Development and approval of biosimilars in Europe

LIS TNF/BIO seminar
20 March 2018, Scandic Nidelven, Trondheim

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Outline

1. Main principles for successful development of biosimilars
2. How to demonstrate analytical and functional similarity
3. Future perspectives for EU biosimilars

Disclaimer: The views expressed are those of the presenter and should not be understood or quoted as being made on behalf of the European Medicines Agency or its scientific Committees
Manufacturing process changes

- Comparability between pre- and post-change versions need to be demonstrated (ICH Q5E)
- Manufacturers and regulators are used to assess the impact of process changes – also in the case of complex biologics


Remicade
\[ \bar{x} 3.33 \text{ Process changes per year} \]

Humira
\[ \bar{x} 2.55 \text{ Process changes per year} \]
The EU regulatory definition of biosimilars

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product.

A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

✓ The scientific principles of similarity assessment are based on those applied for evaluating manufacturing process changes.
Batch to batch variability of biologics

Source: FDA Advisory Committee Meeting 13 July 2016; Sandoz etanercept biosimilar

Measured potency ranges

US-Enbrel 80-104%
Biosimilar 93-101%
EU-Enbrel 76-118%
Quality Target Product Profile (QTPP)

- **Attribute variability (batch to batch variability)** as measured from the reference product, forms the basis for biosimilar development

- QTPP is a **prospective summary** of the quality characteristics of a drug product that ideally will be achieved (ICH Q8)

- Detailed at an **early stage of development**

- The **importance of the quality attributes/ characteristics** for the biological function of the protein need to be understood
  - Single or multiple mode of action?
  - Impact of post-translational modifications?
Typical quality attributes and characteristics to be considered for biosimilar mAbs

**ATTRIBUTES OF THE VARIABLE REGION**
- Deamidation, oxidation
- N-term Pyro-Glu
- Glycosylation
- Glycation
- Conformational changes

**ATTRIBUTES OF THE CONSTANT REGION**
- Deamidation, oxidation
- Glycosylation, glycation
- C-term Lys
- Di-sulfide bond shuffling/ cleavage
- Fragmentation/clipping
- Conformational changes

**PHYSICOCHEMICAL CHARACTERISTICS**
- Structure (primary, higher order structures)
- Molecular mass
- Purity/ impurity profiles
- Charge profile
- Hydrophobicity
- Post-translational modifications

**BIOLOGICAL/ FUNCTIONAL CHARACTERISTICS**
- Binding to target antigen(s)
- Binding to Fcγ receptors, FcRn and complement
- Antigen neutralisation (if relevant)
- Fab- and Fc-associated functions (e.g. ADCC, CDC, reverse signaling)
Rapid advances in analytical sciences

➢ 10 000 fold increase in sensitivity between year 2000 and 2011

➢ 10 million fold increase between year 1990 and 2011!

Slide presented by Tony Mire-Sluis (Amgen) at CASSS Mass Spec 2012
Reverse Engineering Approach

• **Expression system development**
  ✓ All relevant quality attributes should be expressed
  ✓ Expression system differences could result in undesired consequences; atypical glycosylation, higher variability and/or a different impurity profile

• **Upstream process development**
  ✓ To match quality attributes; Media composition, fermentation parameters, growth characteristics etc.

• **Downstream process development**
  ✓ To match product variants; Purification principles and chromatographic parameters used
The "pivotal" evidence for analytical similarity

- Biosimilarity should be demonstrated in an extensive, side-by-side (whenever feasible) comparability exercise
- Quantitative comparability ranges should primarily be based on the measured reference product ranges (QTPP)

The comparability range is established based on results from characterisation studies of the reference product.
What to do when the biosimilar falls outside the comparability range?

• Analytical **identity is not expected**; any differences must be justified in relation to impact on safety and efficacy

• **Clinical data** cannot be used to justify substantial differences

- **Low criticality attributes**; previous knowledge might be sufficient to justify differences
- **Medium to high criticality attributes**; the impact of the difference need to be addressed, for example by using suitable *in vitro* assays

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*20 March 2018*  
LIS TNF/BIO seminar; niklas.ekman@fimea.fi
Successful biosimilar development critically depend on the manufacturers ability to:

1. **Develop** a manufacturing process that consistently produce a close copy version of the reference product

2. **Demonstrate** high similarity through an extensive physicochemical and *in vitro* biological comparability exercise

3. **Understand** the impact of any differences detected

4. **Confirm** similarity with regard to PK, safety and efficacy
Assessment experience from addressing the impact of quality attribute differences observed for a biosimilar monoclonal antibody

Marketing Authorisation Application for Remsima/ Inflectra

1 European public assessment report (EPAR) available at www.ema.europa.eu
Analytical Methods in Structural and Physicochemical Biosimilarity Studies

Primary Structure
- Peptide Mapping (HPLC)
- Peptide Mapping (LC-MS)
- Fragmentation – HC Asn57, HC Asn318, HC Asn364, HC Asn417, LC Asn41
- Oxidation – HC Met256
- C-terminal variant – HC Lys470
- Intact Mass (LC-MS)
  - Light chain
  - Heavy chain K0 - GDF, GDF, GDF, GDF, GDF
- Heavy chain K1 - GDF, GDF, GDF
- Amino Acid Analysis/Molar Absorbivity
  - Aspartic acid, Glutamic acid, Serine, Histidine, Glycine, Threonine, Arginine, Alanine, Tyrosine, Valine, Methionine, Phenylalanine, Isoleucine, Leucine, Lysine, Proline, Molar Absorbivity, Extinction Coefficient
- N-terminal Sequencing
  - Heavy chain
  - Light chain
  - C-terminal Sequencing
  - Heavy chain
  - Light chain

Higher Order Structure
- FTIR
  - Amide I
  - Amide II
  - A
  - B
  - C
- DSC
  - Transition 1
  - Transition 2
  - Transition 3
- CD
- Free Thiol Analysis
- Disulfide Bond
  - H3-H12, 22-68
  - H15-H16, 147-203
  - H20-L19, 222-214
  - H22-H29, 264-324
  - H37-H42, 370-428
  - L3-L7, 23-88
  - L10-L17, 135-140
- Antibody Array
- Protein Concentration (UV

Glycosylation
- Human PAD
  - GDF, GDF, GDF, GDF, GDF, GDF, GDF
  - Non-human PAD
  - GDF, GDF, GDF, GDF, GDF

Purity/Impurity
- SEC-HPLC
- Monomer
- Dimer
- SEC-MALS
- Monomer
- Dimer
- Monomer (MW)
- Dimer (MW)
- AUC
- Monomer
- Higher species
- Non-reduced/Reduced CE-SDS
- Intact IgG (NR)
- dimer (R)
- Non-glycosylated HC (R)
- Sub-visible particles (MFI & HIAC)

Charge Variants
- TEP
- TEP-HPLC
- Peak 1, Peak 2, Peak 3, Peak 4, Peak 5, Peak 6

Excipients
- pH
- Polysorbate 80
- Sucrose

Side presented at FDA Arthritis Advisory Committee Meeting for CT-P13 Feb 09, 2016; http://www.fda.gov/AdvisoryCommittees/Calendar/ucm419688.htm
Primary structure; LC-MS peptide mapping

Higher order structures

Purity/impurity profile

Biological activity; binding and neutralisation of sTNFα

Pictures from Jung et al., mAb 6:5, 1163-1177, 2014 and FDA Arthritis Advisory Committee Meeting for CT-P13, Feb 09, 2016
Summary of analytical similarity assessment

• High similarity between the biosimilar and the reference demonstrated for
  • Primary, secondary and tertiary structures
  • In vitro TNFα neutralisation, binding affinity (soluble and transmembrane TNFα, TNFβ, FcγRIa, FcγRIla, FcRn, C1q), in vitro functional tests (apoptosis, CDC, ADCC using PBMNC effector cells from healthy volunteers)

• Minor differences reported for
  • C-terminal lysine content, aggregates, intact IgG level, charged molecular variants, glycosylation pattern (lower level of afucosylated glycans than Remicade)
  • Binding to FcγRIIIa
### Specific glycan structures may affect safety/immunogenicity, activity and/or clearance

<table>
<thead>
<tr>
<th>Glycan species</th>
<th>Safety/immunogenicity</th>
<th>Biologic activity/efficacy</th>
<th>Clearance (PK/PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactose</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>α1,3-galactose</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Fucose</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>Bisecting GlcNac</td>
<td>Unknown</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>High mannose</td>
<td>Unknown</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>NANA</td>
<td>Unknown</td>
<td>(−)</td>
<td>+</td>
</tr>
<tr>
<td>NGNA</td>
<td>−</td>
<td>Unknown</td>
<td>+</td>
</tr>
<tr>
<td>β1,2-Xylose/α1,3-Fucose</td>
<td>−</td>
<td>Unknown</td>
<td>(−)</td>
</tr>
<tr>
<td>NGHC</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
</tbody>
</table>

*Gal(α1-3)Gal is a non-human glycan structure produced by e.g. many rodent cell lines. Immunogenic in human*

*Afucosylated structures show increased binding to FcγRIII leading to increased ADCC activity*

*Neu5Gc (NGNA) is a sialic acid not present in humans; immunogenic*

*Mannose structures bind to mannose receptors which may result in increased protein clearance*
Potential mechanisms of action for anti-TNFs

**Primary MoA**
- Neutralisation of soluble TNFα

**Additional potential MoAs, especially in inflammatory bowel diseases (IBD)**
- Apoptosis
- Cytokine suppression
- CDC
- ADCC

### Tabular overview of clinical studies

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Design</th>
<th>Objectives</th>
<th>Treatment</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT-P13 1.2 (pilot study)</td>
<td>Prospective Phase 1, randomised, double-blind, parallel-group, multiple single-dose intravenous (i.v.) infusion, multicentre</td>
<td>Primary: To determine Cmax, PK profiles of CT-P13 and Remicade at weeks 0, 2 and 6; Secondary: PK profile, PD, efficacy, and safety of CT-P13 in comparison to Remicade up to week 102;</td>
<td>CT-P13 plus MTX or Remicade plus MTX</td>
<td>RA patients with active disease while receiving MTX: Planned: 20; Randomised: 19; CT-P13: 5; Remicade: 10</td>
</tr>
<tr>
<td>CT-P13 1.1 (PK equivalence, Study name: PLANET AS)</td>
<td>Prospective Phase 1, randomised, double-blind, CT-P13, multiple single-dose i.v. infusion, parallel-group</td>
<td>Primary: To demonstrate comparable PK at steady state in terms AUC, Cmax, between CT-P13 and Remicade determined between weeks 22 and 30; Secondary: long-term efficacy, PK and overall safety up to week 54;</td>
<td>CT-P13 or Remicade</td>
<td>RA patients with active disease: Planned: 246 (ratio 1:1); Randomised: 230; CT-P13: 123; Remicade: 125</td>
</tr>
<tr>
<td>CT-P13 3.1 (Therapeutic equivalence, Study name: PLANET RA)</td>
<td>Prospective Phase 3, randomised, double-blind, multicentre, multiple single-dose i.v. infusion, parallel-group</td>
<td>Primary: To demonstrate that CT-P13 is equivalent to Remicade, in terms of efficacy as determined by clinical response according to ACR20 at week 30; Secondary: long-term efficacy, PK, PD, and overall safety up to week 54;</td>
<td>CT-P13 plus MTX or Remicade plus MTX</td>
<td>RA patients with active disease while receiving MTX: Planned: 304 (ratio 1:1); Randomised: 666; CT-P13: 302; Remicade: 304</td>
</tr>
</tbody>
</table>

Can efficacy and safety data be extrapolated to all Remsima/Inflectra indications applied for?

- Directive 2001/83, part II, Annex 1

   In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.

- As differences in quality attributes potentially involved in the mode of action of infliximab had been detected, the Company was asked to provide evidence that the differences did not result in clinically relevant differences in any of the applied indications.
The difference in afucosylated glycans and FcγRIII binding was confirmed.

- No difference in reverse signaling through tmTNFα
  - Induction of apoptosis
  - Blockade of pro-inflammatory cytokine production

- No difference in blocking soluble hTNFα in an *in vitro* IBD model
  - Suppression of pro-inflammatory cytokine secretion from co-stimulated epithelial cell line
  - Suppression of epithelial cell line apoptosis
• No difference in Regulatory Macrophage function (regMø)
  • Quantity of induced regulatory macrophages, suppression of T cell proliferation, *in vitro* wound healing

• No difference in Antibody-dependent cell-mediated cytotoxicity (ADCC) using;
  • tmhTNFα-Jurkat cells as target cells and PBMCs (from healthy donors or CD patients), NK cells (from healthy donors) whole blood (from healthy donors) as effector cells
  • LPS-stimulated monocytes (from healthy donors or CD patients) as target cells and PBMC as effector cells

❖ Difference in ADCC functional assay detected using
  • tmhTNFα-Jurkat cells as target cells and NK cells from CD patient donors (158V/V or 158V/F genotypes, but not 158F/F) as effector cells
Conclusion from the Remsima assessment

- Functional difference was seen only in an ADCC assay employing artificially high tmTNFα expressing Jurkat target cells in combination with highly purified NK effector cells
- No differences in experimental models regarded as more relevant to the pathophysiological conditions in CD patients
- No published reports describing the induction of ADCC by TNF antagonists in CD patients
- No firm evidence that the FcγRIIIa polymorphism has an impact on the clinical course of CD

Based on the totality of evidence, the CHMP concluded that the differences detected were considered clinically not meaningful and allowed for data extrapolation to all indications
Biosimilars – prerequisites for extrapolation

• **Similar** physicochemical, structural characteristics and biological functions in *in vitro* models

• **Similar** human pharmacokinetics (exposure)

• **Similar** pharmacodynamics, efficacy, safety, and immunogenicity at least in one therapeutic indication

• **Sound scientific justification**
  • Clinical experience and available literature data
  • Mechanism of action of the active substance in each indications
  • Evidence that the lead indication is representative for the other therapeutic indications, both with regard to safety and efficacy

1 For simple biologics, safety and efficacy studies may not always be necessary
"Understanding biosimilars requires a cultural and cognitive change”*

*Janet Woodcock, deputy commissioner of the FDA, 2012
"Understanding biosimilars requires a cultural and cognitive change”*

*Janet Woodcock, deputy commissioner of the FDA, 2012
The future of EU biosimilars – where are we heading?
The potential of Biosimilar Medicines

“Even if the biosimilar product does not end to be the product sold it is likely an essential step to generate a more competitive environment, which *leads to lower prices*.”

“In countries which used to have low usage/availability in the classes the price reductions seem to have a *significant impact on the increased access*.”

“By encouraging manufacturers to *innovate*, the presence of biosimilar medicines in the market *increases choice for patients and physicians*. Furthermore, the presence of biosimilar medicines actually *enables patients to access* these innovative treatments – because the use of more cost-effective biosimilar products frees up funds that can be spent on securing patient access to the latest treatments”

IMS Health: The Impact of Biosimilar Competition, June 2016
IMS Institute for Healthcare Informatics: Delivering on the Potential of Biosimilar Medicines, March 2016
Number of authorised biosimilars and biosimilars under evaluation

![Graph showing the number of authorised products and products under evaluation from 2013 to 2018.](image)

**Authorised products**

**Products under evaluation**
EU Biosimilar product overview (March 2018)

- 76 MAAs submitted
- 58 MAAs post-review
  - 2 Negative
    - Interferon alfa
    - Insulin
  - 12 Withdrawn (pre-approval)
    - Insulin (6)
    - Epoetin (1)
    - Pegfilgrastim (4)
    - Trastuzumab (1)
  - 3 Withdrawn (post-approval)
    - Filgrastim (2)
    - Somatropin (1)
- 44 Positive opinions
- 40 Valid MAs
  - Somatropin (1)
    - Epoetin (5)
    - Filgrastim (7)
    - Infliximab (3)
    - Follitropin alfa (2)
    - Etanercept (2)
    - Insulin glargine (2)
  - Enoxaparin (2)
    - Teriparatide (2)
    - Rituximab (6)
    - Adalimumab (4)
    - Insulin lispro (1)
    - Trastuzumab (2)
    - Bevacizumab (1)
  - Adalimumab (5)
    - Bevacizumab (1)
    - Infliximab (1)
    - Pegfilgrastim (8)
    - Trastuzumab (3)
- 18 MAAs under review
- 1 Awaiting EC decision
  - Insulin glargine (1)
The approval pathway for biosimilars has been effective and highly successful

The EU has the highest number of biosimilar medicines approved, and an extensive experience of their use and safety. **No new or unexpected reverse reactions have been recorded for any of the biosimilars approved in EU.**

Is there anything we could or should do better/ different?
## Available EMA biosimilar guidance

### Definitions and main principles

**Overarching Guideline CHMP/473/04 Rev. 1**  
"Guideline on Similar Biological Medicinal Products"  
Adopted 2005, revised 2014

### General guidelines

**Nonclinical and Clinical**  
EMEA/CHMP/BWP/42832/2005 Rev. 1  
Adopted 2006, revised 2015

**Quality**  
EMA/CHMP/BWP/247713/2012  
Adopted 2006, revised 2014

### Class/product specific guidance

- Somatropin (2006)
- Epoetin (2006, revised 2010)
- Insulin (2006, revised 2015)
- G-CSF (2006, currently under revision)
- LMWH (2009, revised 2017)
- IFNα (2009, currently under revision)
- Monoclonal Abs (2012)
- rFSH (2013)
- IFNβ (2013)

### Other guidelines/RP

- Statistical methodologies for the comparative assessment of quality attributes (draft reflection paper released in 2017)
Current biosimilar development

Comparable quality and *in vitro* function

Large/ complex biologics, e.g. mAbs, fusion proteins

Close to identical analytical & biological properties

Smaller/ less complex biologics, e.g. insulin, filgrastim

Future biosimilar development programs?

Indistinguishable analytical & biological properties

Could such a program one day be applicable for more complex biologics?
Uptake of biosimilars – FI experience

- **Reimbursement** is a prerequisite for the use of biologicals outside hospitals
- For biosimilars that are covered by general reimbursement, prescribers and patients (on treatment) have no special interest in biosimilars because of the **lack of incentives**
- Hospitals are leading the adoption of biosimilars - **economical incentives**
- In Finland, the **market shares** of biosimilars administrated by hospitals are mostly between 50% and 100%; the market share of biosimilar insulin glargine is approximately 1%*

*) QuintilesIMS; The Impact of Biosimilar Competition in Europe, May 2017
Interchangeability of Biosimilars – Position of Finnish Medicines Agency

- Published in 2015, defines the current position of FIMEA towards interchangeability of EU biosimilars and their reference products
- Substitution (at the pharmacy level) is not considered by the current recommendation

Main conclusions from the position paper

• Switches between (non-similar) biological products, for example in the context of hospital tendering processes, are common and usually not problematic

• The clinical crossover studies conducted have given no evidence of adverse effects due to a switch from a reference product to a biosimilar. Also the theoretical basis of such adverse effects is weak

➢ The position of FIMEA is that EU biosimilars are interchangeable with their reference products (under the supervision of a health care person). As with any biological products, the switch should be documented, including brand name and batch number
Product traceability in EudraVigilance

• **Aim of study:** to assess level of precise identification of biologicals in ADR reports received from European clinical practice

• All cases received as spontaneous adverse drug reaction (ADR) between 1 Jan 2011 - 30 Jun 2016, and in which at least one of the suspected or concomitant medicinal products involves a biological for which:

  • **A biosimilar has been approved** in the EEA (epoetin alfa, etanercept, filgrastim, follitropin alfa, infliximab, insulin glargine, somatropin); or
  • **A related product has been approved** in the EEA (human normal immunoglobulin, interferon beta-1a, octocog alfa)
Product traceability in EudraVigilance

<table>
<thead>
<tr>
<th>Product</th>
<th>Total, n</th>
<th>Identifiable product, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept</td>
<td>19,716</td>
<td>19,012 96.4%</td>
</tr>
<tr>
<td>infliximab</td>
<td>12,045</td>
<td>11,342 94.2%</td>
</tr>
<tr>
<td>insulin glargine</td>
<td>2,446</td>
<td>2,364 96.6%</td>
</tr>
<tr>
<td>filgrastim</td>
<td>1,043</td>
<td>934 89.5%</td>
</tr>
<tr>
<td>epoetin alfa</td>
<td>1,084</td>
<td>1,045 96.4%</td>
</tr>
<tr>
<td>somatropin</td>
<td>1,047</td>
<td>1,006 96.1%</td>
</tr>
<tr>
<td>follitropin alfa</td>
<td>448</td>
<td>442 98.7%</td>
</tr>
</tbody>
</table>

Results show **robust levels of overall product identification** for classes of biologicals for which biosimilars are approved, but **overall batch traceability** only 20.5%.

Courtesy of Ana Hidalgo-Simon, EMA

Picture: Freepik.com
Concluding remarks

• The EU’s legal framework has been in place since 2004, first biosimilar was approved in 2006
  • The EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilar medicines and their reference medicines

➢ In order to realize the full potential of biosimilars, also patients on chronic non-hospital treatments need to be switched to the overall cheapest product (the biosimilar or the originator product)
Thank you for your attention!

Acknowledgment
Ana Hidalgo-Simon, EMA

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Any questions or comments?

The pictures used in the presentation were obtained from www.freepik.com, www.unsplash.com and from www.wikipedia.org

Picture: Freepik.com