Regulatory perspectives on biosimilars in Europe

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<th>Year</th>
<th>Drug Name</th>
<th>Company</th>
<th>Status</th>
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<td>Hospira</td>
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Biologics: complex molecules produced from living organisms

A political decision was made in 2004 to allow official copies of existing biological products:
- Based on a reduced dossier
- In parallel with the "generic" concept
- Taking advantage of experience with the comparability of biotech products after a change in manufacturing process

The goal was (is) purely pharmaco-economical

There is no official definition of a biosimilar in the EU

From Joerg Windisch, CSO Sandoz
Biosimilars in the European Union (EU)

The EU Directive and the EMA guidelines

« When a biological MP does not meet all the conditions to be considered as a generic MP, the results of appropriate tests should be provided in order to fulfill the requirements related to safety (pre-clinical tests) or to efficacy (clinical tests) or to both. »

EMA CHMP document 437/04 (“Guideline on Similar Biological Products” = “overarching guideline”), effective 10/2005, states:

« Due to the complexity of biological/biotechnology-derived products the generic approach (i.e. demonstration of bioequivalence with a reference medicinal product) is scientifically not appropriate for these products. The “biosimilar” approach, based on a comparability exercise, will then have to be followed. »

Key points of the CHMP 2005 guideline

1. Biosimilar is NOT “biogeneric”

2. A “comparability exercise” is required

Biosimilarity should be established at all levels in a stepwise fashion
(Quality → Non clinical → Clinical Efficacy & Safety)

The concept is similar to, but more exacting than, the comparisons of internal versions of a biotech product

3. The Quality comparison may be more important than the clinical comparison

4. A Risk Management Plan (RMP) will be needed

NB. Is it really part of the comparability exercise?
To establish that, when used as a therapeutic product, there is **not likely** to be any **clinically significant difference** between the reference product and the test product.

- But the key concept to demonstrate biosimilarity is NOT a therapeutic equivalence trial because this would be insensitive to differences (rather, the concept is a comparability exercise)

- Clinicians and regulators (**and big pharma industry…**) often view this issue differently
## The comparability exercise

<table>
<thead>
<tr>
<th>Comparability (change in manufacturing process)</th>
<th>Biosimilarity</th>
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<tbody>
<tr>
<td>▪ Extensive quality data</td>
<td>▪ Extensive quality data</td>
</tr>
<tr>
<td>▪ Low need for clinical data</td>
<td>▪ High need for clinical data</td>
</tr>
<tr>
<td>▪ Thorough internal knowledge by manufacturer</td>
<td>▪ No internal knowledge</td>
</tr>
<tr>
<td>▪ Noninferiority tests</td>
<td>▪ (Generally) <strong>Therapeutic equivalence</strong></td>
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If the comparison **fails** at any stage, the products cannot be declared biosimilar.
EMA dossier requirements for biosimilars

**Stepwise comparability approach Q → NC → C**

**CTD Module**

- **3 Quality**
- **4 Non-Clinical**
- **5 Clinical**

**Originator**

**Biosimilar**

- Cross reference

**Integrated Comparability Exercise – product specific Quality, Safety and Efficacy**

*Source: Dr Falk Ehmann (EMA)*

*Similarity rather than S/E per se*
Some critical points in the dossier

Quality comparison
• **A key step – possibly the most critical step**
  - Cell culture, impurities – product and process related, sterilisation methods, presence or absence of serum albumin, glycosylation pattern…

Non-clinical comparison
• *In vitro receptor binding & cell-based assays are fundamental*
  - (where model allows) In vivo PK/PD/activity/toxicity

Clinical comparative studies
• *Most sensitive population and endpoints* (healthy volunteers and/or PK/PD/biomarker data may suffice) → **this was easily accepted for growth factors**
  - “Equivalence” study with justified margins (δ) → **uncertainty**!
  - 6-12 month safety data (incl. immunogenicity)
  - *Extrapolation of indications* !!
<table>
<thead>
<tr>
<th>Term(s)</th>
<th>Definition</th>
<th>Implications</th>
</tr>
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<tbody>
<tr>
<td>Biosimilar&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy, and safety, based on a comprehensive comparability exercise.</td>
<td>Only very small differences between biosimilar and reference with reassurance that these are of no clinical relevance. Extrapolation of clinical indications acceptable if scientifically justified.</td>
</tr>
<tr>
<td>Me-too biological/biologic</td>
<td>Biologic medicinal product developed on its own and not directly compared and analyzed against a licensed reference biologic. May or may not have been compared clinically.</td>
<td>Unknown whether and which physicochemical differences exist compared to other biologics of the same product class. Clinical comparison alone usually not sensitive enough to pick up differences of potential relevance. Therefore, extrapolation of clinical indications problematic.</td>
</tr>
<tr>
<td>Noninnovator biological/biologic</td>
<td></td>
<td></td>
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<tr>
<td>Second-generation (next-generation) biological/biologic</td>
<td>Biologic that has been structurally and/or functionally altered to achieve an improved or different clinical performance.</td>
<td>Usually stand-alone developments with a full development program. Clear (and intended) differences in the structure of the active substance, and most probably different clinical behavior due to, for example, different potency or immunogenicity. From a regulatory perspective, a claim for 'better' would have to be substantiated by data showing a clinically relevant advantage over a first- or previous-generation product.</td>
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<td>Biobetter</td>
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<sup>a</sup>Comparable terms defined by the same/similar scientific principles include the WHO's 'similar biotherapeutic products' and Health Canada's (Toronto) 'subsequent-entry biologicals'

BMWP-Biosimilar Medicinal Products Working Party at EMA
EU Biosimilar Guidelines - Overview

Overarching Guideline (CHMP/437/04)
Guideline on Similar Biological Medicinal Products

User guide - CHMP adopted Sep 05

Biotechnology- derived proteins

Quality

Non-clinical

Clinical

Non-clinical

Clinical

Class specific GLs

2006 2007 2008 2009 2010 2011 2012

Somatropin Insulin Epoetin GCSF IFN-alpha Epoetin v2 mAbs FSH IFN-beta Insulin v2

2009 LMWH V2 in 2012
GUIDELINE ON COMPARABILITY OF BIOTECHNOLOGY-DERIVED MEDICINAL PRODUCTS AFTER A CHANGE IN THE MANUFACTURING PROCESS

NON-CLINICAL AND CLINICAL ISSUES

GUIDELINE ON IMMUNOGENICITY ASSESSMENT OF BIOTECHNOLOGY-DERIVED THERAPEUTIC PROTEINS

Some complexities of the system
In principle, the concept of a “biosimilar” is applicable to any biological MP. However, in practice, the success of such a development approach will depend on the ability to characterise the product and therefore to demonstrate the similar nature of the concerned products.

Whether a MP would be acceptable using the “biosimilar” approach depends on the state of the art of the art of analytical procedures, the manufacturing processes employed, as well as clinical and regulatory experiences.

The pharmaceutical form, strength, and route of administration of the similar biological MP should be the same as that of the reference medicinal product. If not, additional data should be provided.

**Ex.** Binocrit® was not able to provide those data for the sc route vs Eprex for chronic renal failure patients. → Binocrit® is only biosimilar for the iv route in CRF patients (Retacrit® is approved for both sc and iv routes in that indication).

« The chosen reference medicinal product must be a MP authorised in the EC on the basis of a complete dossier. »

This requirement will be removed when the revision of the overarching guideline comes into force (possibly end 2013)
4- Legislation vs science

1. Scientific guidelines have no legal force → applicants are invited to justify any lack of compliance

2. Development of guidelines follows science (eg, experience from scientific advice procedures and previous marketing authorization applications)
Outside the EU
To obtain a “SBP” label, a stepwise comparability exercise (quality/nonclinical/clinical) should be performed.

SBPs require regulatory oversight for the management of risks.

Extrapolation of indications is possible provided…

The Affordable Care Act creates an abbreviated licensure pathway for products that are biosimilar or interchangeable with an FDA-licensed biologic reference product.

- Stepwise approach
- FDA intends to consider the “totality of the evidence”
- Scope and magnitude of the clinical studies will depend on the extent of residual uncertainty about biosimilarity.

The contentious points
The debate on biosimilars
In principle, the most sensitive disease model to detect differences in both efficacy and safety should be used in a homogeneous patient population to reduce variability.

In oncology, that would mean response rate rather than (overall) survival, possibly in early stage patients; it would also mean immunocompetent subjects.

But HTA bodies (and clinicians) may require the most relevant population…
1. Without extrapolation, the biosimilar concept is dead

2. Justification of the extrapolated indication (rather than separate demonstration of equivalence) is on a case-by-case basis
   ➔ criteria for the decision? (e.g. mechanism of action, receptor number and affinity…)
   ➔ could guidelines help?
1. Immunogenicity in humans cannot be predicted from animal data → absolute need for **comparative clinical trials** including tests for neutralizing Abs and PK/PD data

2. Consider the risk to the endogenous protein

3. *How long?*

   Usually 1 year pre-licensing if chronic use is intended; the subsequent risk management plan (RMP) is crucial

→ **Traceability (naming) of biosimilars!**
→ **Should be prescribed under brand names**
4- Interchangeability

1. In the EU, biosimilarity refers to a single point in time (date of Marketing Authorization)

2. Designation of interchangeability may imply need for demonstration of “continued biosimilarity” (e.g. with respect to immunogenicity)

3. Interchangeability/automatic switch should remain a national decision
A new era: biosimilar monoclonal antibodies
A new era: biosimilar monoclonal antibodies

April and September 2012: two MAAs to EMA for biosimilar infliximab (at least one from Celltrion, Korea)

Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues

<table>
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<th>Draft Agreed by Similar Biological Medicinal Products Working Party</th>
<th>October 2010</th>
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<td>Adoption by CHMP for release for consultation</td>
<td>18 November 2010</td>
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<tr>
<td>End of consultation (deadline for comments)</td>
<td>31 May 2011</td>
</tr>
<tr>
<td>Final agreed by BMWP</td>
<td>March 2012</td>
</tr>
<tr>
<td>Adoption by CHMP</td>
<td>30 May 2012</td>
</tr>
<tr>
<td>Date for coming into effect</td>
<td>1 December 2012</td>
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Infliximab is a « simple » blockade of TNFα

What about rituximab, trastuzumab….?

Biosimilar monoclonal antibodies (mAbs): the clinical issues are not different but “technically” are we pushing the concept too far?

- Very complex production
- Complex (oncology) indications

**Very complex mechanism of action**
Some Take-Home Messages
1. The biosimilarity concept means a “low likelihood of clinically significant differences”

2. According to (EU) regulators, a product can be biosimilar only if it has successfully gone through the stepwise (Q/S/E) “comparability exercise”

3. Therefore, not all copies of biological products are biosimilar
4. Detection of immunogenicity and RMP are key elements of safety — as for all biotech products; so far there is no safety issue with any biosimilar

5. Traceability should be ensured by prescribing under brand names (and tracing batch numbers...)

6. Interchangeability is a national (or local) issue
7. The clinical focus of the biosimilar exercise is on PK/PD using the most sensitive populations and endpoints, it is not on patient benefit *per se*

8. Extrapolation of indications is key to the biosimilar concept but needs to be justified in all cases

9. **Clinicians should accept these concepts** (*comparability exercise and extrapolated indications*) but should discuss the equivalence margins and the increased level of uncertainty
10. How much “reassurance” are decision makers and clinicians willing to give away in favour of lower prices?

11. The application of the biosimilar concept to mAbs hangs in the balance (in my opinion)
Thank You !!
Back-up slides:

Market Penetration of Biosimilars
FIGURE 3: THREE GEOGRAPHICAL CLUSTERS ARISE, WITH US REPRESENTING A SIGNIFICANT PORTION OF MARKET POTENTIAL (~60%)
Pharmerging economies anticipated to be a potential growth driver

1. US
   Potential leading market for biosimilars
2. Advanced economies
   Established framework for biosimilars, but slow uptake
3. Pharmerging economies
   Biosimilars* already established (looser regulatory pathway) and fast-growing biologics market

Source: IMS Health MIDAS, 2005-2010

* Biosimilars in Europe and Japan defined by regulatory pathway, in pharmerging markets looser approval processes apply for products that resemble biosimilars
FIGURE 4: OVERALL WE CAN IDENTIFY TWO UPTAKE PATTERNS FOR BIOSIMILARS, DIFFERENTIATED VS. COMMODITY
Differentiated markets will pose several challenges to biosimilars

Back-up slides:

Development of biosimilar mAbs
Clinical issues in biosimilar mAbs

- Do not really differ from non-mAb biosimilar products but the guideline insists on:
  1. The comparative PK study (in healthy volunteers or in patients) is key -- if possible, **add PK/PD** (if PD measurements are feasible)
  2. A Phase III equivalence trial is expected in a sufficiently E/S sensitive population (demonstrating patient benefit *per se* is not the goal) – however, a relevant endpoint is key for market access
  3. Extrapolation of indications is possible based on the “overall evidence of biosimilarity”
  4. RMP: post-MA safety studies may be required

April and September 2012: two requests for infliximab biosimilar MAA accepted at EMA, at least one likely from Celltrion (Korea)
Review

Mini Focus: Bioanalysis of Biosimilars

Assessing immunogenicity of biosimilar therapeutic monoclonal antibodies: regulatory and bioanalytical considerations

Immunogenicity of biosimilar mAbs (2)

- ADA incidence and magnitude should always be assessed relative to capacity of ADAs to neutralize the relevant biological activity of the therapeutic mAb.

- Detected differences in ADA incidence or magnitude should not, in themselves, result in a product being classified as ‘not biosimilar’ – the impact of the difference on relevant clinical parameters should be used as the arbiter.

- It follows that it would not be feasible to predefine a margin of difference in ADA incidence or magnitude that would result in the classification of ‘not biosimilar’.

- A single Phase III comparative study in a population that is suitable to demonstrate therapeutic equivalence would be expected to identify the clinical impact of an increase in the level of immunogenicity of a biosimilar product candidate relative to the reference product.
• Although **post-authorization data** might be useful to confirm absence of heightened immunogenicity-related risks in different patient populations, they are **unlikely to be useful** for comparative purposes because of the uncertainties of the longer term treatment outcomes for the reference product - except, perhaps, for anti-TNF agents ?