Safety of Biosimilars: What you really need to know

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The short version of this talk:

• There are NO special safety issues for biosimilars that are any different from the safety issues applicable for ALL biotechnology products

The long version of this talk:

Topics

• Biosimilars; definitions and introduction
• EU Biosimilars – a quick 5 year retrospective
• PV and RMPs for biosimilars
• What safety issues have been seen?
• The “Safety Misinformation” challenge to biosimilars
What is a biosimilar?

There is currently no universally-recognised simple definition for this subgroup of biopharmaceutical products. Like all biopharmaceuticals, involving manufacture by or using living organisms, variability is unavoidable. Because of this variability, current EU terminology avoids the use of the term "biogenetic", as a variable product cannot be identical to a reference product.

In an EU regulatory context, "biosimilar" refers to biopharmaceuticals approved through the formal EU biosimilar approval mechanisms defined in article 10.4 of 2001/83, as amended by 2003/63 and 2004/27, and the associated guidelines.

A similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use.

Biological medicines are medicines that are made by a living organism, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies.

Overarching guideline (CHMP/457/04) defining philosophy and principles:

“The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) is normally applied to chemically derived products. Due to the complexity of biological/biotechnology derived products the generic approach is scientifically not appropriate for these products. The similar biological medicinal approach, based on a comparability exercise, will then have to be followed."
Introduction to biosimilars

- First EU biosimilars approvals were in early 2006 – (Omnitrope and Valtropin, both rhGH) following new legislation passed in 2004 and in effect from end of 2005
- Many additional approvals and new guidelines since 2006

EU Biosimilar approvals to date

<table>
<thead>
<tr>
<th>INN</th>
<th>Biosimilar</th>
<th>Company</th>
<th>Reference</th>
<th>CHMP opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin alfa</td>
<td>Biopharm</td>
<td>Medice</td>
<td>Eprex/Erypro (JnJ/Amgen)</td>
<td>Jan 2007</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Epoetin alfa</td>
<td>Sandoz</td>
<td>Eprex/Erypro (JnJ/Amgen)</td>
<td>Aug 2007</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Epoetin alfa</td>
<td>ABsetned</td>
<td>Eprex/Erypro (JnJ/Amgen)</td>
<td>Aug 2007</td>
</tr>
<tr>
<td>Epoetin zeta</td>
<td>Erythropoietin</td>
<td>Hospira</td>
<td>Eprex/Erypro (JnJ/Amgen)</td>
<td>Dec 2007</td>
</tr>
<tr>
<td>Epoetin zeta</td>
<td>Erythropoietin</td>
<td>Stada</td>
<td>Eprex/Erypro (JnJ/Amgen)</td>
<td>Dec 2007</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Filgrastim</td>
<td>Teva</td>
<td>Neupogen (Amgen)</td>
<td>Feb 2008</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Filgrastim</td>
<td>Teva</td>
<td>Neupogen (Amgen)</td>
<td>Sept 2008</td>
</tr>
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<td>Filgrastim</td>
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</tr>
<tr>
<td>Filgrastim</td>
<td>Filgrastim</td>
<td>Hospira</td>
<td>Neupogen (Amgen)</td>
<td>Mar 2010</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Filgrastim</td>
<td>CT Arzneimittel</td>
<td>Neupogen (Amgen)</td>
<td>Jan 2011</td>
</tr>
</tbody>
</table>

Products which failed to show biosimilarity

<table>
<thead>
<tr>
<th>INN</th>
<th>Biosimilar</th>
<th>Company</th>
<th>Reference</th>
<th>CHMP opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon alfa-2a</td>
<td>Interferon alfa-2a</td>
<td>BioPartners</td>
<td>Roferon-A (Roche)</td>
<td>June 2006</td>
</tr>
<tr>
<td>Human insulin</td>
<td>Human insulin</td>
<td>Marvel</td>
<td>Humulin (Lilly)</td>
<td>Withdrawn Jan 2008</td>
</tr>
<tr>
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</tr>
<tr>
<td>Interferon beta-1a</td>
<td>Interferon beta-1a</td>
<td>BioPartners</td>
<td>Avonex (Biogen)</td>
<td>Feb 2009</td>
</tr>
</tbody>
</table>
INNs for Biosimilars

- INNs are assigned by WHO following application by companies
- Biosimilars usually have the same INN as the reference product with which a satisfactory full comparability exercise has been demonstrated.
- INNs are not currently an issue...
- But in 2006/7 innovative biotech companies attempted to change WHO INN policy so that all biosimilars would need to be given specific and different INNs to their reference products
- This was politics and not science, and this change was rejected by all WHO INN experts
- Nevertheless there are still some attempts to suggest that adequate traceability of products require this, rather than proper reporting of product details

Conclusions on the current EU Regulatory Environment for biosimilars

- EU biosimilars legislation is sensible and flexible
- Appropriate EU guidelines are being developed
- EU dossiers undergo a comprehensive review
- EU approval for biosimilar products is a high hurdle
- PV, RMP and traceability concerns are addressed
- The EU systems for biosimilars represent a global gold standard

PV and RMPs for biosimilars

Are there any differences between PV/RMPs/post-approval studies of biosimilar products and their reference products?
- In the considering the post-approval risk-management program of any biosimilar product we need to distinguish between product-specific safety issues and product-class-specific safety issues
- Usually there should be no difference in risk assessment of the biosimilar and the original reference product
- Manufacturer of biosimilar products will usually focus their post-approval study program on well-known issues that have been established for the reference product
Post approval studies for biosimilars

Why Do Post-Approval Studies for biosimilars?

- To detect rare side effects that cannot be discovered in the clinical development program
- To investigate specific safety issues related to the product-class
- To investigate the product properties in day-to-day clinical setting
- Pharmacovigilance planning studies
- Pharmacoeconomic studies

Same reasons as for every other biotech product

Size of Post-Approval Studies

- Sample size will depend on the frequency of the adverse reaction
- For an incidence rate of ~ 1%, about 300 patients might be sufficient to detect at least one case
- For a very rare adverse reaction such as PRCA it was assessed that at least 20,000 patient years of exposure in each study arm would be needed to detect a 4-fold higher rate (4 in 10,000 versus 1 in 10,000) with 50% power*

* PRIMS registry – (Prospective Immunogenicity Surveillance Registry)

Situations when an EU-RMP is required

- Any product containing a new active substance
- A similar biological medicinal product
- A generic/hybrid medicinal product where a safety concern requiring additional risk minimization activities has been identified with the reference medicinal product
- Application involving a significant change in a marketing authorization (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant change in indication) unless it has been agreed with the Competent Authority that submission is not required
- On request from Authority (both pre- and post-authorization)
- On the initiative of a MAH/MAH when they identify a safety concern with a medicinal product at any stage of its life cycle
Example of RMP for Omnitrope

Risk Management similar to that of originator companies

The pharmacovigilance plan addresses growth hormone specific issues:

- Diabetogenic potential of rhGH treatment in short children born SGA
- Occurrence of malignancies in rhGH-treated patients
- Occurrence and clinical implications of anti-rhGH antibodies
- Risks of rhGH treatment in patients with Prader-Willi Syndrome

Methodology:
- Routine Pharmacovigilance
- PMS Registry
- Phase IV studies

<table>
<thead>
<tr>
<th>Risk issue</th>
<th>Proposed pharmacovigilance activities</th>
<th>Proposed risk minimisation activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetogenic potential of rhGH therapy in short children born SGA</td>
<td>Phase IV prospective, single arm clinical trial in short children born SGA post eligibility</td>
<td>Warning regarding diabetogenic potential in Section 4.4 of IFSC. Rate cases of type 1 diabetes mellitus in Section 6.2 of IFSC.</td>
</tr>
<tr>
<td>Occurrence of malignancies in rhGH treated patients</td>
<td>Registry of patients receiving patients demographic, long term safety including malignancy and other safety issues.</td>
<td>Warning in Section 4.4 regarding occurrence of malignancy. Lowell/waist mentioned as a very rare adverse effect in Section 4.6.</td>
</tr>
<tr>
<td>Risks of rhGH treatment in PWS patients</td>
<td>Registry expected to include patients with PWS and PWS-related demographics, long term safety as well as other safety issues in this group.</td>
<td>Warnings on use of rhGH in PWS is Section 4.14. Respiratory impairment and infection.</td>
</tr>
</tbody>
</table>

Conclusions on PV and RMPs

- Pharmacovigilance requirements are fully in line with those proposed for new drugs.
- RMP requirements for new biotech products and biosimilars are same, and note that these did not exist when many of the original innovator biotechnology products were introduced.
- Claims made that PV and RMP as conducted for biosimilars are "not good enough" do not stand up to any sensible scrutiny.
- Traceability (correctly presented as essential for PV) is achievable via full product name with batch details, as for any biological
Conclusions on RMPS for biosimilars

- In general, the risk assessment of the biosimilar and the reference product is comparable
- Therefore, the post-approval programs of biosimilar and reference product will have to address the same product class specific safety issues
- All programs will contribute to the safety data base of the product class

What real safety issues have been seen with biosimilars?

Epoetin-induced autoimmune PRCA (Pure Red Cell Aplasia)

- rh-epoetin in use since 1987/8
- PRCA extremely rare until 1998
- Peak of PRCA incidence 2001/2
- Majority of cases reported 1996-2003 received Eprex/Erypo (EPO-β, JnJ) outside the USA (195 cases out of about 250 total PRCA)
- In the same period about 11 cases associated with EPO-β (Roche) and 6 cases with EPO-α in USA (Amgen)*

- Multiple theories on causation of PRCA

* Casadevall et al, J Amer Soc Neph 2005
Epoeitin-induced autoimmune PRCA (Pure Red Cell Aplasia)

Formulation change at request of EU regulators for EPO-α (1998, only outside USA); Human serum albumin was replaced by polysorbate 80 (Tween 80)

Rubber stoppers only used for Eprex/Erypro pre-filled syringes (now coated with Teflon since 2004)

Lessons for all biotech products (not specific to biosimilars)
- Immunogenicity cannot be detected in pre-approval clinical studies
- Only robust post-marketing risk management programs will be able to capture these rare events

The Safety Misinformation Challenge to Biosimilars

• The misinformation challenge to biosimilars – to create fear and doubt
• Objectives are to suggest that novel and specific safety issues apply to biosimilars as a product class, and so limit use

(Although all safety issues relevant to biosimilars are fully applicable to all biotech products)

Top 3 results of a Google search on "Safety of Biosimilars" (on 4.5.11)

1. "Biosimilars - What are the Issues?" – a 2004 presentation by Dr Ajay K. Singh describing a study which was ongoing in 2004 reporting on the “safety of 31 biosimilar epos”

2. "Why is patient safety a concern in the biosimilars debate?" - Discussion document on current BIO website

3. "The safety of biosimilars and FDA regulation" – A January 2011 blog on “…the safety standards to which “biosimilars” — copycat version of the original biologics — will be held by the FDA”
“Singh study” methodology

- Ajay K. Singh, MB, MRCP, a nephrologist from Harvard Medical School
- 2004 study on the safety of 31 “biosimilar epos” sourced from Brazil, Colombia, India, Indonesia, Iran, Jordan, Korea, Lebanon, Philippines, Thailand, Venezuela, Vietnam, and Yemen
- Samples were tested against the European quality specifications for epoetin alfa. The epoetin alfa reference standard was used as control
- Study was ongoing in 2004, but does not appear to have been published yet, except as a presentation

“Singh study” conclusions

- Several of the biosimilar epoetins tested were found to be inconsistent in quality and potency
- 26/31 did not conform to all European specifications for epoetin alfa.
- 22/31 samples contained additional forms (basic isoforms), which can reduce clinical efficacy.
- 2 samples were contaminated with impurities (bacterial endotoxin), which poses a risk to patient safety.
- 17/31 samples contained > 2% aggregates, which can influence the immunogenicity profile of the product

“Singh study” and Schellekens 2004 paper on epos

Schellekens, EJHP 3 (2004)
Biosimilar erythropoetins may significantly vary from innovator epoetin alfa

- This published paper reports that from 11 samples (8 manufacturers) sourced from Argentina, China, India, and Korea, 5 failed to meet specifications
- What is the connection between the 2004 Singh study presentation and the 2004 Schellekens publication?
Neither source makes this clear, but both state that they used the same laboratory, J&J Pharmaceutical Technology Laboratory, Raritan, NJ, USA
Safety - The misinformation challenge to biosimilars

Results of a Google Scholar search on “Safety of Biosimilars” (on 4.5.11)
1. Follow-on biologics: challenges of the ‘next generation’
Schellekens, Nephrol. Dial. Transplant. 2005 20 (supp 4)
4. Biosimilars: how similar or dissimilar are they? SD Roger Nephrology 2006
5. Basic Facts about biosimilars Nowicki Kidney / BP Research 2007
6. Biosimilar Therapeutics Schellekens NDT Plus 2009
7. Comparative Testing and Pharmacovigilance of Biosimilars Locatelli and SD Roger NDT 2006 (Suppl 5)
8. Biosimilars: It’s not as simple as cost alone SD Roger J Clin Pharmacy 2008

1. Follow-on biologics: challenges of the ‘next generation’
Schellekens, Nephrol. Dial. Transplant. 2005 20 (supp 4)

Extracts from abstract:
“…verification of the similarity to or substitutability of biosimilars with reference innovator biopharmaceutical products will require much more than a demonstration of pharmacokinetic similarity, which is sufficient for conventional, small molecule generic agents."

“For most products, results of clinical trials demonstrating safety and efficacy are likely to be required. In addition, because of the unpredictability of the onset and incidence of immunogenicity, extended post-marketing surveillance is also important and may be required.”


- Published in Annals of Oncology in 2008, but written in 2007 before any EU biosimilars had been introduced to EU oncology practice
- Appears to be a conventional literature review article

“to review issues associated with the introduction of …biosimilars used in oncology”

“Design: Data obtained by searches of MEDLINE, PubMed…”
Safety - The misinformation challenge to biosimilars


The “Results” section of the abstract of this paper includes statements that challenge the EU review process and the authority of the CHMP and EC:

“When biosimilars are approved in EU…this does not ensure therapeutic equivalence”

“Differences between biosimilars may produce dissimilarities in clinical efficacy, safety, and immunogenicity”

and “switching biosimilars should be considered a change in clinical management”

The misinformation challenge to biosimilars


The “Conclusions” section of the main article clarifies the agenda of this “literature review” (which has been cited 53 times):

“There are potential concerns regarding the use of biosimilars in patients with cancer…”

“…automatic substitution should be prohibited…”

“…extrapolation of clinical data from one therapeutic indication to another…warrants concern.”

Safety - The misinformation challenge to biosimilars


Extracts from abstract:

“The complexity of protein molecules renders it impossible to produce identical copies; this in turn raises questions on the safety of follow-on biosimilar products, particularly with respect to immunogenicity. This review briefly outlines the process of biopharmaceutical production, potential problems that can arise from their long-term use in patients…”
4. Biosimilars: how similar or disimilar are they? SD Roger Nephrology 2006

Extracts from abstract:
“One of the key areas of concern with the introduction of biosimilars into the field of nephrology will be guaranteeing the safety and efficacy of biosimilars.”

“Biopharmaceuticals are inherently more complex, difficult to manufacture and have greater process-related variability that can impact efficacy and safety. Therefore, any potential reduced cost will need to be weighed up against accepting a degree of variability in drug efficacy and safety.”

Safety misinformation on biosimilars continues

Misinformation continues to be published in 2011:

“To date Europe has approved 14 biosimilars with no significant safety issues reported (save for one that was a follow-on biologic called Eprex…which suffered from a significant safety issue in France)”

Taken from a news editorial on biosimilars in Applied Clinical Trials February 2011, page 16

Recent publications

Biosimilars and innovation: an analysis of the possibility of increased competition in biopharmaceuticals.
Blackstone EA, Fuhr JP Jr.

Extracts from abstract:
“Biosimilars raise greater safety issues owing to possible immune responses… Patents may not be as strong for biopharmaceuticals, which are often made by small firms, suggesting the desirability of greater data exclusivity protection. This article suggests that it is better to err on the side of too much protection than too little, given the uncertainties involved.”
Recent publications

SD Roger Biosimilars: current status and future directions.
Excerpts from Abstract:
“...there have been concerns over the degree of similarity of these complex drugs in addition to the hope that their introduction may lower the cost of such expensive medicinal products.
Issues with post-marketing surveillance programmes and their limitations are described.
Clinicians need to be wary of non-transparent promotion of innovator/biosimilar products.”

Recent publications

Niederwieser and Schmitz Biosimilar agents in oncology/haematology: from approval to practice
Excerpts from abstract:
“This review ...highlights current specific issues pertinent to their use in clinical practice in oncology:
...physicians should remain aware of the inherent differences between biosimilar and innovator products.”

Safety - The misinformation challenge to biosimilars

Accurate information and scientific discussion are the best ways to counter misinformation:


Revised and updated second edition was published in April 2011
Thank You