



EAHP Congress 2016
EGA Biosimilar Symposium
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Biosimilars: concerns of prescribers and how to address them as a hospital pharmacist

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Vs16c15

Conflict of Interest Statement



- I declare no personal financial interest in any pharmaceutical business
- I entertain friendly relationships with all innovative and generic / biosimilar companies (AbbVie, Amgen, Biogen, EGA, Mundipharma, Pfizer/Hospira, Roche, Sandoz)
- As a co-founder I have a societal – but not financial - interest in the advocacy of cost-effective treatments via the Generics & Biosimilar Initiative (GaBI)
- My employer – Erasmus University Hospital - receives any honoraria (advisory boards, speakers honoraria) if they let me speak at scientific or commercial meetings.

Agenda



1. Forecast 2020 and where are we now?
2. The Hot Potato
3. Five criteria for acceptance of a drug
4. What kind of misunderstandings many physicians have?
5. The information gap
6. What can we do?



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FDA new drug admissions 1993-2015

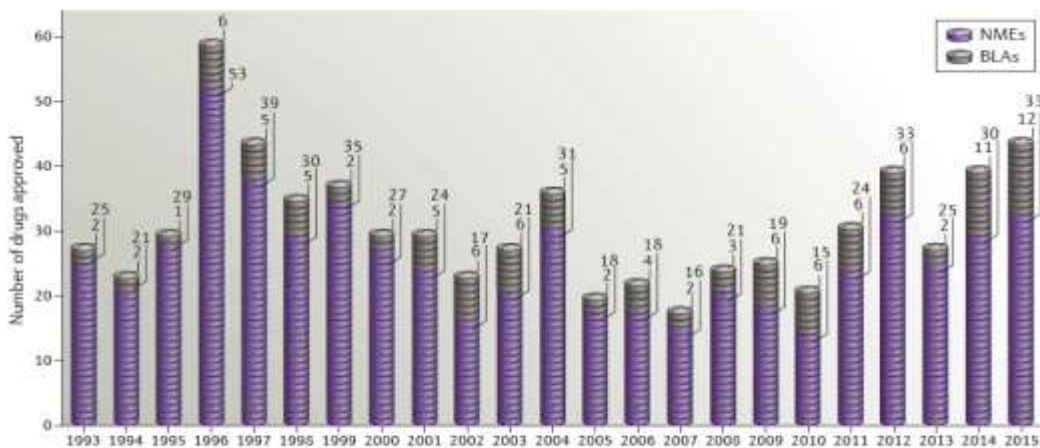


Figure 1 | Novel approvals since 1993. New molecular entities (NMEs) and Biologics License Applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER) since 1993. Approvals by the Center for Biologics Evaluation and Research (CBER) are not included in this drug count. Data are from Drugs@FDA and the FDA.



Sales forecast blockbusters 2014→2019 29 billion dollars extra cost each year

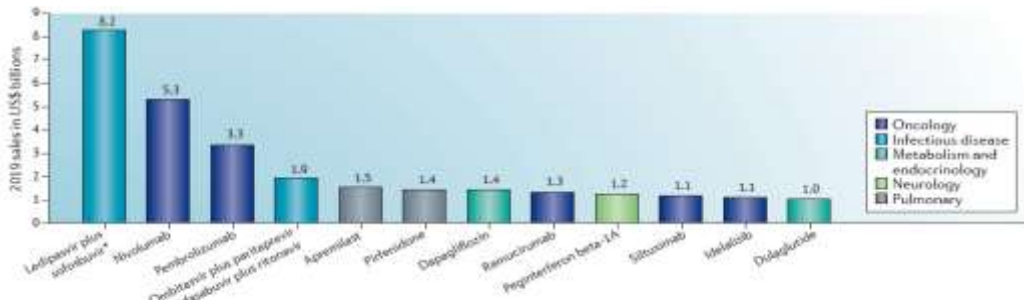


Figure 3 | Anticipated blockbusters approved in 2014. Sales forecasts are average, annual, global estimates for 2019 as compiled by Thomson Reuters Cortellin database. *Sales of Gilead's combination of ledipasvir plus sofosbuvir are expected to peak at US\$12 billion in 2017.

Amgen
Biotech
Workshop



Sales forecast blockbusters 2015-2010 > 36 billion dollars extra cost each year

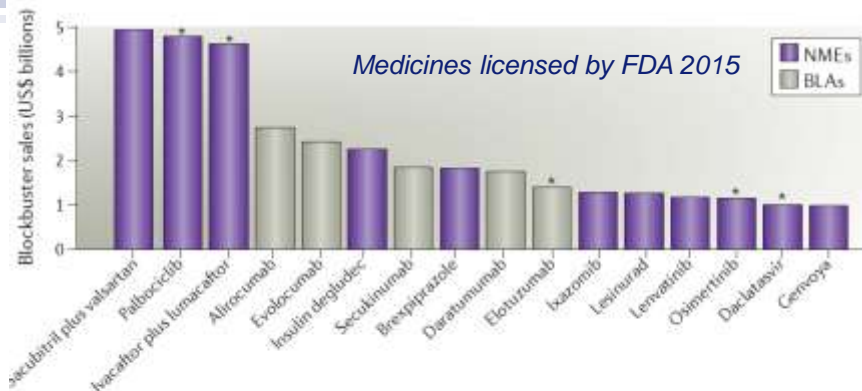
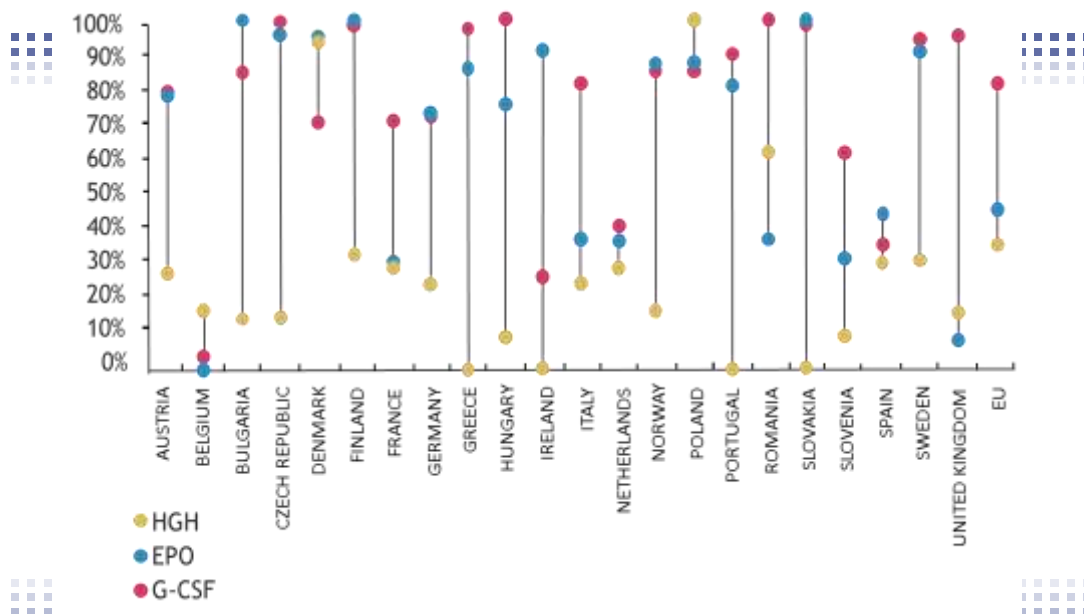


Figure 3 | Anticipated blockbusters approved in 2015. Sales forecasts are average, annual, global consensus sales estimates for 2020 as reported by Thomson Reuters' Cortellin database on 31 December 2015. BLA, Biologics Licence Application; NME, new molecular entity. *Drugs with breakthrough designation.

Mullard, Nat Rev Drug Discovery 15(2016)73

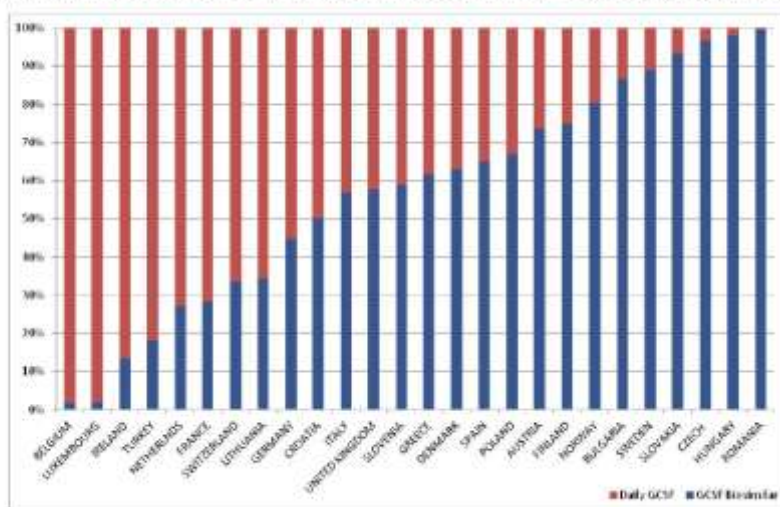
2014: EU Biosimilar uptake as % of accesible market



Or even a more clear example: GCSF (2013)



Volume uptake of GCSF biosimilars in standard units vs. daily GCSF available market products



Source: IMSI Health, MIDAS, July 2013 MAT



In summary

- The total drug bill will grow exponentially with the many blockbuster breakthrough drugs
- The savings-potential of biosimilars is highly underused.
- The question is: why is this so?
- And what can we do about it?

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The hot potato

- When will a physician prescribe a biosimilar and / or when will a pharmacist dispense a biosimilar product?
 - If the physician has sufficient trust in the sameness of the biosimilar
 - If the pharmacist is allowed to dispense a biosimilar
 - And if both have sufficient incentive to do so

- In this presentation we will discuss concerns of prescribers and how we as hospital pharmacists can address these.

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We have unified licensing, but not unified access

Legislation is only part of the story

- There exists a formal legal framework
- Versus a less formal local interpretation with many variations
- Acceptance of a biosimilar is dependent on how different stakeholders act.
 - Physicians, patients, pharmacists, 3rd party payers, policy makers
- Essential to buy in “ownership” from stakeholders like prescribers (e.g. via guidelines)
- This offers a unique opportunity to show added value for pharmacists

“The” biosimilar does not exist

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For a decision to prescribe a drug, information is needed

- Biosimilars are not *identical* but *similar*
- What are then the differences and what could be the consequence?
- A deep understanding of bioequivalence and “biosimilarity” is not easy
- Uncertainty will be smaller if we know the safety profile - both for originator medicines and biosimilars
- Biosimilars are standing on 10 – 15 years of experience of innovator medicines

**Physicians don't like uncertainty
In doubt do not cross!**

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5 reasons why doctors are reluctant to prescribe biosimilars

Biopharmaceuticals

CHALLENGES FOR THE ADOPTION OF FUTURE BIOSIMILARS

Ellen HM Moors, PhD

Hospital pharmacists and physicians are responsible not only for the prescription and delivery of biopharmaceutical drugs, but also for hospital formularies and drug budgets. What are the challenges for these key professionals to adopt biosimilars in the future?



- European J Hospital Pharmacy 13(2007) No5, 57-58

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5 criteria that play a role in adoption of a new drug

Adoption:

“a decision to make full use of an innovation as the best course of action available”

1. Relative advantage

- * Is the innovation perceived as better?
- * What is the added value?
Effectiveness, quality, safety, ease of use, economic factors

2. Compatibility

- * Perception of consistency with past experience and current needs
Does it fit expectations?

Moors EHM, Eur J Hosp Pharmacy Practice 13(2007)No.5, 57-58



5 criteria that play a role in adoption of biosimilars

3. Complexity

- * Perception of degree of difficulty in using the innovation
- * Proving similarity is a serious barrier to biosimilar drug development (when is enough, enough?)

4. Trial data

- * Overall clinical experience before drug is adopted
- * How reliable, informative and convincing are the proof-of-bioequivalence studies?

5. Observations

- * How observable are the results of the innovation?
Biosimilars hardly offer ground breaking research results
Knowledge base *looks* rather small vs. innovative product



Complexity and Trial data

- Doctors have been trained for decades with the principles of “evidence based” medicine, with the controlled clinical trial as a standard.
- Biosimilars are built on a new drug development paradigm
 - Emphasis is on laboratory and pre-clinical work
 - Is based on a similarity exercise
 - The clinical trial is to support similarity, NOT to proof efficacy
- Therefore it is understandable that physicians are reluctant to prescribe these drug

What to choose?



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Acceptance of a new drug dependent on

Affinity with the existing brand-product

(= current value, including habit)

Versus

Attractiveness of the alternative (biosimilar)

(= it implies a change with uncertain outcome)

Without an incentive for change.

A physician will not change it's prescribing habits

Drug prescribing is highly emotion and information driven

Where to obtain convincing information?

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What kind of misunderstandings health care professionals may have?



- Biosimilars
 - May be of less quality as the innovator drug
 - Are poorly supported by research
 - Have not been researched in all indications
 - Differ from the innovator in potentially relevant aspects
 - Have been assessed by regulators who are bureaucrats, who have no clinical experience
 - Used a shortcut in the normally rigorous licensing process

The quality argument

- All pharmaceuticals licensed in the EU have to fulfil the same quality standards, no exception
- Many innovator drugs were developed 20 years ago or more, at that time with state of the art technology

Technology has advanced dramatically in the benefit of biosimilars

- Biosimilars have been developed with 21st century technology.
- Overall we see the same or better quality
 - less aggregates, better stability, less painful injections, even lower drug-antibody titers

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Biosimilars have the same or even better quality

Pharm Res (2011) 28:386–393
DOI 10.1007/s11095-010-0288-2

RESEARCH PAPER

Quality of Original and Biosimilar Epoetin Products

Vera Brinks • Andrea Hawe • Abdul H. H. Basmeh • Liliana Joachin-Rodriguez • Rob Haselberg • Govert W. Somsen • Wim Jiskoot • Huub Schellekens

ABSTRACT

Purpose To compare the quality of therapeutic erythropoietin (EPO) products, including two biosimilars, with respect to content, aggregation, isoform profile and potency.

Methods Two original products, Eprex (epoetin alfa) and Dynepo (epoetin delta), and two biosimilar products, Binocrit (epoetin alfa) and Retacrit (epoetin zeta), were compared using (1) high performance size exclusion chromatography, (2) ELISA, (3) SDS-PAGE, (4) capillary zone electrophoresis and (5) *in-vivo* potency.

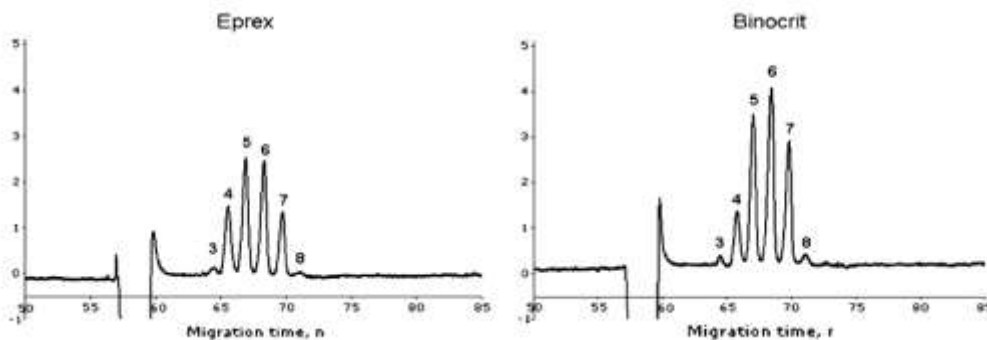
Results Tested EPO products differed in content, isoform composition, and potency.

Conclusion Of the tested products, the biosimilars have the same or even better quality as the originals. Especially, the potency of originals may significantly differ from the value on the label.

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Table II Comparison of Content and Potency of the Four EPO Products Tested

	Declared potency (IU/ml)	Content HP-SEC, UV280nm (IU/ml)	Content ELISA (IU/ml)	In Vivo potency (IU/ml)	Ratio total AUC fluorescence/total AUC UV280 nm from HP-SEC
Eporex	10,000	11,699 ± 453	13,694 ± 273	12,884 (10,860–15,285)	6.57 ± 0.37
Binocrit	10,000	10,961 ± 162	12,942 ± 216	11,404 (9,458–13,752)	6.62 ± 0.27
Retacrit	10,000	9,586 ± 103	11,122 ± 20	11,016 (8,942–13,571)	6.74 ± 0.07
Dynaspo	20,000	20,564 ± 269	23,208 ± 906	15,694 (13,421–18,352)	6.60 ± 0.11



GCSF

Bone Marrow Transplantation (2012) 47, 574–576
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www.nature.com/bmt

LETTER TO THE EDITOR

Experience (1 year) of G-CSF biosimilars in PBSCT for lymphoma and myeloma patients

This study shows that biosimilars of G-CSF are equivalent to classical products in terms of efficacy when used for stimulation after PBSCT in lymphoma and myeloma patients.

Bonnet Cell Cases (2013) 21, 202–203
DOI 10.1007/s00254-013-0613-7

REVIEW ARTICLE

Clinical experience with Zarzio® in Europe: what have we learned?

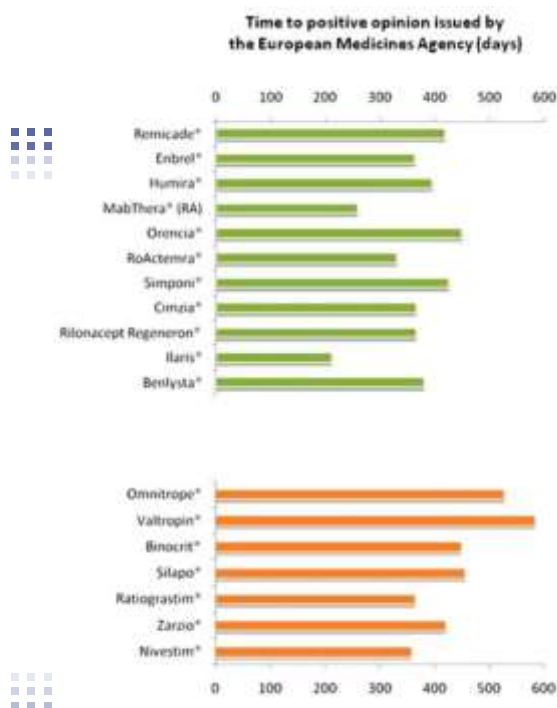
Piero Giaccone · Hans Teack · Karl Verpoint · Maria Sofia Bostak · Nella Salmi · Susmit Agrawal · Nik Wilking · Helen Barber · Michael Hanzheng · Matthew Turner

known safety profile of G-CSF. Initial concerns about the use of biosimilars, at least with regard to biosimilar G-CSFs, appear to be unfounded. Adoption of cost-effective biosimilars should help reduce healthcare costs and improve patient access to biological treatments.

Conflicting acceptance

- Why do physicians have a lack of confidence in fully licensed medicines, once they are coined “biosimilar”?
- Example 1: Omniprote® in the US is a generic medicine (ANDA-route) that is widely prescribed; in the EU the same product is licensed as a biosimilar with hardly any uptake.
- Example 2: The SC forms of trastuzumab and rituximab with completely overhauled formulations and different route of administration were assessed and licensed with a biosimilar-like “abbreviated pathway” and found rapid acceptance by clinicians

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Is the “abbreviated pathway” shorter?

Schneider *Ann Rheum Dis* 72(2013)315-318

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Fingerprinting to ascertain no difference in critical quality attributes

REPORT

Pharmazie, 1163-1173, September/October 2014, Published with license by Taylor & Francis Group, LLC

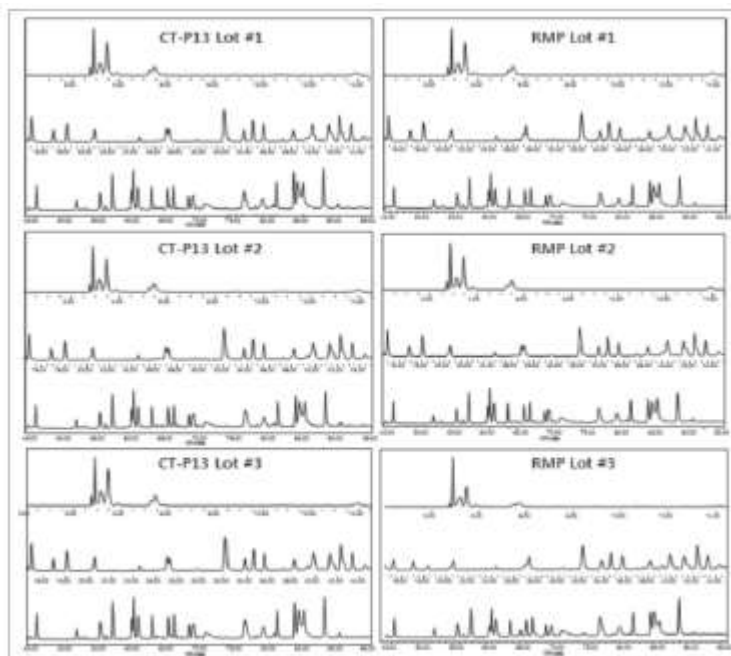
Physicochemical characterization of Remsima®

Soon Kwan Jung¹, Kyoung Hoon Lee², Jae Won Jeon¹, Joon Won Lee¹, Byoung Oh Kwon¹, Yeon Jung Kim¹, Jin Soo Bae¹, Dong-Il Kim², Soo Young Lee², and Shin Jae Chang¹⁻²

¹R&D Division, CellGen Inc., Incheon, Korea; ²Department of Biological Engineering, Inha University, Incheon, Korea

Keywords: infliximab, biosimilar, CT-P13, characterization, comparability, Remsima®, Remicade®, reference medicinal product (RMP)

Remsima® (infliximab) was recently approved as the world's first biosimilar monoclonal antibody (mAb) in both the European Union and Korea. To achieve this, extensive physicochemical characterization of Remsima® in relation to Remicade® was conducted in order to demonstrate the highly similar properties between the two molecules. A multitude of state-of-the-art analyses revealed that Remsima® has identical primary as well as indistinguishable higher order structures compared with the original product. Monomer and aggregate contents of Remsima® were also found to be comparable with those of Remicade®. In terms of charge isoforms, although Remsima® was observed to contain slightly less basic variants than the original antibody, the difference was shown to be largely due to the presence of C-terminal lysine. On the other hand, this lysine was found to be rapidly clipped inside serum *in vitro* and *in vivo*, suggesting it has no effect on the biological potency or safety of the drug. Analysis of the glycan contents of the antibodies showed comparable glycan types and distributions. Recent results of clinical studies have further confirmed that the two antibody products are highly similar to each other. Based on this research as well as previous clinical and non-clinical comparability studies, Remsima® can be considered as a highly similar molecule to Remicade® in terms of physicochemical properties, efficacy, and safety for its final approval as a biosimilar product to Remicade®.



Peptide mapping
(HPLC)

Figure 1. Expanded chromatograms of peptide mapping.

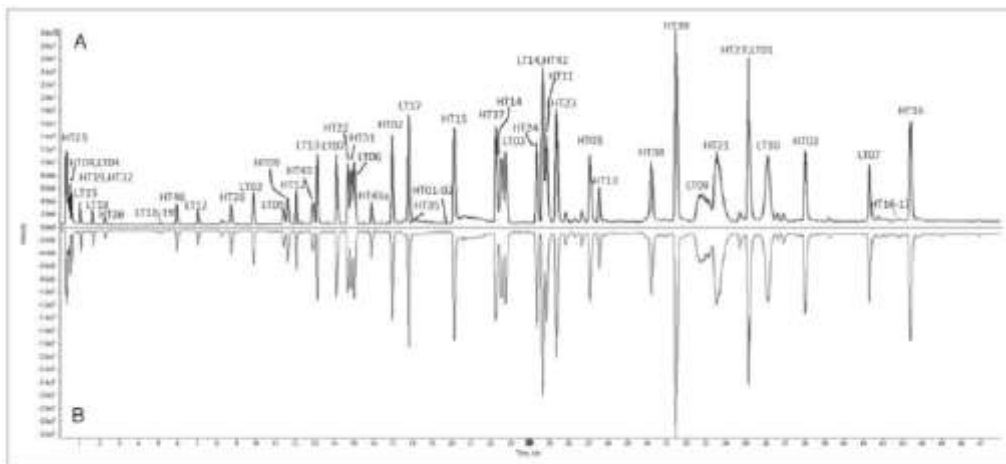


Figure 2. Comparison of Total Ion Chromatogram of LC-ESI-MS peptide mapping between (A) CT-P13 and (B) RMP, and peptide peak assignment.

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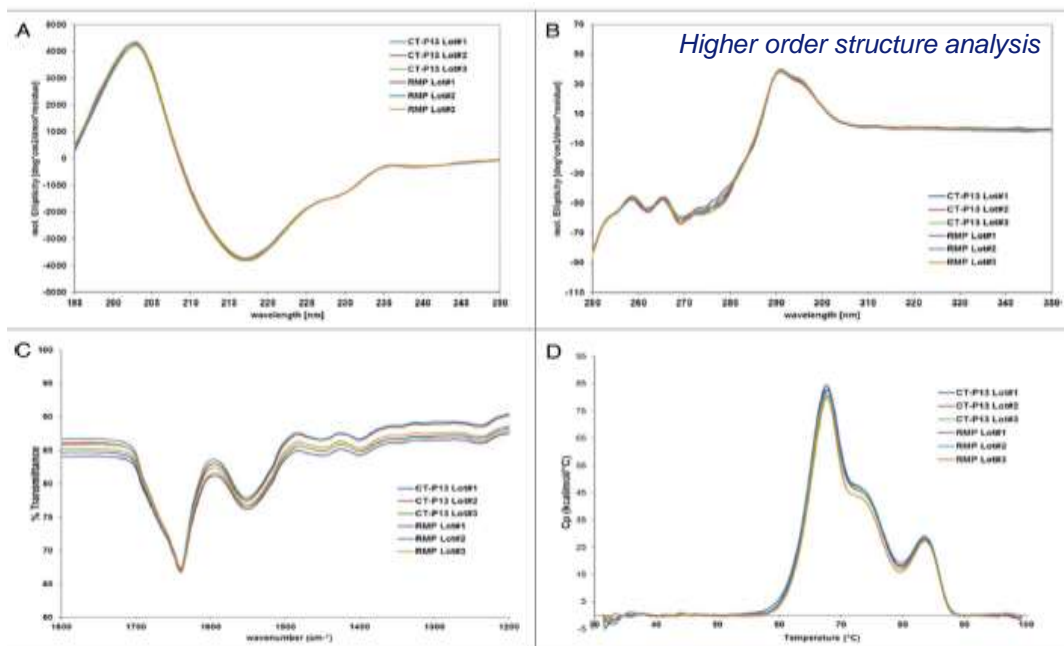


Figure 3. Higher order structure analysis: (A) Far-UV CD; (B) Near-UV CD; (C) FT-IR; (D) DSC.

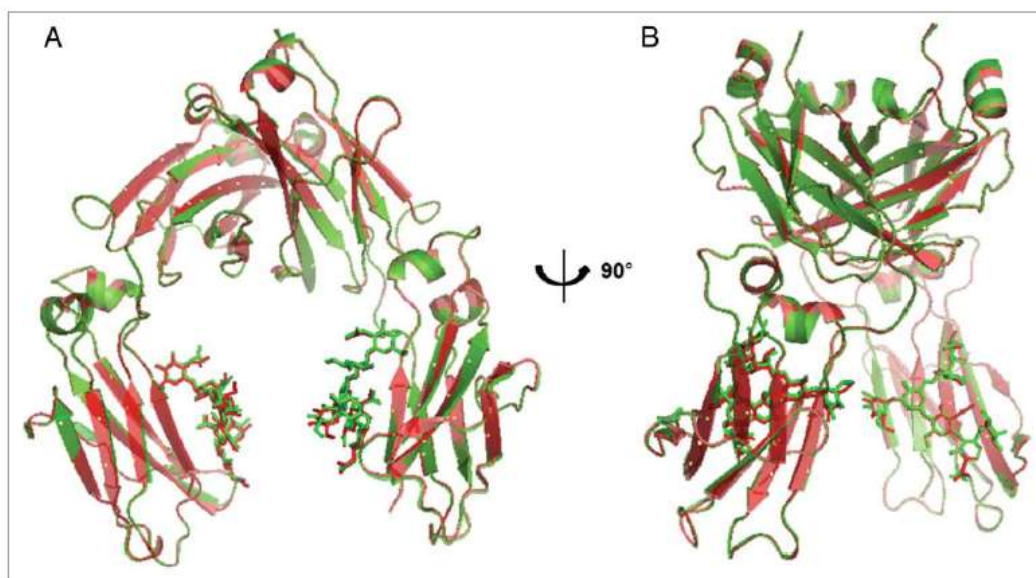


Figure 5. Superimposition of CT-P13 Fc (green) and RMP Fc (red) crystal structures: (A) front view; (B) side view.



Biosimilars create uncertainty with prescribers

▪ Innovative medicines

- Offer a clear advantage – whether real or not
- Marketeers promise a solution for a therapeutic problem
- And hence, the physician is prepared to take a certain risk

▪ Biosimilars

- Don't offer prescriber and patient a clear therapeutic advantage
- May offer a modest price advantage for the patient / 3rd party payer
- They may carry – as with any other new drug – some risk

Doctors and patients don't like trouble with their medicines



The market place makes it even more confusing

- Innovative companies have high stakes
 - Are seeding doubt among prescribers and patients with “you never know”.
 - Have invested for years in a strong prescriber relationship

- The biosimilar industry initially was reluctant with high quality scientific information; it came too late or it was impossible to find
 - Smaller marketing budgets
 - Traditionally, they do not have – as yet – a relationship with prescribers.

It is an uneven playing field

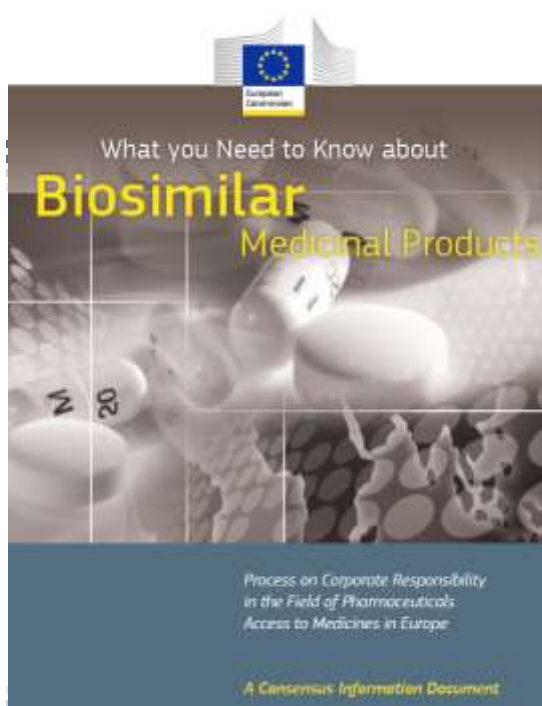
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EU commission published consensus paper (April 2013), very useful for all policy makers involved in biosimilars (but to difficult to find)

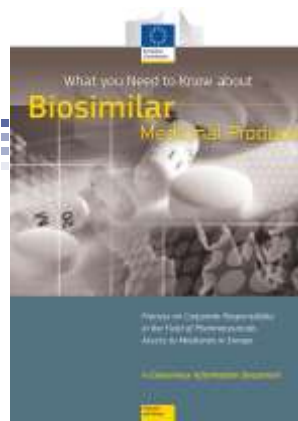
Quote:

“Biosimilar medicinal products have been used safely in clinical practice in the European Union since 2006 “

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How to build trust in biosimilars?

- **Reduce the information gap**
 - Regulators can communicate their knowledge actively to medical professionals:
 - “The past 10 year there has not been a single incident with biosimilars”
 - The assessment system worked as expected
 - Raised mistrust was not justified and we learned better in the meantime
- **Avoid trouble around switching**
 - Convince prescribers on the (financial) advantages for the society, without compromising quality of treatment.



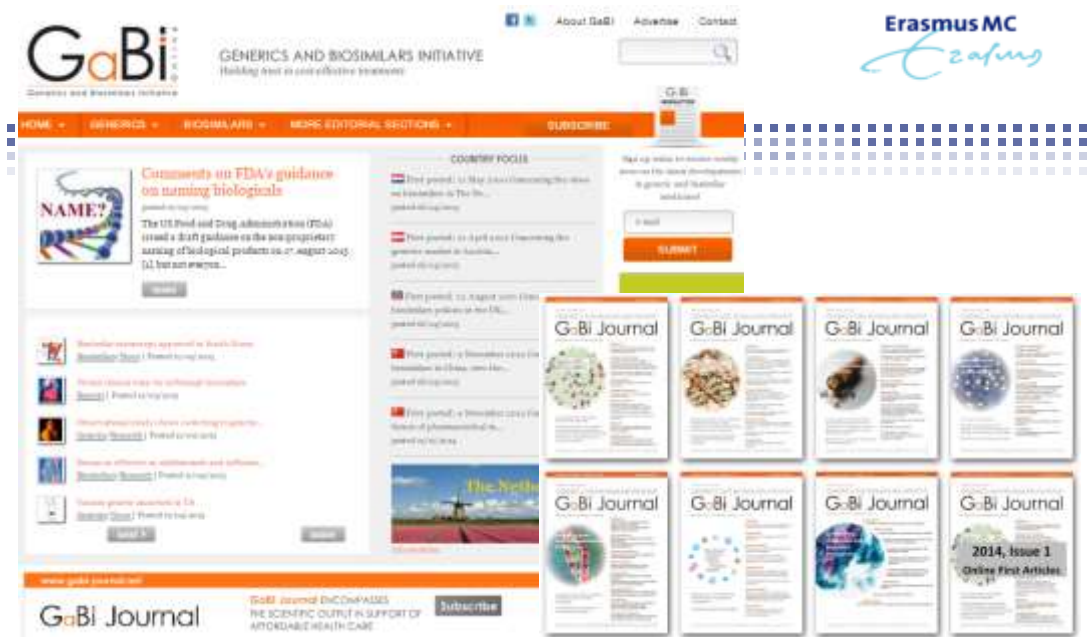
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2008: Closing the information gap (www.gabionline.net)



- Umbrella initiative to build trust in cost-effective treatments:
 - One-stop website with comprehensive information on generics and biosimilars
 - Peer reviewed open access scientific journal
 - Scientific symposia
 - Educational meetings
 - Patient information



www.gabionline.net (15/16)

www.gabi-journal.net

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In summary

- Biosimilars once licensed, fulfill very high quality requirements, equal to any other biotech drug. Thus, they can be prescribed without reservation
 - For new patients
 - To change patients from innovator to biosimilar in a stable way
- There exist formal and informal barriers towards market acceptance
 - Barriers need to be removed to make it a sustainable savings option
- Critical to have support from stakeholders; requires a lot of education
 - Hospital pharmacists can play a critical role in this education effort
- Biosimilars may contribute to an affordable health care market for all



GaBI is supporting you.
Please support GaBI.

GaBi

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*GaBI will be happy to publish
your bioequivalence studies*

Thank you for your attention



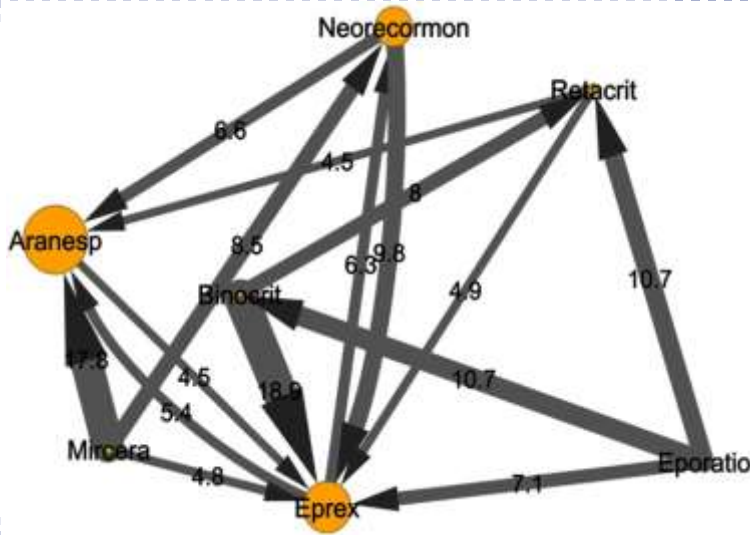
Contact: a.vulto@erasmusmc.nl

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- This presentation is partly based on a MBA-thesis of Mrs. Clara Jonker-Exler, pharmacist ErasmusMC Pharmacy
 - **“Market entry of biosimilar monoclonal antibodies; current barriers, how they could be removed and what will be the economic and other impacts of their removal”**
 - Imperial College London, UK, May 2014
 - Downloadable from: <http://thesis.eur.nl/pub/16597/>
 - Contact: c.jonker-exler@erasmusmc.nl or claartjejonkerexler@yahoo.com

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Switching of EPO in the first year did not increase immunogenicity (Italy)



Ingrasciotta et al.
BioDrugs
29(2015)275