

ROUNDTABLE ON BIOSIMILARS

with participation by European Regulators and Medical Societies



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Interchangeability and substitution of biosimilars – a German perspective

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Interchangeability of Biosimilars



European Medical Societies
Roundtable on Biosimilars

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The views presented here are my own and do not necessarily reflect the views of the Paul-Ehrlich-Institut.

Interchangeability of Biosimilars

- **Definitions EU and US**
- **Implications in EU countries**
- **What we know so far :**
Review of switching studies involving biologics and biosimilars
- **Interchangeability: Theoretical considerations**
- **Interchangeability: Difficulties in designing studies**
- **Closing remarks**

Biosimilars may be approved in the EU !

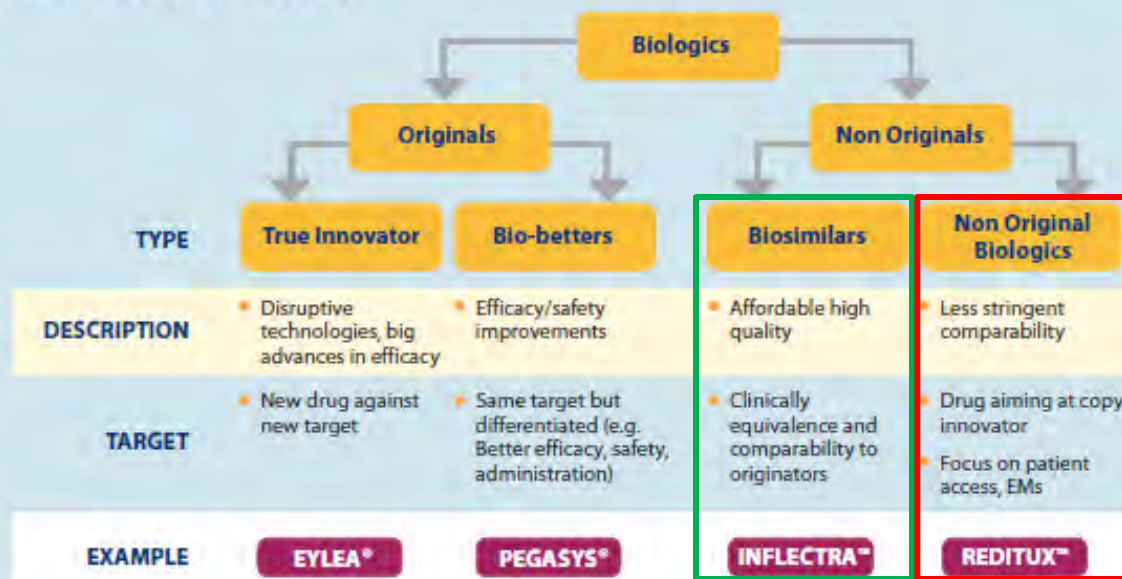
Not: Non Original Biologics

Importance of nomenclature...

A Biosimilar by Any Other Name...

To support consistent analyses across geographies, therapies, and manufacturers, IMS Health has established an industry-verified categorization of biologics. Although not every product fits neatly into these classifications, the schema applies in most instances.

CLASSIFICATION OF BIOLOGICS



Within IMS MIDAS®, biosimilars are those biologics that are non-original copies of innovative brands and that have been approved for marketing via a dedicated regulatory pathway, such as has been created in the EU, U.S., and Japan. Non-original biologics (NOBs) are those copies of innovative brands that have not been approved through such a dedicated pathway. Typically, they are introduced in emerging markets.

Definitions of interchangeability largely agreed within EU

Importance of nomenclature...

Switching

The **decision by the treating physician** to exchange one medicine with another medicine with the same therapeutic intent in a given patient.

Interchangeability

means the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient **on the initiative, or with the agreement of the prescriber.**

Substitution

practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level **without consulting the prescriber.**
There is no “substitutability determination” at EU level

Automatic Substitution (EU)

practice whereby a pharmacist **is obliged to dispense** one medicine instead of another equivalent and interchangeable medicine due to national or local requirements (**without consulting the prescriber**)

Definition in US



U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

Definition: Interchangeability

Interchangeable or Interchangeability means:

- the biological product is **biosimilar** to the reference product;
- it can be expected to produce the **same clinical result** as the reference product **in any given patient**; and
- for a product that is administered more than once to an individual, the risk in terms of **safety or diminished efficacy of alternating or switching** between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

Note: The interchangeable product **may be substituted** for the reference product without the intervention of the health care provider who prescribed the reference product.

Biologics Price Competition and Innovation Act of 2009,
Pub. L. 111-148, Sect. 7001-7003, 124 Stat. 119. Mar. 23, 2010.

→ Different EU and US nomenclature hampers debate

Handling of Interchangeability is not the same in EU countries:

Ireland

- If it is planned to change the medicine a patient receives from a reference to a biosimilar medicine or vice versa, **the treating physician should be involved**
- This should involve a **discussion between the prescriber / patient, and prescriber /dispensing pharmacist.**

Holland

- New patients can be treated with a biosimilar right away
- **No uncontrolled exchange between biological medicinal products** (regardless of whether they are innovator products or biosimilar medicinal products)
- Switching between biological medicines is possible, **but only if patient is well informed** and there is **adequate clinical monitoring.**
- Discussions with patient organizations on educational material

Finland

- Switches between biological products are common and usually not problematic, e.g. in the context of hospital tendering processes.
- For time being, there is no evidence for adverse effects due to the switch from a reference product to a biosimilar
- The **patient needs to be informed** of switch as of any other change in the medication.
- Biosimilars are interchangeable with their reference products under the **supervision of a health care person.**

Interchangeability: PEI position updated Dec 08, 2015

1. Confidence in regulatory system
2. Scientific principles
3. „Therapiefreiheit“ = Freedom of choice of therapy



The screenshot shows the Paul Ehrlich Institute website. The header includes the logo and name of the Paul Ehrlich-Institut. The navigation bar contains links for Information, Institute, Research, Medicinal Products, In vitro Diagnostics, Meetings, and Service. The left sidebar lists various product categories, including Allergens, Antibodies / Immunoglobulines / Fusion Proteins, and Monoclonal Antibodies. The main content area is titled 'Position of Paul-Ehrlich-Institut regarding the use of biosimilars' and includes a search bar and a paragraph explaining the institute's stance on biosimilars. A red box highlights a specific paragraph in the text.

Paul-Ehrlich-Institut

Information Institute Research Medicinal Products In vitro Diagnostics Meetings Service

Antibodies / Immunoglobulines / Fusion Proteins

Monoclonal Antibodies

Position of Paul-Ehrlich-Institut regarding the use of biosimilars

(search words: interchangeability, substitution)

As part of the marketing authorisation procedure, in which the risk/benefit balance of a product is assessed, the Committee for Medicinal Products for Human Use (CHMP) primarily evaluates the direct comparison of the pharmaceutical quality, efficacy, and safety of a product for which a marketing authorization application has been submitted and not its interchangeability.

According to the current status of the discussion at the CHMP and its working parties, biosimilars can in principle be used in the same way as originator products after equivalence has been proven and the marketing authorisation has been granted. This implies that they can be administered to both, patients who have not previously been treated with biologics and those who previously have received the originator product. The Paul-Ehrlich-Institut holds the view that any treatment decision of the physician must be based on scientific data, especially with regard to proven high-grade comparability of a biosimilar to its originator product and the scientific plausibility of all data included in the discussion.

Vacancies Sitemap

The treating physician should at any rate ascertain that any adverse effects that may occur during treatment with Remsima or Inflectra, and even the original product Remicade, be reported adequately within the pharmacovigilance system, so that they can be followed up. The new pharmacovigilance guideline (Guideline on good pharmacovigilance practice, Module VI Risk management systems, EMA/873138/2011 Rev 1*) states that the Identification of a biological medicinal product in a pharmacovigilance report requires the relevant brand name (Remsima, Inflectra or Remicade) and the batch number in addition to the active substance.

If a prescription only shows the name of the active substance, the pharmacist should contact the treating physician and clarify which of the two substances is intended to be used, and should also ensure that the pharmacovigilance guideline is observed.

What we know so far

Switching studies involving biologics/biosimilars

(1) Review of EPARS of all approved biosimilars, accessed January 2015

The European public assessment reports (EPARs) available at the website of EMA describe the development programs of the authorized biosimilars and provide substantial evidence for the safety of the switch.

- No new AES or increased frequencies for biosimilars and
- No product specific label changes necessary for any marketed biosimilar

= Real life proof that switching has no adverse impact

Ref: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=VC0b01ac058001d124

What we know so far

Switching studies involving biosimilars

(1) Review of EPARS of all approved biosimilars, accessed January 2015 –cont'd

Omnitrope (somatropin):

44 patients with the reference product and 45 patients treated with the first version of the biosimilar were compared in a clinical trial.

Efficacy and safety of the products were comparable but Biosimilar was more immunogenic due to impurities.

In the next part of the study, the same patients were switched to new, improved versions of the biosimilar. **No changes in efficacy or safety were observed and ADAs continuously decreased after the switch to the improved biosimilar.**

Epoetin Alfa: Hexal, Binocrit, Abseamed (Epoetin alfa, HX575):

Randomized pivotal efficacy and safety study with 314 **patients with renal anemia** treated with the reference product intravenously switched to HX575 and followed for 54 weeks.

Additional 117 patients were later switched from the reference product to the biosimilar and followed for 26 weeks.

Overall, no differences in safety or efficacy profiles were demonstrated following the switches.

What we know so far

Switching studies involving biosimilars

(1) Review of EPARS of all approved biosimilars, accessed January 2015 –cont'd

Epoetin Alfa : Silapo, Retacrit

A randomized double-blind, **cross-over**, active controlled phase III trial in 313 **patients with renal anemia** found similar safety and efficacy profiles between the biosimilar and the reference product.

The biosimilar and the reference products had similar safety and efficacy profiles after switching.

Zarzio (filgrastim): Two pharmacokinetic (PK) and pharmacodynamic (PD) **cross-over studies** with s.c. administration involved 96 **healthy volunteers**. Two PK and PD studies with single administration and cross-over studies involved 50 **patients**. The biosimilar and the reference products had similar safety and efficacy profiles after switching.

Abasaglar(insulin glargine): The phase III study in type I diabetes compared the biosimilar insulin glargine to the reference product in 536 adult patients in combination with mealtime insulin lispro. **Eighty four per cent of the patients were on the reference product before randomisation into the biosimilar or the reference product arms**. In this subgroup, no relevant differences in efficacy, safety, and immunogenicity between the switch-to-biosimilar group and the reference group were observed

What we know so far

Switching studies involving biosimilars

(2) Switching from Originator to Biosimilar Human Growth Hormone

Flodmark C-E, Lilja K, Woehling H, Järvholm K. Switching. From Originator to Biosimilar Human Growth Hormone Using Dialogue Teamwork: Single-Center Experience From Sweden. *Biol Ther* 2013; **3**:35-43.

Romer T, Zabransky M, Walczak M, Szalecki M, Balzer S. Effect of switching recombinant human growth hormone: comparative analysis of phase 3 clinical data. *Biol Ther*. 2011;**1**:005.

Rashid N, Saenger P, Wu YL, et al. Switching to Omnitrope® from Other Recombinant Human Growth Hormone Therapies: Retrospective Study in an Integrated Healthcare System. *Biol Ther*. 2014 **4**: 27–39

Conclusion:

Patients successfully switched with no negative impact on growth, and no serious or unexpected adverse drug reactions

What we know so far

Switching studies involving biologics/biosimilars

- (3) Review of 58 clinical trials (PV data bases, literature, clinical trial data bases), 193 adverse event report summaries for safety of switching between therapeutic proteins
(HGH:13 clin. trials, EPO 35 crossover clin. trials, Filgrastim 10 clin. trials)

Covers switching between originators in a product class and also between originator and biosimilar

→ No evidence that switching to and from different biopharmaceuticals leads to safety concerns

Reference:

H.Ebbers, M. Muenzberg, H. Schellekens

The safety of switching between therapeutic proteins. *Expert Opin Biol Ther* 2012;**12**:1473-85

(4) Interchangeability Remsima (Biosimilar Infliximab)

PLANETRA Study (extension study of 302/455 Rheumatoid Arthritis patients for another year):
158/302 Patients were maintained and 144/302 Patienten were switched on Infliximab-Biosimilar

Efficacy outcome		CT-P13 throughout study (N=151)	Switched from INX to CT-P13 in extension phase (N=142)
ACR20, n (%)	Wk 54	116 (76.8)	110 (77.5)
	Wk 78	108 (71.5)	111 (78.2)
	Wk 102	109 (72.2)	102 (71.8)
ACR50, n (%)	Wk 54	69 (45.7)	71 (50.0)
	Wk 78	73 (48.3)	68 (47.9)
	Wk 102	73 (48.3)	73 (51.4)
ACR70, n (%)	Wk 54	33 (21.9)	34 (23.9)
	Wk 78	37 (24.5)	42 (29.6)
	Wk 102	37 (24.5)	37 (26.1)
DAS28-CRP	Baseline (BL, wk 0)	5.8	5.8
	Δ from BL at Wk 54	-2.4	-2.4
	Δ from BL at Wk 78	-2.4	-2.6
	Δ from BL at Wk 102	-2.4	-2.5
DAS28-ESR	BL (wk 0)	6.6	6.6
	Δ from BL at Wk 54	-2.5	-2.6
	Δ from BL at Wk 78	-2.6	-2.8
	Δ from BL at Wk 102	-2.6	-2.7
Safety outcome		CT-P13 throughout study (N=159)	Switched from INX to CT-P13 in extension phase (N=143)
TEAEs, n		226	180
pts with ≥1 TEAE, n (%)		85 (53.5)	77 (53.8)
Mild		37 (23.3)	38 (26.6)
Moderate		39 (24.5)	31 (21.7)
Severe		7 (4.4)	8 (5.6)
Life-threatening		1 (0.6)	0
Death		1 (0.6)	0
pts with ≥1 TESAE, n (%)		12 (7.5)	13 (9.1)
pts with ≥1 infection, n (%)		50 (31.4)	47 (32.9)
ADA positive, n (%)		78 (49.1)	69 (49.3)
		Wk 54	71 (50.4)
		Wk 78	66 (49.6)
		Wk 102	64 (46.4)
			64 (49.6)

What we know so far

Switching studies involving biologics

Switches from one biological to another biological product in Rheumatoid Arthritis

94% of US rheumatologists **switch from one anti-TNF to another** as distinct as switching from infliximab or etanercept, to adalimumab after detecting a lack of response or side effects providing an effective next choice of therapy **without triggering adverse events that would lead to a disvarouble risk benefit balance.**

References:

[Jt Bone Spine.](#) 2006;73:718- 24.

[Clin Rheumatol.](#) 2011 Nov;30(11):1447-54.

[Scand J Rheumatol.](#) 2005 Sep-Oct;34(5):353-8

[Rheumatology \(Oxford\).](#) 2008 Jul;47(7):1000-5.

What we know so far

Switching studies involving **biologics** and biosimilars

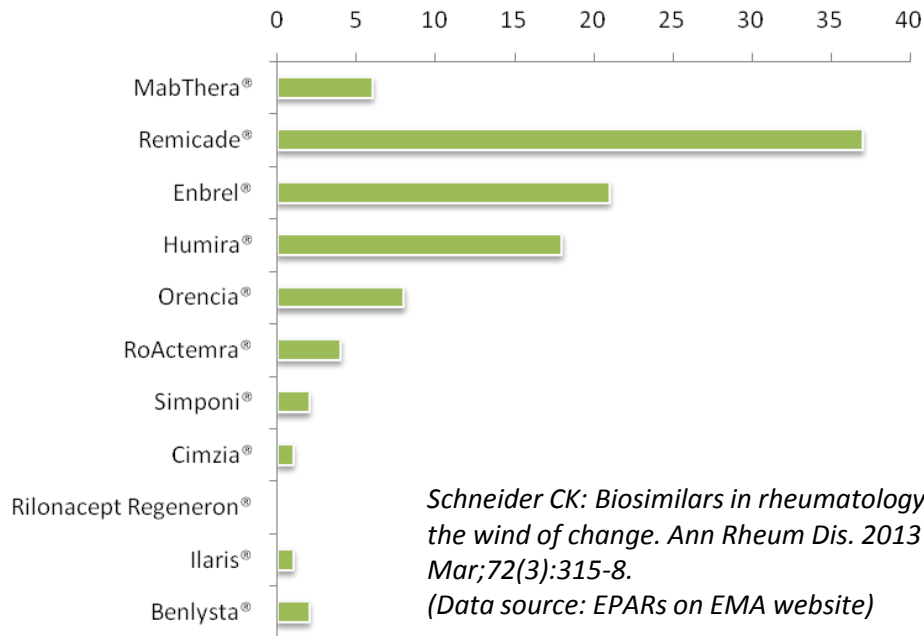
In summary:

Review of many small to mid sized clinical trials leads to conclusion that they do not show any safety/efficacy signals that would justify extensive, longlasting studies.

Interchangeability: Theoretical considerations

Changes in the manufacturing process of biologicals

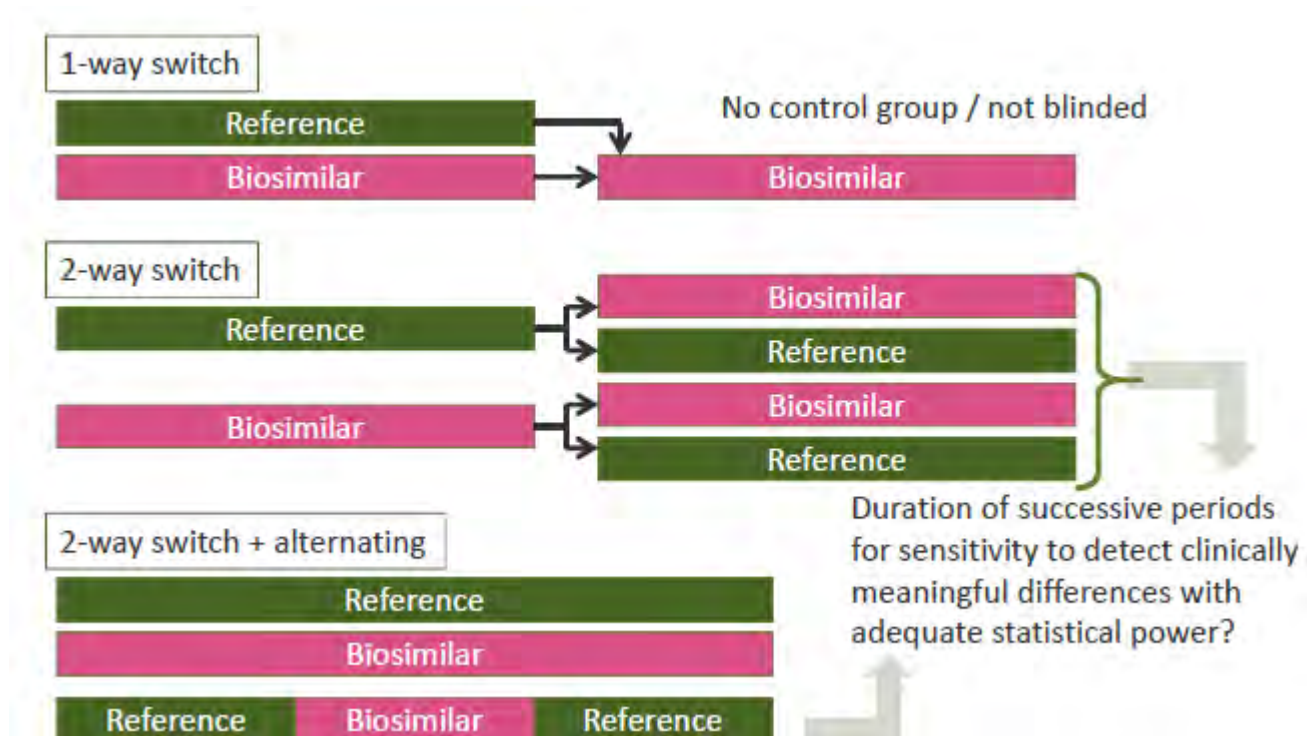
Number of post-marketing changes
in the manufacturing process of mAbs



- BWP/CHMP have experience in judging impact of differences in quality attributes.
- Different versions of same active substance are used interchangeably without necessity of clinical studies

Interchangeability: Difficulties in designing studies

Ref: Ebbers H & Chamberlain P. GaBi Journal 2014



Additional FDA Guidance Documents for Industry planned:

Considerations in Demonstrating Interchangeability to a Reference Product
Draft published on internet in May 2015

<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM273001.pdf>

Can an applicant obtain a **determination of interchangeability** between its proposed product and the reference product **in an original 351(k) application**?

(Proposed Answer): Yes. Under the BPCI Act, FDA can make a determination of interchangeability in a 351(k) application or any supplement to a 351(k) application.

An interchangeable product must be shown to be biosimilar to the reference product and meet the other standards described in section 351(k)(4) of the PHS Act.

At this time, it would be **difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application** given the statutory standard for interchangeability and the **sequential nature of that assessment**.

FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product.

In Summary: Interchangeability of Biosimilars

- **Biosimilars licensed in the EU are interchangeable with their reference product since** clinically significant differences have been ruled out with EU licensure.
- Value of EPAR in reviewing study results leading to approval
- Review of many small to mid sized clinical trials leads to conclusion that they do not show any safety signals that would justify extensive studies.
- No change in dosage or dosing regimen is warranted when a patient is switched from a reference product to its biosimilar.
- Manufacturing changes lead to **different versions of same active substance which are also used interchangeably** without necessity of clinical (switching) studies

In Summary: Interchangeability of Biosimilars

- Theoretical considerations which trial designs would be appropriate suggest that such trials would need to be very large and time consuming. Still not clear which trials would be conclusive.
- The switch itself is not expected to cause adverse effects whereas, switching a patient to an inferior product could be problematic.
- However, inferior products (=“Non-Original Biologics”) would not be approved in the EU.
- Risk of rare adverse effects may best be addressed by the Risk Management Plans as with any other medicinal product.

Thanks for your attention !

