Who needs biosimilars?

Prof. Dr. Huub Schellekens
Utrecht University
Treaty of Tordesillas

1494
The kings of Spain and Portugal divide the world
The generic paradigm

- Only applicable to small molecules taken orally
- Based on the assumption that pharmaceutical equivalence and bioequivalence = therapeutic equivalence
- Has led to the introduction of many safe, effective and affordable drugs
- Is important part of the innovation cycle
The arguments for a separate pathway for biologics
Biologicals are much larger with more complicated structures than classical drugs.

- **Interferon beta**
  - Molecular weight 19,000

- **Aspirin**
  - Molecular weight 180
The Biological and Clinical Properties of Biologics cannot be predicted from physical chemical analyses.

The analytical tools for biologics are 10-100 times less sensitive than for classical drugs.
Biologics are produced by living cells

- Biologicals are produced under controlled conditions
- Newly generated proteins undergo complex post-translational modifications:
  - Very sensitive to production conditions
  - Minor changes can have major impacts on biological activity

E. coli bacterium producing interferon gamma

Roger SD. Nephrology 2006;11:341–6;
Dews I. Clinical Research Focus 2006;17:5–10;
Biologics are heterogeneous

Different epoetins from around the world – Isoelectric focusing

Schellekens H and Combe C et al. Poster ERA-EDTA Congress 2004
Immunogenicity, the main issue for biosimilars

- Current analytical methods cannot fully predict biological properties
- The immune system can detect alterations in products missed by analytical methods
- Immunogenicity of biopharmaceuticals may have serious clinical consequences
Biopharmaceuticals differ from conventional drugs

<table>
<thead>
<tr>
<th>Generic</th>
<th>Biosimilar*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical and therapeutic equivalent of original low molecular weight drug whose patent has expired</td>
<td>Biological product referring, but not identical, to an existing product, submitted for separate marketing approval following patent expiration</td>
</tr>
</tbody>
</table>
Quality Clinical & Non-clinical Immunogenicity Assessment

Overarching Guideline (CHMP 437/04)
Guideline on Similar Biological Medicinal Products
Defines concept, principles and provides user guide

Quality
CHMP/BWP/49348/04

Clinical & Non-clinical
CHMP/BMWP/42832/05

Immunogenicity Assessment
CHMP/BMWP/14327/06

Product Specific
EPO Insulin
G-CSF HGH
LMWH IFNa
Principles of the EMA approach for biosimilars

- Full quality dossier, including comparisons with original
- Limited preclinical dossier including PK comparison with original
- Clinical similarity. Hard clinical endpoint not needed
- Extrapolation possible
- Risk management plan needed with postmarketing safety studies including immunogenicity
Guideline biosimilars WHO

- Clinical data necessary
- Immunogenicity should always be tested
- Pharmacovigilance essential
Experience with biosimilars in the EU
### What do we currently have in the EU?

<table>
<thead>
<tr>
<th>INN Reference product</th>
<th>Marketing Authorisation Holder</th>
<th>Date of EC Approval</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatropin</td>
<td>Sandoz GmbH</td>
<td>12 April 2006</td>
<td>Omnitrope®</td>
</tr>
<tr>
<td></td>
<td>Biopartners GmbH</td>
<td>24 April 2006</td>
<td>Valtropin</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Sandoz GmbH</td>
<td>28 Aug 2007</td>
<td>Binocrit</td>
</tr>
<tr>
<td></td>
<td>Hexal GmbH</td>
<td>28 Aug 2007</td>
<td>Epoetin alfa HEXAL</td>
</tr>
<tr>
<td></td>
<td>Medice Arzmittel</td>
<td>28 Aug 2007</td>
<td>Abseamed</td>
</tr>
<tr>
<td></td>
<td>Hospira UK</td>
<td>18 Dec 2007</td>
<td>Retacrit</td>
</tr>
<tr>
<td></td>
<td>STADA Arzneimittel GmbH</td>
<td>18 Dec 2007</td>
<td>Silapo</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Ratiopharm GmbH</td>
<td>15 Sept 2008</td>
<td>Ratiograstim</td>
</tr>
<tr>
<td></td>
<td>Teva Generics GmbH</td>
<td>15 Sept 2008</td>
<td>TevaGrastim</td>
</tr>
<tr>
<td></td>
<td>CT Arzneimittel GmbH</td>
<td>15 Sept 2008</td>
<td>Biograstim</td>
</tr>
<tr>
<td></td>
<td>Sandoz GmbH</td>
<td>15 Sept 2008</td>
<td>Zarzio</td>
</tr>
<tr>
<td></td>
<td>Hexal GmbH</td>
<td>6 Feb 2009</td>
<td>Filgrastim HEXAL</td>
</tr>
<tr>
<td></td>
<td>Hospira UK</td>
<td>8 June 2010</td>
<td>Nivestim</td>
</tr>
</tbody>
</table>
Differences between biosimilar epoetins and the reference product

- Level of impurities
- Formulation
- Glycosylation
- Potency
Monitoring of the quality of the biosimilar by utrecht university

10 batches of Retacrit, Binocrit, Neorecormon and Eprex will be tested
“Of the tested products, the biosimilars have the same or even better quality as the originals”

Study compared 2 originators, Eprex, Dynepo and two biosimilar products, Binocrit and Retacrit using:

(1) high performance size exclusion chromatography
(2) ELISA
(3) SDS-PAGE
(4) capillary zone electrophoresis
(5) in-vivo potency

... the potency of originals may significantly differ from the value on the label”
Ongoing study in Bangkok

- 19 epoetins available in Thailand registered by the classical generic pathway
- All CKD patients treated with epoetin in registry
- All batches used are being analyzed in Utrecht University
- Study blinded until June 2013
Outstanding issues biosimilars

- Substitution
- Exchangeability
  - Population level
  - Individual level
Biosimilar substitution policies

- **Substitution possible**
  - ROMANIA
  - CYPRUS
  - ESTONIA
  - IRELAND
  - POLAND
  - MALTA
  - PORTUGAL
  - LITHUANIA
  - LATVIA
  - SLOVENIA

- **Biosimilar substitution possible?**
  - ? No clear position on biosimilar substitution?

- **Rx by brand name recommended for biosimilar products**
  - UNITED KINGDOM
  - NETHERLANDS
  - NORWAY

- **Evaluation on case-by-case basis**
  - DENMARK
  - FINLAND
  - HUNGARY
  - SLOVAKIA
  - GERMANY
  - SWEDEN
  - BELGIUM
  - FRANCE
  - ITALY

- **Generic substitution not allowed or Rx by brand name only**
  - CZECH REPUBLIC
  - AUSTRIA
  - GREECE
  - BULGARIA

- **Official position unfavourable to biosimilar substitution**
  - ITALY
  - BELGIUM

- **Legislative provision not allowing biosimilar substitution**
  - SPAIN
  - SWEDEN

- **? No clear position on biosimilar substitution?**
  - UNITED KINGDOM
Exchangeability

- Metanalysis of switching data of current bioisimilars
- Database of Sandoz
- Drug safety databases
- Data from large clinic in the Netherlands

No clinical/biological effect of switching identified
Aspects under discussion in new versions of EMA biosimilar guidelines
Quality aspects

Several different batches of the reference medicinal product should be used to generate a representative quality profile. The relative age of the different batches of reference medicinal product should also be considered.

The development and documentation for biosimilars should cover two complementary aspects:

i) molecular characteristics and quality attributes (QA) of the target product profile should be comparable to the reference medicinal product;

ii) performance and consistency of the manufacturing process of the biosimilar on its own

Amino acid sequences should be identical

Different expression system and formulation possible

Biosimilar is allowed its own life cycle
The feasibility of biosimilar monoclonal antibodies
The next generation of biosimilars: monoclonal antibodies

- More complex than current biosimilars
- More than one active site
- However, the assays for all these activities are well established
- Glycosylation will be the most important quality issue
- Most important clinical issues
  - Endpoint for clinical similarity
  - Extrapolation of indications
Sample size calculations assuming various effect size differences Avastin trial NO16966 (Saltz, 2008)

<table>
<thead>
<tr>
<th>Time to event Endpoint</th>
<th>Placebo efficacy (HR 97.5% CI)†</th>
<th>Innovator efficacy (HR 1.05)</th>
<th>Sample size required (δ= HR 1.05)</th>
<th>Sample size required (δ= HR 1.1)</th>
<th>Sample size required (δ= HR 1.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS*</td>
<td>19.9 months (0.84[0.76-1.03])</td>
<td>21.3 months (0.83[0.72-0.95])</td>
<td>15760</td>
<td>4130</td>
<td>1130</td>
</tr>
<tr>
<td>PFS*</td>
<td>8.0 months (0.83[0.72-0.95])</td>
<td>9.4 months (0.83[0.72-0.95])</td>
<td>11242</td>
<td>2946</td>
<td>806</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Binary Endpoint†</th>
<th>Placebo efficacy †</th>
<th>Innovator efficacy † (δ = 10% of Δ Bev &amp; PBO)</th>
<th>Sample size required (δ= 10% of Δ Bev &amp; PBO)</th>
<th>Sample size required (δ = 25% of Δ Bev &amp; PBO)</th>
<th>Sample size required (δ= 50% of Δ Bev &amp; PBO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One year survival</td>
<td>72.1%</td>
<td>126566 (δ=1.09%)</td>
<td>20254 (δ= 1.45%)</td>
<td>5066 (δ= 2.9%)</td>
<td></td>
</tr>
<tr>
<td>One year PFS</td>
<td>25.4%</td>
<td>166976 (δ=0.56%)</td>
<td>26716 (δ= 1.41%)</td>
<td>6678 (δ= 2.82%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.4%</td>
<td>24268 (δ=1.25%)</td>
<td>3887 (δ=3.125%)</td>
<td>978 (δ=6.25%)</td>
<td></td>
</tr>
</tbody>
</table>

*OS: Overall Survival  PFS: Progression Free Survival
### Characteristics essential to be shared for extrapolation of indications

<table>
<thead>
<tr>
<th>Type of extrapolation</th>
<th></th>
<th>Scope of extrapolation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Efficacy</strong></td>
<td></td>
<td><strong>Safety</strong></td>
<td><strong>Immunogenicity</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Product</td>
<td>1. Dose</td>
<td>1. Immune status of the patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Target</td>
<td>2. route of administration</td>
<td>2. Dose and length of treatment</td>
<td></td>
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<tr>
<td></td>
<td>5. Clearance</td>
<td>6. Co-morbidity</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>6. Route of administration Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease 1. Pathogenesis</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>2. Co-morbidity</td>
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<tr>
<td></td>
<td>3. Biomarkers</td>
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<tr>
<td></td>
<td>4. Dose/response</td>
<td></td>
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<tr>
<td></td>
<td>Patient 1. Age, gender</td>
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</tr>
<tr>
<td></td>
<td>2. Genetic/ethnic background</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>3. Co-medication</td>
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</tr>
</tbody>
</table>

| **Population** | 1. Pathogenesis | 1. Dose and length of treatment | 1. Age |
|               |          | 5. Route of administration | 5. Route of administration |

| **Both indication and population** | All of the above | All of the above | All of the above |
Factors in favor of penetration of biosimilar monoclonals

- No competition by second generation products
- Price reduction will be more than with the current biosimilars
- Exchange not really an issue
- Oncologists are very aware about price issues
- New markets
The future biosimilar pathway

Physical chemical characterization sufficient?
Both the FDA as well as the EMA suggest this:

“Advances in manufacturing science and Quality-by-Design approaches may facilitate production processes that can better match a reference product’s fingerprint. Such a strategy could further quantify the overall similarity between two molecules and may lead to additional bases for a more selective and targeted approach to subsequent animal and/or clinical studies.”

Draft FDA biosimilar Quality Guideline
But

- How to translate level of quality to size of clinical trials
- The more sophisticated the analytical tools the more differences will be seen between original and biosimilar
- Only for simple non-glycosylated biologics such as insulin physical chemical characterization will suffice in the future.
Conclusions

- Mainly big companies involved
- Quality of biosimilars on the EU high
- Still a lot of low quality biologics (“bioquestionables”) around
- The penetration of the market of monoclonal antibodies will be much faster than with the first generation of biosimilars