KATHOLIEKE UNIVERSITEIT LEUVEN

Biologicals and Biosimilars, What's in a name?

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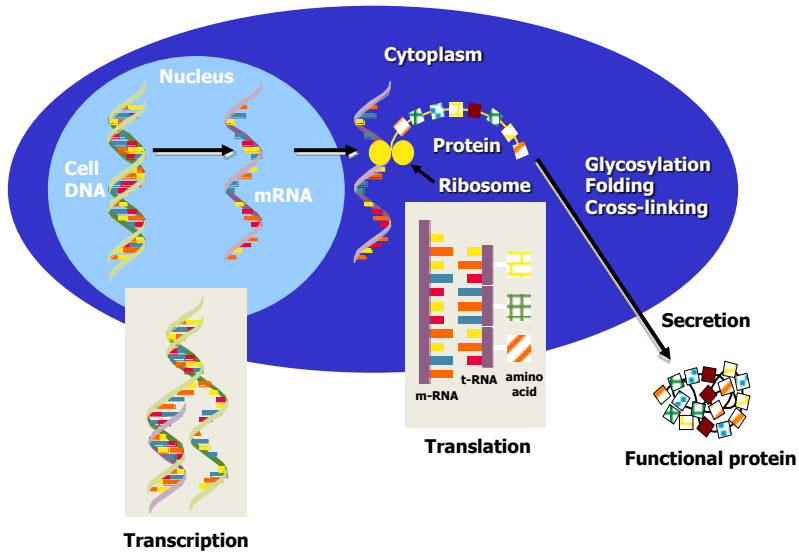
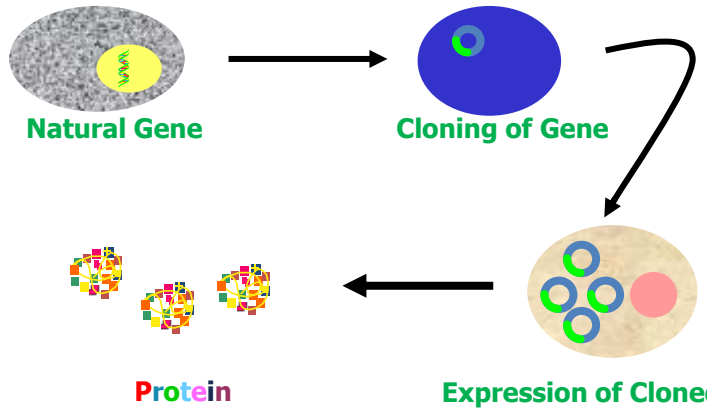
Biological medicinal product

A well-defined biological product prepared by the use of living systems, such as organisms, tissue cultures or cells.

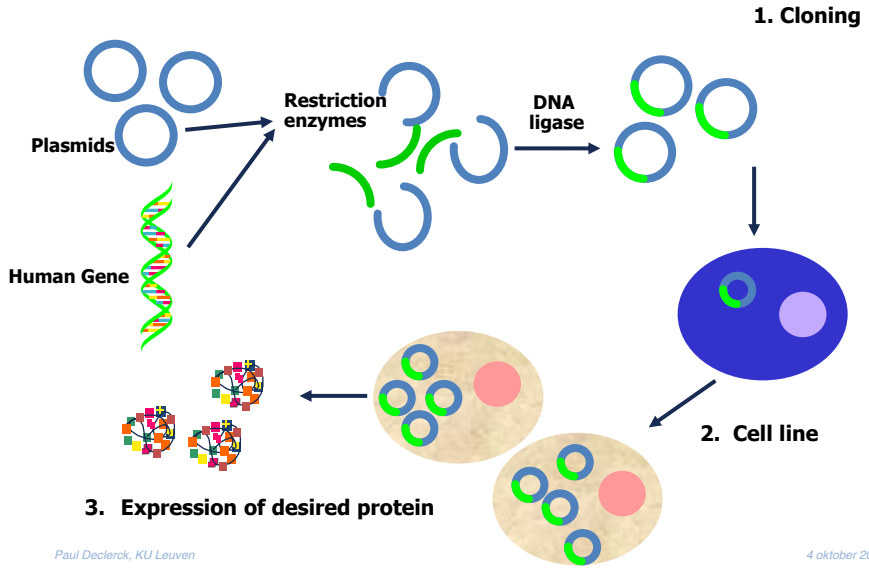
From Gene to Protein



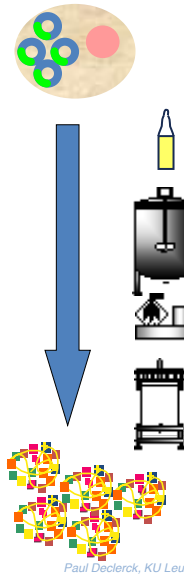
Genetic code is universal !



Recombinant Protein Production



Recombinant Protein Production



Unit Operation	Specific to Product
Cell Expansion	Cell line, growth media, method of expansion
Cell Production in Bioreactors	Cell line, growth media, bioreactor conditions
Recover through filtration or centrifugation	Operating conditions
Purification through chromatography	Binding and elution conditions
Characterization and Stability	Methods, reagents, reference standards

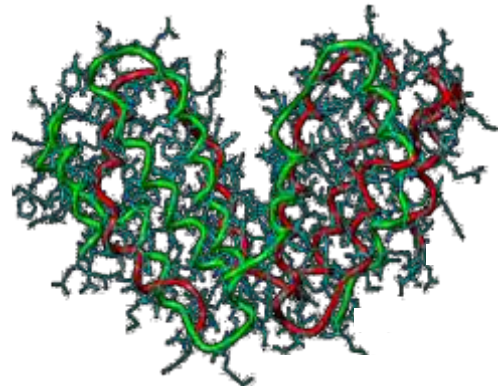
Quality Control Analyses

Cell Banks	Bulk product	Process validation	Final product batches
8+ tests eg, •Karyotype •Infectious/ oncogenic screen •Genetic stability	20+ tests eg, •Amino acid sequence •Peptide maps •IEF •HPLC •SDS-PAGE •RIA •Receptor binding •Bioassays	10+ tests eg, •Endotoxin spiking •Protein challenges •Protein yield •Adventitious agents	30+ tests eg, •Peptide maps •IEF •HPLC •SDS-PAGE •Purity •ELISA •Potency •Stability tests

Chemical *vs* Biotech drugs


Small chemical entity	Large, complex biomolecule
Chemical synthesis	Cell cultures
Defined structure	Heterogeneous structures
Not or less sensitive to process changes	Extremely sensitive to process changes
Relatively stable	Variable; sensitive to conditions
Not or less immunogenic	Immunogenic

Chemical *vs* Biotech drugs



Aspirin: molecular weight 180

Interferon: molecular weight 19.000

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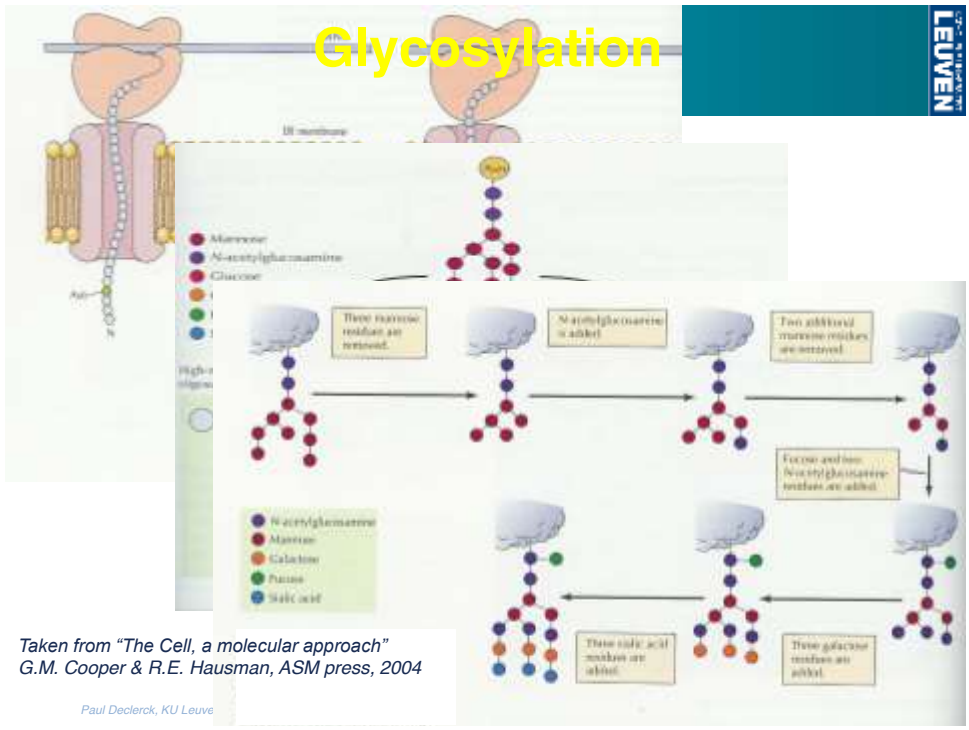
Glycosylation



Taken from "The Cell, a molecular approach"
G.M. Cooper & R.E. Hausman, ASM press, 2004

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"Other" modifications

- Deamidation (e.g. Asn to Asp)
- Racemization (L to D)
- Oxidation (Met, Tyr, His, Trp)
- Disulfide exchange
- …..

- Presence and frequency dependent on:
  - pH
  - Additives
  - Impurities
  - Temperature

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Product variants

- Always present
- Large number of possible variants
- Impossible to unambiguously identify
- Determined by the entire process
- Reproducibility to be guaranteed by consistency in the production process
- Safety also to be proven by clinical studies

Product variants

- 428 aa; 20 Met; on average 0.3 % oxidized;
- Position Met^{19}, Met^{205} and Met^{320} (2:1:3);
- 100 molecules protein: 6 Met oxidized.

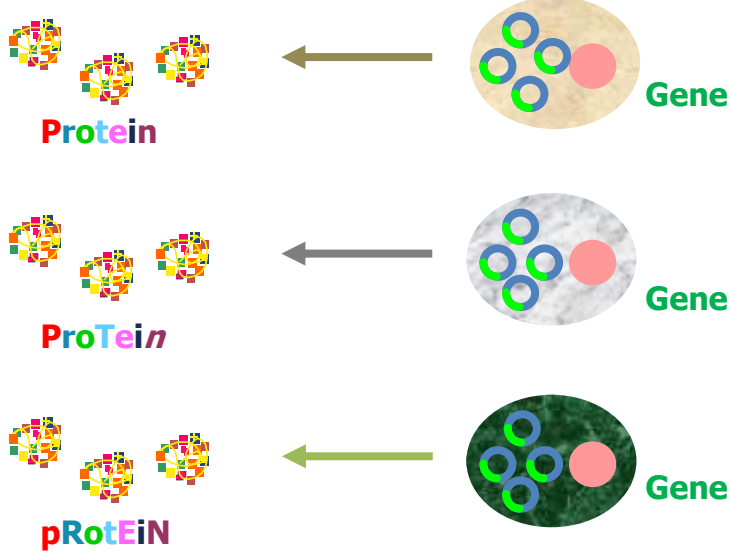
1	M^{19}	M^{205}	M^{320}	428
	Ox	**Ox**	**Ox**	1
	Ox	-	**Ox**	1
	-	-	**Ox**	1
	-	-	-	97
	Ox	-	-	1
	Ox	-	-	1
	-	**Ox**	-	1
	-	-	**Ox**	1
	-	-	**Ox**	1
	-	-	**Ox**	1
	-	-	-	94

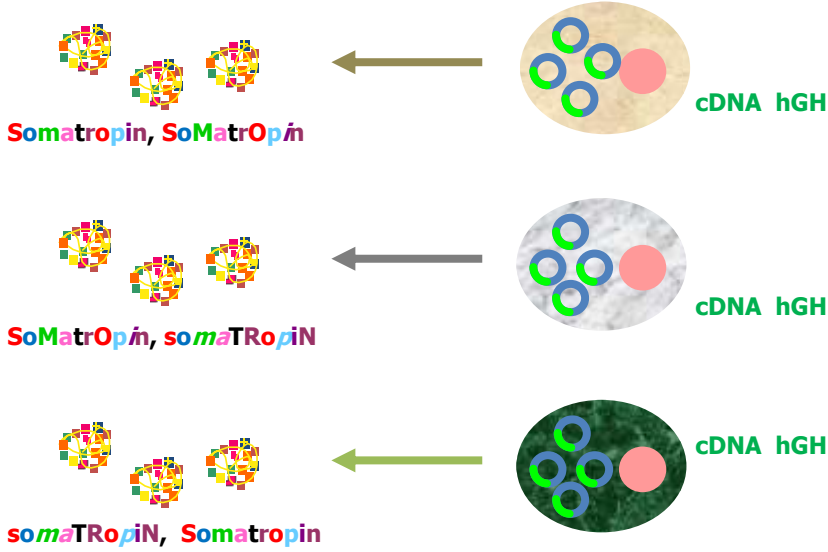
Biological product variants

- Always present
- Large number of possible variants
- Impossible to unambiguously identify
- Determined by the entire process
- Reproducibility to be guaranteed by consistency in the production process

The process determines the product

The process determines the product





A new concept

Somatropin, SoMatrOpin

somaTRopiN, Somatropin

SoMatrOpin, somaTRopiN

- Identical ?
- Comparable ?
- Dissimilar ?

Biosimilar

- Physicochemical characteristics
- Impurities
- Clinical properties

- Reference ?

Criteria ?

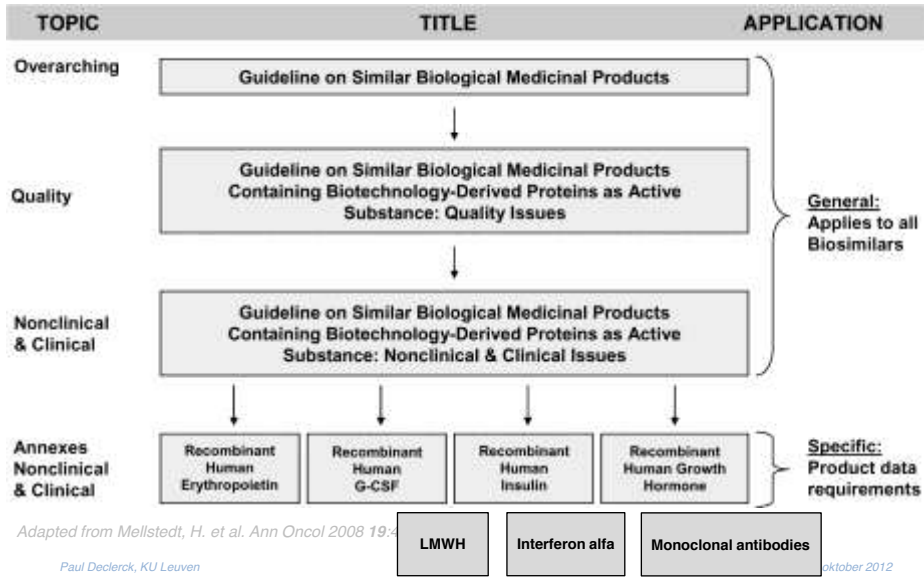
European Medicines Agency EMA

- Similar biological medicinal product:

  '*… biological medicinal product claimed to be "similar" to an approved reference biological medicinal product…*'

- Quality, Safety and Efficacy
- Comparability exercises
- Guidelines

Overview of EMA guidelines for biosimilars



Adapted from Mellstedt, H. et al. Ann Oncol 2008 19:4

Original *vs.* biosimilar

CMC	Nonclinical	Clinical

• Drug substance
  • Manufacture
  • Characterisation
  • Control
  • Reference standard
  • Container
  • Stability
• Drug product
  • Description
  • Development
  • Manufacture
  • Control
  • Reference standard
  • Container
  • Stability
	• Pharmacology
	  • Primary pharm.
	  • Secondary pharm.
	  • Safety pharm.
	  • Interactions
	• Pharmacokinetics
	  • ADME
	  • Interactions
	• Toxicology
	  • Single dose
	  • Repeat dose
	  • Genotoxicity
	  • Carcinogenicity
	  • Reproduction
	  • Local tolerance
		• Pharmacology
		• Pharmacokinetics
		  • Single dose
		  • Repeat dose
		  • Special populations
		• Efficacy and safety
		  • Dose finding
		  • Schedule finding
		  • Pivotal
		  • Indication 1
		  • Indication 2
		  • Indication 3
		  • Indication 4
		• Post-marketing studies

Original *vs.* biosimilar

CMC	Nonclinical	Clinical

• Drug substance
  • Manufacture
  • Characterisation
  • Control
  • Reference standard
  • Container
  • Stability
• Drug product
  • Description
  • Development
  • Manufacture
  • Control
  • Reference standard
  • Container
  • Stability
• Comparability data
  • Analytical comparison with reference product
	• Pharmacology
	  • Primary pharm
	  • Secondary pharm.
	  • Safety pharm.
	  • Interactions
	• Pharmacokinetics
	  • ADME
	  • Interactions
	• Toxicology
	  • Single dose
	  • Repeat dose
	  • Genotoxicity
	  • Carcinogenicity
	  • Reproduction
	  • Local tolerance
		• Pharmacology
		• Pharmacokinetics (Study #1)
		  • Single dose
		  • Repeat dose
		  • Special populations
		• Efficacy and safety (Study #2)
		  • Dose finding
		  • Schedule finding
		  • Pivotal
		  • Indication 1
		  • Indication 2
		  • Indication 3
		  • Indication 4
		• Post-marketing studies
		  • Safety in larger population
		  • Efficacy in other indications
		  • Immunogenicity

Registration of biosimilars (Europe)

- 2 refused by the EU commission:
  - *Interferon alpha-2a* (2006)
  - *Interferon beta-1a* (2009)
- 3 withdrawn:
  - *Insulin* (2008)
    - Insulin Rapid
    - Insulin Long
    - Insulin 30/70 Mix

Registration of biosimilars (Europe)

- 14 approved by the EU Commission
  - *2 Human growth hormone* (2006)
  - *3 Epoietin alfa* (2007)
  - *2 Epoietin zeta* (2007)
  - *4 Filgrastim* (2008)
  - *2 Filgrastim* (2009)
  - *1 Filgrastim* (2010)

Registration of biosimilars (Europe)

- 7 under review (09/2012)
  - 3 Insulin human
  - 1 Follitropin alfa
  - 2 Infliximab
  - 1 Filgrastim

How similar is similar?

Biosimilar ESA [1]

- **"Differences were observed at the glycosylation level"**
- **"Phosphorylated high mannose type structures were detected at higher levels than in Reference ESA"**
- **"Lower values on N-glycolyl-neuramic acid and diacetylated neuramic acids as compared to Reference ESA"**
- **"Peptide map showed differences … in O-linked glycan due to a higher sialylation and lower content of the oxidized variant"**

Biosimilar hGH [2]

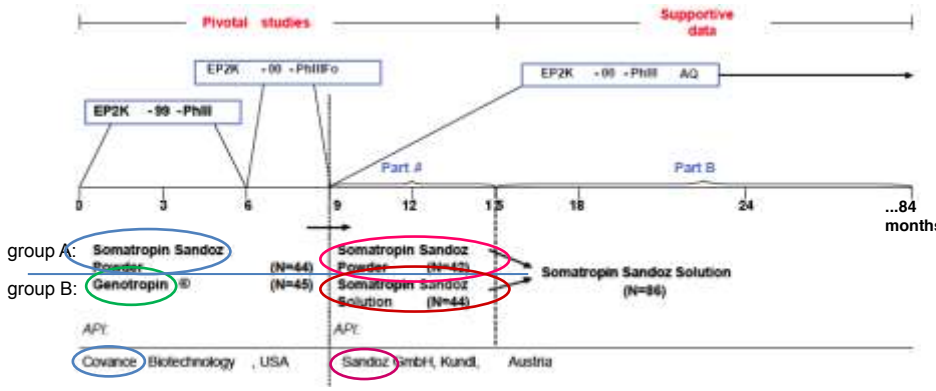
- **"The results of this study … demonstrate that Biosimilar rhGH produced at full scale is comparable to Reference Product"**
- **"The impurity profile of Biosimilar hGH shares some similarity with Reference hGH; however the profiles are not identical"**
- **" … impurities, … , are present in the Biosimilar hGH batches and are not in any Reference hGH batches"**
- **"Additionally, there appears to be a higher level of deamidated variants in the Biosimilar hGH samples"**

Similar, not identical – as predicted, differences observed

[1] European Public Assessment Report on a particular biosimilar ESA.
[2] Summary Basis of Approval of a particular biosimilar hGH

Clinical evidence

- **efficacy:** 1 study consisting of 3 substudies

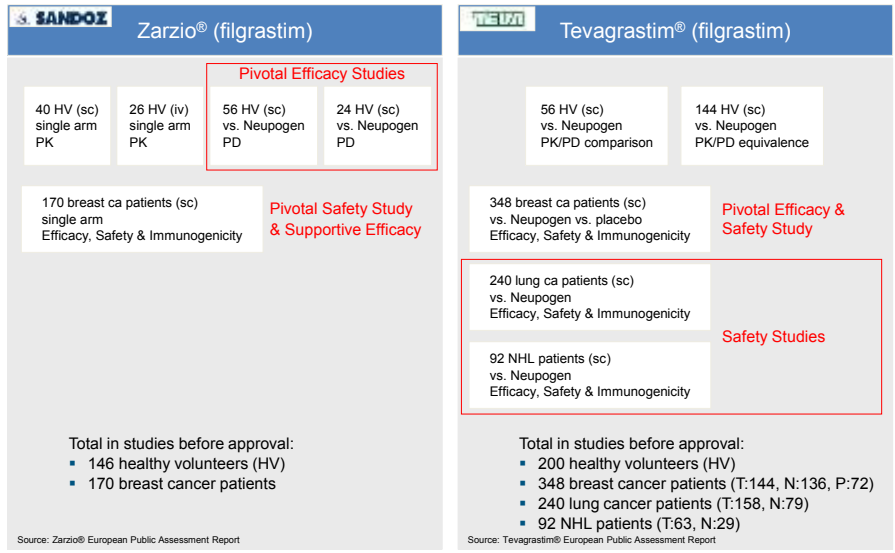


•Romer T. *et al.* Horm Res 2009;72:359-369
•Omnitrope EPAR. Scientific discussion
•Declerck P. J. *et al.* Curr Med Res & Opinion 2010; 26: 1219-1229

EMA Biosimilar G-CSF guideline

Non-clinical studies	Comparative pharmacology & 1-month toxicology
Human PK & PD studies	Comparative *vs.* innovator in healthy volunteers Single dose (SC & IV); PD markers ANC and $CD34^+$
Efficacy studies	Comparative equivalence study *vs.* innovator in chemotherapy-induced neutropenia (CIN) *OR* PD study *vs.* innovator in healthy volunteers (if justified)
Extrapolation	Yes Equivalence in CIN may allow extrapolation to other indications, if mechanism of action is the same
Safety	Evaluate AE's & immunogenicity in CIN study 6-month treatment duration
Post-Approval Commitments	Immunogenicity & rare serious AEs Safety & lack of efficacy in extrapolated indications

Clinical studies: nature and extent may vary, even within the same class



Registration of biosimilars (Europe)

- Naming confusing
- Limited clinical experience
- Extrapolation for some indications
- SmPC misleading

- Prescription practices
- Pharmacovigilance

Epoietin alfa

- Eprex®: 11 studies including 6,626 pts (reference)
- Binocrit®: 2 studies including 388 pts (biosimilar)

SmPC Binocrit refers to 11 studies/6,626 pts !

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Filgrastrim

Indication	√ Clinical trial data ⇨Extrapolation		
	Neupogen® (Reference)	Zarzio®	Tevagrastim®
Chemotherapy-induced neutropenia (except CML and MDS)	√ (n = 3,932)	√ n = 170	√ n = 140/158/63
AML receiving chemotherapy	√ (n = 297)	⇨	⇨
Stem Cell Transplantation	√ (n = 1,802)	⇨	⇨
Paediatrics	√ (n = 1,063)	⇨	⇨
Mobilization of PBPC	√ (n = 1,025)	⇨	⇨
Severe congenital, cyclic, or idiopathic neutropenia	√ (n = 1,293)	⇨	⇨
HIV-related neutropenia	√ (n = 530)	⇨	⇨

Manufacturing change *vs.* Biosimilar

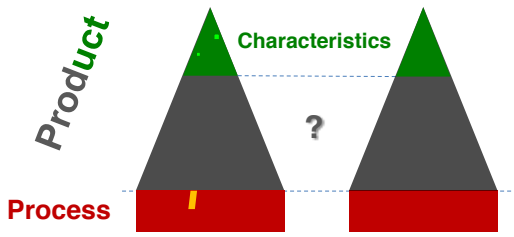
Manufacturing change

- Same cell line
- Same process with a change
- Comparison pre/post based upon numerous analyses/characteristics
- Reference material available at each step

Biosimilar

- Newly developed cell line
- Entirely new process
- Comparison *vs.* reference based upon less analyses/characteristics (proprietary info lacking)
- Reference API not available

Manufacturing change *vs.* Biosimilar

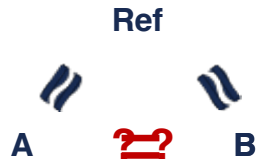


Manufacturing change ***vs.*** **Originator**

Biosimilarity ≠ Interchangeability

- Not identical to reference
- Claim for interchangeability needs to be proven (in both directions!) and holds only for the two products evaluated
- Two or more biosimilars from the same reference product have not been compared to each other.

Biological drugs



Biological drugs

- No substitution
- Physician control over prescribing
- Appropriate (brand)naming required

Conclusions

- Complex molecules
- Properties are process-dependent
- Biosimilars are similar but not identical to reference product
- Non-substitutable
- Limited clinical experience
- Follow-up measures