Current regulatory strategies: Extrapolation and Interchangeability

2 nd ASEAN

Educational Workshop on

Regulatory Considerations of Biosimilars

June 23, 2019

Dr. Elena Wolff-Holz

Paul Ehrlich Institut
Federal Agency for Vaccines and Biomedicines
Elena.Wolff-Holz@pei.de

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

Definition of a Biosimilar exists in Europe since 2001

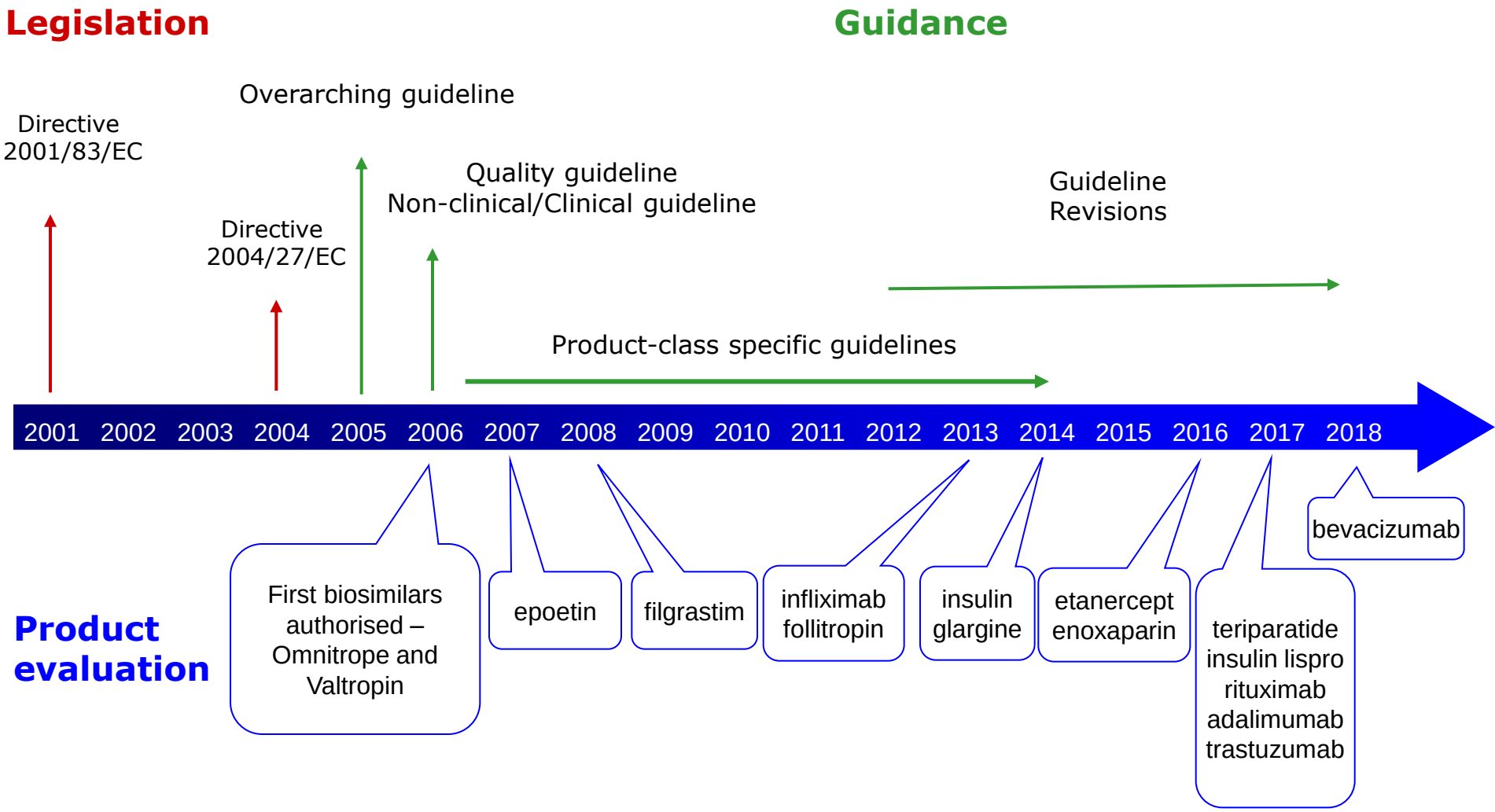
..... it´s a LAW

Directive 2001/83/EC (as amended)

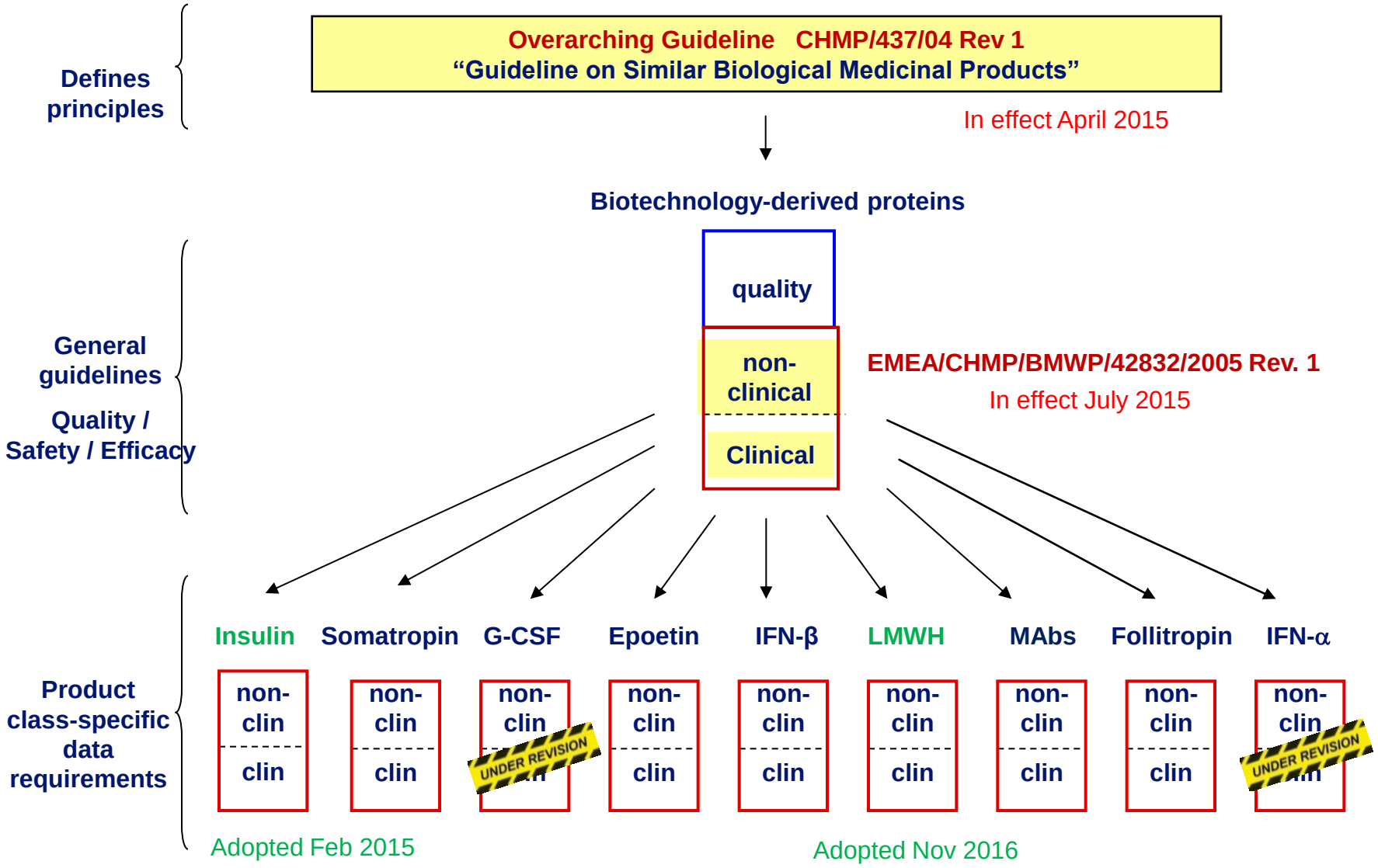
Article 10: „Generics“ and legal basis for „biosimilars“

- ✓ Article 10(2a): *„Generic medicinal product ” shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, (…). ”*
- ✓ Article 10(4): *„Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. ”*

Evolution of Biosimilars in the EU



Guidance on biosimilar development in the EU



Biosimilars in Europe (04 April 2019)*

85

MAAs submitted

78

MAAs reviewed

7

MAAs under review

Adalimumab (2)
Etanercept (1)
Infliximab (1)
Pegfilgrastim (1)
Rituximab (2)

EMA scientific committees and working parties

2 Negative
Interferon alfa
Insulin

16 Withdrawn (*pre-approval*)
Insulin (6)
Bevacizumab (1)
Epoetin (1)
Pegfilgrastim (6)
Trastuzumab (1)
Adalimumab (1)

60 Positive opinions

53 **MAs**

Somatropin (1)
Epoetin (5)
Filgrastim (7)
Infliximab (4)
Follitropin alfa (2)
Etanercept (2)
Bevacizumab (2)
Insulin glargine (2)
Enoxaparin (2)
Teriparatide (2)
Rituximab (6)
Adalimumab (7)
Insulin lispro (1)
Trastuzumab (5)
Pegfilgrastim (5)

2 Awaiting EC decision
Adalimumab (2)

5 Withdrawn (*post-approval*)
Filgrastim (2)
Somatropin (1)
Insulin glargine (1)
Adalimumab (1)

* Information on the EMA website

Biosimilars in Europe, 04 April 2019 www.ema.europa.eu

	Medicine	Common name	MA Holder	Status	MA Date
1	Hyrimoz	adalimumab	Sandoz	Authorised	Jul. 18
	Hefiya	adalimumab	Sandoz	Authorised	Jul. 18
	Halimatoz	adalimumab	Sandoz	Authorised	Jul. 18
	Cyltezo	adalimumab	Boehringer Ing	~~Withdrawn~~	Nov. 17
	Solymbic	adalimumab	Amgen	~~Withdrawn~~	Mrz. 17
	Hulio	adalimumab	Mylan	Authorised	Sep. 18
	Amgevita	adalimumab	Amgen	Authorised	Mrz. 17
	Imraldi	adalimumab	Samsung	Authorised	Aug. 17
2	Mvasi	bevacizumab	Amgen	Authorised	Jan. 18
3	Inhixa	enoxaparin	Techdow	Authorised	Sep. 16
	Thorinane	enoxaparin	Pharmathen	Authorised	Sep. 16
4	Abseamed	epoetin alfa	Medice	Authorised	Aug. 07
	Binocrit	epoetin alfa	Sandoz	Authorised	Aug. 07
	Epoetin Alfa	epoetin alfa	Hexal	Authorised	Aug. 07
	Silapo	epoetin zeta	Stada	Authorised	Dez. 07
	Retacrit	epoetin zeta	Hospira	Authorised	Dez. 07
5	Benepali	etanercept	Samsung	Authorised	Jan. 16
	Erelzi	etanercept	Sandoz	Authorised	Jun. 17
6	Accofil	filgrastim	Accord	Authorised	Sep. 14
	Nivestim	filgrastim	Pfizer	Authorised	Jun. 10
	Grastofil	filgrastim	Apotex	Authorised	Okt. 13
	Ratiograstim	filgrastim	Ratiopharm	Authorised	Sep. 08
	Zarzio	filgrastim	Sandoz	Authorised	Feb. 09
	Tevagrastim	filgrastim	Teva	Authorised	Sep. 08
	Filgrastim Hexal	filgrastim	Hexal	Authorised	Feb. 09
	Biograstim	filgrastim	AbZ-Pharma	~~Withdrawn~~	Sep. 08
	Filgrastim	filgrastim	Ratiopharm	~~Withdrawn~~	Sep. 08
7	Bemfola	follitropin alfa	Gedeon Richter	Authorised	Mrz. 14
	Ovaleap	follitropin alfa	Teva	Authorised	Sep. 13
8	Zessly	infliximab	Sandoz	Authorised	Mai. 18
	Flixabi	infliximab	Samsung	Authorised	Mai. 16
	Remsima	infliximab	Celltrion	Authorised	Sep. 13
	Inflectra	infliximab	Pfizer	Authorised	Sep. 13
9	Lusduna	insulin glargine	MSD	~~Withdrawn~~	Jan. 17
	Semglee	insulin glargine	Mylan	Authorised	Mrz. 18
	Abasaglar (Abasria)	insulin glargine	Eli Lilly	Authorised	Sep. 14
10	Solumarv	insulin human	Marvel Life	~~Refused~~	
	Insulin lispro Sanofi	insulin lispro	sanofi-aventis	~~Authorised~~	Jul. 17
11	Ziextenzo	pegfilgrastim	Sandoz	Authorised	Nov. 18
	Pelgraz	pegfilgrastim	Accord Health	Authorised	Sep. 18
	Fulphila	pegfilgrastim	Mylan	Authorised	Nov. 18
	Pelmeg	pegfilgrastim	Cinfa	Authorised	Nov. 18
	Udenyca	pegfilgrastim	ERA	Authorised	Sep. 18
	Alpheon	interferon alfa-2a	BioPartners	~~Refused~~	
12	Truxima	rituximab	Celltrion	Authorised	Feb. 17
	Ritemvia	rituximab	Celltrion	Authorised	Jul. 17
	Rituzena (Tuxella)	rituximab	Celltrion	Authorised	Jul. 17
	Blitzima	rituximab	Celltrion	Authorised	Jul. 17
	Riximyo	rituximab	Sandoz	Authorised	Jun. 17
	Rixathon	rituximab	Sandoz	Authorised	Jun. 17
13	Omnitrope	somatropin	Sandoz	Authorised	Apr. 06
	Valtropin	somatropin	BioPartners	~~Withdrawn~~	Apr. 06
14	Movymia	teriparatide	STADA	Authorised	Jan. 17
	Terrosa	teriparatide	Gedeon Richter	Authorised	Jan. 17
15	Kanjinti	trastuzumab	Amgen	Authorised	Mai. 18
	Herzuma	trastuzumab	Celltrion	Authorised	Feb. 18
	Ogivri	trastuzumab	Mylan	Authorised	Dez. 18
	Ontruzant	trastuzumab	Samsung	Authorised	Nov. 17
	Trazimera	trastuzumab	Pfizer	Authorised	Jul. 18

53 products* = brand names

exist for

15 different
Reference Products

Incl. 1 bevacizumab Zirabev, Pfizer
+1 adalimumab, Idacio, Fresenius

Extrapolation and Interchangeability

- Update on Biosimilars in the EU
  - ✓Framework (legal basis, overview guidelines)
  - ✓Nomenclature and available biosimilars in Europe
- Extrapolation
- Interchangeability

Extrapolation
in the clinical development of biosimilars

Extrapolation is not a new concept

- Concept has been emphasized in new Overarching Guidelines and Product specific GLs

- Extrapolation is integral part of regulatory guidance and clinical practice

  - Always assumed for manufacturing changes according to ICH Q5E
  - Line extensions of originators
  - Biosimilar concept
  - What about Line extensions of Biosimilars?

Extrapolation
in the clinical development of biosimilars

Extrapolation is not a new concept

- Concept has been emphasized in new Overarching Guidelines and Product specific GLs

- Extrapolation is integral part of regulatory guidance and clinical practice

  - Always assumed for manufacturing changes according to ICH Q5E
  - Line extensions of originators
  - Biosimilar concept
  - What about Line extensions of Biosimilars?

Concept of extrapolation has been emphasized in new Overarching Guidelines

"The overarching guideline", CHMP/437/04 Rev. 1

3.1. Application of the biosimilar approach

If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification.

3.3. Principles of establishing biosimilarity

In specific circumstances, a confirmatory clinical trial may not be necessary. This requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product.

Generally, the aim of clinical data is to address slight differences shown at previous steps and to confirm comparable clinical performance of the biosimilar and the reference product

Clinical data cannot be used to justify substantial differences in quality attributes

Concept of extrapolation has been emphasized in new Overarching Guidelines

„Overarching Guideline: non-clinical and clinical issues“

EMEA/CHMP/BMWP/42832/2005 Rev. 1

Normally, comparative efficacy trials are required for the demonstration of clinical comparability in adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blind.

The study population should be representative (changed from: most sensitive) of approved therapeutic indication(s) of the RMP–and separate demonstration for each of the claimed indications may be necessary.

However, in certain cases,

- PK/PD studies may be sufficient for comparability

- Extrapolation of efficacy and safety from one therapeutic indication to another may be justified

Concept of extrapolation has been emphasized in new Overarching Guidelines

„Overarching Guideline: non-clinical and clinical issues“
EMEA/CHMP/BMWP/42832/2005 Rev. 1

In certain cases, PK/PD studies may be sufficient for comparability, if

- Comparable dose-response or concentration-response relationship has been demonstrated (a multiple dose-exposure-response study with comparison in ascending part of dose response curve)
- PD marker/biomarker is an accepted/validated surrogate marker or a combination of markers can be selected based on sound pharmacological principles, including dose/concentration sensitivity (e.g. G-CSF, early viral load in chron. Hep C, euglycaemic clamp test to compare two insulins, MRI of disease lesions to compare two β-interferons)
- Predefined equivalence margins are mandatory

Concept of extrapolation has been emphasized in new Overarching Guidelines

„Overarching Guideline: non-clinical and clinical issues“
EMEA/CHMP/BMWP/42832/2005 Rev. 1

Extrapolation:

- Requires scientific justification (not automatically granted)
- Is possible IF overall data on biosimilarity allow for it
- „Totality of-evidence“

Concept of extrapolation has been emphasized in new Overarching Guidelines

„Overarching Guideline: non-clinical and clinical issues“
EMEA/CHMP/BMWP/42832/2005 Rev. 1

Extrapolation

- **Additional data (= clinical or nonclinical !)** may be required if
  - Different active sites of the RMP are present which may have a different impact in different therapeutic indications
  - Active substance reacts with different receptors which are involved in different indications (e.g. s TNF and mTNF)
  - Studied therapeutic indication is not relevant for the others in terms of efficacy or safety (e.g. extrapolation from R.A to oncology indications)
  - Different safety profile in different therapeutic indications

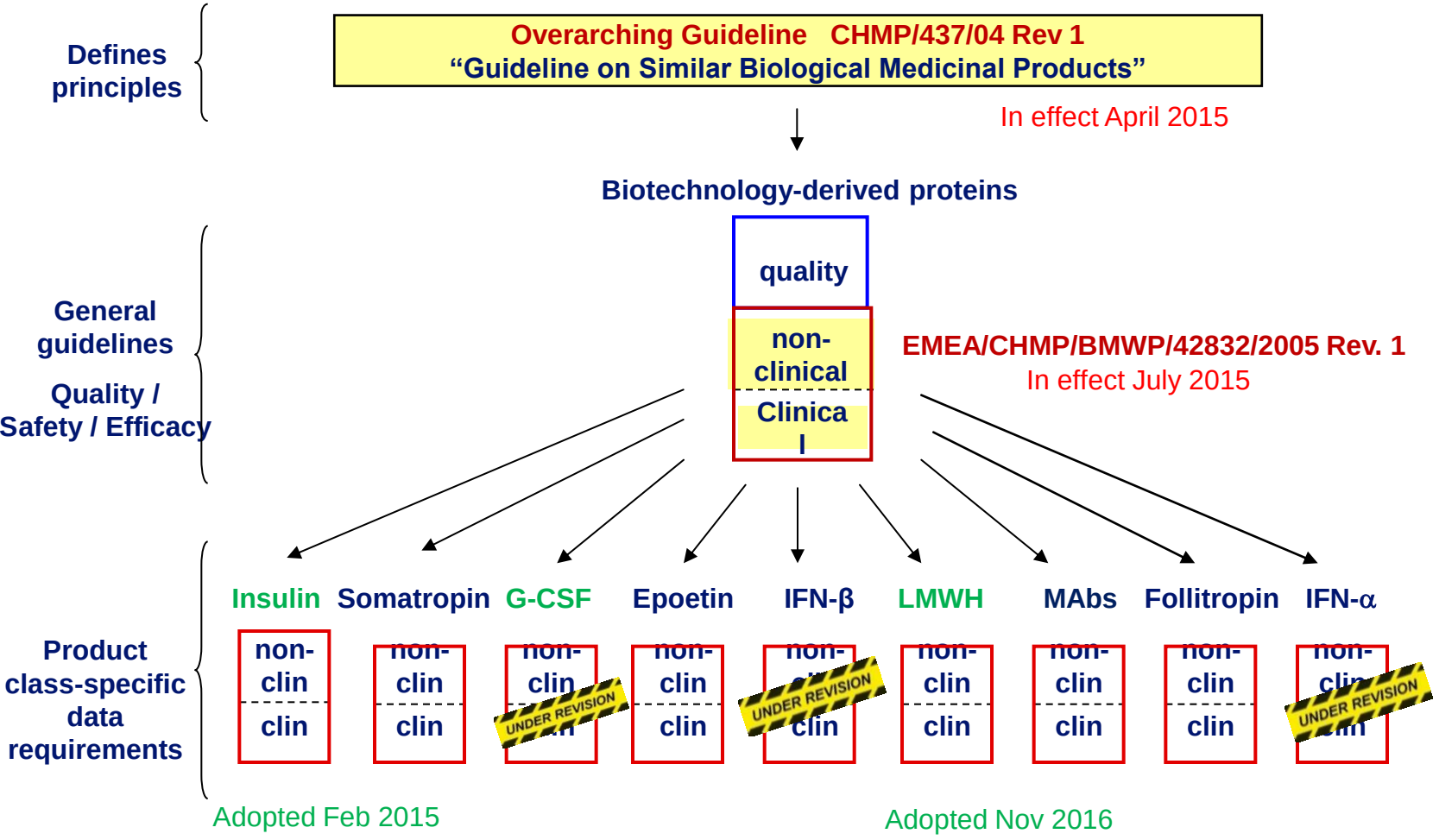
Extrapolation is specified in regulatory guidance documents

Product-specific biosimilar guideline on…	Extrapolation
LMWHs (low-mol weight heparins) EMEA/CHMP/BMWP/118264/2007	**Extrapolation of efficacy data:** Prevention of venous thromboembolism → prevention of arterial thromboembolism
R-insulin and insulin analogues EMEA/CHMP/BMWP/32775/2005 _Rev 2	**Extrapolation of efficacy data** Demonstration of similar PK +/- PD profiles and absence of safety issues with subcutaneous use (in Healthy volunteers) will allow extrapolation to intravenous use and to other indications and patient populations licensed for the reference product. If a rapid- or a short-acting biosimilar insulin is intended for use in pumps, additional stability data may be required.
R-h FSH follicle stimulating hormone EMA/CHMP/BMWP/671292/2010	**Extrapolation of efficacy data** Recommended model: Infertile ovulatory women undergoing Assisted Repr. Techniques (ART) with “oocytes retrieved” as EP→ •Women with Anovulation (including polycystic ovarian syndrome unresponsive to standard treatment); •Women with severe LH and FSH deficiency •Stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism

Extrapolation is specified in regulatory guidance documents

(Product-specific) biosimilar guideline on…	Extrapolation
Recombinant erythropoietins EMEA/CHMP/BMWP/301636/2008 Corr.* (2010)	**Extrapolation of efficacy data** Demonstration of efficacy and safety in renal anaemia will allow extrapolation to other indications of the reference medicinal product with the same route of administration.
Recombinant GCSF EMEA/CHMP/BMWP/31329/2005	**Extrapolation of efficacy data** Demonstration of the clinical comparability in the chemotherapy-induced neutropenia model will allow the extrapolation of the results to the other indications (incl. mobilization of stem cells in healthy donors)
Overarching GL: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1	**Extrapolation of routes of administration** It is possible to waive the evaluation of **intravenous administration** if biosimilar comparability in both absorption and elimination has been demonstrated for the **subcutaneous route**

Guidance on biosimilar development in the EU



"Pivotal evidence for similar efficacy will be derived from the similarity demonstrated in physicochemical, functional, pharmacokinetic and pharmacodynamic comparisons. A dedicated comparative efficacy trial is therefore not considered necessary."

Extrapolation
in the clinical development of biosimilars

Extrapolation is not a new concept

- Concept has been emphasized in new Overarching Guidelines and Product specific GLs

- Extrapolation is integral part of regulatory guidance and clinical practice

  - Always assumed for manufacturing changes according to ICH Q5E
  - Line extensions of originators
  - Biosimilar concept
  - What about Line extensions of Biosimilars?

Extrapolation is not a new concept

Concept of having to go through multiple iterations of process changes and having to show comparability is not new → it´s a common regulatory requirement

•Change of the manufacturing process leads to
a new version of the active substance

•The manufacturer has to demonstrate comparability of the versions from the old and the new manufacturing process (ICH guideline Q5E)

•Typically, clinical data is not required to substantiate manufacturing change.

•But if at all, then one clinical trial in one therapeutic indication with extrapolation to all therapeutic indications is sufficient

Manufacturing changes authorized by EMA

(EPARs of 29 mabs: Total manufacturing changes = 404):

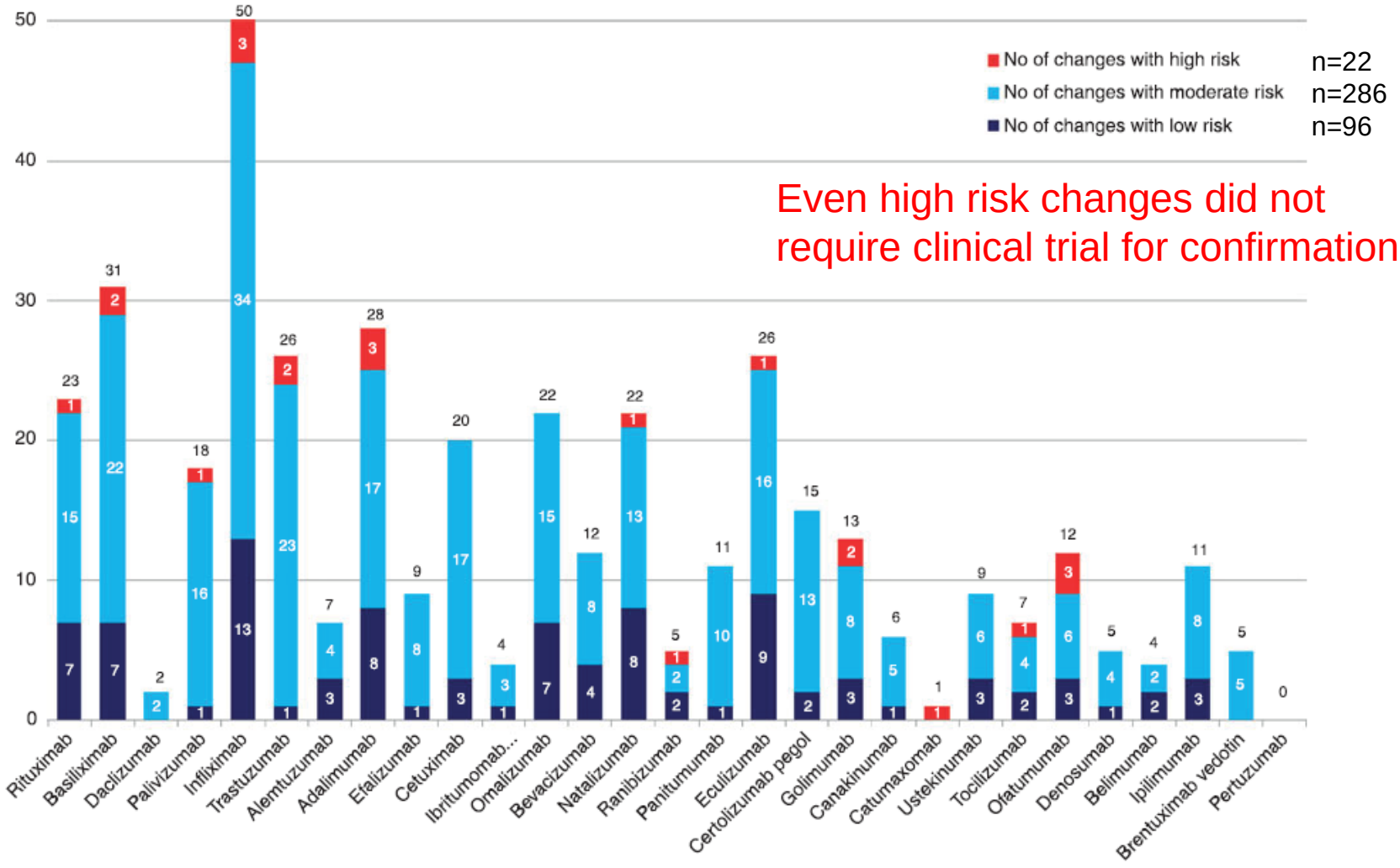


Figure 2. Number of manufacturing changes for monoclonal antibodies in their European Public Assessment Reports according to risk category (during the search period all non-proprietary names relate only to the trade named medicines listed in Table 1).

Vezér B, Buzás Zs, Sebeszta M, Zrubka Z.: Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. Curr Med Res Opin. 2016 May;32(5):829-34

Extrapolation
in the clinical development of biosimilars

Extrapolation is not a new concept

- Concept has been emphasized in new Overarching Guidelines and Product specific GLs

- Is integral part of regulatory guidance and clinical practice

  - Always assumed for manufacturing changes according to ICH Q5E
  - Line extensions of originators
  - Biosimilar concept
  - What about Line extensions of Biosimilars?

Extrapolation is specified in regulatory guidance documents

(Product-specific) biosimilar guideline on…	Extrapolation
Recombinant erythropoietins EMEA/CHMP/BMWP/301636/2008 Corr.* (2010)	**Extrapolation of efficacy data** Demonstration of efficacy and safety in renal anaemia will allow extrapolation to other indications of the reference medicinal product with the same route of administration.
Recombinant GCSF EMEA/CHMP/BMWP/31329/2005	**Extrapolation of efficacy data** Demonstration of the clinical comparability in the chemotherapy-induced neutropenia model will allow the extrapolation of the results to the other indications (incl. mobilization of stem cells in healthy donors)
Overarching GL: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1	**Extrapolation of routes of administration** It is possible to waive the evaluation of **intravenous administration** if biosimilar comparability in both absorption and elimination has been demonstrated for the **subcutaneous route**
Also generally allowed in **Line extensions (=abridged application)**	**Extrapolation of efficacy data** **e.g. Herceptin s.c. one clinical Phase 3 trial conducted (vs i.v.) in early breast cancer (EBC) with neoadjuvant Rx.** Recomb. hyaluronidase = permeation enhancer was classified as excipient, thus allowing different formulation EP: Ctrough and pCR only Extrapolation to all breast ca indications (gastric ca not requested)

Extrapolation
in the clinical development of biosimilars

Extrapolation is not a new concept

- Concept has been emphasized in new Overarching Guidelines and Product specific GLs

- Is integral part of regulatory guidance and clinical practice

  - Always assumed for manufacturing changes according to ICH Q5E
  - Line extensions of originators
  - Biosimilar concept
    - EXAMPLES: Filgrastim, Epoetin, Insulin
    - EXAMPLES: Therapeutic monoclonal Abs for Autoimmune Disease and Oncology
  - What about Line extensions of Biosimilars?

Extrapolation: not a new concept

Biosimilars: the science of extrapolation

Martina Weise,[1] Pekka Kurki,[2] Elena Wolff-Holz,[3] Marie-Christine Bielsky,[4] and Christian K. Schneider[5,6]

[1]Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany; [2]Finnish Medicines Agency, Helsinki, Finland; [3]Paul-Ehrlich-Institut, Langen, Germany; [4] Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; [5]Danish Health and Medicines Authority, Copenhagen, Denmark; and [6]Twincore Centre for Experimental and Clinical Infection Research, Hannover, Germany

(*Blood*. 2014;124(22):3191-3196)

Extrapolation of data is already an established scientific and regulatory principle that has been exercised for many years, for example, in the case of major changes in the manufacturing process of originator biologicals. In such cases, clinical data are typically generated in one indication and, taking into account the overall information gained from the comparability exercise, may then be extrapolated to the other indications. In fact, the authors are not aware of any case where additional clinical studies with the changed product in other or even all approved indications have been provided by the marketing authorisation holders, or have been considered necessary by regulators.

The science of extrapolation

Weise et al. Blood. 2014;124 (22) :3191-6.

Scientific arguments supporting the extrapolation of indications for biosimilar epoetin (renal anemia, oncology) :

- ✓ All licensed biosimilar epoetins exhibit the same amino acid sequence as their reference product
- ✓ Although epoetins are heavily glycosylated (165 aa 34 kDa) and rather complex molecules characterisation is possible with state-of-the-art methods
- ✓ All licensed biosimilar epoetins demonstrated high level of similarity in molecular structure and biological activity with their RMP.
- ✓ The desired pharmacological effect of epoetin is mediated by a single cell receptor
- ✓ mechanism of action is the same in all approved indications.

The science of extrapolation

Weise et al. Blood. 2014;124 (22) :3191-6.

Scientific arguments supporting the extrapolation of indications for biosimilar epoetin (renal anemia, oncology) :

- ✓ The observation of equivalent effects on reticulocyte count and Hb values provides considerable reassurance that adverse events that are related to exaggerated pharmacological effects can be expected at similar frequencies, also at the high doses used in oncology patients.
- ✓ No differences in the safety profile and anti-epoetin antibody response was detected between the biosimilar and their reference products
- ✓ Extrapolation of immunogenicity data is possible from the population at increased risk (renal anaemia), to the population at low risk (cancer patients on chemotherapy).

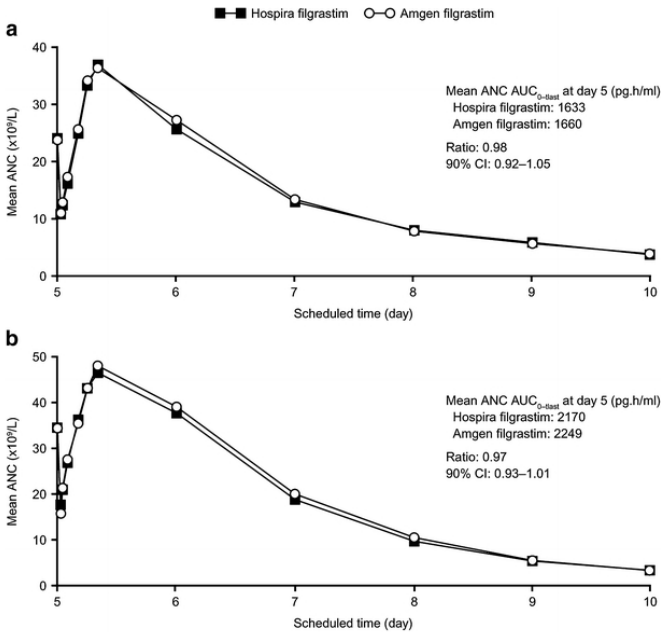
The science of extrapolation

Weise et al. Blood. 2014;124 (22) :3191-6.

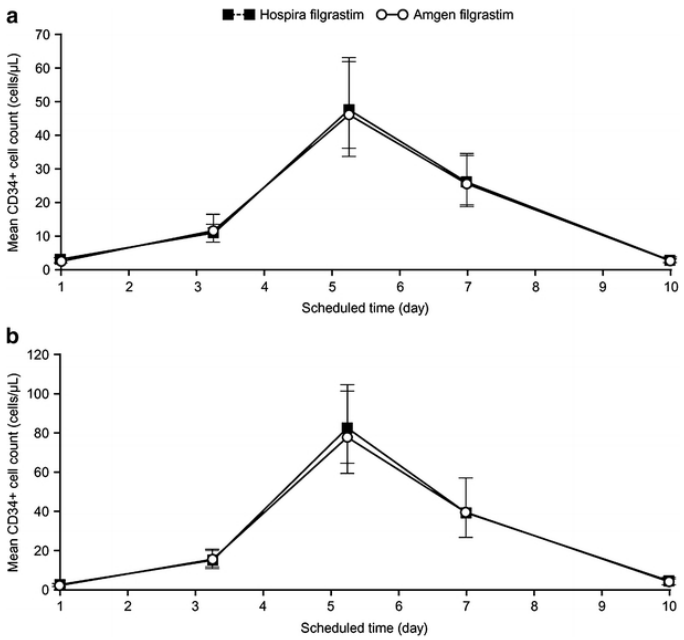
Scientific arguments supporting the extrapolation of indications for biosimilar filgrastrim (treatment of neutropenia, mobilisation of PBC in patients and healthy donors):

- ✓ Filgrastim is a very well characterisable, 20 kDa, non-glycosylated molecule
- ✓ All licensed biosimilar filgrastims demonstrate high level of similarity in molecular structure and biological activity with their RMP.
- ✓ Pharmacokinetic profiles are comparable ensuring equivalent exposure
- ✓ All pharmacological actions of filgrastim are mediated via a single affinity class cell receptor

Biosimilar Filgrastim



Mean ANC over time in subjects given Hospira filgrastim or Amgen filgrastim; **a** 5-µg/kg dose group and **b** 10-µg/kg dose group. Data shown are geometric means. Samples taken outside each schedule timepoint window have been excluded. *ANC* absolute neutrophil count, $AUC_{0–tlast}$ area under the curve from time 0 to the last time point, *CI* confidence interval



Mean CD34+ cell count over time in subjects given Hospira filgrastim o Amgen filgrastim; **a** 5-µg/kg dose group and **b** 10-µg/kg dose group. Da shown are geometric mean values with lower and upper 95% confidenc intervals

Waller, Ann Hematol 2010

The science of extrapolation

Weise et al. Blood. 2014;124 (22) :3191-6.

Scientific arguments supporting the extrapolation of indications for biosimilar filgrastrim (treatment of neutropenia, mobilisation of PBC in patients and healthy donors):

- ✓ Comparable pharmacodynamic activities were confirmed in healthy subjects and/or patients.
- ✓ The safety and immunogenicity profiles were found to be comparable to those of the reference product, in patients and in pharmacology studies in healthy subjects.
- ✓ Immunogenicity is not a specific concern for filgrastim as anti-filgrastim antibodies are infrequent and have not been associated with relevant clinical effects.

Extrapolation
in the clinical development of biosimilars

Extrapolation is not a new concept

- Concept has been emphasized in new Overarching Guidelines and Product specific GLs

- Is integral part of regulatory guidance and clinical practice

  - Always assumed for manufacturing changes according to ICH Q5E
  - Line extensions of originators
  - Biosimilar concept
    - EXAMPLES: Filgrastim, Epoetin, Insulin
    - EXAMPLES: Therapeutic monoclonal Abs **for Autoimmune Disease** and Oncology
  - What about Line extensions of Biosimilars?

The science of extrapolation

Weise et al. Blood. 2014;124 (22) :3191-6.

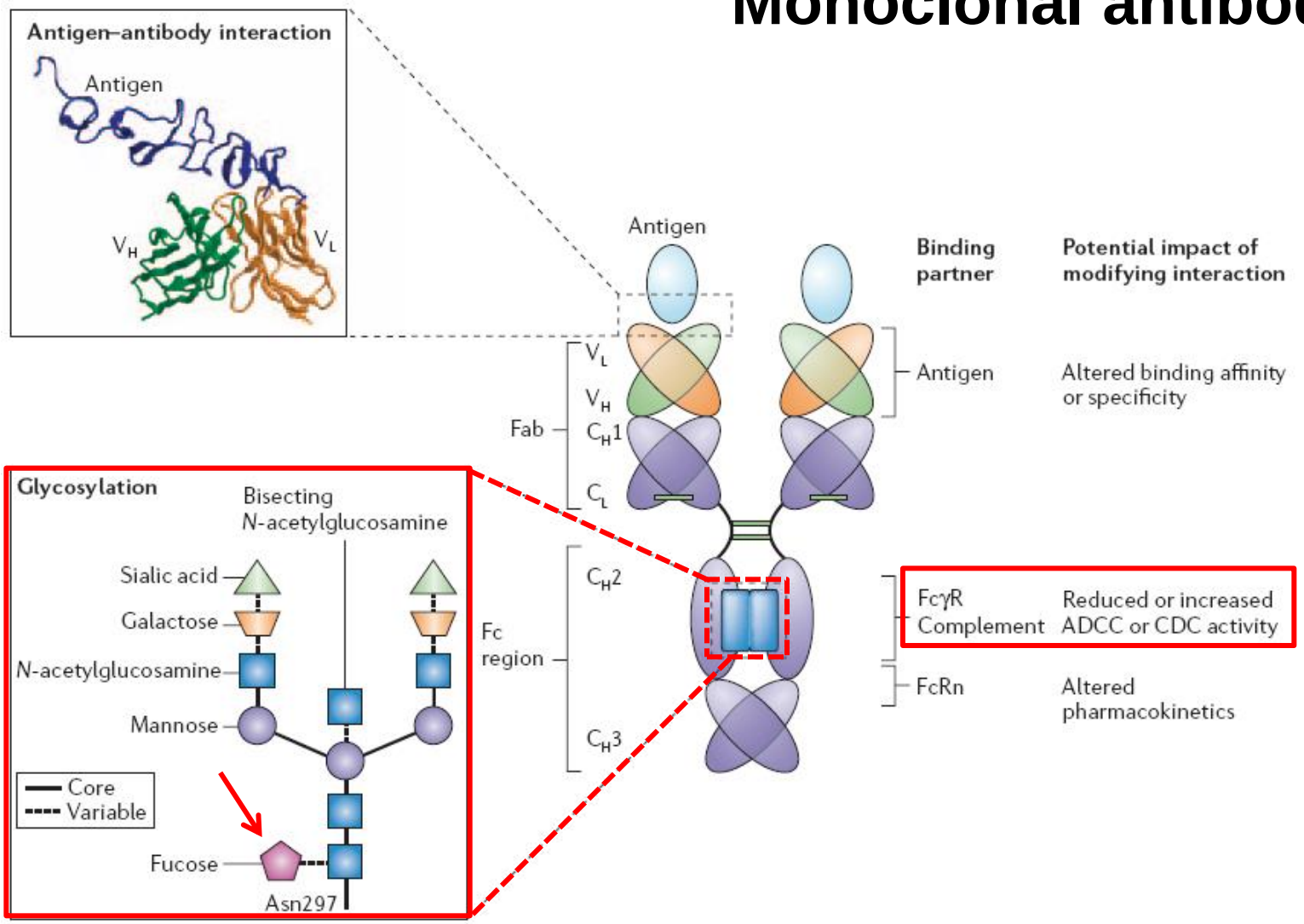
Scientific arguments supporting the extrapolation of indications for biosimilar infliximab (autoimmune diseases):

✓Extensive analytical tests showed physicochemical and structural comparability except for a small difference in the proportion of afucosylated forms

✓The biosimilar and the reference infliximab demonstrated comparable binding to complement receptor and all types of Fc-receptors except for FcγRIIIa/b, **translating into lower ADCC activity** in one particular assay.

→ **Further studies concerning FcγRIIIa/b revealed t**his difference disappeared under more physiological conditions, questioning the clinical relevance of the observed difference

Monoclonal antibody

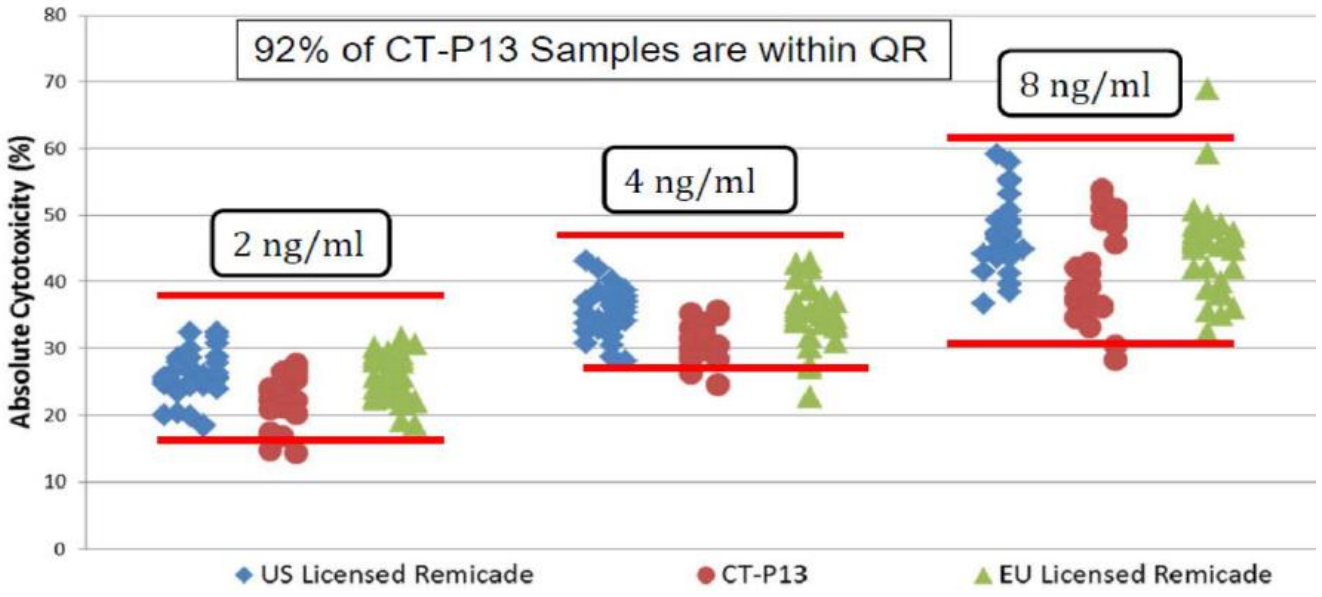


Carter PJ: Potent antibody therapeutics by design, Nature Rev Immunol 6, 343 (2006)

CT-P13 : Importance of difference in ADCC ?

20% difference in mean ADCC Aktivity in most sensitive *in vitro* test with t Jurkatcells (very high titers tmTNF) as target cells and NK-cells ls effectorcells

Figure 9. ADCC of CT-P13, US-licensed Remicade, and EU-approved Remicade Using NK Cells as Effector Cells

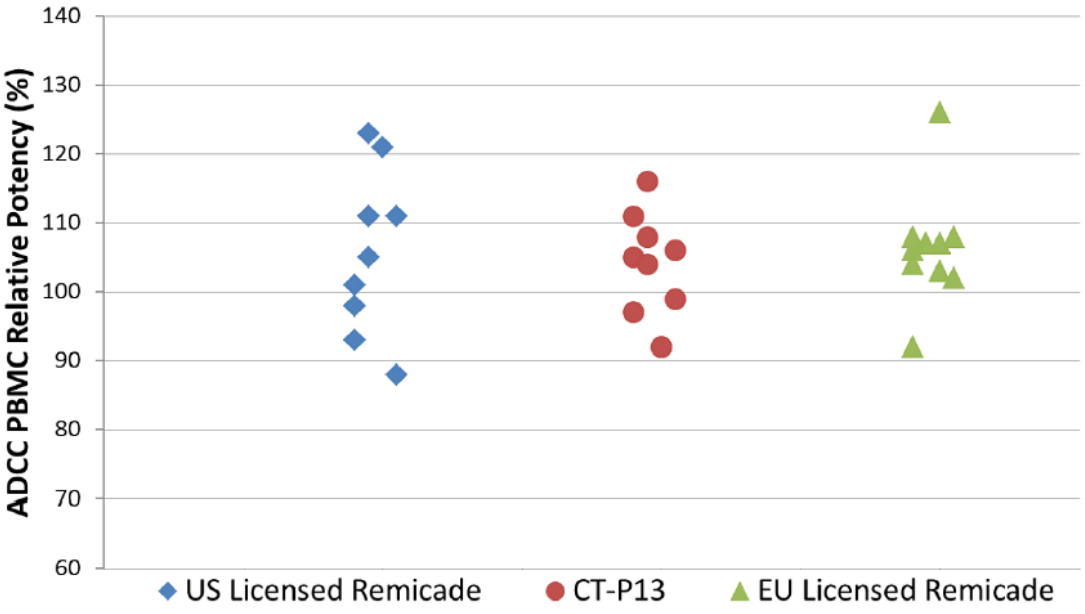


Source: CDER Clinical Review Template on CT-P13, available at www.fda.gov

CT-P13 : Importance of difference in ADCC ?

No difference in ADCC under more physiologic condirions (e.g. addit ion of serum to NK-cell-Assay or use of PBMC)

Figure 8. ADCC of CT-P13, US-licensed Remicade, and EU-approved Remicade Using PBMC as Effector Cells



Source: CDER Clinical Review Template on CT-P13, available at www.fda.gov

No ADCC response when LPS-stimulated Monocyts were used as target cells and PBMC as effectorcells → ADCC poss. Nit important in IBD

α TNF Overview of authorized indications

Which studies are important across indications

???

Indication	Infliximab Remicade®	Adalimumab Humira®	Golimumab Simponi®	Certolizumab-peg Cimzia®	Etanercept Enbrel®
Rheumatoide Arthritis	✓	✓	✓	✓	✓
Juvenile Rheumatoide Arthritis		✓			✓
Psoriasis	✓	✓			✓
Psoriatrische Arthritis	✓	✓	✓	✓	✓
Morbus Crohn	✓	✓		EU: Negativ USA: Positiv	Negativ
Colitis ulcerosa	✓	✓	✓		Negativ
Ankylosierende Spondylitis	✓	✓	✓	✓	✓
Hidradenitis suppurativa		✓			

Mechanism of action of anti TNFα	Infliximab Chimeric IgG1 Remicade®	Adalimumab Human IgG1 Humira®	Certolizumab peg Fab-peg (no Fc) Cimzia®	Etanercept Fusion protein with small Fc part Enbrel®
Binding soluble TNF				
Elim. by complex formation	✓	✓	✓	✓
Binding affinity	✓	✓	✓	✓
Attenuation of angiogenesis + adhesion molecule expression	reduced trafficking of inflammat. cells (macroph, T- cells into inflamed tiss.)	reduced trafficking	reduced trafficking	reduced trafficking
Binding of membranous TNF				
Binding of monocytes, macrophages, T-cells)	✓	✓	✓	✓
→ ADCC	high	high	—	Low / high
→ CDC	high	high	—	Low / high
Binding to FcRn (clearance)	✓	✓	—	diff Fc CH2 / No Fc CH1 — diff PK
Reverse signalling of membranous TNF, alters function of immune cell				
Apoptosis of CD3+ T-cells in lamina propria of CD pat.	high	high	—	✓ (less)
Cytokine suppression, e.g. inhibition of LPS induced Cytokine release (e.g. IL-ß)	✓	✓	✓	—

Modified table from Tracey, D. et al. Pharmacology Therapeutics 117 (2008) 244-279

CT-P13 Summary Comparability studies

- **More than 50 analytical tests for characterising und comparing with originator**
  - Comparable primary, secondary, tertiary structure
    - Comparable post-translationae profile
    - Comparable biologic acitivity
- **Clinical studies with patients with ankylosing spondylitis and with patients with rheumatoid arthritis**
  - Comparable pharmacokinetcs
  - Comparable efficacy, safety incl. immunogenicity
  - Post approval studies confirmed effect

* ***European Public Assessment Report on Remsima @ www.ema.europa.eu***

Extrapolation
in the clinical development of biosimilars

Extrapolation is not a new concept

- Concept has been emphasized in new Overarching Guidelines and Product specific GLs

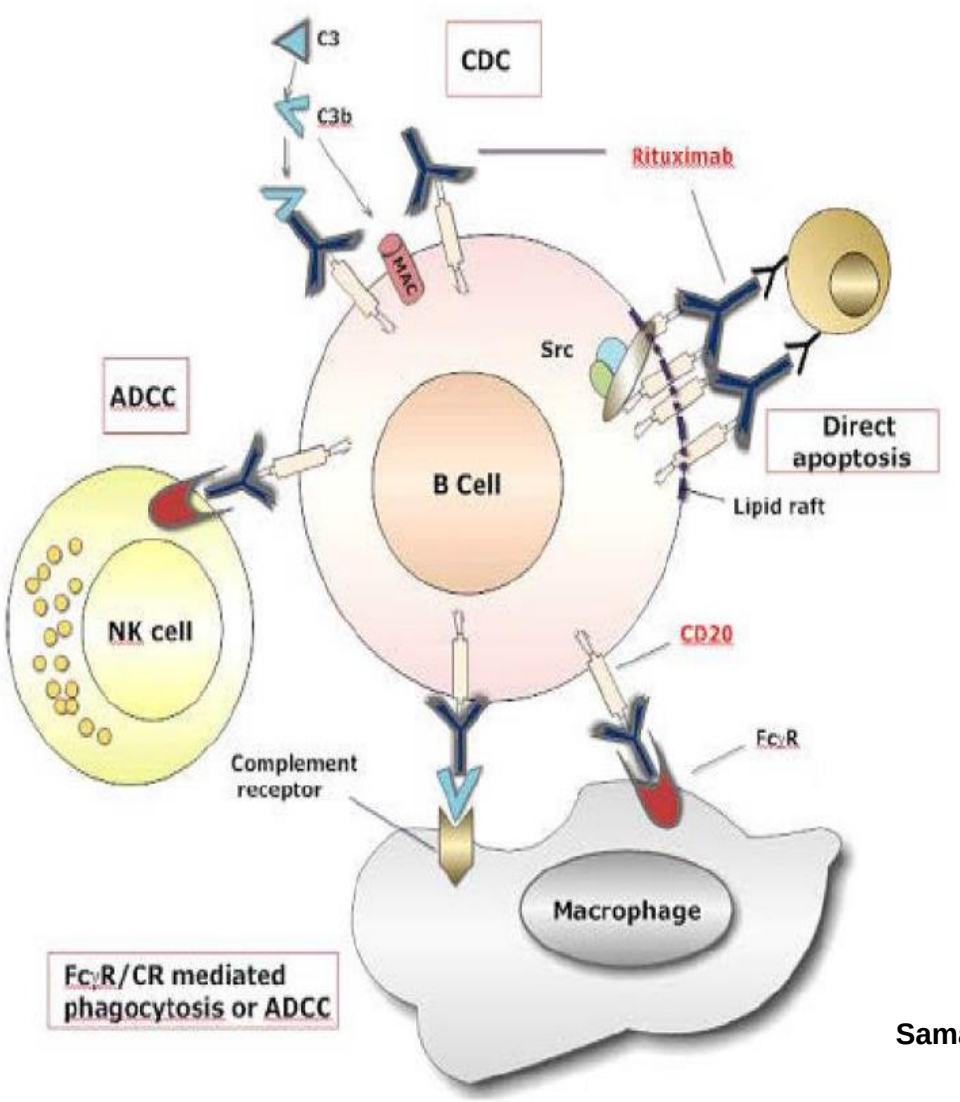
- Is integral part of regulatory guidance and clinical practice

  - Always assumed for manufacturing changes according to ICH Q5E
  - Line extensions of originators
  - Biosimilar concept
    - EXAMPLES: Filgrastim, Epoetin, Insulin
    - EXAMPLES: Therapeutic monoclonal Abs for Autoimmune Disease and **Oncology**

Comparability studies Rituximab Biosimilars versus Mabthera – Overview of comparative quality studies

Molecular parameter	Methods for control and characterisation	Key findings
Primary structure	Amino acid analysis Molar absorptivity N-terminal sequencing C-terminal sequencing Peptide mapping by HPLC Determination of intact mass	Identical primary structure Intact mass comparable
Secondary and higher order structure	Fourier Transform Infra-Red spectroscopy Circular Dichroism Differential Scanning Calorimetry	Highly similar secondary and higher order structure. • Similar post-translational modifications included deamidation, oxidation and C-terminal lysine variants, • highly similar number and distribution of charged variants • highly similar glycosylation profiles, • highly similar monosaccharide (Fucose, N-acetyglucosamine, Galactose and Mannose) sugar contents • Highly similar sialic acid (N-acetylneuraminic acid (NANA) contents • similar levels of residual process-related impurities such as host cell protein, Host Cell DNA and rProtein A were shown.

Mechanism of rituximab-mediated cell death



Direct apoptosis induction in vitro is mainly seen in rapidly dividing Burkitt lymphoma cells but is very hard to demonstrate in some other lymphoma cell types.

FcR polymorphism(s) have impact on in vivo response in Follicular lymphoma (FL) suggesting that ADCC is more important in FL but less important in CLL

CD20 levels on the B cell surface, and B cell count differ largely between NHL and Rheumatoid Arthritis (RA) patients due to the range of tumour burden among patients.

Samantha M. Jaglowski et al. Blood 2010;116:3705-3714

Ab-dependent cellulae Phagocytosis (ADCP)

Comparability studies Rituximab Biosimilars versus Mabthera –Overview of comparative preclinical studies

Molecular parameter	Methods for control and characterisation	Key findings
Binding assays and *in vitro* bioassays	Binding affinity to CD20 C1q binding affinity Fcγ receptors (FcγRIIIa-V, FcγRIIIa-F, FcγRIIIb, FcγRIIa, FcγRIIb and FcγRI) binding affinity and FcRn binding affinity CDC ADCC Apoptosis bei FACS analysis	Highly similar binding affinity to CD20 (the primary mechanism of action of rituximab) A similar correlation between glycosylation and Fc function of Truxima and MabThera/Rituxan was shown Highly similar biological activities in assays representative of the known and putative mechanisms of action of Rituximab.

Clinical comparability studies Rituximab Biosimilars vs Mabthera

Rituximab CT-P10 Truxima
FDA: approved; EMA: approved

Study CT-P10 1.1 and extension study CT-P10 1.3 in **patients with Rheumatoid Arthritis**

- 2-arm, 72 week follow up, N=151
- **Pivotal PK** (primary), PD, efficacy and safety (secondary) of Truxima vs Mabthera

Parameter	Treatment	N	Geometric Mean	Ratio (%) of Geometric Means	90% CI of Ratio (%)
PK population					
$AUC_{0\text{-last}}$ (day•µg/mL)	CT-P10 1000 mg	96	7838.62	97.72	89.23 - 107.00
	MabThera 1000 mg	45	8021.86		
C_{max} (µg/mL)[a]	CT-P10 1000 mg	96	465.94	97.57	91.96 - 103.53
	MabThera 1000 mg	45	477.52		
$AUC_{0\text{-last}}$ (day•µg/mL)	CT-P10 1000 mg	96	7859.29	96.90	88.10 - 106.58
	MabThera 1000 mg	45	8110.54		
C_{max} (µg/mL)[b]	CT-P10 1000 mg	96	465.76	95.77	89.40 - 102.60
	MabThera 1000 mg	45	486.32		

Clinical comparability studies of Rituximab Biosimilars vs Mabthera

Rituximab GP2013 Rixathon
FDA:withdrawn; EMA: approved

Study GP13-201 in **patients with Rheumatoid Arthritis**

- 2 arm, 52 week follow up, N = 173
- **Pivotal PK** (primary), **PD** (key secondary), safety and efficacy of Rixathon vs Mabthera (Part 1), Rixathon vs Rituxan (Part 2)

Parameter	Statistics	GP2013 N= 86	MabThera N= 86
$AUC_{(0\text{-}Inf)}$ (day*mcg/mL)	n	75	70
	Mean (SD)	8005.04 (2653.757)	7563.06 (3000.580)
	CV% mean	33.15	39.67
	Geometric mean	7582.73	7046.23
	CV% geometric mean	34.25	39.54
	Median	7633.41	7441.26
	Minimum - Maximum	3973.1 - 13648.2	2054.7 - 20614.9

Clinical comparability studies of Rituximab Biosimilars vs Mabthera
EPARs; http://www.ema.europa.eu

Rituximab CT-P10 Truxima FDA: approved EMA: approved	Rituximab GP2013 Rixathon FDA: application withdrawn EMA: approved
Study CT-P10 1.1 and extension study CT-P10 1.3 in **patients with Rheumatoid Arthritis** • 2-arm, 72 week follow up, N=154 • **Pivotal PK** (primary), PD, efficacy and safety (secondary) of Truxima vs Mabthera	**Study GP13-201** in **patients with Rheumatoid Arthritis** • 2 arm, 52 week follow up, N = 173 • **Pivotal PK** (primary), **PD** (key secondary), safety and efficacy of Rixathon vs Mabthera (Part 1), Rixathon vs Rituxan (Part 2)
Study CT-P10 3.2 in **patients with Rheumatoid Arthritis** • 3-arm, 76 week follow up, **N=372 patients** • (Part 1) **PK** of Truxima vs Rituxan and Mabthera (primary) • (Part 2) **Efficacy** of Truxima vs Rituxan and Mabthera (primary) PK, PD, Safety, Efficacy of Truxima vs Rituxan (secondary, Parts 1&2)	**Study GP13-301 (Pivotal)** in **patients with Advanced FOLLICULAR LYMPHOMA (AFL)** • 2 arms, follow up: 3 years **N= 627 patients induction** **N = 462 patients maintenance** • **Efficacy,** safety **and PK** of • Rixathon vs Mabthera • in combination with other therapies followed by maintenance therapy
Study CT-P10 3.3 (supportive) in patients with **Advanced FOLLICULAR LYMPHOMA (AFL)** • 2-arm, 3 year follow up, N=121 • (Part 1) PK of Truxima vs Rituxan (primary) • (Part 2) Efficacy of Truxima vs Rituxan (non inferiority) (primary) • Efficacy, PD, Safety of Truxima vs Rituxan (secondary, Parts 1&2)	

Extrapolation
in the clinical development of biosimilars

Extrapolation is not a new concept

- Concept has been emphasized in new Overarching Guidelines and Product specific GLs

- Is integral part of regulatory guidance and clinical practice

  - Always assumed for manufacturing changes according to ICH Q5E
  - Line extensions of originators
  - Biosimilar concept

Overarching Guideline CHMP/437/04 Rev. 1: Biosimilar versus RMP

Must be the same (clinical aspects)

- **Posology**
- **Route of adminstration**

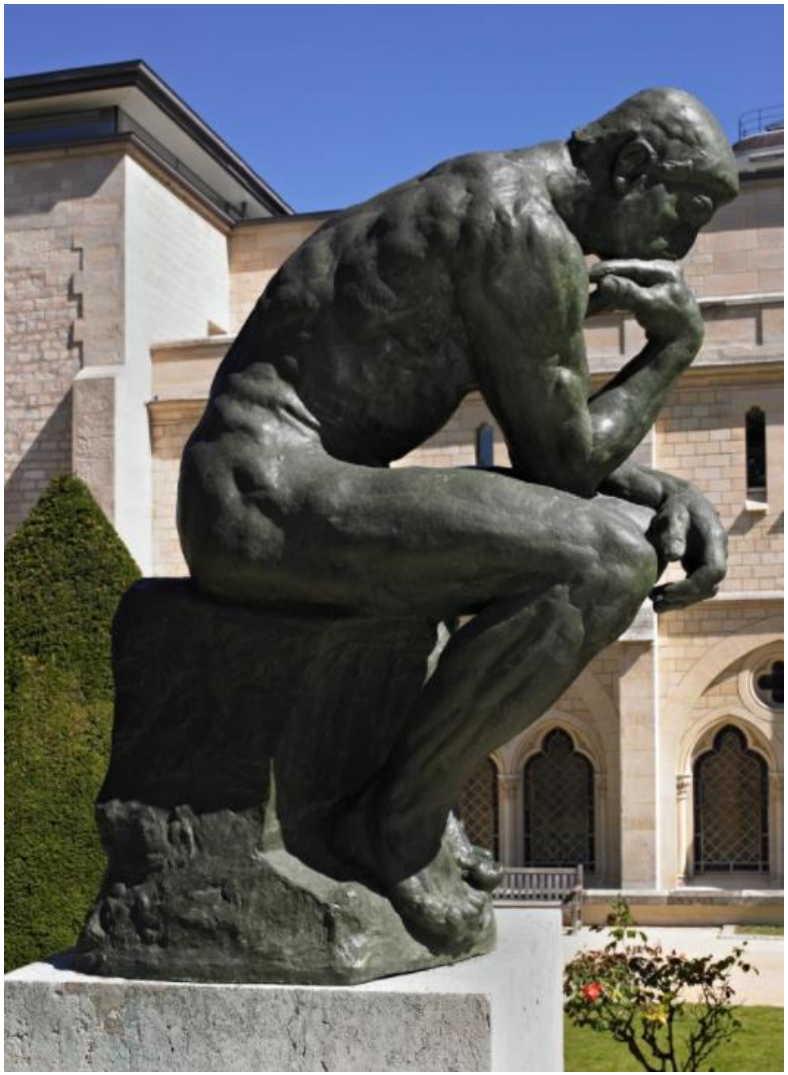
Deviations which require justification (quality aspects)

- **Strength** (e.g.30 mg/ml versus 60 mg/ml)
- **Pharm. Form** (e.g. solution for injection, freeze-dried powder)
- Formulation (drug substance, microaggregates, stabilizers, salts, excipients…)
- Excipients (also depend on route of administration)
- Presentation (vial vs multidose vial vs PFS vs pen or autoinjector) incl different container/closure system

→**In practice the same posology could be obtained from different pharmaceutical forms or strengths**

→ **Body weight versus fixed dosing may have implications for some indications**

Thanks for your attention !!



Extrapolation and Interchangeability

- Update on Biosimilars in the EU
  - ✓Framework (legal basis, overview guidelines)
  - ✓Available biosimilars in Europe
- Extrapolation
- Interchangeability

Status Quo: Still an emotional debate

- Who decides?
- Impact on Immunogenicity?
- Impact of Immunogenicity ?
  - ✓ Loss of efficacy?
  - ✓ Increase in infusion reactions or other AEs?
- Pharmacovigilance possible?

→ Need to look at experience gained so far !!

- Before marketing authorization
- After marketing authorization
- Pharmacovigilance

Definitions of interchangeability largely agreed within EU
Importance of nomenclature…

Interchangeability
Refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another.
Replacement can be done by

1. Switching
The decision by the treating physician to exchange one medicine with another medicine with the same therapeutic intent in patients who are undergoing treatment.

2. 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

3. 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)

BioDrugs
DOI 10.1007/s40259-017-0227-4

CURRENT OPINION

A 'Global Reference' Comparator for Biosimilar Development

Christopher J. Webster[1] · Gillian R. Woollett[2]

Abstract Major drug regulators have indicated in guidance their flexibility to accept some development data for biosimilars generated with reference product versions licensed outside their own jurisdictions, but most authorities require new bridging studies between these versions and the versions of them licensed locally. The costs of these studies are not trivial in absolute terms and, due to the multiplier effect of required repetition by each biosimilar sponsor, their collective costs are substantial. Yet versions of biologics licensed in different jurisdictions usually share the same development data, and any manufacturing changes between versions have been justified by a rigorous comparability process. The fact that a biosimilar is usually expected to be licensed in multiple jurisdictions, in each case as similar to the local reference product, confirms that minor analytical differences between versions of reference biologics are typically inconsequential for clinical outcomes and licensing. A greatly simplified basis for selecting a reference comparator, that does not require conducting new bridging studies, is proposed and justified based on the shared data of the reference product versions as well as the proof offered where biosimilars have already been approved. The relevance of this proposal to the interchangeability designation available in the US is discussed.

✉ Gillian R. Woollett
gwoollett@avalere.com

[1] BioApprovals, Acton, MA 01720, USA

[2] FDA Regulatory Strategy and Policy, Avalere Inc, 1350 Connecticut Avenue, NW, Suite 900, Washington, DC 20036, USA

Published online: 19 May 2017

Key Points

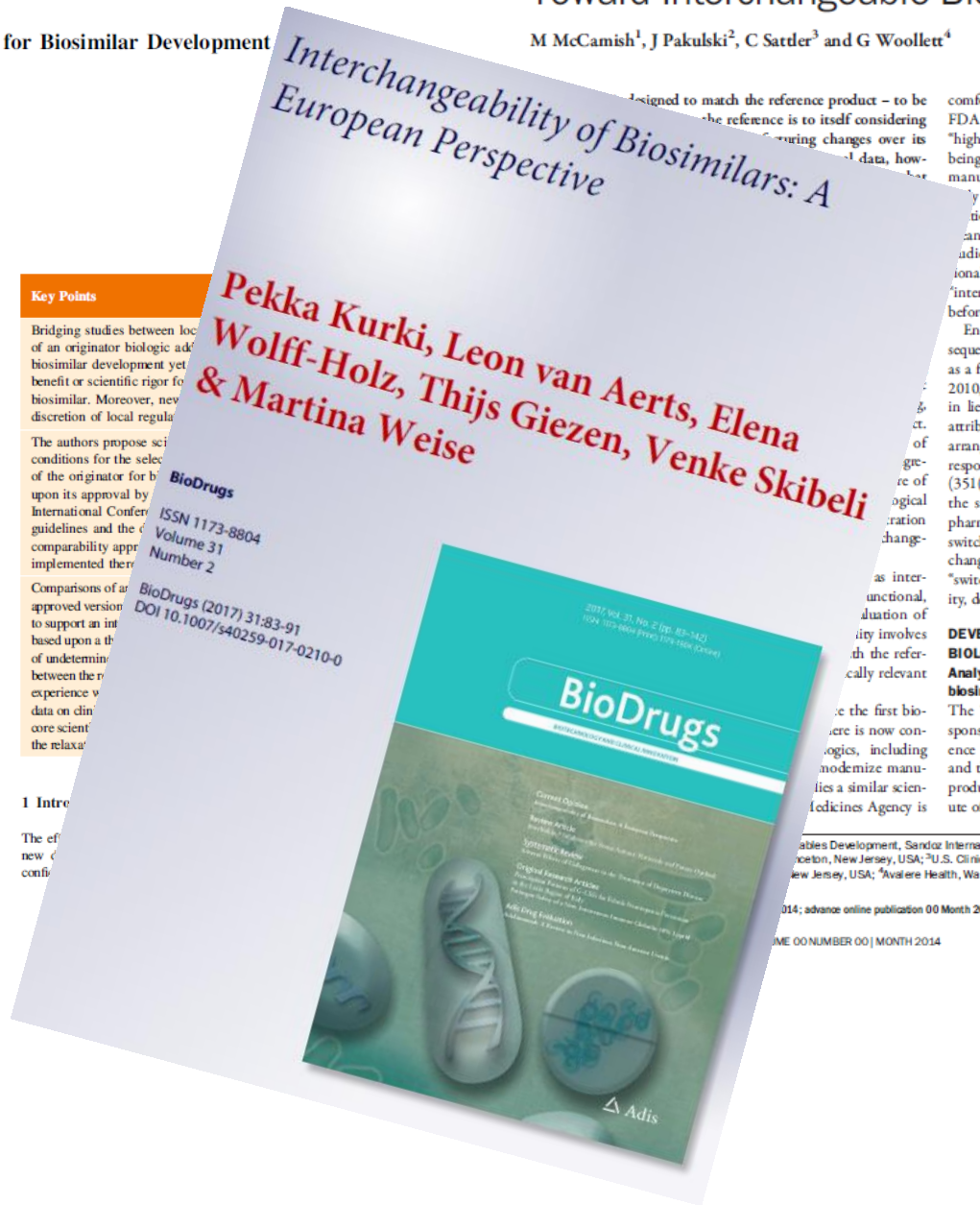
Bridging studies between loc
of an originator biologic ad
biosimilar development yet
benefit or scientific rigor fo
biosimilar. Moreover, nev
discretion of local regula

The authors propose sc
conditions for the selec
of the originator for b
upon its approval by
International Confer
guidelines and the
comparability appr
implemented there

Comparisons of a
approved version
to support an int
based upon a th
of undetermin
between the r
experience w
data on clin
core scient
the relaxa

1 Intro

The ef
new
confi



Toward Interchangeable Biologics

M McCamish[1], J Pakulski[2], C Sattler[3] and G Woollett[4]

signed to match the reference product – to be
he reference is to itself considering
uring changes over its
l data, how-
ber

comfortable calling both approaches comparability, whereas the FDA distinguishes the two. Nonetheless, both settings invoke the "highly similar" analytical standard for the two products that are being compared (biosimilar to reference vs. pre to post-manufacturing change products), and both require an increasingly comprehensive understanding of structure-function relationships in order for the determination of "no clinically meaningful differences" to be accepted absent complete clinical studies in every indication. Immunogenicity studies are an additional consideration for biosimilars and particularly "interchangeable" biologics although generally not required before a manufacturing change.

Enoxaparin is used in critical care indications with lethal consequence if the product does not work. In approving enoxaparin as a fully substitutable complex generic drug of biologic origin in 2010, the FDA identified five criteria for addressing "sameness" in lieu of comparative clinical trials (including physicochemical attributes and fragmentation methods; sourcing; nature and arrangement of components; anticoagulant assays, and human responses).[3] Biosimilars utilize a different regulatory pathway (351(k)), but ultimately approval and interchangeability requires the same confidence that the biosimilar has the "same" active pharmaceutical ingredient as the reference product, and can be switched without impact on the patient. FDA guidance on interchangeability is not yet available. Data expected will likely include "switching studies" in patients, while monitoring immunogenicity, demonstrating no difference compared to no switching.

DEVELOPMENT OF A BIOSIMILAR/INTERCHANGEABLE BIOLOGIC

Analytical studies provide the basis for a determination of biosimilarity

The "design space" for a biosimilar is created by the biosimilar sponsor's in-depth analysis of multiple lots of their chosen reference product. This provides the specifications for the biosimilar and the justification for clinical acceptability when the biosimilar product attributes fall within the ranges of each analytical attribute of the reference product.

...ables Development, Sandoz International GmbH, Holzkirchen, Germany; [2]U.S. Biopharmaceutical ...ceton, New Jersey, USA; [3]U.S. Clinical Development and Medical Affairs, Biopharmaceuticals North ...ew Jersey, USA; [4]Avalere Health, Washington, DC, USA. Correspondence: G Woollett (GWoollett@Avalere.

...014; advance online publication 00 Month 2014. doi:10.1002/cpt.39

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=WC0b01ac058001d124

What we know so far

Switching studies involving biosimilars

(1) Review of EPARS of all approved biosimilars – 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.

Of these, 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

(2) Switching studies involving biologics/biosimilars

CLINICAL EXPERIENCE WITH INFLIXIMAB BIOSIMILAR - SWITCH FROM REMICADE;
Expert Opin. Biol. Ther. (2015) 15(12)

39 patients with different rheumatic diseases
Median time on INX: 4.1 years
31/39 patients received concomitant MTX
Blood tests for INX levels and anti-INX Abs taken before first INB infusion, results not available at 1st INB infusion

Patients' symptom level and disease activity available in clinical database for

- pain
- fatigue
- patient global health (PtGlobal) and disease activity (PtAct) and
- doctor global assessment of activity (DrGlob) on 0-100mm VAS, HAQ on 0-3,
- ESR and CRP.

Time-dependent area under the curve (AUC) was computed for each variable for

- time elapsed before biologic treatment
- during INX and
- during INB treatments

What we know so far

(2) Switching studies involving biologics/biosimilars

CLINICAL EXPERIENCE WITH INFLIXIMAB BIOSIMILAR - SWITCH FROM REMICADE; Expert Opin. Biol. Ther. (2015) 15(12)

Repeated measures were analyzed using generalized estimating equations (GEE) models with an unstructured correlation structure.

Results:

NO difficulties with handling of IFB or infusion rxns

11/39 (28.2%) patients discontinued:

6 subjective reasons...fear of inferior drug, no objective AES or deterioration !!!
3 due to INB –ADAs --no AES
1 latent tbc (on INX 12 mo)
1 neurofibromatosis (on INX: 5 yrs)

What we know so far

(3) Switching studies involving biologics/biosimilars

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)

PLANETAS Study (extension study with 174/210 Ankylosing Spondylitis patients for another year): 88/ 174 Patienten were maintained and 86/174 were switched on Infliximab-Biosimilar

Efficacy outcome		CT-P13 throughout study (N=88)	Switched from INX to CT-P13 in extension phase (N=86)
ASAS20, n (%)	Wk 54	62 (70.5)	65 (75.6)
	Wk 78	61 (70.1)	64 (77.1)
	Wk 102	67 (80.7)	60 (76.9)
ASAS40, n (%)	Wk 54	51 (58.0)	46 (53.5)
	Wk 78	50 (57.5)	43 (51.8)
	Wk 102	53 (63.9)	48 (61.5)
ASAS partial remission, n (%)	Wk 54	18 (20.5)	17 (19.8)
	Wk 78	19 (21.8)	18 (21.7)
	Wk 102	23 (27.7)	22 (28.2)
ASDAS-CRP	Baseline (BL)	3.86	3.85
	Mean Δ from BL at Wk 54	−1.77	−1.74
	Mean Δ from BL at Wk 78	−1.88	−1.68
	Mean Δ from BL at Wk 102	−2.03	−1.81

Safety outcome		CT-P13 throughout study (N=90)	Switched from INX to CT-P13 in extension phase (N=84)
TEAEs, n		103	162
pts with ≥1 TEAE, n (%)		44 (48.9)	60 (71.4)
Mild		20 (22.2)	27 (32.1)
Moderate		21 (23.3)	28 (33.3)
Severe		3 (3.3)	5 (6.0)
pts with ≥1 TESAE, n (%)		4 (4.4)	4 (4.8)
pts with ≥1 infection, n (%)		23 (25.6)	29 (34.5)
ADA positive, n (%)	Wk 54	20 (22.2)	22 (26.2)
	Wk 78	21 (24.4)	25 (31.3)
	Wk 102	21 (25.0)	23 (30.7)

ADA, anti-drug antibodies; ASAS, Assessment of SpondyloArthritis international Society; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score C-reactive protein; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

W. Park, Abstract L15, presented at ACR 2013, San Diego, 29th October, 2013

Ann Rheum Dis 2016; published online April 26. DOI:10.1136/annrheumdis-2015-208783.

(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 (%)	Wk 54	78 (49.1)	69 (49.3)
	Wk 78	71 (50.4)	66 (49.6)
	Wk 102	64 (46.4)	64 (49.6)

Yoo, DH et al. Abstract L1, ACR 2013, San Diego, 29 Oct, 2013

Ann Rheum Dis 2016; published online April 29. DOI:10.1136/annrheumdis-2015-208786.

(5) Interchangeability Remsima

PHARMACOTHERAPY

Biosimilar switching — "To set a form upon desired change"

Jonathan Kay and Kevin L. Winthrop

The highly anticipated NOR-SWITCH trial results provide valuable information for patients and physicians concerned about the effects of switching between a biologic agent and a biosimilar product. However, the possibility of frequent switches, potentially involving more than one biosimilar, raises more questions.

Refers to Jørgensen, K. K. *et al.* Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet* http://dx.doi.org/10.1016/S0140-6736(17)30068-5 (2017)

www.nature.com/nrrheum
doi:10.1038/nrrheum.2017.79
Published online 1 Jun 2017

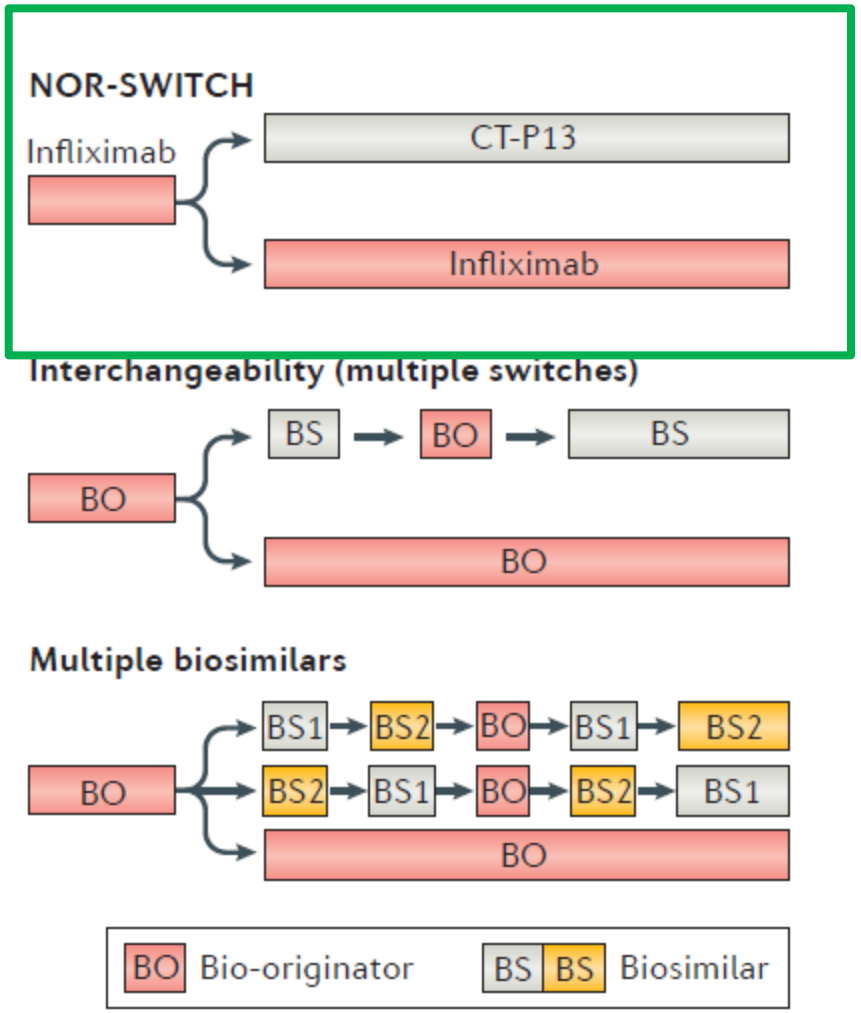


Figure 1 | **Clinical trials are needed to explore the effects of switching repeatedly between a bio-originator and its biosimilar or between multiple biosimilars.** The NOR-SWITCH study evaluated the transition from infliximab to its biosimilar CT-P13.

NOR-SWITCH published

Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial

Kristin K Jørgensen*, Inge C Olsen*, Guro L Goll*, Merete Lorentzen*, Nils Bolstad, Espen A Haavardsholm, Knut E A Lundin, Cato Mørk, Jørgen Jahnsen†, Tore K Kvien†, on behalf of the NOR-SWITCH study group

Lancet 2017; 389: 2304–16
Published Online May 11, 2017 http://dx.doi.org/10.1016/S0140-6736(17)30068-5
This online publication has been corrected. The corrected version first appeared at thelancet.com on May 23, 2017

See Editorial page 2263
See Comment page 2266

*Contributed equally as first authors
†Contributed equally as senior authors
Department of Gastroenterology, Akershus University Hospital, Lørenskog, Norway (K K Jørgensen PhD, Prof J Jahnsen PhD); Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway (I C Olsen PhD, G L Goll PhD, Prof E A Haavardsholm PhD, Prof T K Kvien PhD); Department of Dermatology (M Lorentzen MD) and Department of Gastroenterology (Prof K E A Lundin PhD), Oslo University Hospital, Rikshospitalet, Oslo, Norway; Department of Medical Biochemistry, Oslo University Hospital, Radiumhospitalet, Oslo, Norway (N Bolstad MD); Faculty of Medicine (Prof E A Haavardsholm, Prof K E A Lundin, Prof J Jahnsen, Prof T K Kvien) and Centre for Immune Regulation (Prof K E A Lundin), University of Oslo, Oslo, Norway; and Institute of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway (Prof C Mørk PhD)

Summary

Background TNF inhibitors have improved treatment of Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis, but are expensive therapies. The aim of NOR-SWITCH was to examine switching from originator infliximab to the less expensive biosimilar CT-P13 regarding efficacy, safety, and immunogenicity.

Methods The study is a randomised, non-inferiority, double-blind, phase 4 trial with 52 weeks of follow-up. Adult patients on stable treatment with infliximab originator treated in a hospital setting for at least 6 months were eligible for participation. Patients with informed consent were randomised in a 1:1 ratio to either continued infliximab originator or to switch to CT-P13 treatment, with unchanged dosing regimen. Data were collected at infusion visits in 40 Norwegian study centres. Patients, assessors, and patient care providers were masked to treatment allocation. The primary endpoint was disease worsening during 52-week follow-up. 394 patients in the primary per-protocol set were needed to show a non-inferiority margin of 15%, assuming 30% disease worsening in each group. This trial is registered with ClinicalTrials.gov, number NCT02148640.

Findings Between Oct 24, 2014, and July 8, 2015, 482 patients were enrolled and randomised (241 to infliximab originator, 241 to CT-P13 group; one patient was excluded from the full analysis and safety set for CT-P13) and 408 were included in the per-protocol set (202 in the infliximab originator group and 206 in the CT-P13 group). 155 (32%) patients in the full analysis set had Crohn's disease, 93 (19%) had ulcerative colitis, 91 (19%) had spondyloarthritis, 77 (16%) had rheumatoid arthritis, 30 (6%) had psoriatic arthritis, and 35 (7%) had chronic plaque psoriasis. Disease worsening occurred in 53 (26%) patients in the infliximab originator group and 61 (30%) patients in the CT-P13 group (per-protocol set; adjusted treatment difference −4·4%, 95% CI −12·7 to 3·9). The frequency of adverse events was similar between groups (for serious adverse events, 24 [10%] for infliximab originator *vs* 21 [9%] for CT-P13; for overall adverse events, 168 [70%] *vs* 164 [68%]; and for adverse events leading to discontinuation, nine [4%] *vs* eight [3%], respectively).

Interpretation The NOR-SWITCH trial showed that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator according to a prespecified non-inferiority margin of 15%. The study was not powered to show non-inferiority in individual diseases.

Funding Norwegian Ministry of Health and Care Services.

Introduction

Infliximab is a chimeric IgG1 antibody approved for treatment of Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis. Across all these indications, infliximab and other tumour necrosis factor (TNF) inhibitors have substantially improved disease management.[1] However, access to TNF inhibitors varies and is inversely related to socioeconomic conditions in each country.[2] The patent for the infliximab originator (Remicade; Janssen Biologics, The Netherlands) expired in 2015 in Europe and in many other parts of the world.

The biosimilar infliximab CT-P13 was approved by the European Medicines Agency in 2013 and by the US Food and Drug Administration in 2016.

Randomised controlled trials in patients who have not previously received TNF inhibitors, comparing infliximab originator with CT-P13, have been done in ankylosing spondylitis (PLANETAS,[3] a phase 1 study) and rheumatoid arthritis (PLANETRA,[4] a phase 3 study). However, according to guidance for regulatory approval of biosimilars, CT-P13 has been approved for all six relevant indications.[5–7] This extrapolation of indication has been debated in clinical communities, especially gastroenterology,[8,9] because the mechanisms of action for infliximab might differ between indications.[10,11] Several other TNF inhibitor biosimilars have been approved or are under regulatory review and will be available for therapeutic use in the coming years.[6,12]

In Norway, an annual tender system for TNF inhibitors and related biological drugs was established in 2007.

NEWS & VIEWS

PHARMACOTHERAPY

Biosimilar switching — "To set a form upon desired change"

Jonathan Kay and Kevin L. Winthrop

The highly anticipated NOR-SWITCH trial results provide valuable information for patients and physicians concerned about the effects of switching between a biologic agent and a biosimilar product. However, the possibility of frequent switches, potentially involving more than one biosimilar, raises more questions.

Refers to Jørgensen, K. K. *et al.* Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet* http://dx.doi.org/10.1016/S0140-6736(17)30068-5 (2017)

www.nature.com/nrrheum
doi:10.1038/nrrheum.2017.79
Published online 1 Jun 2017

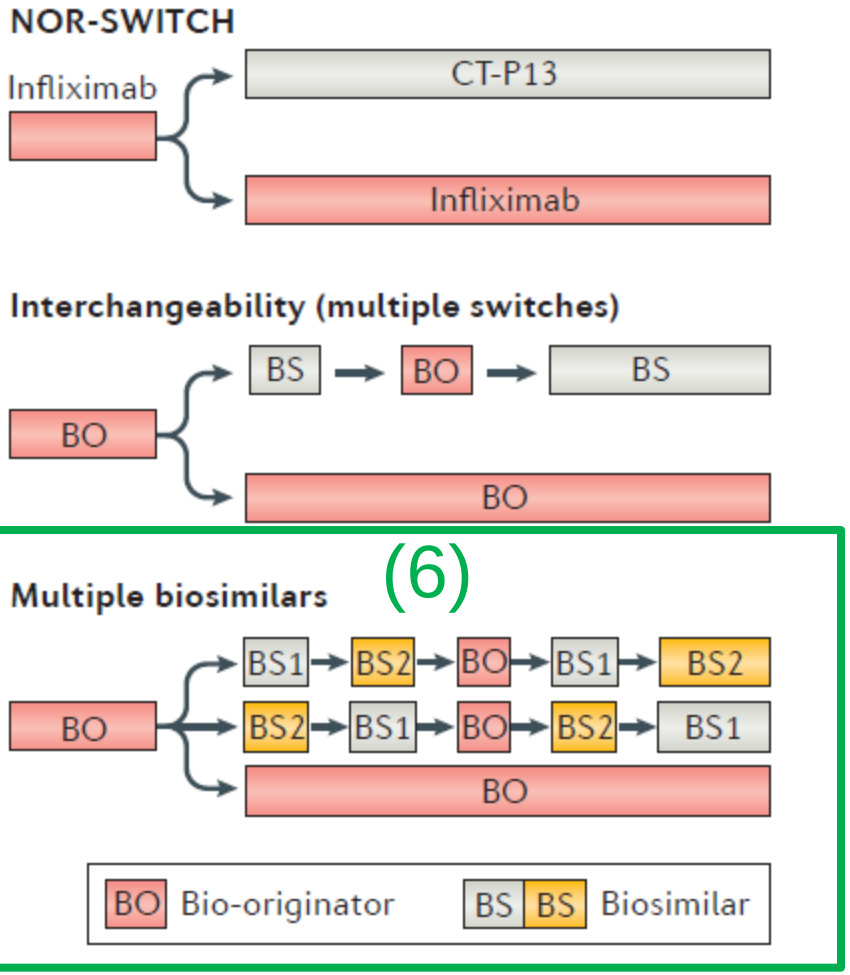
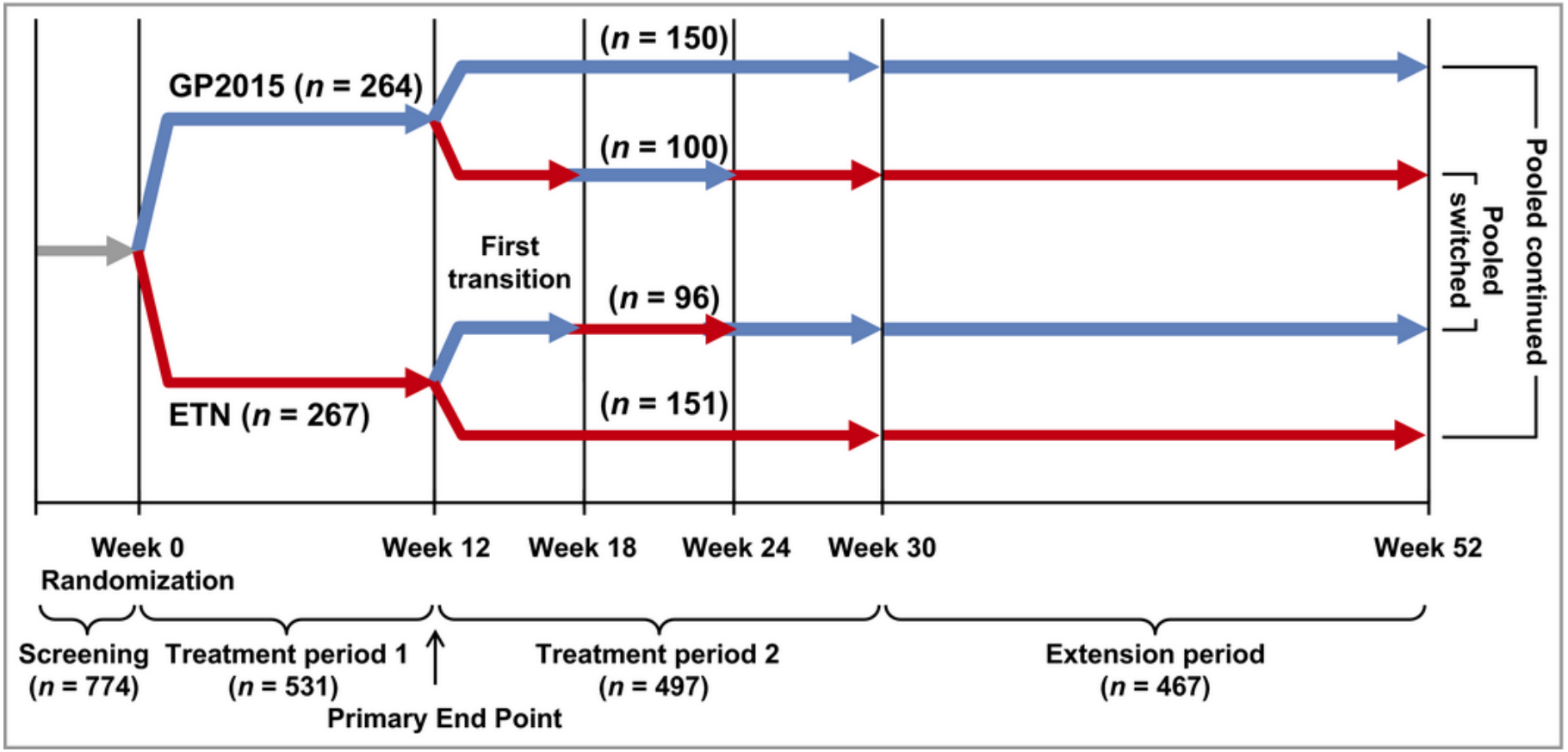


Figure 1 | **Clinical trials are needed to explore the effects of switching repeatedly between a bio-originator and its biosimilar or between multiple biosimilars.** The NOR-SWITCH study evaluated the transition from infliximab to its biosimilar CT-P13.

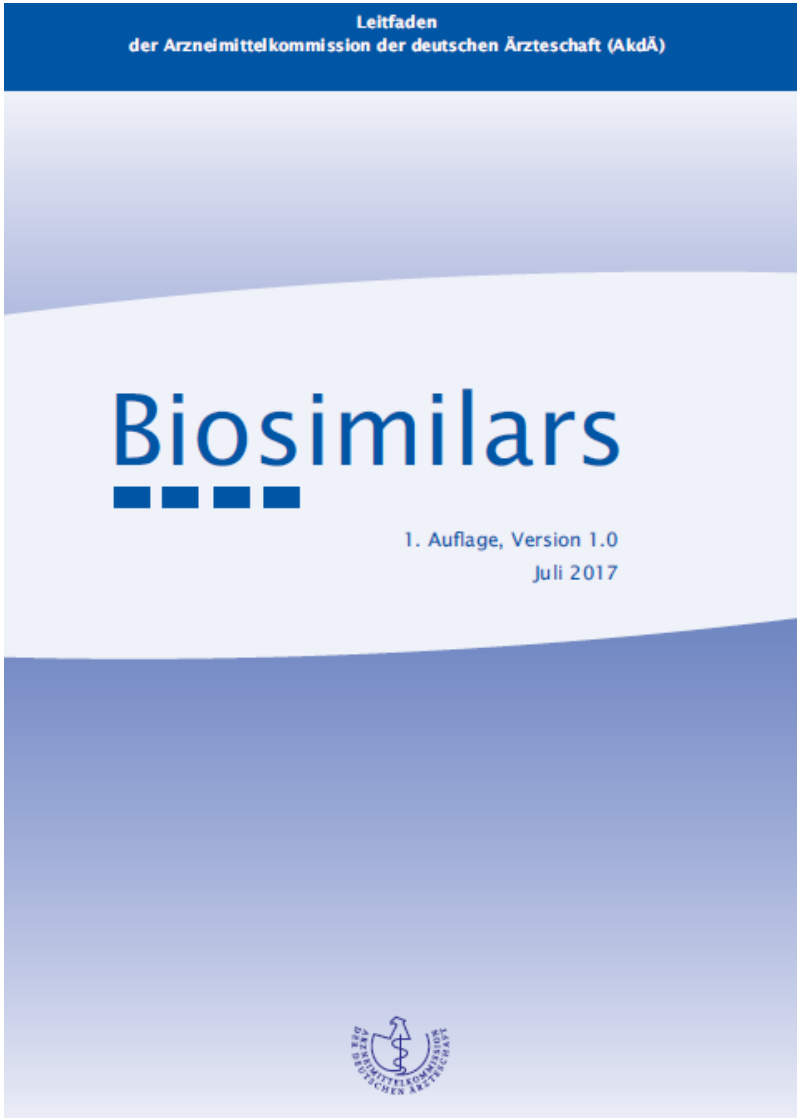
The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis



C.E.M. Griffiths et al, BrJD 176, 4, 928-938, 10.1111/bjd.15152

Short Half life etanercept: T1/2= 115 hr

What we know so far



(8) Switch-Studien mit Biosimilars

Inzwischen sind Daten aus zahlreichen Switch-Studien mit Crossover-Design mit unterschiedlichen Biosimilars verfügbar

siehe Tabelle 10:

105 Studien !!

Beim Switch einer laufenden Therapie mit einem biologischen Referenzarzneimittel auf ein Biosimilar wurden in klinischen Studien keine (signifikanten) Unterschiede hinsichtlich der Wirksamkeit oder Sicherheit zwischen Referenzarzneimittel und Biosimilar festgestellt.

Drugs
https://doi.org/10.1007/s40265-018-0881-y

SYSTEMATIC REVIEW

Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes

Hillel P. Cohen[1] · Andrew Blauvelt[2] · Robert M. Rifkin[3] · Silvio Danese[4] · Sameer B. Gokhale[5] · Gillian Woollett[6]

Abstract

Introduction To evaluate the possibility that switching from reference biologic medicines to biosimilars could lead to altered clinical outcomes, including enhanced immunogenicity, compromised safety, or diminished efficacy for patients, a systematic literature review was conducted of all switching studies between related biologics (including biosimilars).

Methods A systematic search was conducted using the Medline® and Embase® databases up to 30 June 2017 employing specific medical subject heading terms. Additionally, the snowball method and a hand search were also applied. Publications were considered if they contained efficacy or safety information related to a switch from a reference medicine to a biosimilar. Non-English, non-human studies, editorials, notes, and short surveys were excluded.

Results Primary data were available from 90 studies that enrolled 14,225 unique individuals. They included protein medicines used in supportive care as well as those use therapeutic agents. The medicines contained seven di ent molecular entities that were used to treat 14 dise The great majority of the publications did not report ferences in immunogenicity, safety, or efficacy. The ra and intensity of safety signals reported after switching reference medicines to biosimilars were the same as t already known from continued use of the refer medicines alone. Three large multiple switch studies different biosimilars did not show differences in efficac safety after multiple switches between reference medi and biosimilar. Two publications reported a loss of effi or increased dropout rates.

Conclusions While use of each biologic must be asse individually, these results provide reassurance to health professionals and the public that the risk of imm genicity-related safety concerns or diminished efficac unchanged after switching from a reference biologic biosimilar medicine.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40265-018-0881-y) contains supplementary material, which is available to authorized users.

✉ Hillel P. Cohen
hillel.cohen@sandoz.com

[1] Sandoz Inc., 100 College Road West, Princeton, NJ 08540, USA

[2] Oregon Medical Research Center, Portland, OR, USA

[3] Rocky Mountain Cancer Centers, Denver, CO, USA

[4] IBD Center, Humanitas Clinical and Research Hospital, Milan, Italy

[5] Novartis Ltd., Hyderabad, India

Curr Rheumatol Rep (2017) 19:37
DOI 10.1007/s11926-017-0658-4

BIOSIMILARS (E MYSLER, SECTION EDITOR)

Switching Between Reference Biologics and Biosimilars for the Treatment of Rheumatology, Gastroenterology, and Dermatology Inflammatory Conditions: Considerations for the Clinician

Robert Moots[1,2] · Valderilio Azevedo[3] · Javier L. Coindreau[4] · Thomas Dörner[5] · Ehab Mahgoub[4] · Eduardo Mysler[6] · Morton Scheinberg[7] · Lisa Marshall[4]

Abstract

Purpose of Review Biosimilars of the reference biologic therapeutics infliximab, etanercept, adalimumab, and rituximab are entering the market. Clinical and real-world data on the effects of reference → biosimilar switching are limited. This review was carried out to assess the current body of switching data.

Recent Findings Fifty-three switching studies were identified. Infliximab publications covered CT-P13 (25 studies), SB2 (1), infliximab NK (1), and unspecified infliximab biosimilars (2). Etanercept publications covered SB4 (2) and GP2015 (2). Adalimumab publications covered ABP 501 (2) and SB5 (1). Rituximab publications covered CT-P10 (1). Efficacy and safety data generally showed no differences between patients who switched treatments versus those who did not. No differences were seen pre- and post-switch. Immunogenicity data were presented in 19/37 (51%) studies.

Summary Additional data from switching studies of these therapies are still required, as is continuing pharmacovigilance. Switching should remain a case-by-case clinical decision made by the physician and patient on an individual basis supported by scientific evidence.

Keywords Biologics · Biosimilars · Switching · Clinical trials · Real world data

This article is part of the Topical Collection on *Biosimilars*

Electronic supplementary material The online version of this article (doi:10.1007/s11926-017-0658-4) contains supplementary material, which is available to authorized users.

✉ Robert Moots
rjmoots@liv.ac.uk

[1] University of Liverpool, Liverpool, UK

[2] Department of Musculoskeletal Biology, Institute of Ageing and Chronic Disease, Clinical Sciences Centre, Aintree University Hospital, Longmoor Lane, Liverpool L9 7AL, UK

[3] Federal University of Parana and Edumed Health Research Center and Biotech, Curitiba, Brazil

[4] Pfizer Inc, Collegeville, PA, USA

[5] Department of Medicine, Rheumatology and Clinical Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany

[6] Organización Médica de Investigación, Buenos Aires, Argentina

[7] Hospital Israelita Albert Einstein, São Paulo, Brazil

Introduction

Biosimilars are biologic products assessed by regulatory agencies to be similar to a licensed reference product in terms of quality, safety, and efficacy. Different agencies have their own definitions of biosimilarity [1–3], and regional regulatory requirements for biosimilars have been discussed elsewhere [4]. Proposed biosimilar products include both candidate biosimilars (copies of licensed reference products still in development) and intended copies (products marketed without first undergoing rigorous comparative evaluations) [5]. The development of proposed biosimilar products has increased as reference drugs lose patent exclusivity, with the anticipated effect of increasing patient access through reduced costs.

A key question for health care professionals (HCPs) contemplating prescribing biosimilar drugs is "Should the biosimilar immediately replace the reference product currently in use by the stable patient?" When considering this, HCPs should take into account not only the efficacy and safety of the biosimilar, but also any possible effects of switching patients

90 studies

7 molecular entities

14 disease indications

14,225 individuals enrolled

Overall, the results suggest a low risk of either a safety concern or a loss of efficacy after switching to a biosimilar.

Summary

- **Biosimilars licensed in the EU are interchangeable with their reference product since clinically significant differences have been ruled out with EU licensure**
- **Review of many post-authorization small to mid-sized clinical trials plus NOR-Switch trial 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**
- **Real life experience has not led to necessity to withdraw any biosimilar or change SmPC**

Acknowledgements:

All contributors (experts, observers, other WPs) to BMWP

- **Sean Barry**
- **Marie-Christine Bielsky**
- **Karen De Smet**
- **Niklas Ekman (Vice-Chair)**
- **Thijs Giezen**
- **Nanna Aaby Kruse**
- **Alexandre Moreau**
- **Leon van Aerts**
- **Martina Weise**

- **Jan Müller-Berghaus, PEI**
- **Pekka Kurki, Finnish Medicines Agency**
- **Ina-Christine Rondak; European Medicines Agency**
- **Ana Hidalgo-Simon, European Medicines Agency**
- **Antonella Baron, European Medicine Agency**