KU LEUVEN

Biologicals and Biosimilars

The rules of engagement in Europe

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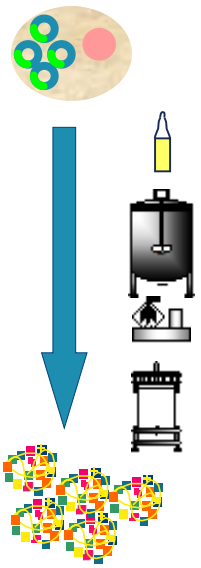
Disclosing Financial Relationships

- speakers' fee for lectures for various pharmaceutical companies
- honoraria for (non-product specific) advisory board meetings for various pharmaceutical companies

Biological medicinal product

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

Recombinant Protein Production

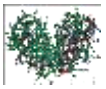
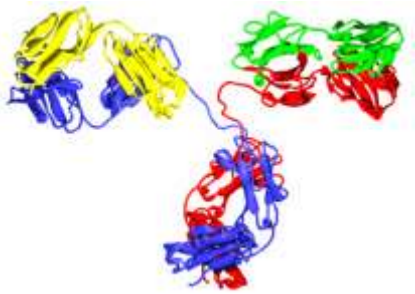


Unit Operation	Specific to Product
Cell Expansion	Cell line, growth media, method of expansion
Cell Production in Bioreactors	Cell line, growth media, bioreactor conditions
Recover through filtration or centrifugation	Operating conditions
Purification through chromatography	Binding and elution conditions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

Paul Declerck, 2016 03 16

Chemical versus Biological drug



Aspirin Interferon Monoclonal Antibody

Chemical versus Biological drug

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**

Molecular basis of heterogeneity

- Glycosylation
- Phosphorylation
- Sulfation
- Methylation
- N-acylation
- S-Nitrosylation
- ….
- cell type and culture conditions

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

- External conditions (pH, additives, temperature....)

> 10^8 variants

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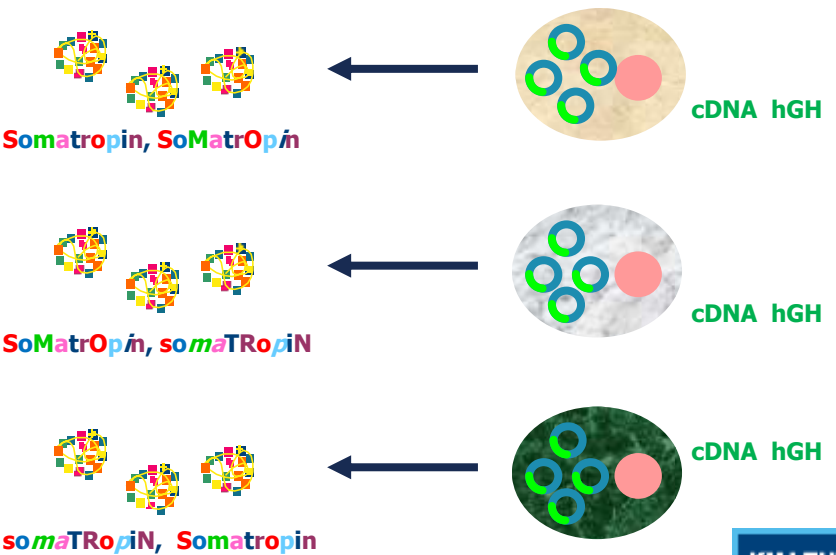
Biological medicinal product

- 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



European Medicines Agency (EMA)

- Similar biological medicinal product:

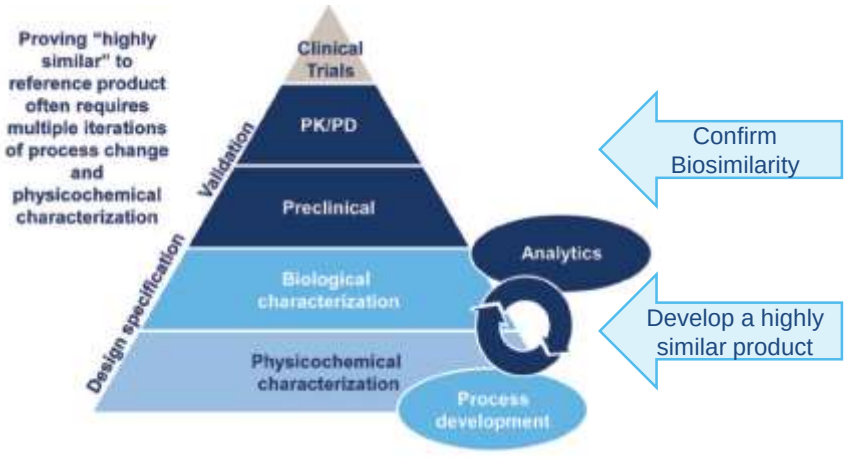
'A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the European Economic Area.

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.'

- Guidelines for development and registration since 2006

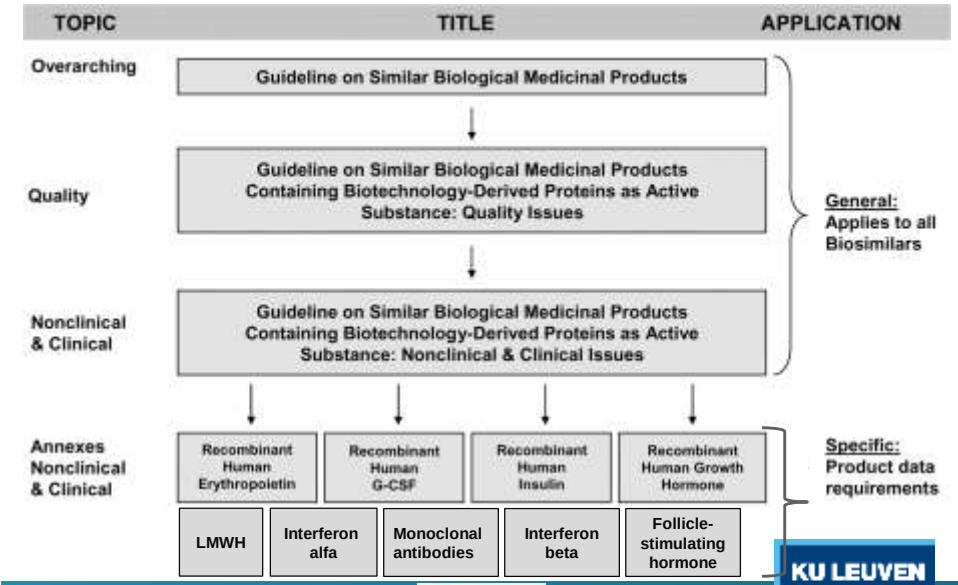
EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf (accessed Dec 2015).

Concept of biosimilar development



McCamish. MAbs. 2011;3(2):209-17

EMA guidelines for biosimilars



Registration requirements (Biosimilar)

Quality	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)

- 22 approved in Europa (02/2016)
  - *2 Human growth hormone* (2006)
  - *3 Epoietin alfa* (2007)
  - *2 Epoietin zeta* (2007)
  - *4 Filgrastim* (2008)
  - *2 Filgrastim* (2009)
  - *1 Filgrastim* (2010)
  - *2 Infliximab* (2013)
  - *1 Filgrastim* (2013)
  - *1 Follitropin alfa* (2013)
  - *1 Follitropin alfa* (2014)
  - *1 Insulin glargine (2014)*
  - *1 Filgrastim (2014)*
  - *1 Etanercept (2016)*

Registration of biosimilars (Europe)

- 11 under review (02/2016)
  - *1 Etanercept*
  - *1 Infliximab*
  - *2 Enoxaparin*
  - *1 Rituximab*
  - *3 Pegfilgrastim*
  - *2 Adalimumab*
  - *1 Insulin glargine*

How similar are biosimilars ?

Biosimilar ESA (*)

- "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 (*)

- "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"

Biosimilar IFX (*)

- "….. all major physicochemical characteristics and biological activities of biosimilar IFX were comparable to those of the reference product"
- "….difference in the amount of afucosylated infliximab, translating into a lower binding affinity towards FcγRIIIa receptors and a lower *ex vivo* antibody-dependent cellular cytotoxicity (ADCC) activity…."
- "… less intact IgG …. , mainly due to a higher proportion of non-assembled form. …. unlikely to impact its biological activity"
- "a higher level of C-terminal lysine variability"
- "…slightly higher level of aggregates …"

Biosimilars are Similar, not identical

(*) Based upon European Public Assessment Report on respective biosimilars.

Infliximab: *extrapolation of indications*

Remicade approved indications		Remsima/Inflectra approved indications
• Rheumatoid arthritis	• **PK study in AS (Phase I, 250 patients)**	• Rheumatoid arthritis
• Adult Crohn's disease	• **Equivalence trial in RA (Phase III, 606 patients)**	• Adult Crohn's disease
• Paediatric Crohn's disease		• Paediatric Crohn's disease
• Ulcerative colitis		• Ulcerative colitis
• Paediatric ulcerative colitis		• Paediatric ulcerative colitis
• Ankylosing spondylitis		• Ankylosing spondylitis
• Psoriatic arthritis		• Psoriatic arthritis
• Psoriasis		• Psoriasis

extrapolated indications in light blue

REMSIMA European Public Assessment Report.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-Public_assessment_report/human/002576/WC500151486.pdf assessed January 27, 2014

Biosimilarity ≠ Interchangeability

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

Conclusions

- Complex (multi-domain) molecules
- Properties are process-dependent
- Biosimilars are similar but not identical to reference product
- Approved: pharmaceutical quality demonstrated
- Approved: limited clinical experience
- Non-interchangeable (during treatment)
- Follow-up measures