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

<table>
<thead>
<tr>
<th>Unit Operation</th>
<th>Specific to Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Expansion</td>
<td>Cell line, growth media, method of expansion</td>
</tr>
<tr>
<td>Cell Production in Bioreactors</td>
<td>Cell line, growth media, bioreactor conditions</td>
</tr>
<tr>
<td>Recover through filtration or centrifugation</td>
<td>Operating conditions</td>
</tr>
<tr>
<td>Purification through chromatography</td>
<td>Binding and elution conditions</td>
</tr>
<tr>
<td>Characterization and Stability</td>
<td>Methods, reagents, reference standards</td>
</tr>
</tbody>
</table>
Chemical versus Biological drug

Aspirin                   Interferon                                Monoclonal Antibody

Chemical versus Biological drug

<table>
<thead>
<tr>
<th>Small chemical entity</th>
<th>Large, complex biomolecule</th>
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<tbody>
<tr>
<td>Chemical synthesis</td>
<td>Cell cultures</td>
</tr>
<tr>
<td>Defined structure</td>
<td>Heterogeneous structures</td>
</tr>
<tr>
<td>Not or less sensitive to process changes</td>
<td>Extremely sensitive to process changes</td>
</tr>
<tr>
<td>Relatively stable</td>
<td>Variable; sensitive to conditions</td>
</tr>
<tr>
<td>Not or less immunogenic</td>
<td>Immunogenic</td>
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</table>
**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**

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Biological medicinal products

- 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
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

Concept of biosimilar development

Proving “highly similar” to reference product often requires multiple iterations of process change and physicochemical characterization.
## EMA guidelines for biosimilars

<table>
<thead>
<tr>
<th>TOPIC</th>
<th>TITLE</th>
<th>APPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overarching</td>
<td>Guideline on Similar Biological Medicinal Products</td>
<td>General: Applies to all Biosimilars</td>
</tr>
<tr>
<td>Quality</td>
<td>Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues</td>
<td></td>
</tr>
<tr>
<td>Nonclinical &amp; Clinical</td>
<td>Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical &amp; Clinical Issues</td>
<td></td>
</tr>
<tr>
<td>Annexes Nonclinical &amp; Clinical</td>
<td>Recombinant Human Erythropoietin</td>
<td>Product data requirements</td>
</tr>
<tr>
<td></td>
<td>Recombinant Human G-CSF</td>
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<tr>
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<td>Recombinant Human Insulin</td>
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<tr>
<td></td>
<td>Recombinant Human Growth Hormone</td>
<td></td>
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<tr>
<td></td>
<td>LMWH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interferon alfa</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monoclonal antibodies</td>
<td></td>
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<tr>
<td></td>
<td>Interferon beta</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follicle-stimulating hormone</td>
<td></td>
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</table>

### 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
- Efficacy and safety
  - Dose finding
  - Schedule finding
- Toxicology
  - Single dose
  - Repeat dose
  - Genotoxicity
- Interactions
  - Safety in larger population
  - Efficacy in other indications
  - Immunogenicity
- Post-marketing studies
  - Indication 1
  - Indication 2
  - Indication 3
  - Indication 4

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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?

<table>
<thead>
<tr>
<th><strong>Biosimilar ESA</strong> (*)</th>
<th><strong>Biosimilar hGH</strong></th>
<th><strong>Biosimilar IFX</strong> (*)</th>
</tr>
</thead>
</table>
| • Differences were observed at the glycosylation level | • The results of this study ... demonstrate that Biosimilar rhGH produced at full scale is comparable to Reference Product | • "... all major physicochemical characteristics and biological activities of biosimilar IFX were comparable to those of the reference product"
| • Phosphorylated high mannose type structures were detected at higher levels than in Reference ESA | • "...impurities, ... are present in the Biosimilar hGH batches and are not in any Reference hGH batches" | • "...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..."
| • Lower values on N-glycolyl-neuramic acid and diacytelylated neuramic acids as compared to Reference ESA | • "...Additionally, there appears to be a higher level of deamidated variants in the Biosimilar hGH samples" | • "...less intact IgG,..., mainly due to a higher proportion of non-assembled form,... unlikely to impact its biological activity"
| • Peptide map showed differences ... in O-linked glycan due to a higher sialylation and lower content of the oxidized variant | • • Peptide map showed differences ... in O-linked glycan due to a higher sialylation and lower content of the oxidized variant | • "a higher level of C-terminal lysine variability"

**Biosimilars are Similar, not identical**

Based upon European Public Assessment Report on respective biosimilars.

### Infliximab: 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

**Remsima/Inflectra approved indications**
- PK study in AS (Phase I, 250 patients)
- Equivalence trial in RA (Phase III, 606 patients)

**REMSIMA European Public Assessment Report.**
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