Understanding the Science of Extrapolation and Defining Interchangeability

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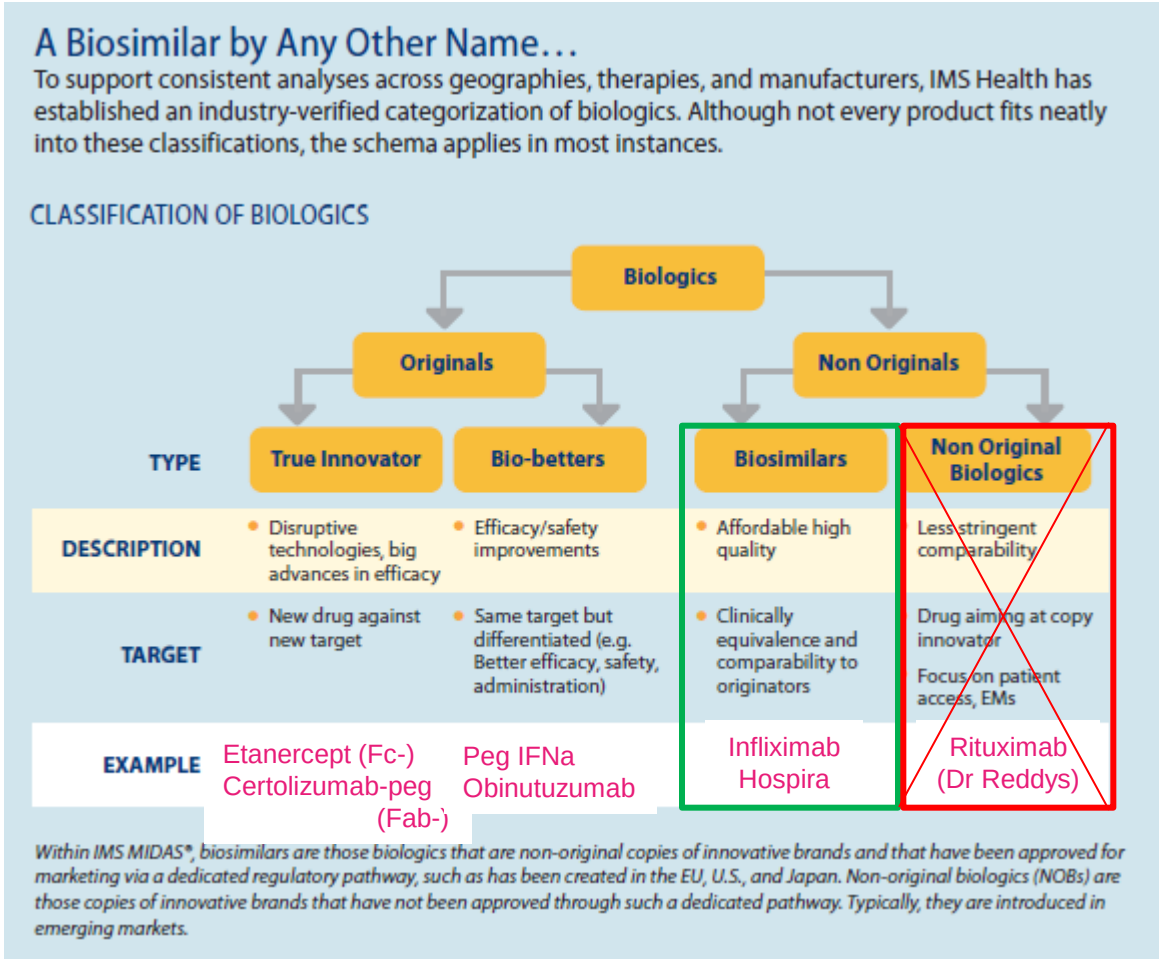
The views presented here are my own and do not necessarily reflect the views of the Paul-Ehrlich-Institut.

Understanding the Science of Extrapolation and Interchangeability

- Nomenclature
- Regulatory framework in EU
- The science of extrapolation
- Interchangeability
- Closing remarks

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.

Source: IMS HEALTH

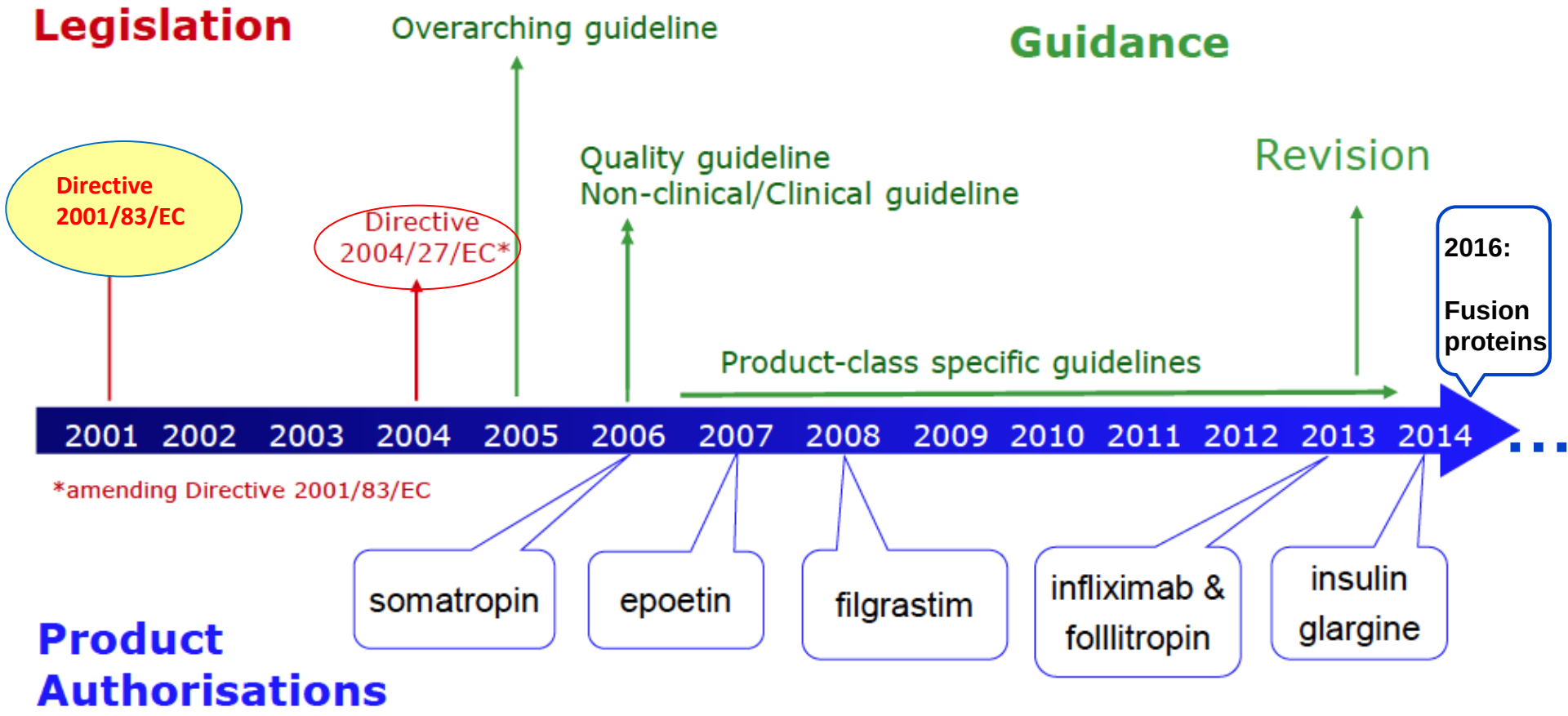
Definition of a Biosimilar exists in Europe since 2001 ……. it´s a LAW

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



Significant number of regulatory applications in pipeline for 15 different biological substances

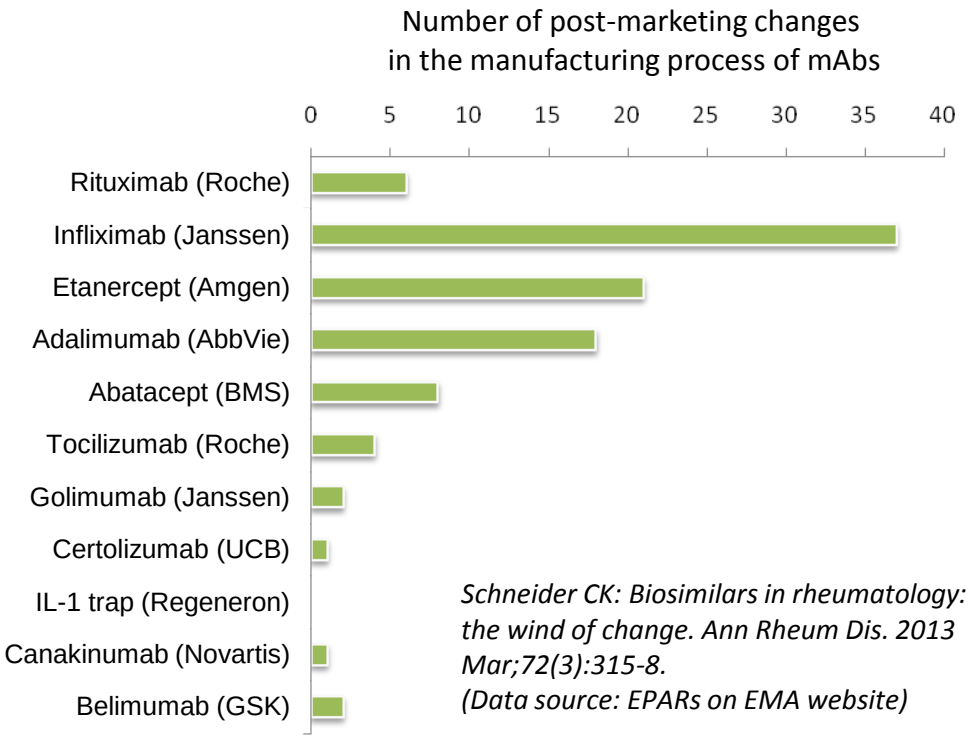
Biosimilars in the EU (May 2016; EMA website)

now: 13 distinct Biosimilars (20 Products!)

exist for 7 different Reference products

Active Substance	MAH	Status	Authorisation
insulin glargine	Eli Lilly	authorized	September 14
insulin human	Marvel Lifesciences	**refused**	Nov 15
somatropin	Sandoz	authorized	April 06
somatropin	BioPartners	**withdrawn**	Apr 06
IFN alfa-2a	BioPartners	**refused**	September 06
epoetin alfa	Sandoz	authorized	August 07
epoetin alfa	Sandoz	authorized	August 07
epoetin alfa	Hexal AG	authorized	August 07
epoetin zeta	Hospira UK Limited	authorized	Dezember 07
epoetin zeta	Stada	authorized	Dezember 07
filgrastim	AbZ-Pharma	authorized	September 08
filgrastim	Ratiopharm	**withdrawn**	September 08
filgrastim	Ratiopharm	authorized	September 08
filgrastim	Teva Generics	authorized	September 08
filgrastim	Hexal AG	authorized	Februar 09
filgrastim	Sandoz	authorized	Februar 09
filgrastim	Hospira UK Ltd.	authorized	Juni 10
filgrastim	Apotex Europe BV	authorized	Oktober 13
filgrastim	Accord Healthcare Ltd	authorized	September 14
infliximab	Celltrion Hungary	authorized	September 13
infliximab	Hospira UK	authorized	September 13
follitropin alfa	Teva	authorized	September 13
follitropin alfa	Finox Biotech	authorized	March 14
etanercept	Samsung Bioepis	authorized	January 2016

Changes in the manufacturing process of biologicals occur frequently and extrapolation applies!



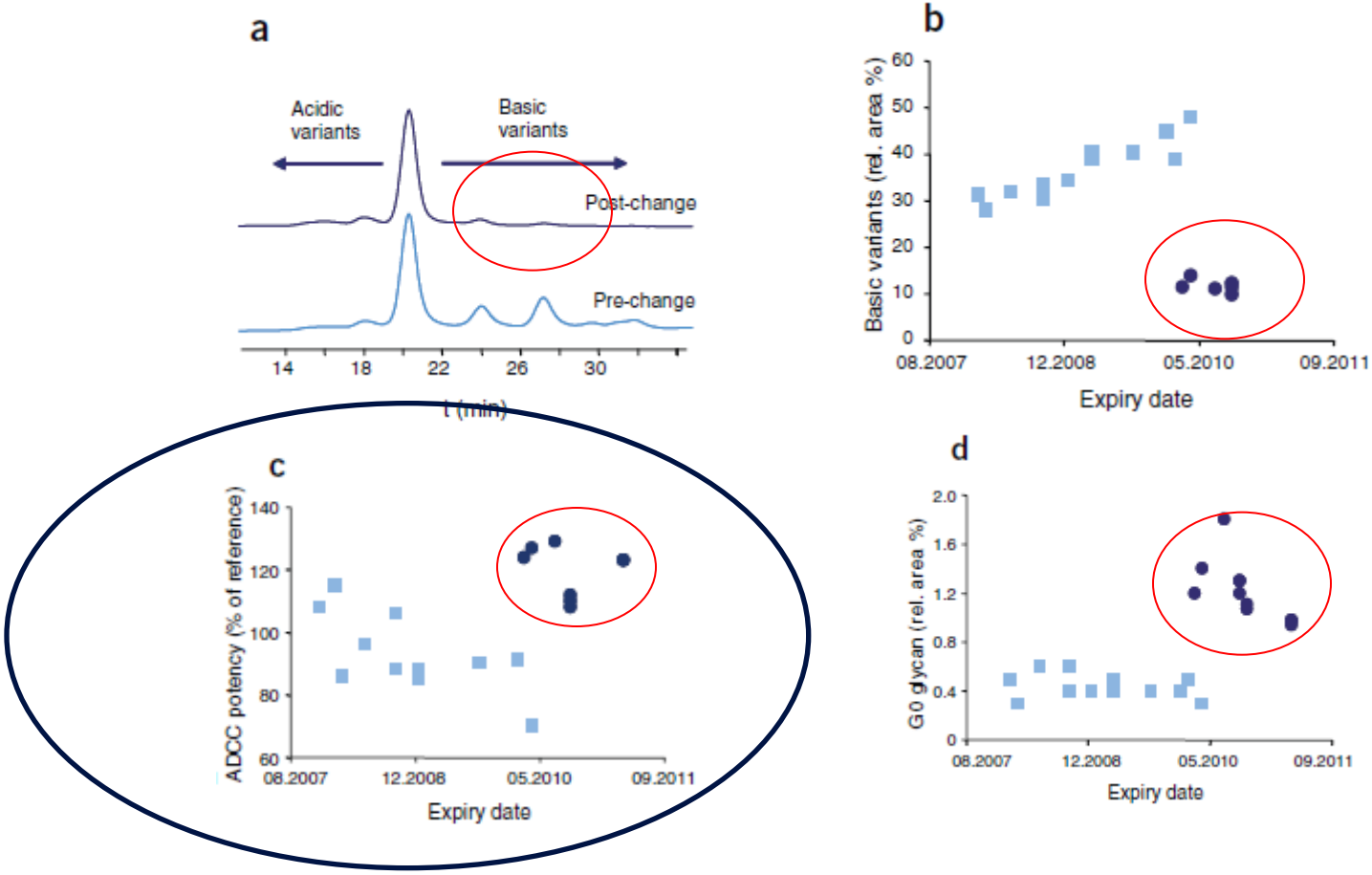
Schneider CK: Biosimilars in rheumatology: the wind of change. Ann Rheum Dis. 2013 Mar;72(3):315-8.
(Data source: EPARs on EMA website)

Changes in the manufacturing process

- ➔ Different versions of the active substance
- ➔ Comparability exercise (pre-change vs. post-change product) to ensure unchanged efficacy and safety
- ➔ 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
- ➔ BWP/CHMP have experience in judging impact of differences in quality attributes.

Comparability Exercise
for different versions of the same active substance

New version of the active substance implies …similar (!) and not identical



Rituximab with expiry dates from Sep 2007 to Oct 2011

Using cation exchange chromatography (a), % basic variants (b), ADCC (c) and glycan mapping (d)

Schiestl, Nature Biotechnology Vol. 29 ; 4 , 2011

Bridging is done by Comparability Exercise

Technical term to show that two biological / biotechnological products are „similar“ or „comparable“

1) **Scenario 1:** After a change in the manufacturing process of a given product (pre- and post-change product from the same manufacturer)

   Manufacturer has all the data and experience, i.e.

   Quality Target Product Profile (QTPP) with ranges

2) **Scenario 2:** In a biosimilarity exercise (two products from different manufacturers)

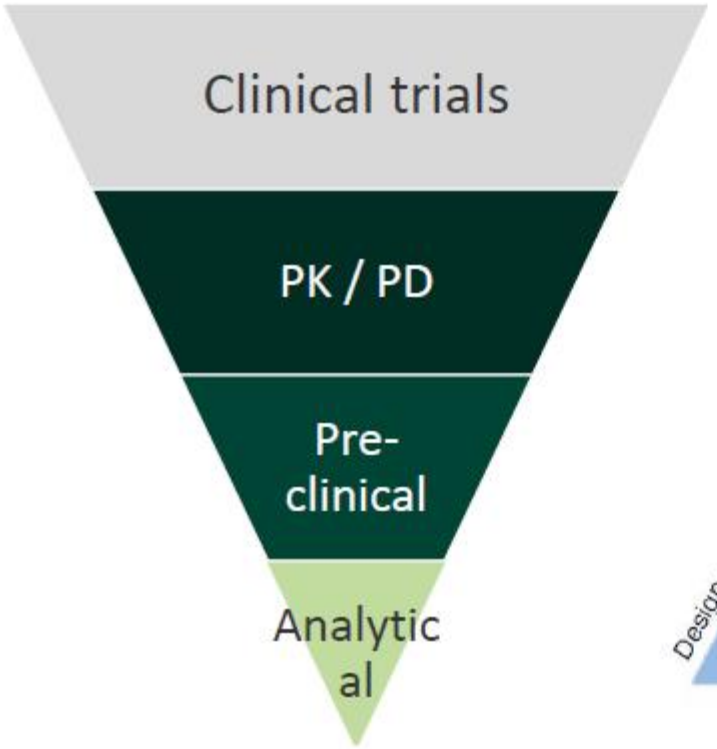
   Manufacturer does not have the data from the originator company (intellectul property)

   → **reverse engineering**!

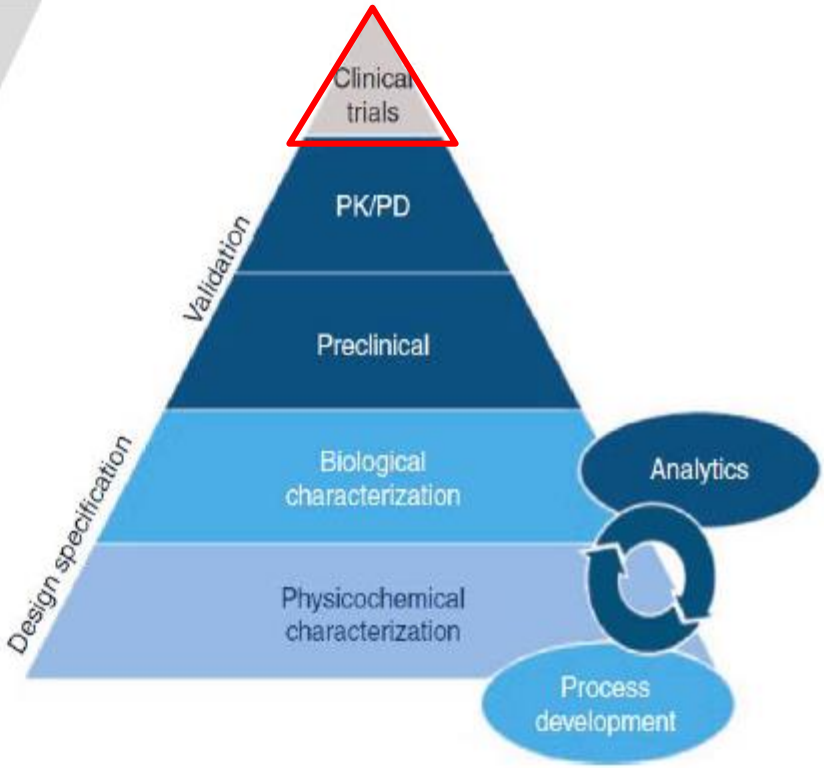
   → Only then: side by side comparison of Qualtity Attributes

The biosimilar development paradigm turns „world upside down“

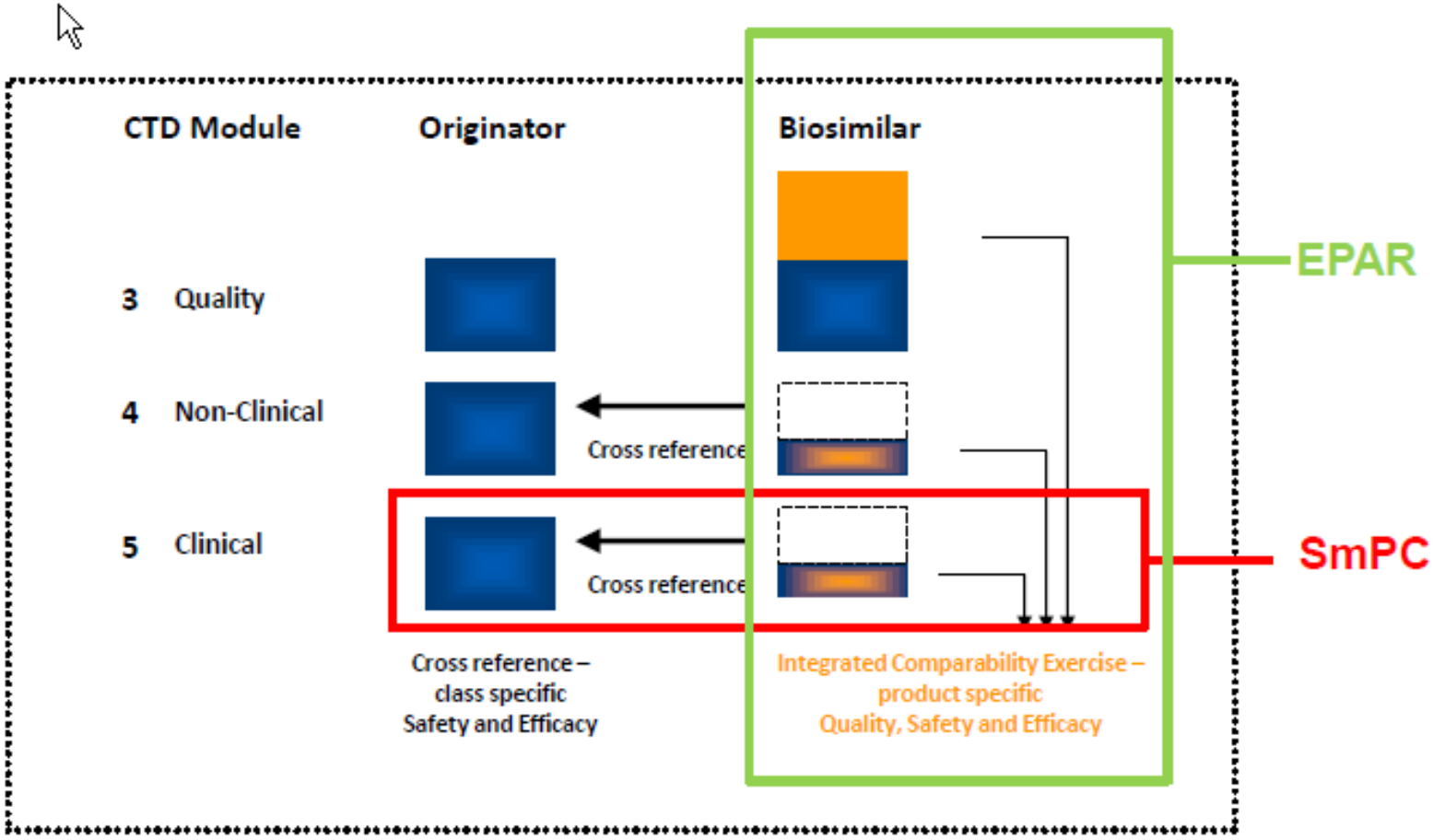
Originals, Biobetters



Biosimilars



Important source of information for Biosimilars is European Public Assessment Report (EPAR)



Considerations for extrapolation

Usually unproblematic when

- same MoA/receptor is involved and no unique safety concern exists
- same receptor but different target-cell specific downstream signalling ➔ no reason to request additional data
- Different active sites of the biologic agent or different target receptors ➔ additional data necessary (e.g. functional assays and/or PD parameters and/or clinical data)

Binding and functional tests for anti TNF products

Mechanism of action of anti TNFα	Infliximab Chimeric IgG1	Adalimumab Human IgG1	Certolizumab peg Fab-peg (no Fc)	Etanercept Fusion protein with small Fc part
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 diff PK No Fc CH1
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

The science of extrapolation

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

Extrapolation **Biosimilar Infliximab**

- ✓ 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** of sTNFα and tmTNFα except for FcγR IIIa/b, translating into lower ADCC activity in one particular assay with Jurkat cells as target cells with abnormally high tmTNFα and NK as effector cells.
- ✓ → **Further studies concerning FcγRIIIa/b** revealed this difference disappeared under more physiological conditions, questioning the clinical relevance of the observed difference
- ✓ A large 250 patient multiple-dose PK study in patients with ankylosing spondylitis demonstrated comparable safety, efficacy and immunogenicity.
- ✓ Equivalent efficacy as well as comparable safety and immunogenicity was demonstrated in a 600 patient randomised controlled phase 3 clinical trial in rheumatoid arthritis.

The science of extrapolation

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

→Extrapolation of safety and efficacy should be possible if quality and (pre-)clinical tests demonstrate comparability!

- Identical primary, secondary, and tertiary structure
- Comparable post-translational profile
- Comparable *in vitro* binding and functional characteristics
- Comparable pharmacokinetics
- Equivalent efficacy and comparable safety and immunogenicity

How could two comparable versions of an active substance behave differently in different therapeutic indications?

Post-marketing studies confirmed efficacy and safety in IBD

Table 1. Summary of clinical experience with CT-P13 in IBD.

Country	Patient numbers	Efficacy	Safety	Ref.
South Korea	173 (CD = 95, UC = 78)	Response: 79.5 and 72.2% in CD and UC at week 30 Remission: 59.0 and 37.0% in CD and UC at week 30	No unexpected AEs, well tolerated	[52]
South Korea	110 (CD = 59, UC = 51)	Naïve: response 95.5 and 91.3% in CD and UC at week 30; remission 77.3 and 47.8% in CD and UC at week 30 Switch: the efficacy of CT-P13 was maintained in 92.6 and 66.7% of CD and UC patients, respectively	AEs related to CT-P13 occurred in 11.8% of UC patients	[53]
South Korea	17 (CD = 8, UC = 9)	Response: Mayo/CDAI: ~87.5% at week 8 in switch and naïve	One UC patient experienced arthralgia	[51]
Hungary	90 (CD = 57, UC = 33)	Significant decrease in CDAI and partial Mayo score	Four allergic reactions	[54]
Hungary	12 (UC)	Mucosal healing: 78% after induction therapy	Not reported	[55]
Norway	78 (CD = 46, UC = 32)	Remission: 79 and 56% in CD and UC at week 14	There were no unexpected AEs reported	[63]
Poland	32 (pediatric CD)	Switch: pediatric CDAI: 48 (start of RMP) →8.5 (at switch to CT-P13) →7.5 (CT-P13 at week 8)	No unexpected AEs	[58]
Poland	12 (pediatric CD)	Pediatric CDAI: 52.5 →5 after induction dose	AEs were observed in 2/12 (17%) pts	[56]
Poland	6 (pediatric UC)	Pediatric UCAI: 47.5 at initiation →28.3 at week 10	Not reported	[57]
Ireland	36 (14 for CT-P13, 22 for RMP)	Clinical efficacy results were not reported Surgery: 4 and 0 in CT-P13 and RMP-treated patients, respectively (in two cases, surgery was performed within 2 weeks and the remainder within 6 weeks of initiating CT-P13)		[59]

AE: adverse event; CD: Crohn's Disease; CDAI: Crohn's disease activity index; UC: Ulcerative colitis; UCAI: Ulcerative colitis activity index

Walter Reinisch, Edouard Louis & Silvio Danese; Expert Review of Gastroenterology & Hepatology, 2015

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.

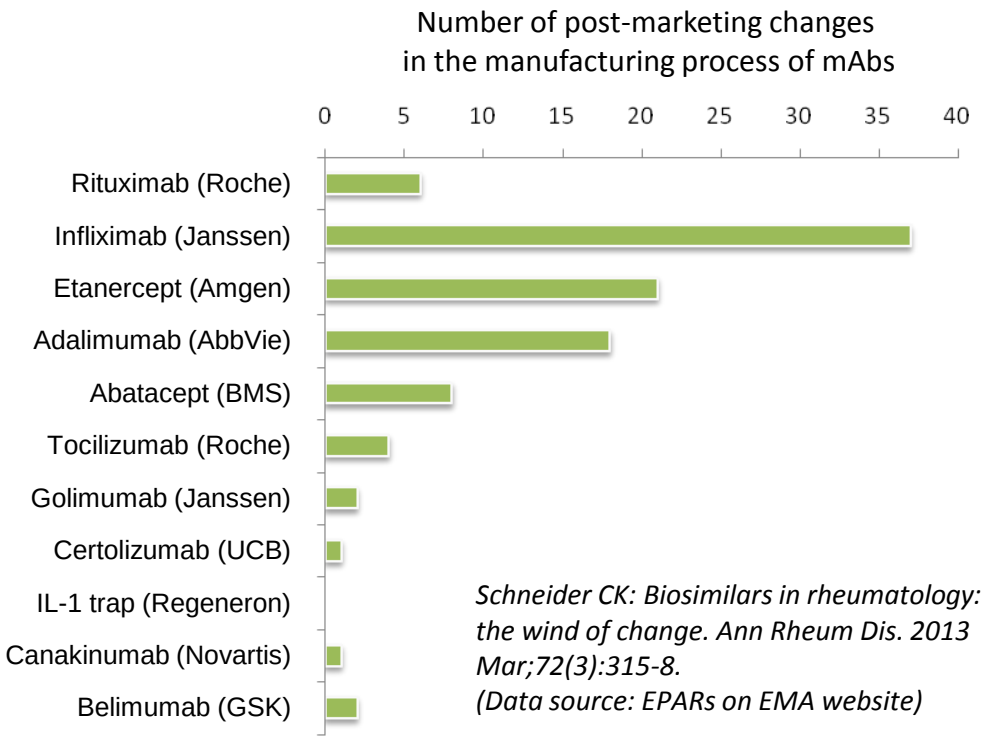
Note: The interchangeable product **may be substituted** for the reference product without the intervention of the health care provider who prescribed the reference product.

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

Interchangeability: Theoretical considerations

Changes in the manufacturing process of biologicals



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(Data source: EPARs on EMA website)

Different versions of same active substance are

de facto

being used interchangeably without necessity for clinical studies

What we know so far
Switching studies involving biologics/biosimilars

Review of EPARS of all approved biosimilars

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 biologics/biosimilars

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 an unfavourable risk-benefit balance.

References:

Joint 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
Interchangeability Biosimilar Infliximab

PLANETRA Study (extension study of 302/455 Rheumatoid Arthritis patients for another year):
158/302 Patients were maintained and 144/302 Patients 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

Interchangeability: PEI position updated Dec 08, 2015

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

Interchangeability: PEI position updated Dec 08, 2015

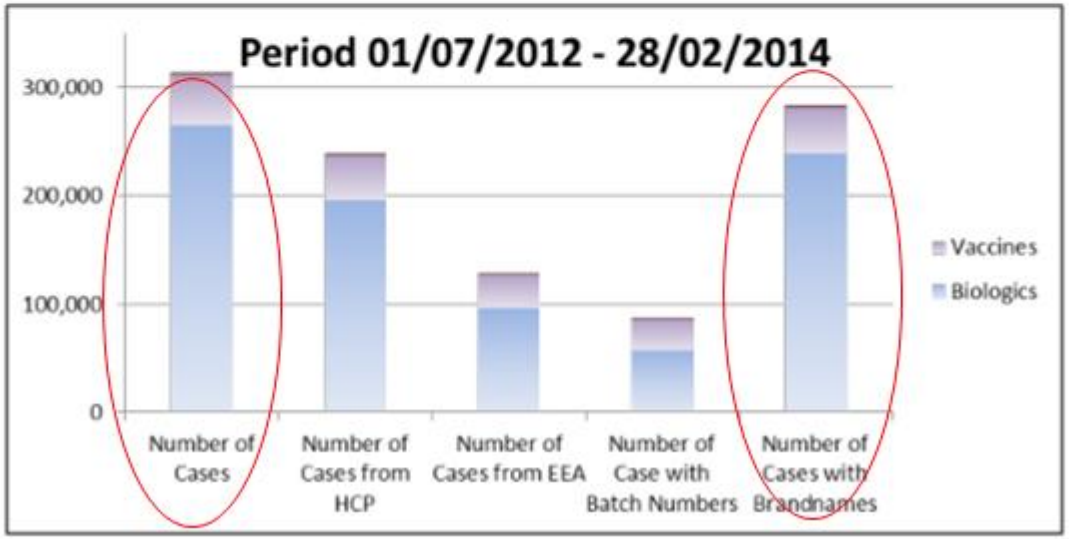
The treating physician should at any rate ascertain that any adverse effects that may occur during treatment with Remsima or Inflectra, and even the original product Remicade, be reported adequately within the pharmacovigilance system, so that they can be followed up. The new pharmacovigilance guideline (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.

Adverse reaction reporting and biologics

Period 01/07/2012 - 28/02/2014

	Number of Cases	% Cases from HCP	% Cases from EEA countries	% Case with Batch Numbers	% Cases with Brandnames
Biologics	264,796	74	36	22	90
Vaccines	48,765	88	67	62	89



→So far excellent compliance and
→excellent results (= no new AEs for biosimilars) reported

Summary: Extrapolation of Biosimilars

- Extrapolation is not a new concept and is based on sound scientific principles
- In case of remaining doubt, additional binding, functional and/or clinical data are required
- Regulators in the EU take a careful approach in order not to jeopardize the safety and wellbeing of patients
- Explanation of the reasons for extrapolation granted by CHMP is presented in the EPAR
- Much real life experience with extrapolation exists

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
- There is a value of EPAR in reviewing study results leading to approval
- Review of many post-authorization 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
- Real life experience has not led to necessity to withdraw any biosimilar or change SmPC

Thanks for your attention !