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The European Biosimilar Quality Experience

Professor Paul Declerck
Laboratory for Therapeutic and Diagnostic Antibodies

paul.declerck@kuleuven.be

Disclosures

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

Learning Objectives

- Gain detailed insight in the concept of biosimilarity
- Gain insight in the challenges of the evaluation and approval process of a biosimilar
- Acquire knowledge on the current European experience with respect to the quality evaluation of biosimilars

Biological medicinal product

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

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paul.declerck@kuleuven.be

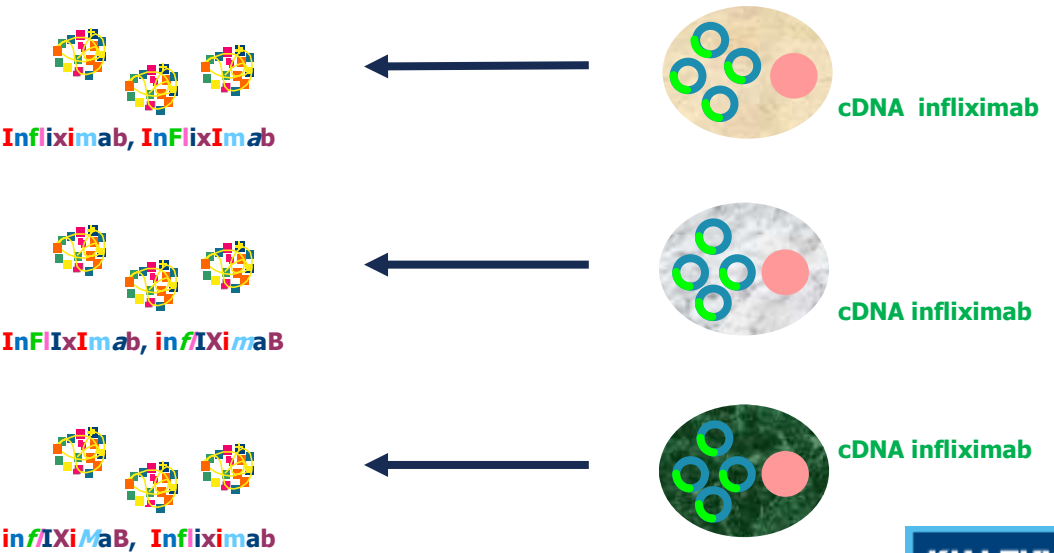
Molecular basis of heterogeneity

- 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

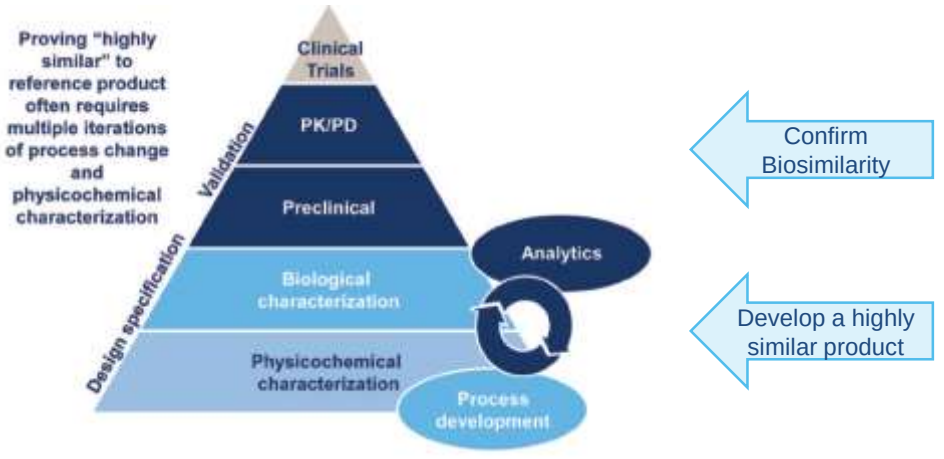
The process determines the product



Guidelines

- Biosimilars (EMA, 2006)
- Similar biotherapeutic products (WHO, 2010)
- Biosimilars (Australia, Canada, Japan, Korea, …; FDA 2015)
- Quality, safety and efficacy
- Extensive comparison with authorised reference product

Concept of biosimilar development



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

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
  - Single dose
  - Repeat dose
  - Special populations

Study #1

- Efficacy and safety
  - Dose finding
  - Schedule finding
  - Pivotal
    - Indication 1
    - Indication 2
    - Indication 3
    - Indication 4

Study #2

- Post-marketing studies
  - Safety in larger population
  - Efficacy in other indications
  - Immunogenicity

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Registration of biosimilars (Europe)

- 2 refused by the EU commission:
  - *Interferon alpha-2a* (2006)
  - *Insulin human* (2015)
- 9 withdrawn during evaluation procedure:
  - *Insulin* (2008)
    - Insulin Rapid
    - Insulin Long
    - Insulin 30/70 Mix
  - *Insulin* (2012)
    - Solumarv
    - Isomarv medium
    - Combimarv
  - *"2" Pegfilgrastim* (2016)
  - *Pegfilgrastim* (2017)

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Why refused?

Solumarv (human insulin)

- Insufficient details on manufacturing process
- Insufficiently demonstrated whether clinical study batches are representative for market batches
- Insufficiently shown that quality of proposed biosimilar is comparable to the reference product

From European Public Assesment Report Solumarv®

Why refused?

Pegfilgrastim (RGB-02)

- *Study results had not shown that RGB-02 was handled by the body in the same way as the reference medicine* (EMA/822769/2016)

Pegfilgrastim (LA-EP2006)

- *Study results were not able to show that the concentrations of pegfilgrastim in blood were the same after taking LA-EP2006 and reference medicine* (EMA/47326/2017)
- *Lack of a certificate of Good Manufacturing Practice (GMP) for the medicine's manufacturing site* (EMA/47326/2017)

Registration of biosimilars (Europe)

- 31 approved in Europa (02/2017)

- *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)
- *2 Insulin glargine* (2014, 2016)
- *1 Filgrastim* (2014)
- *1 Etanercept* (2016)
- *1 Infliximab* (2016)
- *2 Enoxaparin* (2016)
- *2 Teriparatide* (2016)
- *1 Rituximab* (2017)
- *2 Adalimumab* (2017)

- *1 Pegfilgrastim* (2015) ("bio-identical")
- *1 Etanercept* (2017)("bio-identical")

Registration of biosimilars (Europe)

- 14 under review (02/2017)

- *1 Etanercept*
- *2 Rituximab*
- *2 Pegfilgrastim*
- *2 Adalimumab*
- *1 Insulin glargine*
- *3 Trastuzumab*
- *1 Insulin Lispro*
- *2 Bevacizumab*

Physicochemical Comparability Tests: Analytics Set the Foundation (AS, DP, RMP)

Test Method	Compares...
Amino acid analysis	Amino acid composition
Peptide mapping (LC-MS) in combination with MS/MS	Peptide coverage and chemical modifications
Peptide mapping (HPLC)	Tryptic peptide map by visual inspection
N-terminal sequencing	N-terminal sequences
C-terminal sequencing	C-terminal sequences
Reduced mass	Molecular weights by mass spectrometry
Disulfide bonds	Disulfide bonds location
Free thiol analysis	Amount of free sulfhydryl groups
FTIR	Secondary structures
CD	Secondary structure
DSC	Thermal stability; also determines thermal transition temperatures

Test Method	Compares…
Purity/Impurity	
SEC-HPLC	Aggregate content and monomeric purity
CE-SDS (reduced/nonreduced)	Electrophoretic mobility and purity under nonreducing and reducing conditions
Charged Isoforms	
IEF	Isoelectric point(s)
IEC-HPLC	Charge variant distribution
Glycosylation	
Sialic acid analysis	Sialic acid content
Monosaccharide analysis	Neutral and amino sugar composition
Oligosaccharide profiling	Glycosylation pattern (eg,G0F, G1F, G2F)
N-linked glycan analysis	Oligosaccharide structures, attachment sites, and distribution
Content	
UV_{280}	Protein concentration
ELISA	API content

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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.

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How similar are biosimilars ?

Immunological events

SB2 versus Infliximab reference

- Higher incidence of ADA formation in patients (47 % *vs.* 38 % at day 71)
- Impact of ADA on efficacy is not clear (CHMP: Divergent opinion 14/36 negative)
- Data from studies in presence of MTX → extrapolation of immunogenicity to other indications?

From European Public Assesment Report Flixabi®

How similar are biosimilars ?

Immunological events

SB4 versus Etanercept reference

- Significantly lower incidence of ADA formation in patients (overall 1 % *vs.* 13 %)
- Impact of assay methodology –low drug tolerance: data affected by trough levels, the latter were different at wk 4/8, thus reanalysis after excluding ADA data at wk 4/8
- Reanalysis excluding wk 4 and 8: 0.3 *vs.* 0.7%
- *"…. it is premature to conclude that SB4 is less immunogenic than reference …."*

From European Public Assesment Report Benepali®

How similar are biosimilars ?

Physicochemical / Immunological events

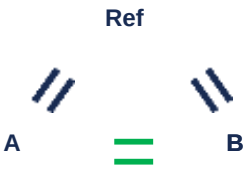
XM17 versus FSH reference

- *Quality evaluation*: more non-human sialic acid (Neu5Gc) in XM17
- "*…The absolute quantity of Neu5Gc in Ovaleap is negligible compared to the dietary intake of this non-human sialic acid…* "

From European Public Assesment Report Ovaleap®

Chemical drugs

generic A and B



Biological drugs

Biosimilar A and B

Biosimilarity does not automatically imply Interchangeability

Conclusions

- The concept for biosimilar development is well-defined
- The process for approval is rigorous
- Pharmaceutical quality of approved biosimilar is guaranteed
- Differences in quality attributes are always present
- Major challenges include the identification of the potential clinical relevance of differences in quality attributes and non-clinical properties

Conclusions

- Residual uncertainties (scientifically or statistically) have so far always been deemed to have no impact on safety and efficacy
- EPARs contain some but limited information to judge the final outcome of the approval process
- EPARs contain heterogenous information not consistent between different biosimilars for the same reference product

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