Title:  Biosimilar: rigorous evidence of equivalence.

Author(s):  Fernando de Mora, MBA, PhD

Fernando de Mora, PhD, MBA
Professor
Department of Pharmacology, Therapeutics and Toxicology

Universidad Autónoma de Barcelona

SPAIN
Biosimilars' stringent regulation: the focus is on patients

Biosimilar: the totality of the evidence

What is not a biosimilar?

Biosimilars: the evidence behind extrapolation and switch

Conclusion:
Biosimilars added value

Is the structure of the active substance of any given original biological product identical from batch-to-batch?

NO
Chemically-synthesized medicine
(NO living organism)

Biological medicine:
Complexity

↑↑↑ Size, structural and manufacturing complexity

↑↑↑ Batch-to-batch VARIABILITY

Original active substance:
Rituximab

Glycans
Pre and post-change batches

Batches after
Manufacturing change

Batches before
Manufacturing change

Batch-to-batch clinically acceptable physicochemical variability
Will they open?

IT DEPENDS

If this shape changes WILL NOT AFFECT

If this shape changes MAY AFFECT

Biosimilar: in essence the same

EMA/WHO standard: biosimilar and originator share essentially the same active substance, are given via the same route, at the same dose, and for the same indications
Biosimilar etanercept: acceptable differences

Originator’s batches

Is the difference biosimilar/originator of any clinical concern?

A comprehensive physicochemical and functional comparability exercise

Analytical (physicochemical and functional) comparability: the most sensitive comparison

Patient trials: confirmatory

Physicochemical comparability: 90 attributes (charge, di-sulphide, HOS, glycosylation..)
Functional comparability: Fab, Fc.. > 30 studies

The foundation of biosimilarity is analytical comparability

EPAR. 27 June 2013 EMA/CHMP/589317/2013 Committee for Medicinal Products for Human Use (CHMP)
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EMA: the pioneer agency

Reference regulatory agencies share with EMA, biosimilars regulatory/scientific principles
Biosimilars versus “Non-comparable biologic, NCB” or “intended copy”

Less stringent regulatory framework

Biosimilar Regulatory framework

Can they be called biosimilars?

Investment: intended copy << Biosimilar
Clinical risk: intended copy >> Biosimilar

Biosimilars or NCB?


Healthcare warning
Withdrawn from market

Side effects suggest that EMA/WHO standards have not been followed: isn’t “biosimilarity” questionable?
Biosimilar is a biosimilar

Less stringent regulatory framework

Term “biosimilar”: NOT APPLICABLE to any biologic
Only if EMA/WHO standard

The “regulatory walk”:
A worldwide trend towards EMA/WHO

Legal frameworks acknowledge specific requirements for biosimilars

How demanding/appropriate are the guidelines being put in place? WHO-like?
Do authorities closely outlook their implementation or application?
Are evaluators properly trained to assess a dossier?

Differentiate intended copy from biosimilar
FOR PATIENT SAFETY
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Applicable to BIOSIMILARS (EMA/WHO standard)
Caution with intended copy !!!

Are clinical trials of an original biologic performed for every targeted indication/population?

NO
Approval by extrapolation: originators (1)

- Children / Young adults
  - YES Co-morbidity
  - NO Co-morbidity
  - Co-treat
    - Ethnic group – origin (caucasian, asian, etc..)
- Adults / geriatric
  - NO Co-morbidity
  +

It is beyond reach to perform a clinical trial that covers all the patient populations to be treated

Approval for non-studied patient populations = Extrapolation

Approval by extrapolation: originators (2)

27 June 2013
EMA/CHMP/751770/2012/corr1
Committee for Medicinal Products for Human Use (CHMP)

- Efficacy endpoint and the extrapolation of the efficacy data to the metastatic breast cancer setting was considered acceptable. Overall, a comparable efficacy of a fixed dose of trastuzumab SC with

<table>
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<th>IV Formulation trastuzumab</th>
<th>SQ formulation trastuzumab</th>
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<td>Comparative trial in patients: Early breast cancer</td>
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- IV / SQ Equivalent
- Approved by extrapolation

The new SQ original trastuzumab formulation was approved for “metastatic” tumour by EXTRAPOLATION
Position of the British Society of Gastroenterology

1. Prescribing by brand name e.g. use Remicade rather than infliximab
2. For patients already on therapy, avoidance of switching from parent drug to biosimilar, or vice versa, at least until we have safety data
3. The use of a prospective registry of all biological use in IBD to capture safety data, rare and new side effects. We recommend the IBD Registry (www.ibdbiologicsaudit.org)

Infliximab: BSG recommends original-to-biosimilar switch in an EXTRAPOLATED indication!!

Original biologicals: switch to an active ingredient without identical primary sequence

Human insulin

Darbepoietin

Insulin analog

Erythropoietin


Exchange among biomedicines that DO NOT meet a fundamental biosimilarity criterion: identical aminoacid sequence
Switching from plasma Factor VIII to recombinant Factor VIII does not trigger immunogenicity, despite biosimilarity not reached.

Switch among highly similar biomedicines

Switching between medicines subject to a stringent comparability exercise IS SAFE.
Original-biosimilar switch: the position of the European Medicines Agency

Interchangeability of Biosimilars: A European Perspective

Pekka Karkkila, Leon van Arnhem, Elena Wolff, Henk te Meer, Thijs Ginjaer, Veronika Kühn, Martina Wolff

Key Points

Biosimilars are copy versions of an already existing biological medicinal product. They are high-quality products and as efficacious and safe as the original biological medicines. Because of the high similarity, there is no reason to believe that the body’s immune system would react differently to the biosimilar compared with the original biological upon a switch. This view is supported by the current experience with biosimilars on the market and by literature data.

In our opinion, switching patients from the original to a biosimilar medicine or vice versa can be considered safe.

Acceptable Switch

Exchanging original and biosimilar versions may be considered safe

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CONCLUSION

Only if its development follows EMA/WHO (or alike) standards, a biosimilar can be considered a safe alternative to the original reference product.

Therefore, the development of a biosimilar needs to follow EMA/WHO (or alike) standards for the sake of the patient.

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Thank you...