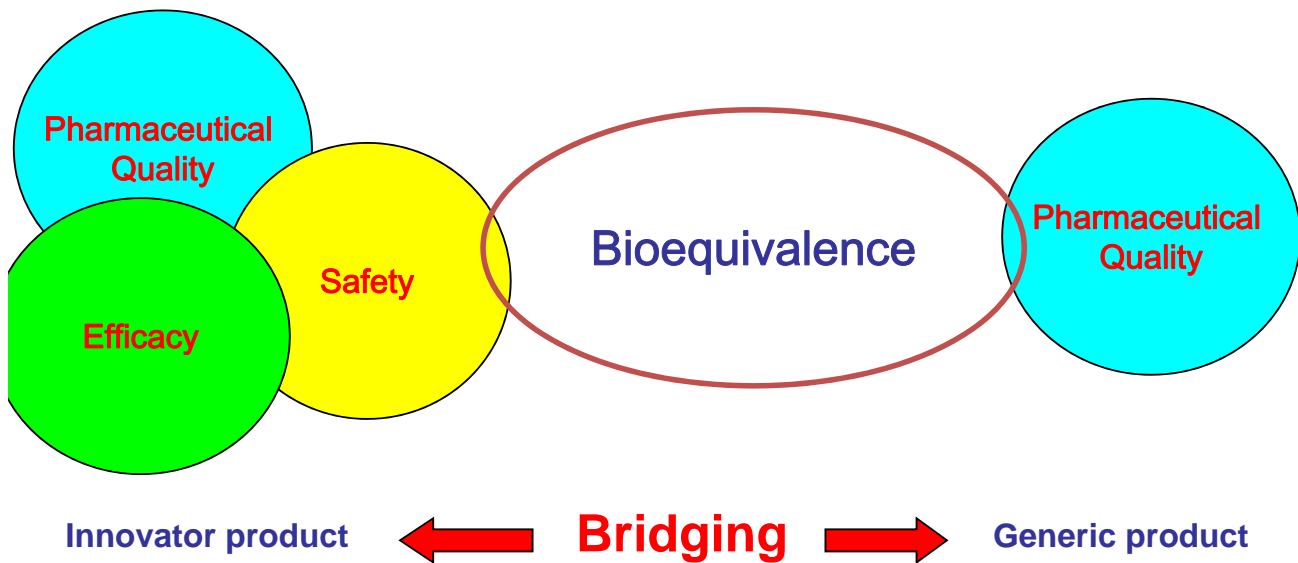
Why?



Registration of Synthetic New Chemical Entity: Decision Basis



..... and its generic fellows



Innovator product = generic product

- same efficacy
- same safety
- same indications
- same dose regimen

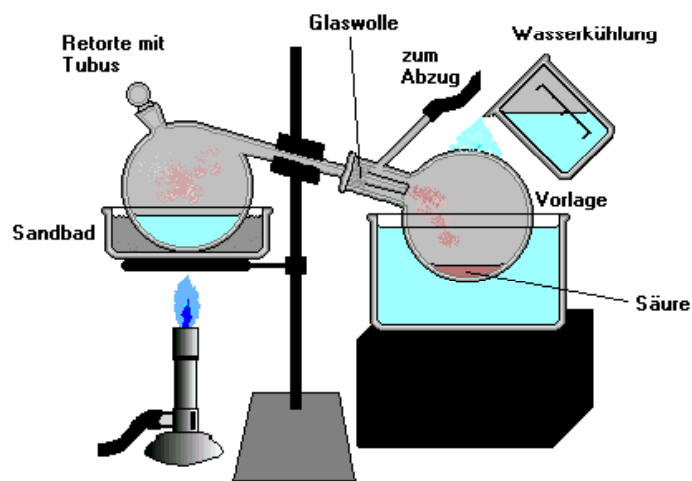
➔ **INTERCHANGEABILITY**

➔ **SUBSTITUTION**

The Synthetic versus biotechnology-derived Medicinal Products – What is the difference?

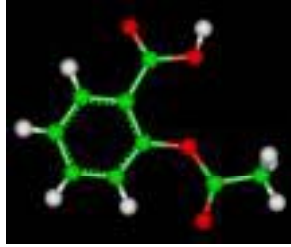
The synthetic medicinal product

From starting Material to Product

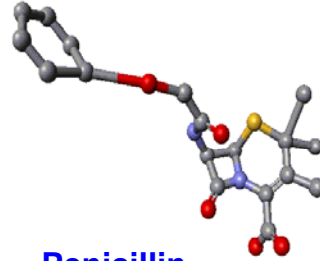


The synthetic medicinal product

The Product



Aspirin



Penicillin

- simple
- small
- easily characterized
- clean

The biotechnology-derived Medicinal Products

The biotechnology-derived Medicinal Products

SPIEGEL ONLINE WIRTSCHAFT KURSE:

Ressort wählen ▾ Aktuell Börse Depot Fonds Derivate

Home > Wirtschaft

17. März 2005 [Druckversion](#) | [Versenden](#) | [Leserbrief](#)

PHARMAINDUSTRIE

Die Kopisten stoßen an Grenzen

Biotech-Wirkstoffe werden eher gebraut als chemisch konstruiert. In riesigen Fermentern schwimmen Kulturen genetisch veränderter Bakterien in Nährlösung. Aus dieser Biosuppe werden die Wirkstoffe extrahiert und gereinigt. Sie bestehen aus Proteinen, die auch natürlich vorkommen - oder ähneln diesen zumindest.

Aber wenn sie erst einmal ein taugliches Molekül gefunden haben, ist dessen Produktion meist einfach - auch für Nachahmer.

Deshalb spielen Patente eine so

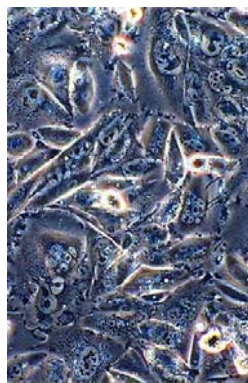
Molekulare Struktur von Insulin: Unübersichtliche Gebilde erschweren die Qualitätskontrolle

The biotechnology-derived Medicinal Products

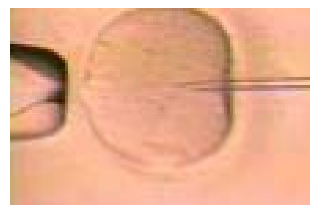
From starting Material to Product



Source of „production site“



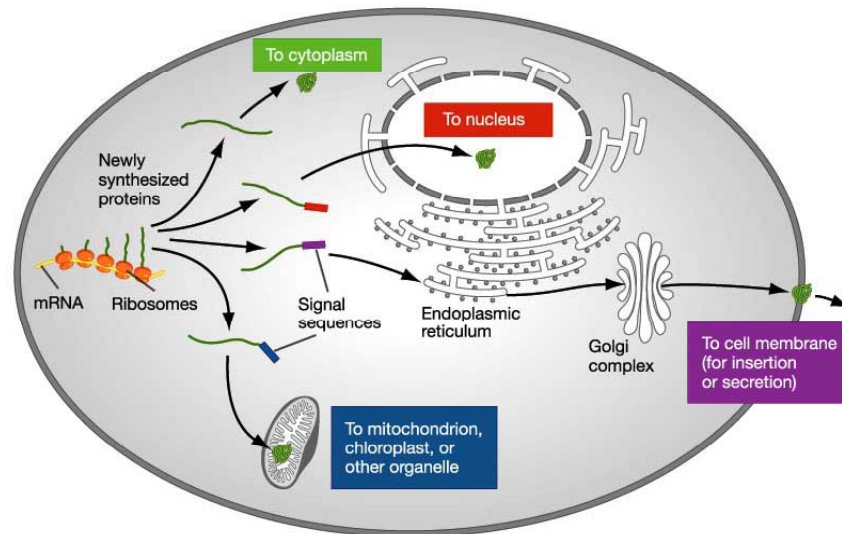
„Production site“



Gene transfer

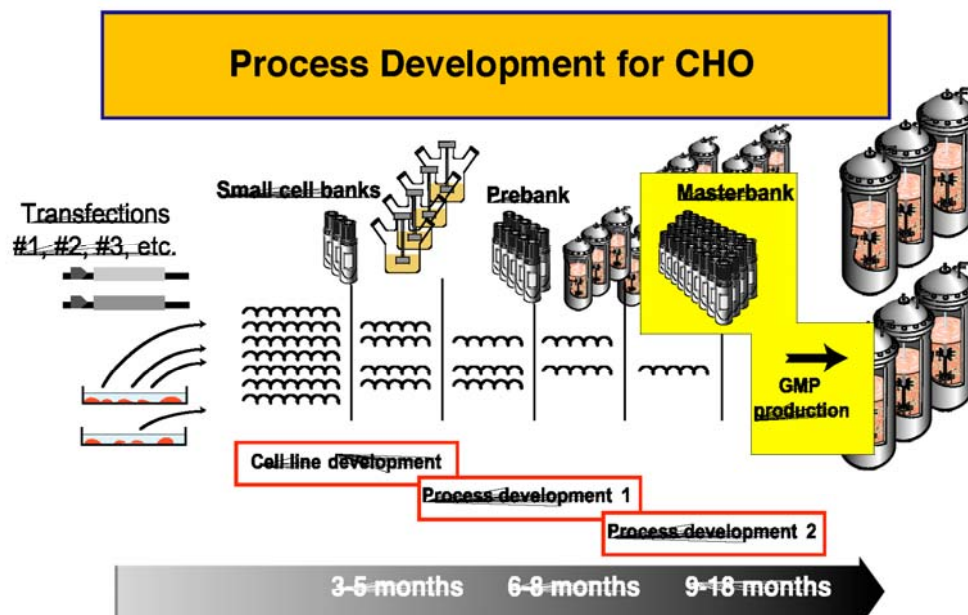
The biotechnology-derived Medicinal Products

From starting Material to Product



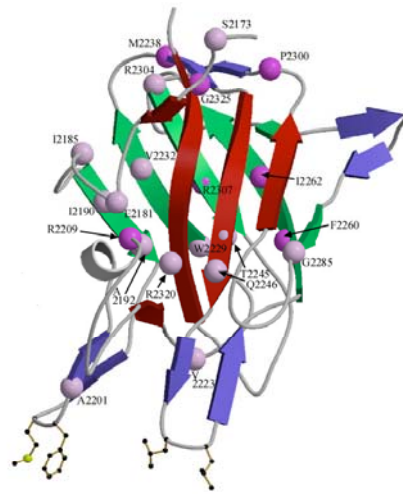
The biotechnology-derived Medicinal Products

Prozess: Vom Plasmid bis zum Bioreaktor



The biotechnology-derived Medicinal Products

The Product



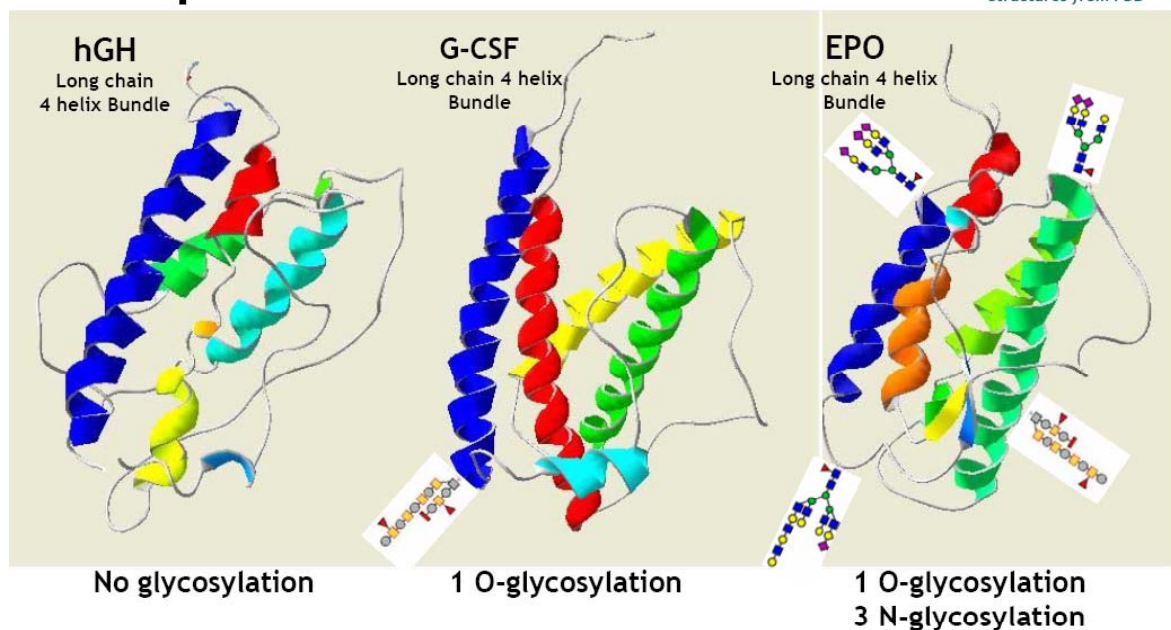
Factor VIII

Fred Hutchinson Cancer Research Center

- Production site complex
- Product very large
- Heterogeneity in structure
- Difficult to characterize
- Difficult to clean

The biotechnology-derived Medicinal Products

Difference in post-translational modification



Synthetic versus biotechnology-derived Medicinal Products

Difference in complexity

<u>Product</u>	<u>Molecular Weight (Dalton)</u>	<u>Number of Amino Acids</u>
Chemically-Based		
Propranolol	259	-
Aspirin	180	-
Biologic		
Calcitonin	4,500	32
Hu Growth Hormone	22,000	191
Erythropoietin	ca. 30,000	165
Factor VIII	ca. 264,000	2332

Synthetic versus biotechnology-derived Medicinal Products

„The process makes the product“

**Any change in the production may
change the product**

**Any change in the product may
change the efficacy and safety**

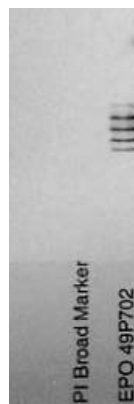
Major Challenges

- Differences in 3-D structure
- Batch reproducibility
- Impurities

May affect efficacy and safety

Example: Erythropoietin

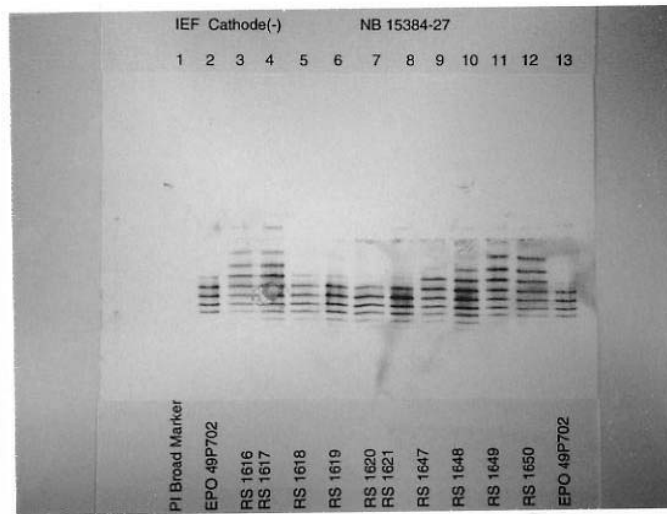
Eprex Gelelectrophorese / MW / Eprex



Schellekens, H., Biosimilar Epoetins: How Similar Are They? Eur. J. of Hosp. Scien., Mar 04, 43-47

Example: Erythropoietin

Effect of changing the production site

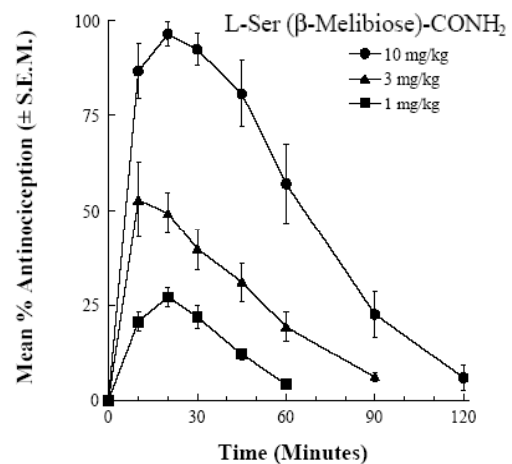
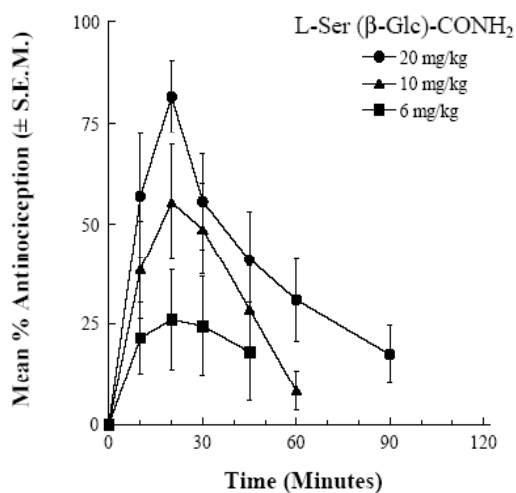


Schellekens, H., Biosimilar Epoetins: How Similar Are They? *Eur. J. of Hosp. Scien.*, Mar 04, 43-47

The risk – difference in efficacy

Structural differences and effect on bioavailability

Site of Carbohydrate Linkage – Opioid Glycopeptide (Elmagbari et al.)



The risk – difference in efficacy

Structural differences and the effect on tissue distribution

Biodistribution of Radiolabeled Glycoforms in Mice*

Tissue	Form 1	Form 2	Form 3	Form 4
Blood	100%	108%	103%	217%
Liver	100%	51%	13%	4%
Lungs	100%	22%	56%	289%
Bone Marrow	---	---	*	---

* Neoglycopeptides (derived from fibrinogen, thyroglobulin)
25 minutes post-dose, cpm \times 10⁸ gm tissue

Gupta and Surolia. 1994
Glycoconjugate Journal

The risk – difference in safety

The event, which changed perception

The New England Journal of Medicine

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FEBRUARY 14, 2002

NUMBER 7

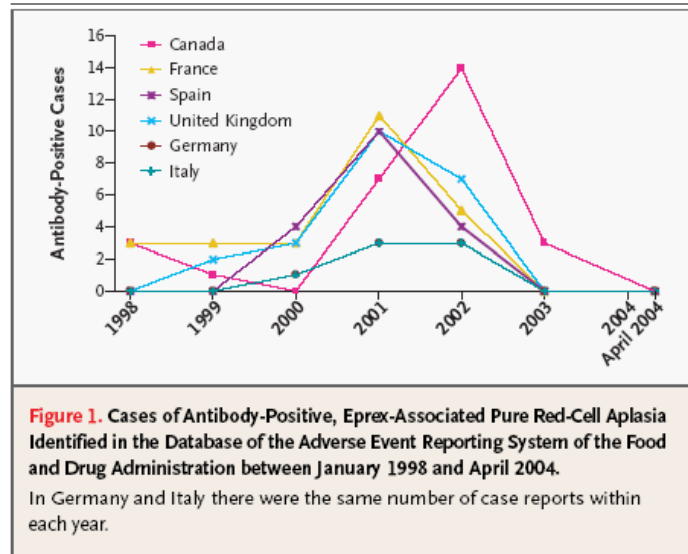


PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

NICOLE CASADEVALL, M.D., JOELLE NATAF, M.D., BÉATRICE VIRON, M.D., AMIR KOLTA, M.D.,
JEAN-JACQUES KILADJIAN, M.D., PHILIPPE MARTIN-DUPONT, M.D., PATRICK MICHAUD, M.D., THOMAS PAPO, M.D.,
VALÉRIE UGO, M.D., IRÈNE TEYSSANDIER, B.S., BRUNO VARET, M.D., AND PATRICK MAYEUX, PH.D.

The risk – difference in safety

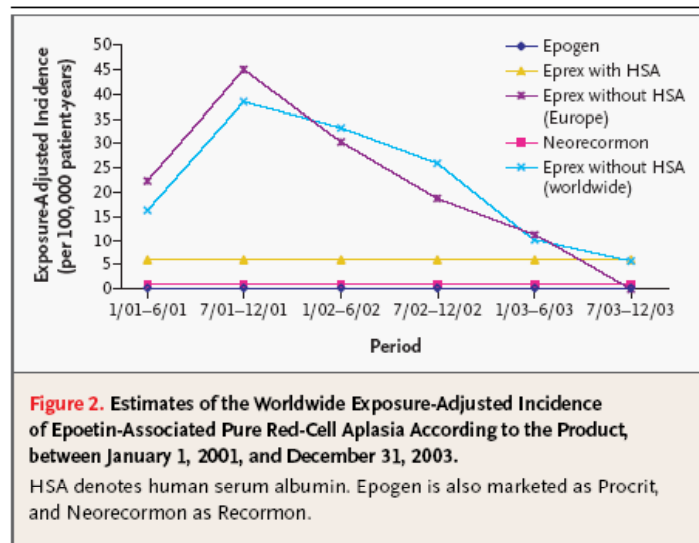
... the observation



Bennett C.NJM, 2004; 351, 1403

The risk – difference in safety

... and the analysis



Bennett C.NJM, 2004; 351, 1403

Biosimilars – Evolutionary Development of a New Term

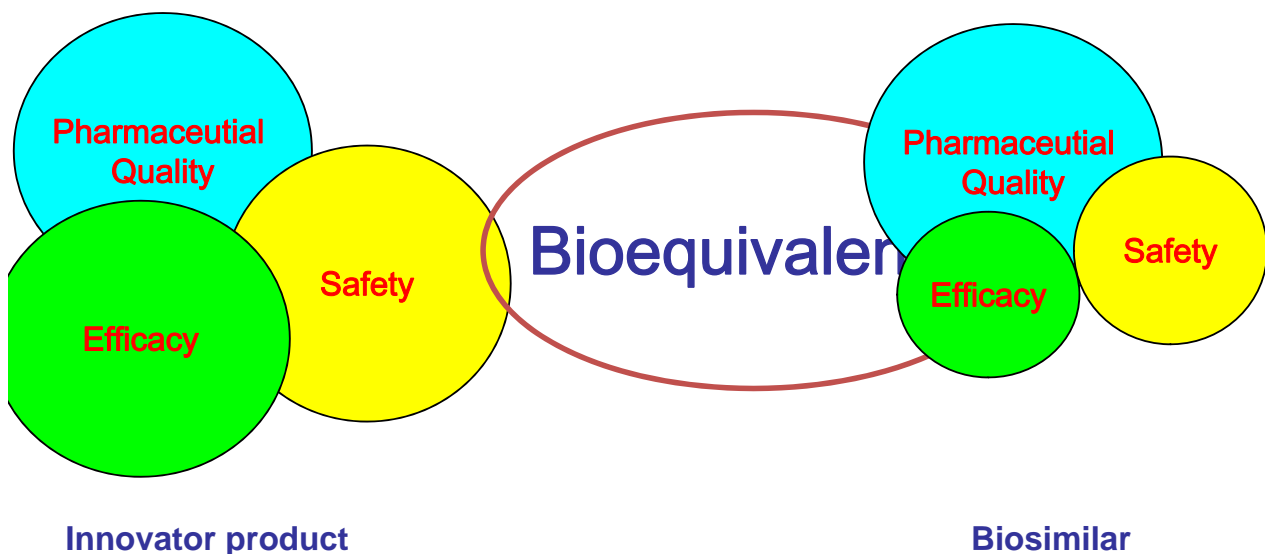
~~from Generic~~

~~to Biogeneric~~

to Biosimilar (Follow-on Protein)



Question:
Decision basis for registration of a biosimilar?



The buzz word:

COMPARABILITY

No prove of efficacy (already proven with original product)

No prove of safety

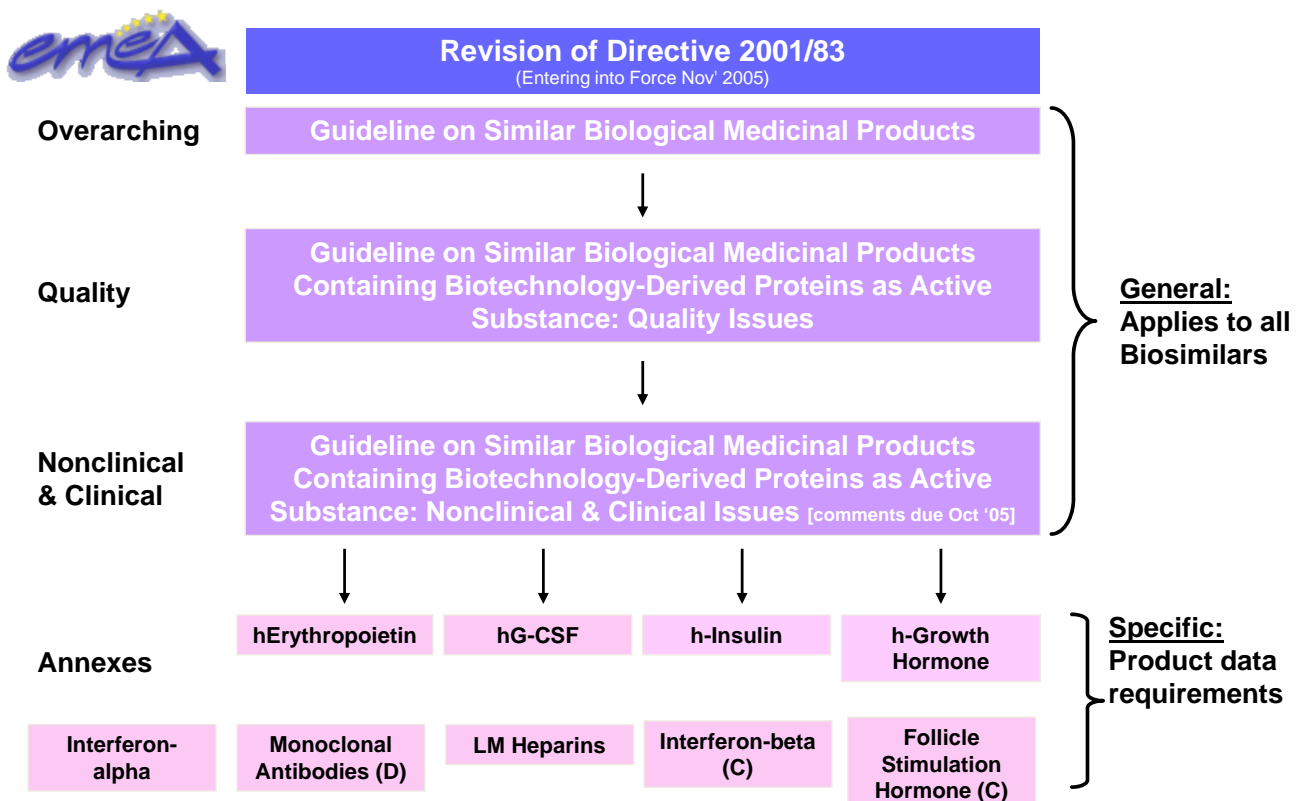
PROVE OF COMPARABILITY IN SAFETY AND EFFICACY

BUT

Immunogenicity, long term follow up

Risk Management Plan

Cautious approach of the regulatory bodies



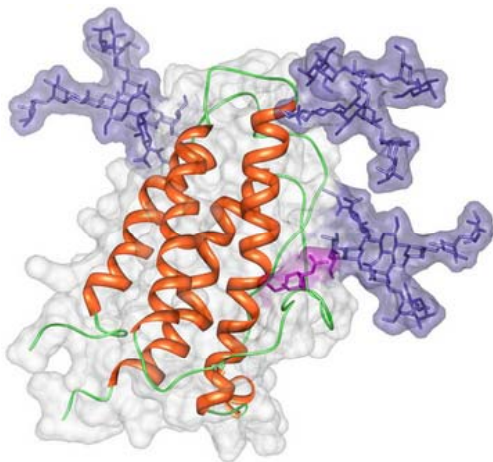
Elements considered in Guidelines

- Complexity of Molecule – risk of structural differences
- Comparability on the molecular level (quality documentation)
- Comparability on pre-clinical level
- Comparability on clinical level
 - efficacy
 - safety
- Most sensitive indication
- Extrapolation to other indications
- Risk Assessment – Post Marketing Surveillance

INTERCHANGEABILITY



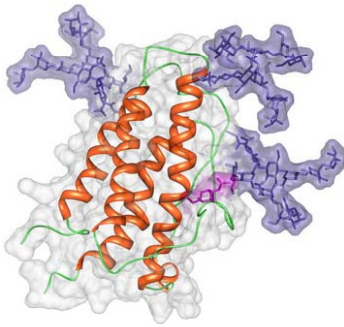
Example Erythropoietin



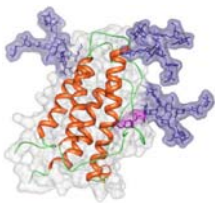
Recombinant human Erythropoietin, 165 residues, expressed in CHO cells.

Molecular weight is approx. **30'000**
(40% sugar moiety)

Example Erythropoietin



Complexity of molecule requires extensive clinical study program, including correction and maintenance phase and post-marketing fu



Example Erythropoietin

ORIGINALPRÄPARATE:

DIU

Präparat	INN (Wirkstoffbezeichnung)	Vertreiber	Wirkstoffhersteller	Zelllinie
Aranesp®	Darbepoetin alfa	Amgen	Amgen	CHO-Zellen
Erypo®	Epoetin alfa	Janssen-Cilag	Johnson & Johnson	CHO-Zellen
Neorecormon®	Epoetin beta	Roche	Roche	CHO-Zellen
Micera®	Methoxy-Polyethylen-glycol-Epoetin beta	Roche	Roche	CHO-Zellen
Biopoin®	Epoetin theta	CT Arzneimittel	Merckle Biotec	CHO-Zellen
Eporatio®	Epoetin theta	Ratiopharm	Merckle Biotec	CHO-Zellen

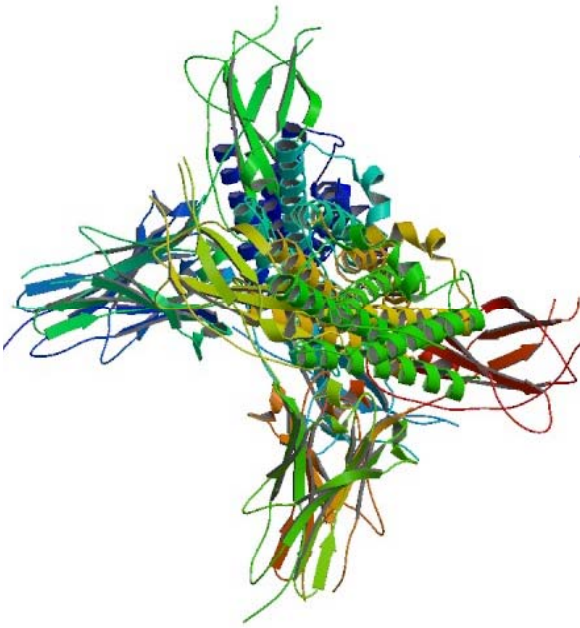
CHO = Chinese Hamster Ovary

BIOSIMILARS:

Präparat	INN (Wirkstoffbezeichnung)	Vertreiber	Wirkstoffhersteller	Zelllinie	Referenzprodukt
Abseamed®	Epoetin alfa	medice	Rentschler	CHO-Zellen	Erypo®
Epoetin alfa Hexal®	Epoetin alfa	Hexal	Rentschler	CHO-Zellen	Erypo®
Binocrit®	Epoetin alfa	Sandoz	Rentschler	CHO-Zellen	Erypo®
Retacrit®	Epoetin zeta	Hospira	Norbitec	CHO-Zellen	Erypo®
Silapo®	Epoetin zeta	Stada	Norbitec	CHO-Zellen	Erypo®

CHO = Chinese Hamster Ovary

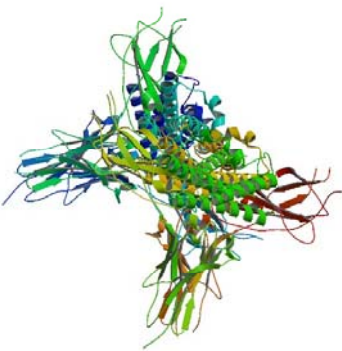
Example Filgrastim



Recombinant human G-CSF (Granulocyte colony stimulating factor), 175 residues, expressed in E. coli. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in E coli.

Molecular weight is **18'802.8 g/mol**

Example Filgrastim



- **Relative simple molecule**
- **Low Immunogenicity**

requires minimal clinical study program



Example Filgrastim

DIU

ORIGINALPRÄPARATE:

Präparat	INN (Wirkstoffbezeichnung)	Vertreiber	Wirkstoffhersteller	Zelllinie
Neupogen®	Filgrastim	Amgen	Amgen	E.coli
Granocyte®	Lenograstim	Chugai Pharma	Chugai Pharma	CHO-Zellen
Neulasta®	Pegfilgrastim	Amgen	Amgen	E.coli

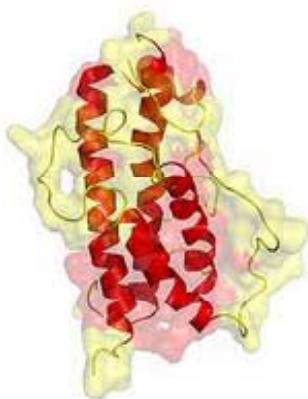
CHO = Chinese Hamster Ovary

BIOSIMILARS:

Präparat	INN (Wirkstoffbezeichnung)	Vertreiber	Wirkstoffhersteller	Zelllinie	Referenzprodukt
Filgrastim Hexal®	Filgrastim	Hexal	Sandoz	E.coli	Neupogen®
Zarzio®	Filgrastim	Sandoz	Sandoz	E.coli	Neupogen®
Biograstim®	Filgrastim	ct Arzneimittel	SICOR Biotech	E.coli	Neupogen®
Filgrastim ratiopharm®	Filgrastim	ratiopharm	SICOR Biotech	E.coli	Neupogen®
Ratiograstim®	Filgrastim	ratiopharm	SICOR Biotech	E.coli	Neupogen®
Tevagrastim®	Filgrastim	Teva	SICOR Biotech	E.coli	Neupogen®

vfa, 12. Feb 2011

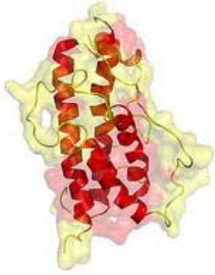
Example Somatotropin



Recombinant human growth hormone, 91 residues, expressed in E. coli. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis.

Molecular weight is **22'000**

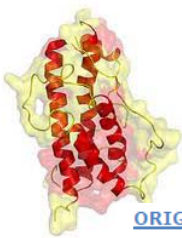
Example Somatotropin



- 6 original products on market with little difference in efficacy and safety
- Relative simple molecule
- Low Immunogenicity

requires minimal clinical study program

Example Somatotropin



ORIGINALPRÄPARATE:

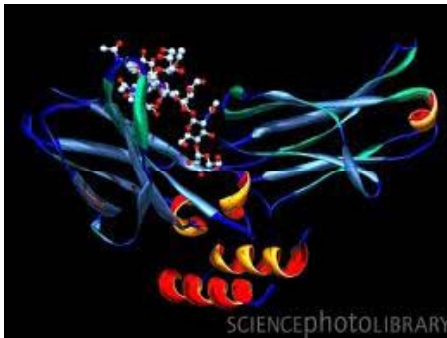
Präparat	INN (Wirkstoffbezeichnung)	Vertreiber	Wirkstoffhersteller	Zelllinie
Genotropin®	Somatropin	Pharmacia/Pfizer	Genentech	E.coli
Humatrope®	Somatropin	Lilly	Lilly	E.coli
Norditropin®	Somatropin	Novo Nordisk	Novo Nordisk	E.coli
Nutropinag®	Somatropin	Ipsen	Genentech	E.coli
Saizen®	Somatropin	Merck Serono	Merck Serono	Mauszellen C127
Zomacton®	Somatropin	Ferring	Ferring	E.coli

BIOSIMILARS:

Präparat	INN (Wirkstoffbezeichnung)	Vertreiber	Wirkstoffhersteller	Zelllinie	Referenzprodukt
Omnitrope®	Somatropin	Sandoz	Sandoz	E.coli	Genotropin®
Valtropin®*	Somatropin	BioPartners	LG Life Sciences Ltd.	Saccharom. cerevisiae	Humatrope®

*In Deutschland ist Valtropin nicht marktrelevant.

Example Rituximab



Monoclonal chimeric (mouse / human) antibody against CD20 mainly present in B-cell. 2 heavy chain of 451 amino acid, 2 light chains of 213 amino acids, produced in CHO Cells, highly complex molecule

Molecular weight is **145'000 kD**

- Highly complex molecule

CHALLENGE

But see below

vfa, 12. Feb 2011

Novartis Issues Challenge To Roche By Launching Copycat Clinical Trials.

The [Financial Times](#) (1/11, Simonian) reports Novartis has issued a challenge to its competitor Roche by launching clinical trials into its own version of biosimilar rituximab, the top selling cancer and rheumatoid arthritis treatment that Roche sells under the brand names Rituxan and Mabthera. Sandoz, the Novartis subsidiary who specializes in "copycat" generic versions of drugs will soon begin the trials.

DIA Daily 1-2011

Novartis Rituxan goes into Phase II

Rituxan is a huge earner for Roche, and Novartis says it ranks among the top three biologics worldwide, with 2009 sales of \$5.60 billion. Sandoz boss Jeff George notes that this "key development milestone" demonstrates that the firm is on track to maintain its global leadership position in biosimilars in the medium to long term.

Biosimilars – Chance oder Risiko?

Guideline on similar biological medicinal products
containing monoclonal antibodies

Draft

Draft Agreed by Similar Biological Medicinal Products Working Party	October 2010
Adoption by CHMP for release for consultation	18 November 2010
End of consultation (deadline for comments)	31 May 2011



Open Questions / Disputes

- **Interchangeability**
- **Substitution**
- **Nomenclature (INN) resolved**
- **Information in Package Insert**
- **Pharmakovigilance**

- **Extrapolation to other indications**

