Biosimilars –
Regulation strategies and pathway in the EU (and US)
Experience gained and Perspectives

DVFA Symposium, Frankfurt 8 June

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Scientific secretariat of the ‘Biosimilar’ Working Party
European Medicines Agency (EMA)
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The European Medicines Agency (EMA) is a decentralised body of the EU - Celebrated 15th anniversary in Jan. 2010.

The mission of the Agency is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health.

Responsible for centralised procedure and co-ordination of EU network + plays a role in stimulating innovation and research in the pharmaceutical sector.
The Committee for Medicinal Products for Human Use (CHMP)

CHMP
Chairperson: Dr. E. Abadie

max. 5 Co-opted CHMP members

BWP
CPWP
GTWP
PhVWP
PgWP
VWP
EWP
QWP
PCWP
BPWP
SWP
SAWP
BMWP

SAGs
NRG
HCWP
QRD

Chair: Dr Christian Schneider, PEI
5 years to built the world's tallest building 2009

(21 September 2004 – 4 January 2010)
"I believe that this nation should commit itself to achieving the goal, before this decade is out, of landing a man on the moon and returning him safely to earth."

J F Kennedy, Inauguration speech, 1961

July 20, 1969, American Neil Armstrong
It takes more than 10 years and 1$ Bn to bring an innovative product with a new active substance on the market.

Biologicals are more complex and expensive to develop than small entity drugs.

Can/will public sector cope with the continuously rising costs for the health care system?
What is a similar biological medicinal product “Biosimilar”? 

- Published guidance on Biosimilar / FOPP / SEB / FOB in different jurisdictions 
  - SEB (Subsequent Entry Biologicals) 
  - FOPP (Follow on Protein Products) 
  - FOB (Follow on Biologicals) 

- Biosimilars ≠ ME-TOO or 2nd generation Biologicals 

- Possibility that different concepts in different regions developed (EU / India / Korea / China / US?) 

- Avoid double standards 
  - India and Korea already authorised “Biosimilar” monoclonal Abs 

- WHO guideline 
  - for entire world 

**Clear definition of EU Biosimilar concept**
Why „biosimilar“ (and not „biogeneric“)?

Aspirin
180 Daltons

Insulin
5 700 Daltons

MAb
150 000 Daltons

Source: Cecil Nick, Parexel
Legislation and its implementation


- Implementation

- Structures
  - Initial guidance (2Q 2004)
  - Biosimilar Working Party (BMWP) (established 2005, multidisciplinary)

- Products
  - Scientific advices
  - First Biosimilar opinion (2006 Omnitrope)
Overarching Guideline (CHMP/437/04).
“Guideline on Similar Biological Medicinal Products”

Biotechnology-derived proteins

Quality

Non-clinical
Clinical

General guidelines
Quality / Safety
Efficacy

Defines principles

Product class specific data requirements

Insulin
Somatropin
GCSF
Epoetin
IFN-α
LMMH

Non-clinical
Non-clinical
Non-clinical
Non-clinical
Non-clinical
Non-clinical

Clinical
Clinical
Clinical
Clinical
Clinical
Clinical
Dossier requirements for Biosimilars

<table>
<thead>
<tr>
<th>Module 1 - Normal Requirements</th>
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<tbody>
<tr>
<td>Module 2 - Normal Requirements</td>
</tr>
<tr>
<td>Quality, Module 3 - FULL</td>
</tr>
<tr>
<td>+ CE</td>
</tr>
<tr>
<td>Non-clinical, Module 4 - Reduced</td>
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<tr>
<td>= CE</td>
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<tr>
<td>Clinical, Module 5 - Reduced</td>
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<td>= CE</td>
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Integrated CE
(Comparability Exercise)
Experience gained
Scientific Advice

Scientific Advice for Biosimilars

Number of applications

Follow-up advice
First advice

2003 2004 2005 2006 2007 2008 2009
**Biosimilar MAA Procedures**

<table>
<thead>
<tr>
<th></th>
<th>Product Name</th>
<th>Manufacturer</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Omnitrope (somatropin)</td>
<td>Sandoz</td>
<td>Authorised</td>
</tr>
<tr>
<td>2</td>
<td>Valtropin (somatropin)</td>
<td>Biopartners</td>
<td>Authorised</td>
</tr>
<tr>
<td>3</td>
<td>Alpheon (interferon alfa)</td>
<td>Biopartners</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>Binocrit (epoetin alfa)</td>
<td>Sandoz</td>
<td>Authorised</td>
</tr>
<tr>
<td>5</td>
<td>Epoetin alfa Hexal (epoetin alfa)</td>
<td>Hexal</td>
<td>Authorised</td>
</tr>
<tr>
<td>6</td>
<td>Abseamed (epoetin alfa)</td>
<td>Medice</td>
<td>Authorised</td>
</tr>
<tr>
<td>7</td>
<td>Silapo (epoetin zeta)</td>
<td>Stada</td>
<td>Authorised</td>
</tr>
<tr>
<td>8</td>
<td>Retacrit (epoetin zeta)</td>
<td>Hospira</td>
<td>Authorised</td>
</tr>
<tr>
<td>9</td>
<td>Insulin Marvel Short (human insulin)</td>
<td>Marvel Life Sci’</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>10</td>
<td>Insulin Marvel Intermediate (human insulin)</td>
<td>Marvel Life Sci’</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>11</td>
<td>Insulin Marvel Long (human insulin)</td>
<td>Marvel Life Sci’</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>12</td>
<td>Filgrastim Ratiopharm (filgrastim)</td>
<td>Ratiopharm</td>
<td>Authorised</td>
</tr>
<tr>
<td>13</td>
<td>Ratiograstim (filgrastim)</td>
<td>Ratiopharm</td>
<td>Authorised</td>
</tr>
<tr>
<td>14</td>
<td>Biograstim (filgrastim)</td>
<td>CT Arzneimittel</td>
<td>Authorised</td>
</tr>
<tr>
<td>15</td>
<td>Tevagrastim (filgrastim)</td>
<td>Teva</td>
<td>Authorised</td>
</tr>
<tr>
<td>16</td>
<td>Filgrastim Hexal (filgrastim)</td>
<td>Hexal</td>
<td>Authorised</td>
</tr>
<tr>
<td>17</td>
<td>Zarzio (filgrastim)</td>
<td>Sandoz</td>
<td>Authorised</td>
</tr>
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Perspectives

Are we ready for more complex biologicals being authorised via the biosimilar pathway?
Current situation

Biosimilars currently authorised are „small biologicals“ (less complex)

However

- Different expression systems have been used (Valtropin® = yeast Humatrope® = E coli)

- Recently Biosimilar class specific guidance has been finalised for more complex products, e.g. alpha-interferons or LMWH
Implications of recently published guidance

*Similar biological medicinal products containing low molecular weight heparins (LMWH) – (Non-)Clinical Issues.*

- LMWHs are heterogeneous (polysaccharides)
- Mode of action is not completely understood
- LMWH are licensed for various indications, including:
  - Treatment and prophylaxis of deep venous thrombosis
  - Prevention of complications of acute coronary syndromes (unstable angina, non-STEMI and STEMI)
- Recommendation for establishing equivalent efficacy: Prevention of venous thromboembolism (VTE) in surgical patients with high risk
- May allow extrapolation to other indications if adequately justified.
Implications of recently published guidance

Reflection Paper on Interferon alfa

- **Interferon-alpha** licensed for cancer indications and for treatment of viral hepatitis C

- Several PD effects; relation to efficacy unknown and potentially different in the two „major“ indications

- Concept of „PD fingerprint“, ie measurement of PD markers and their comparison even if their correlation to clinical efficacy is unclear:
  - β2 microglobulin
  - Neopterin
  - Serum 2´, 5´-oligoadenylate synthetase activity

- „Biosimilar“ endpoint rather than „benefit“ endpoint *(virological response at week 12)*
How far can we go?

In principle, the concept of “similar biological medicinal products” applies to any biological medicine. Guideline CPMP/BWP/437/04

Feasible? Possible?
Perspectives: BMWP workplan for 2010

I. EMEA/CHMP guidelines

- Revision of Guideline on Similar Biological Medicinal Products containing Recombinant Erythropoietins (EMEA/CHMP/BMWP/301636/2008) Finalisation of the revision of guideline

- Guideline on Immunogenicity Assessment of monoclonal antibodies intended for in vivo Clinical use Preparation of guideline

- Guideline on Similar Biological Medicinal Products containing Follitropin alpha Preparation of guideline

- Guideline on Similar Biological Medicinal Products containing Monoclonal Antibodies Preparation of guideline

- Guideline on Similar Biological Medicinal Products containing beta-Interferon Preparation of guideline

- Maintenance and revision of existing guidelines (overarching and non-clinical and Clinical) in light of gained experience.

II. Activities with external parties

- Meeting with interested parties (e.g., learned societies, patients’ organisations, Academia networks)

- Cooperation and reinforcing the networking and exchange of experience, e.g. FDA, Health Canada and other Agencies
“Towards Biosimilar monoclonal Abs”

<table>
<thead>
<tr>
<th>Pros for biosimilar approach</th>
<th>Cons for biosimilar approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>The structural characterization, manufacture and regulatory history of mAbs are reasonably well established</td>
<td>Every mAb is unique and small structural changes can have significant functional consequences. Even the same expression system and similar culture conditions might lead to a distinct product profile (e.g., impurities or microheterogeneity). Some methods for physicochemical characterization might not be sufficiently sensitive to establish similarity conclusively.</td>
</tr>
<tr>
<td>Readily available potency assays, most of which are relevant (that is, they correlate with the rationale of the product)</td>
<td>Potency assays might not be able to discriminate differences (see above).</td>
</tr>
<tr>
<td>In most cases, understanding of mAb function is reasonably well established, facilitating the planning of nonclinical studies as regards endpoints and other criteria</td>
<td>The efficacy and safety of mAbs are in most cases highly species specific, which makes performing nonclinical studies more difficult and potentially expensive.</td>
</tr>
<tr>
<td>Safety profile is generally reasonably well established</td>
<td>Safety profile might differ due to factors like differences in impurity profile, immunogenicity and others.</td>
</tr>
<tr>
<td>Efficacy profile is generally reasonably well established</td>
<td>Efficacy from one indication might not be transferable to other indications if the reference product is licensed for several clinical conditions. Equivalence/noninferiority study against reference product might require many more patients than stand-alone trials</td>
</tr>
</tbody>
</table>

Schneider CK and Kalinke U (2008), Nature Biotechnology 26(9): 985-990
Spectrum of Uncertainty

Can these ever be biosimilar?

Can these be bioidentical?

Complexity of Product

Source: Cecil Nick
Other Regulatory challenges
Interchangeability / Substitution I

- Substitution policies and interchangeability are decisions outside the remits of the EMA.

- Interchangeability may have different meanings in different territories.

- The EMA, based on the assessment of the Marketing Authorisation Application (MAA), provides information on quality, safety and efficacy data and as for all products a Plan for Risk Management and Pharmacovigilance.

- This information can be considered by Health Authorities and Health Care Professionals when making decisions on interchangeability or substitution of medicines.
Interchangeability / Substitution II

Relevant Scientific elements:

- **Product related**
  - Conclusion on similarity of the product
  - Comparative Pre-Clinical and Clinical data
  - Experience with biosimilars and originator
  - Safety profile of the originator
  - RMP specifications

- **Patient related**
  - Therapeutic indication
  - Naïve vs. previously treated patient
  - Patient monitoring
  - Information to patient
Challenge of global Biosimilar development

- **EU definition of 'reference medicinal product':** Article 10 point 2 (a): ‘reference medicinal product’ shall mean a medicinal product authorised under article 6, in accordance with the provisions of Article 8.

- Art. 10(2) lit. (a) of Directive 2001/83/EC contains the requirement that a **MA has been granted for the reference product in the Community.**

- **Directive** does not specify for the development product set up, however...

- “**Overarching**” Biosimilar guidance (CHMP/437/04) states:”...the chosen reference medicinal product must be **authorised in the Community, on the basis of a complete dossier...and...should be used throughout the comparability program for quality, safety and efficacy studies... data generated from comparability studies with medicinal products authorised outside the Community may only provide supportive information.”

- **Points to consider:**
  - Biosimilars evolved from generics legislation - therefore same principles are applied for reference product.
  - At time of drafting GL no external reference product with the potential of poor(er) quality and no accessible dossier was desired.
  - Comparability should provide a homogenous data set through all disciplines - using different products dilutes comparability assessment.
# Regulatory Hurdles for global Biosimilar development

<table>
<thead>
<tr>
<th>EU Development</th>
<th>Requirements</th>
<th>US Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓</td>
<td>physico-chemical and biological comparison with reference product of both regions</td>
<td>✓</td>
</tr>
<tr>
<td>✓</td>
<td>appropriate comparative pre-clinical testing with reference product of both regions</td>
<td>✓</td>
</tr>
<tr>
<td>✓</td>
<td>comparative PK/PD clinical phase I studies with reference product of both regions</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td><strong>ONE</strong> comparative clinical phase III studies with reference product from one region only (against either EU or US reference product)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Sandoz
Recent developments in the US

‘Biological Price Competition and Innovation Act of 2009’
H.R. 3590 signed by President Obama and became law
March 23, 2010

→ A Regulatory Pathway for Biosimilars in the US
Key Features:

» Biosimilar applications are reviewed by the same FDA division as the reference product

» Two standards for biosimilar approval → biosimilarity vs. interchangeability

» Twelve years of market exclusivity for reference products (Biosimilar applicant can file 4 years after licensure of reference product)

» One year market exclusivity for first approved interchangeable biosimilar product

» Complex confidential patent exchanges and litigation regulations
Biosimilarity vs Interchangeability

**Biosimilar:**
- requires demonstration that product is "highly similar", including preclinical and clinical studies (including immunogenicity, PK and PD)
- FDA to develop guidance on NC/C data requirements

**Interchangeability:** biosimilar requirements (as above) *and*
- expected to produce same clinical result... in any patient
- Safety risks or diminished efficacy of alternating or switching between use of the Biosimilar and reference product is equal to the risk of continuously using the reference product
Market exclusivity:

Reference Product Exclusivity-Evergreening Limitations

- No new exclusivity for supplements or subsequent applications for a new indication, route of administration, dosage form, or strength of a previously licensed biologic, however

- A modification to the structure of a biological product results in an additional 12 years of marketing exclusivity for the new structure **provided** it also results in a change in indication(s), route of administration, dosing, delivery or strength, or a change in safety, potency or purity.

Biosimilar Market Exclusivity

- First Biosimilar applicant that has been approved a determination of **interchangeability** (not first to file) is eligible for **one year** of Biosimilar ME

- Different market exclusivity periods apply in case of patent litigations
FDA responsibility:

- to define and draft guidance what is meant by “highly similar”?
- to determine what requirements for showing biosimilarity is necessary in terms of non-clinical and clinical requirements.
- Product class specific guidance in line with EMA (European Medicines Agency)
Conclusions

• Evolving regulatory activity being successfully implemented and monitored in the EU

• BMWP committed to keep track with the progress in the field
  – The development of novel methodologies for better characterisation of biosimilarity
  – The development of novel methodologies for tackling consequences (e.g. immunogenicity)
  – Experience from Scientific Advice, MAA and RM/PhV

• Open dialogue: Informal discussion / Briefing meetings on new technologies or regulatory challenges with stakeholders

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