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Biosimilars

Scientific Challenges and Implications

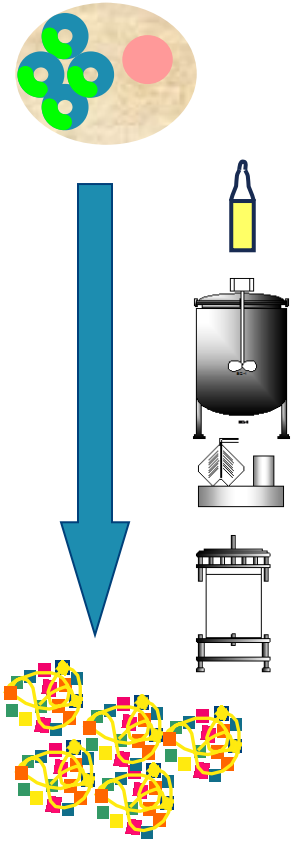
Professor Paul Declerck
Laboratory for Therapeutic and Diagnostic Antibodies

paul.declerck@pharm.kuleuven.be

Biological medicinal product

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

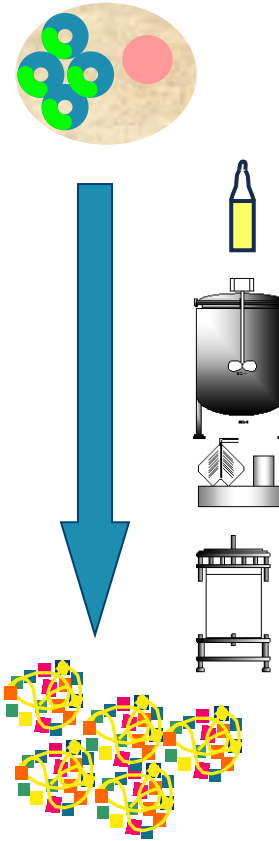
Recombinant Protein Production



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

Bioreactor

Recombinant Protein Production



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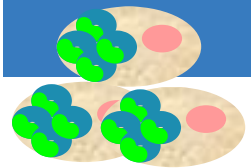
Recombinant Protein Production

Cell Banks

10+ tests

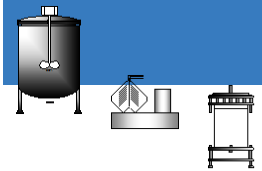
eg,
- Karyotype
- Infectious/ oncogenic screen
- Gene stability



Process validation

20+ tests

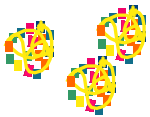
eg,
- Endotoxin spiking
- Protein challenges
- Protein yield
- Adventitious agents



Bulk product

20+ tests

eg,
- Amino acid sequence
- Peptide maps
- IEF
- HPLC
- SDS-PAGE
- RIA
- Receptor binding
- Bioassays



Final product batches

30+ tests

eg,
- Peptide maps
- IEF
- HPLC
- SDS-PAGE
- Purity
- ELISA
- Potency
- Stability tests

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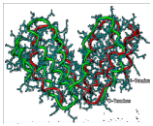
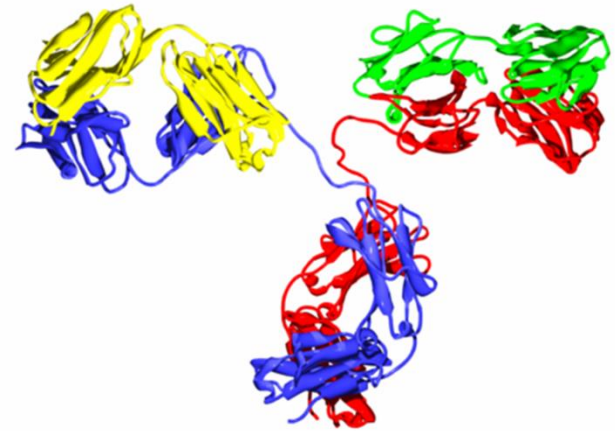
Chemical versus Biological drug





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

Post-translational modifications (glycosylation)

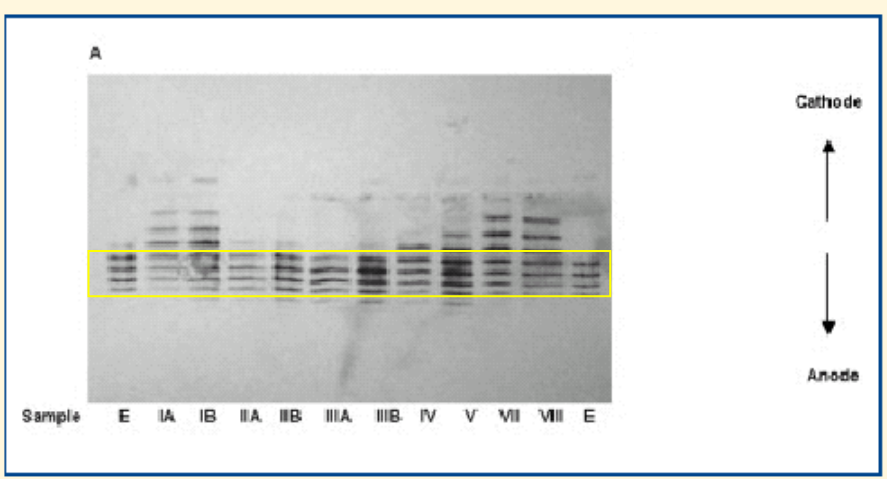


Figure 1
Isoelectric Focusing / Western Blot. Isoform distribution of each sample is shown.

Schellekens H. Nephrol Dial Transplant 2005

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

Chemical versus Biological drug

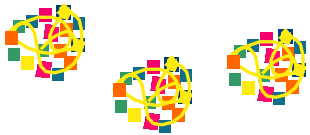
Small chemical entity	Large, complex biomolecule
Chemical synthesis	Cell cultures
Defined structure	Heterogeneous structures
Not or less sensitive to process changes	Extremely sensitive to process changes
Relatively stable	Variable; sensitive to conditions
Not or less immunogenic	Immunogenic

Biological Product variants

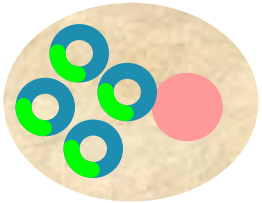
- Always present
- Large number of possible variants
- Impossible to unambiguously identify
- Determined by the entire process
- Reproducibility to be guaranteed by consistency in the production process

The process determines the product

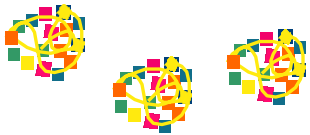
The process determines the product



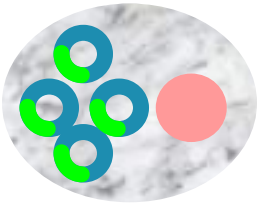
Somatropin, SoMatrOpín



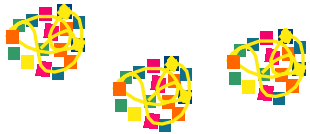
cDNA hGH



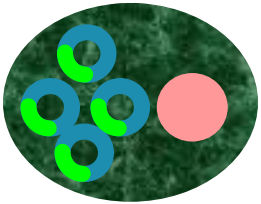
SoMatrOpín, somaTRopiN



cDNA hGH



somaTRopiN, Somatropin



cDNA hGH

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A new concept

Somatropin, SoMatrOpin

somaTRopiN, Somatropin

SoMatrOpin, somaTRopiN

- Identical ?
- Comparable ?
- Dissimilar ?

Biosimilar

- Physicochemical characteristics
- Impurities
- Clinical properties

European Medicines Agency (EMA)

'A similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use.'

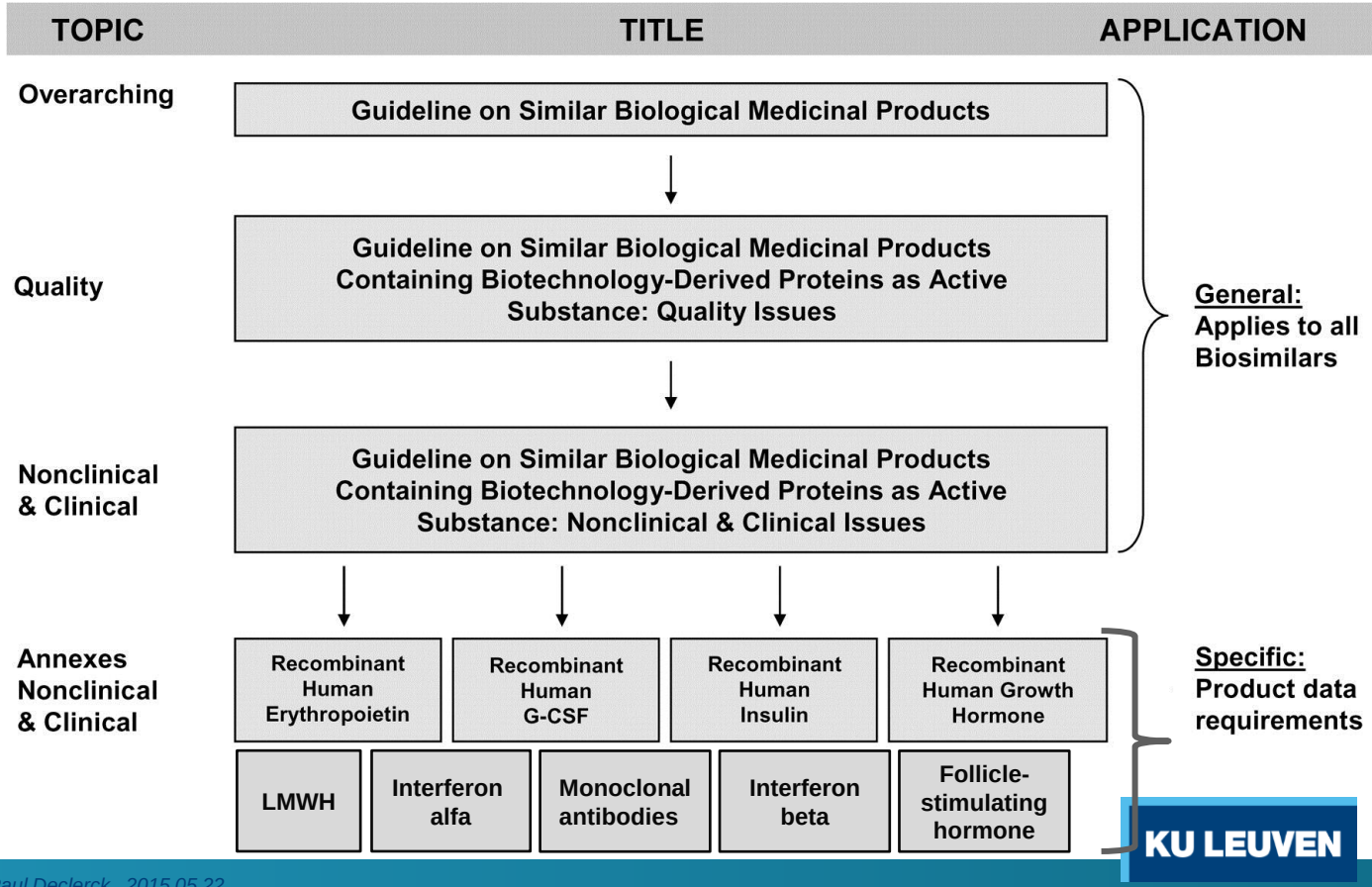
Guidelines

- Biosimilars (EMA, 2006; Australia, Canada, Japan, Korea, …)
- Similar Biotherapeutic Products (WHO, 2010)
- Biosimilars (FDA, draft 2012; final April 2015)

- Quality, Safety and Efficacy
- Comparability exercises

- Authorized reference product

EMA guidelines for biosimilars



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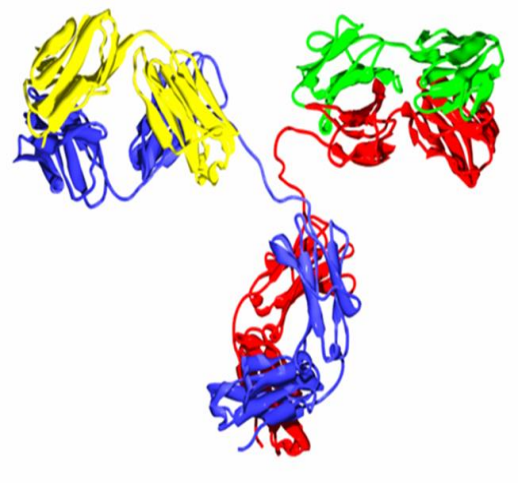
Biosimilar monoclonal antibodies

- Binding to target
- Binding to
  - FcγRI, FcγRII, FcγRIII
  - FcRn
  - C1q



- *Fab*-associated functions (*neutralization, activation, ...*)
- *Fc*-associated functions (*ADCC, CDC, complement activation, ...*)

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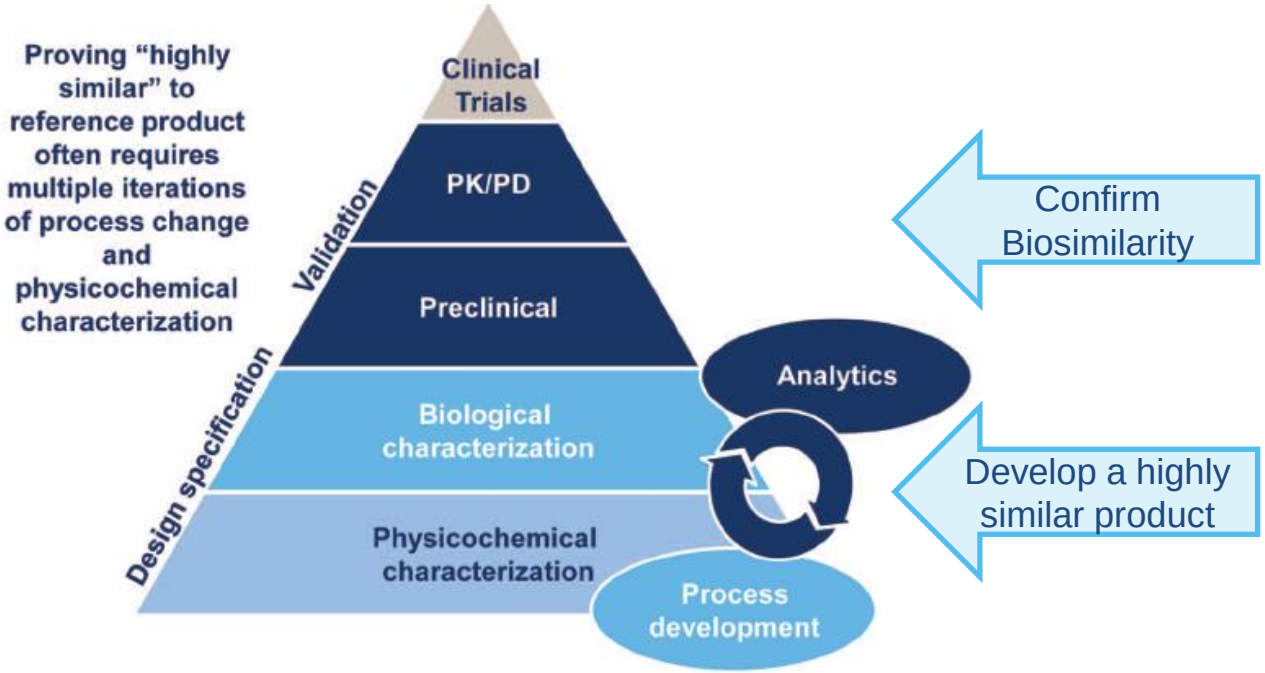
Concept of biosimilar development



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

Registration requirements (Original)

Quality

- Drug substance
  - Manufacture
  - Characterisation
  - Control
  - Reference standard
  - Container
  - Stability
- Drug product
  - Description
  - Development
  - Manufacture
  - Control
  - Reference standard
  - Container
  - Stability

Nonclinical

- Pharmacology
  - Primary pharm.
  - Secondary pharm.
  - Safety pharm.
  - Interactions
- Pharmacokinetics
  - ADME
  - Interactions
- Toxicology
  - Single dose
  - Repeat dose
  - Genotoxicity
  - Carcinogenicity
  - Reproduction
  - Local tolerance

Clinical

- 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

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Registration requirements (Biosimilar)

Quality

- 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

Nonclinical

- Pharmacology
  - Primary pharm.
  - Secondary pharm.
  - Safety pharm.
  - Interactions
- Pharmacokinetics
  - ADME
  - Interactions
- Toxicology
  - Single dose
  - Repeat dose
  - Genotoxicity
  - Carcinogenicity
  - Reproduction
  - Local tolerance

Clinical

- 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)
- 6 withdrawn:
  - *Insulin* (2008)
    - Insulin Rapid
    - Insulin Long
    - Insulin 30/70 Mix
  - *Insulin* (2012)
    - Solumarv
    - Isomarv medium
    - Combimarv

Registration of biosimilars (Europe)

- 21 approved in Europa (05/2015)
  - *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)*

Registration of biosimilars (Europe)

- 4 under review (05/2015)
  - *1 Insulin human*
  - *1 Etanercept*
  - *1 Infliximab*
  - *1 Enoxaparin*

Registration of biosimilars

- Canada
  - *2 Infliximab (2014)*
- US
  - *1 Filgrastim (2015)*

How similar is similar ?

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 …"

Similar, not identical – as predicted differences are observed

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

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How similar are biosimilars ?

Primary end point: number of oocytes retrieved

	Gonal-f® n=123	Bemfola® n=249
Number of oocytes Mean (SD)	11 (6)	11 (5)

Pregnancy follow up

	Gonal-f®	Bemfola®
Pregnancy rate per patient	41 %	34 %
Take-home baby rate	41 %	32 %

From European Public Assesment Report Bemfola

Biosimilars: *extrapolation of indications*

Remicade approved indications

- Rheumatoid arthritis
- Adult Crohn's disease
- Paediatric Crohn's disease
- Ulcerative colitis
- Paediatric ulcerative colitis
- Ankylosing spondylitis
- Psoriatic arthritis
- Psoriasis

- **PK study in AS (Phase I, 250 patients)**
- **Equivalence trial in RA (Phase III, 606 patients)**

- **randomised, double-blind, comparative study in active Crohn's disease planned**

Remsima/Inflectra approved indications

- Rheumatoid arthritis
- Adult Crohn's disease
- Paediatric Crohn's disease
- Ulcerative colitis
- Paediatric ulcerative colitis
- Ankylosing spondylitis
- Psoriatic arthritis
- 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

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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
- Follow-up measures

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