SANDOZ A Novartis Division

Hot air or hot topic?

Join the biosimilar debate!

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Join the biosimilar debate!

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Introduction

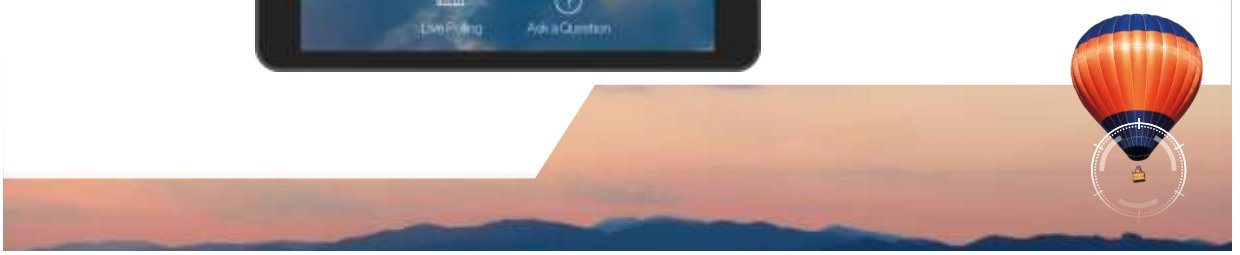
Catherine Hood

Housekeeping

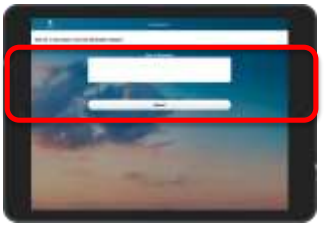
- Please turn all mobile phones off / to silent
- Use the meeting app to:
  - Ask questions throughout the presentations
  - Provide your vote
  - Complete the evaluation form

Event App

- Your event app will be pre loaded on to the ipad

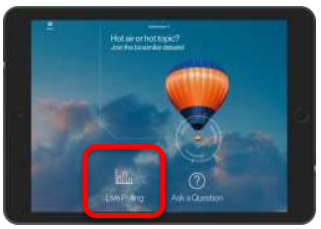


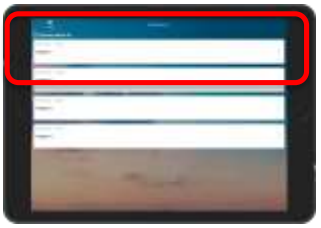
Q & A

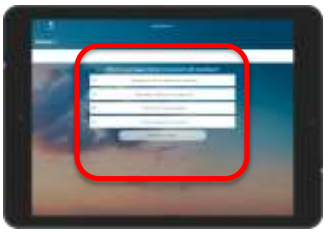


- Click on Ask a Question on the home screen
- Enter your questions
- Click submit

Live Polling







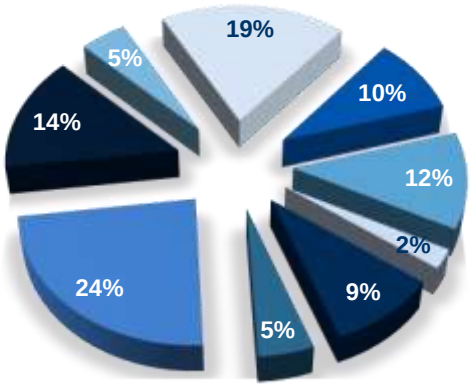
- Click on Live Polling on the home screen
- Choose the debate
- Choose your answer and click submit

An introduction to biosimilars

- The first biosimilar approved in Europe was somatropin in 2006[1]
  - Currently, 23 biosimilars are available for use[1]
- Biosimilars are important alternatives to reference biologics as they may simultaneously:
  - reduce healthcare spending[2]
  - increase access to biologics[2]
- Use of biosimilars does not compromise patient outcomes[2]

1. EMA. EPARs for biosimilars. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125. Accessed 14 March 2017. 2. Zelenetz D. Oncol Hematol Rev 2016; 12:22–8.

Pre-meeting survey results



- Understanding structural similarity between a biosimilar and the
- Concerns about biosimilar safety
- Incomplete understanding of approval criteria for biosimilars
- Challenges in communicating biosimilar data to clinicians
- Queries regarding the immunogenicity of biosimilars
- Interpreting analytical data for biosimilars
- Understanding the significance of pharmacokinetic/pharmacodynamics
- The concept of extrapolation for clinical indications

Agenda

The analytical techniques used to establish similarity
Martin Schiestl
Chief Science Officer, Sandoz GmbH, Kundl, Austria

The regulatory pathway for biosimilars
Steffen Thirstrup
Adjunct Professor, Faculty of Health Sciences, School of Pharmacy, University of Copenhagen, Copenhagen, Denmark

The concept of extrapolation
Arnold Vulto
Professor of Hospital Pharmacy & Practical Therapeutics, Erasmus University Medical Center, Rotterdam, The Netherlands

Immunogenicity concerns with biosimilars
Alain Astier
Head of Department of Pharmacy, Henri Mondor University Hospital, Paris, France

Disclosures

- **Dr Martin Schiestl**
  - Full-time employee of Sandoz Biopharmaceuticals
- **Professor Steffen Thirstrup**
  - Full-time employee of NDA Advisory Services, Ltd
- **Professor Alain Astier**
  - Research grants: Biosedra, Pfizer
  - Consulting fees: Amgen, Pfizer, Sandoz
  - Funding member of an academic-based startup: Biotopic Pharmaceuticals
- **Professor Arnold Vulto**
  - No personal financial interest in any pharmaceutical company
  - Friendly relationships with all innovative and generic / biosimilar companies (a.o. AbbVie, Amgen, Biogen, EGA, Hospira, Mundipharma, Roche, Sandoz)
  - Co-founder with societal but not financial interest in the advocacy of cost-effective treatments via the Generics & Biosimilar Initiative (GaBI)
  - Honoraria paid to employer Erasmus University Medical Center

The debate

- Please imagine our faculty are in a hot air balloon losing altitude – someone must be ejected from the basket if they are not to crash!
- Three rounds of debate
- In each round, every faculty member presents evidence to counteract their barrier
- After each round, you can vote again on your most important barrier
- Final decisive vote – who will be ejected from the balloon?!

Let's vote now!

- Which of the topics below do you regard as the most important barrier to use of biosimilars?

A. The analytical techniques used to establish similarity
B. The regulatory pathway for biosimilars
C. The concept of extrapolation
D. Immunogenicity concerns with biosimilars

Vote Now

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Let the debate begin!

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Hot air or hot topic?

Join the biosimilar debate!

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Balloon debate: Round 1

Sandoz Biopharmaceuticals

The analytical techniques used to establish similarity

Martin Schiestl, Chief Science Officer
Sandoz Biopharmaceuticals

EAHP, Cannes, March 23, 2017
HQ/BIO/16-0013k

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Issue 1

Understanding the new drug development paradigm for biosimilars

Martin Schiestl

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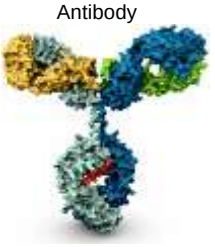
Biologics are different from small molecules – and from one another

Paracetamol	Filgrastim (a growth factor)	Antibody
		
▪ Small molecule	▪ Protein (w/o sugars)	▪ Glycoprotein (with variable sugars)
▪ Chemical synthesis	▪ Made using bacteria	▪ Made using mammalian cells
▪ Single substance	▪ Single substance	▪ Mixture of glycovariants having the same amino acid sequence
	▪ 1 chain, 175 amino acids	▪ 4 chains, 1 330 amino acids
▪ 151 Da	▪ 18 803 Da	▪ 144 000 Da
▪ MoA ambiguous	▪ Receptor binding only	▪ Receptor binding, effector functions

Note: Illustrations not to scale.
MoA = mode of action.
Kozlowski S, et al. N Engl J Med 2011;365(5):385–8; Revers L & Furczon E. Canadian Pharmacists Journal 2010;143(3):134–9; Revers L & Furczon E. Canadian Pharmacists Journal 2010;143(4):184–91.

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What is a biosimilar?

Biosimilarity means

- That the biologic product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components
- There are **no clinically meaningful differences** between the biologic product and the reference product in terms of safety, purity, and potency of the product

An approved biosimilar medicine and its reference medicine contain **essentially the same** active ingredient and are expected to have the **same** safety and efficacy profile

"Biosimilar" is a **regulatory term** to refer to a product that has been approved via a stringent regulatory biosimilar pathway

Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf; European Commission (EC).Consensus Information Document: What you need to know about Biosimilar Medicinal Products. Available at: http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/en/renditions/native. Accessed 2016 June 02.

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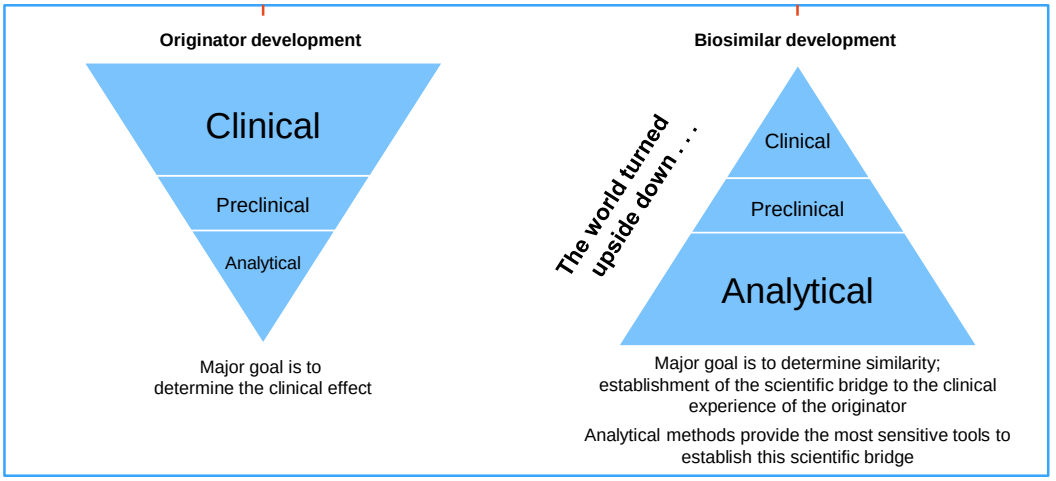
Development of a biosimilar requires a paradigm shift



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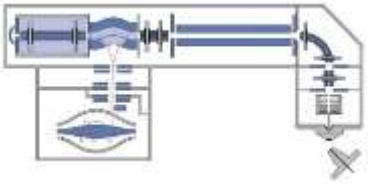
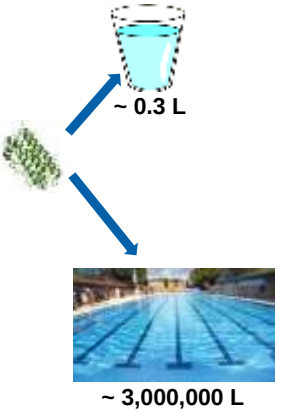
Powerful tools have evolved to allow comprehensive characterisation

Year	MS detection limit for peptides (pmol)
1990	100
1993	10
1997	1
2000	0.1
2003	0.01
2005	0.001
2008	0.0001
2011	0.00001

Mass spectrometry





10 million-fold increase

MS = mass spectrometry.
Adapted from presentation by Anthony Mire-Sluis, 9th Symposium on the Practical Applications of Mass Spectrometry in the Biotechnology Industry (Mass Spec 2012) September 11-14, 2012, San Diego, CA, USA.

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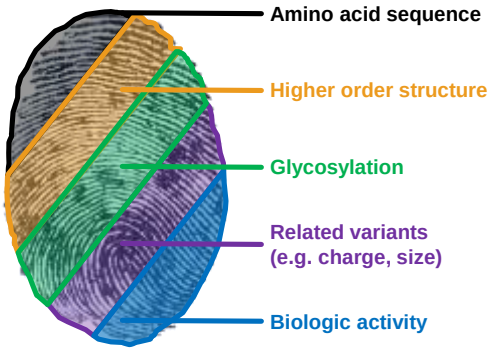
Biosimilar and reference medicine must match in all relevant attributes



- Characterisation using over 40 different analytical methods
- Approximately 100 different quality attributes
- Attributes often analysed with multiple methods (redundancy)

Sandoz-generated/owned slide.
Windisch J. EGA's perspective on the draft quality guideline, 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500154191.pdf. Accessed 2016 March 18.

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The regulatory pathway for biosimilars

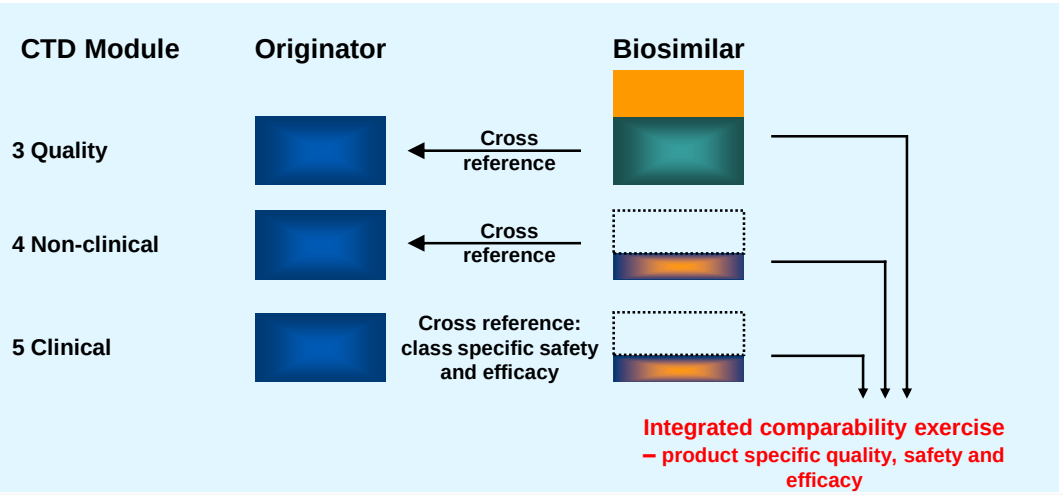
Prof Steffen Thirstrup, MD, PhD

Issue 1

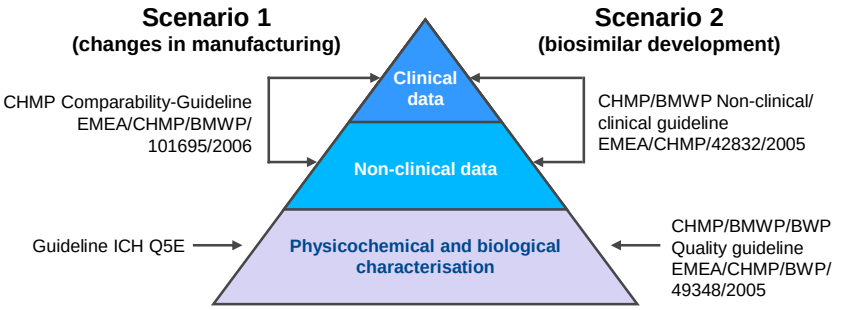
WELL-DEFINED AND SOLID SCIENTIFIC PRINCIPLES

Steffen Thirstrup

Dossier requirements for biosimilars contained in Common Technical Documents (CTDs)

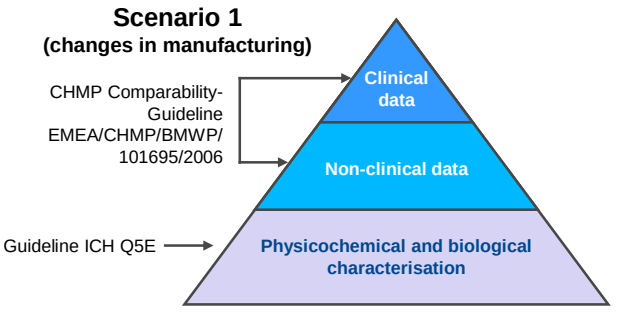


Comparability exercise – same principles in two different scenarios



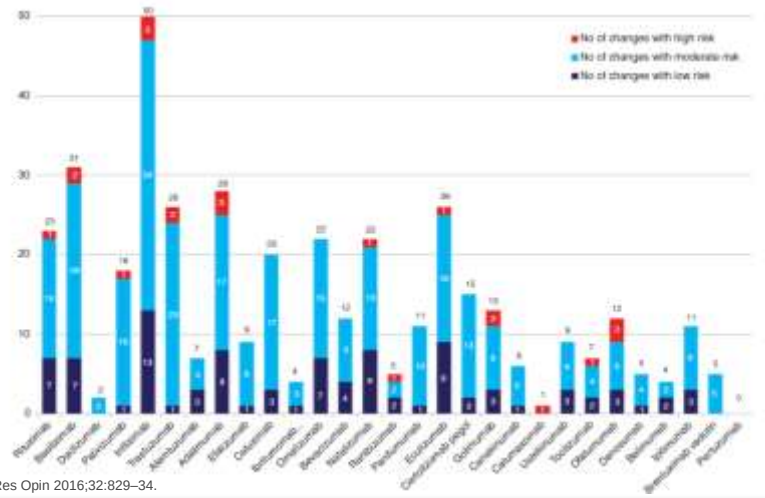
US Food and Drug Administration (FDA). ICH Q5E: Comparability of biotechnological/biological products subject to changes in their manufacturing process [online]. Available from: http://www.fda.gov/OHRMS/DOCKETS/98fr/2004d-0118-gdl0001.pdf [Accessed 03 June 2016];
European Medicines agency (EMA). Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process: non-clinical and clinical issus [online]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003935.pdf [Accessed 3 June 2016];
European Medicines Agency (EMA). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues [online]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf [Accessed 03 June 2016];
European Medicines Agency (EMA). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (rev 1) [online]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf [Accessed 03 June 2016].

Comparability exercise – same principles in two different scenarios



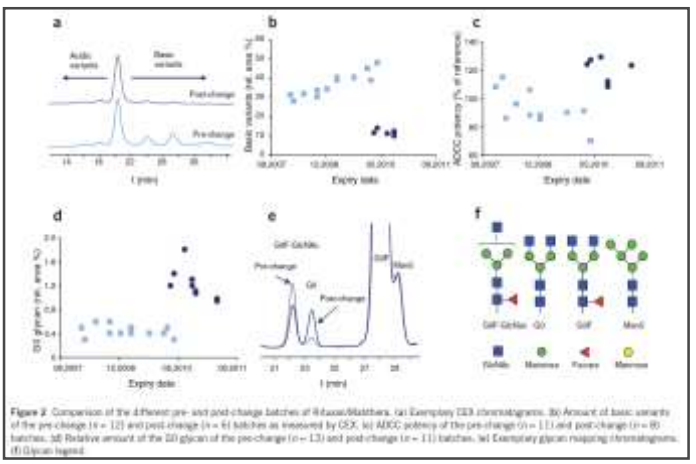
US Food and Drug Administration (FDA). ICH Q5E: Comparability of biotechnological/biological products subject to changes in their manufacturing process [online]. Available from: http://www.fda.gov/OHRMS/DOCKETS/98fr/2004d-0118-gdl0001.pdf [Accessed 03 June 2016];
European Medicines agency (EMA). Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process: non-clinical and clinical issues [online]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003935.pdf [Accessed 3 June 2016].

Changes to originator biologicals



Vezer B, et al. Curr Med Res Opin 2016;32:829–34.

Manufacturing changes in originator products – rituximab

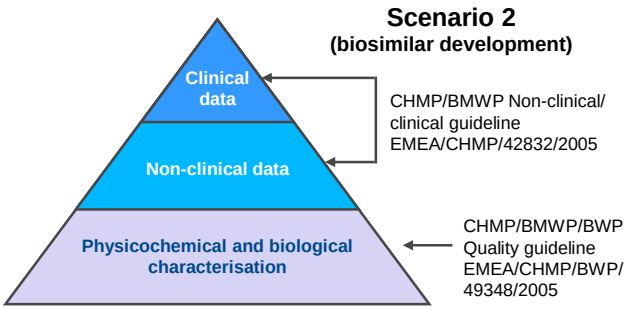


Manufacturing resulting in:
Changes in glycosylation
Increased ADCC potency

Regulatory review:
Unchanged benefit:risk ratio
Approved <u>without</u> clinical data

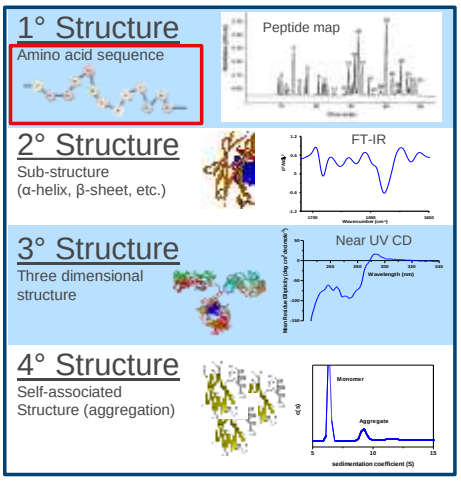
ADCC = antibody-dependent cellular cytotoxicity
Schiestl M, et al. Nature Biotechnol 2011:29(4):310–2.

Comparability exercise – same principles in two different scenarios



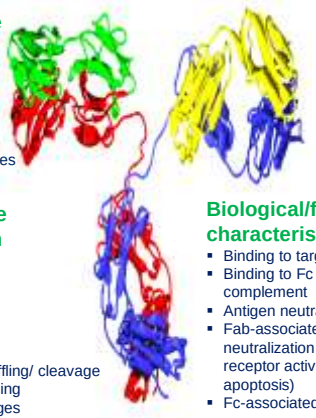
European Medicines Agency (EMA). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues [online]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf [Accessed 03 June 2016]; European Medicines Agency (EMA). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (rev 1) [online]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf [Accessed 03 June 2016].

Typical quality attributes to be evaluated in similarity assessment of a mAb



Attributes of the variable region
- Deamidation
- Oxidation
- N-term Pyro-Glu
- Glycosylation
- Glycation
- Conformation changes

Attributes of the constant region
- Deamidation
- Oxidation
- Acetylation
- Glycation
- Glycosylation
- C-term Lys
- Di-sulfide bond shuffling/ cleavage
- Fragmentation/clipping
- Conformation changes



Physicochemical characteristics
- Structure (primary, higher order structures)
- Molecular mass
- Purity/ impurity profiles
- Charge profile
- Hydrophobicity
- O- and N-glycans

Biological/functional characteristics
- Binding to target antigen(s)
- Binding to Fc γ receptors, FcRn and complement
- Antigen neutralisation (if relevant)
- Fab-associated functions (e.g. neutralization of a soluble ligand, receptor activation, induction of apoptosis)
- Fc-associated functions (ADCC and DC)

Erasmus MC
University Medical Center Rotterdam

The Concept of Extrapolation

Arnold G. Vulto FCP, Ph.D.
Professor of Hospital Pharmacy & Practical Therapeutics
Hospital Pharmacy ErasmusMC,
Rotterdam. The Netherlands

Erasmus MC
University Medical Center Rotterdam

Issue 1: Extrapolation has a sound scientific basis

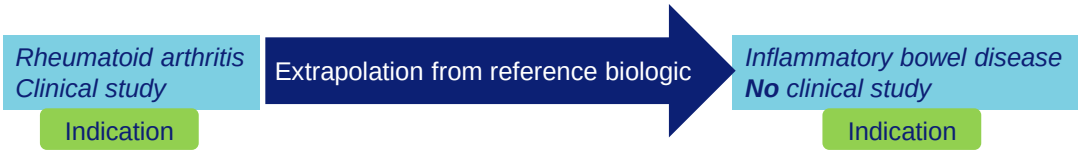
Arnold G. Vulto

Erasmus MC

Extrapolation of indication: What is it?

Approval of the biosimilar for another clinical indication of the reference product, without clinical data of the biosimilar in this indication

- Based on the principle that *if the molecule is the same, it will do the same*



- Regulatory decision – convincing evidence must be provided

Perspectives

Erasmus MC

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]

- Scientific and regulatory point of view: active substance in biosimilar is another version of that within the reference medicine
- Important questions for extrapolation:
  - **Mode of action** known in each indication?
  - Same **target receptors** in each indication?
  - Differences in **safety issues** across indications?
  - Can we **assign functional moieties** in the molecule to certain properties?

Weise M, et al. Blood 2014;124:3191-6.

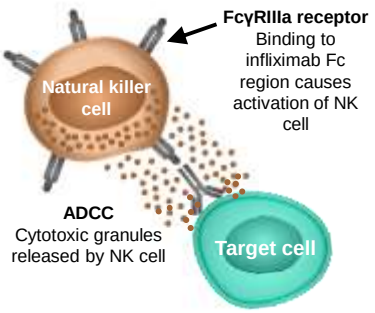
Erasmus MC

Example: infliximab biosimilar compared with reference infliximab

Extensive analytical comparability, **except for small difference in fucosylation**

Comparable binding to sTNFα, tmTNFα, complement receptor and **all Fc-receptors, except for FcγRIIIa/b**

Lower ADCC activity in vitro for the biosimilar vs reference medicine, in one particular assay



- **Further studies:** difference disappeared under conditions representative of physiology
- **Clinical relevance** of observed difference?

ADCC, antibody dependent cell-mediated cytotoxicity; NK, natural killer; sTNFα, soluble tumor necrosis factor; tmTNFα, transmembrane tumor necrosis factor

Weise M, et al. Blood 2014;124:3191-6.

Extrapolation of indications is an established regulatory concept

"The IPRF Biosimilar Working Group considers that the extrapolation of indication(s) of a biosimilar product could be accepted on the basis of the **totality of the evidence** generated from analytical, non-clinical and clinical comparability data"

"Extrapolation of clinical data to other indications could be acceptable, **with adequate justification,** when biosimilar comparability has been demonstrated in one indication"

International Pharmaceutical Regulators Forum. IPRF Biosimilar Working Group Draft Reflection Paper on Extrapolation of Indications in Authorization of Biosimilar Products. 25 July 2016. Available at: https://www.i-p-r-f.org/index.php/en/news/template-draft-reflection-paper-bwg-consultation-process/

50

If the molecule is the same, it will do the same, in all indications of the reference product

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UPEC FACULTÉ DE MÉDECINE

ECCO ECCO ECCO ECCO ECCO

ESOP

HENRI MONDOR hm

Immunogenicity concerns with biosimilars

Prof. Alain Astier. Pharm D, PhD,
Vice-President ESOP
Head of Pharmacy department ; CHU Henri Mondor,
School of Medicine , University Paris Est Créteil, France.

Sandoz Satellite
Hot air or hot topic? Join the biosimilar debate!
23 March 2017
EAHP Cannes, France

Immunogenicity concerns with biosimilars

ISSUE 1

Alain Astier

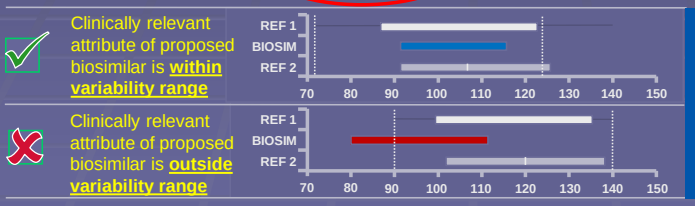
The living world is inseparable from the notion of variability

Biosimilars are designed to be highly comparable in all quality attributes

- Identical amino acid sequence
- Highly similar higher-order (spatial) structure

- Affinity
- Selectivity
- PK
- Effector function
- Solubility
- Immunogenicity

ESSENTIALLY THE SAME



The range, defined by the variability of the originator product, is very narrow

Schematic developed by Sandoz (18 November 2014).

Immunogenicity of proteins

- Frequent antibody induction
- Induction not explainable by simple classical immunological reaction
- Antibodies can induce severe effects
- Two mechanisms evoked:
  - Neo-antigen reaction
  - Rupture of immune tolerance

A. Astier; SFPO Nice, 11 Oct 2007

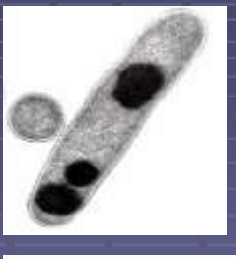
Characteristics of immunogenic response

	Neo-antigen	Tolerance break
Type of reaction	▪ **Immediate** and acute anaphylactic reaction	▪ **Slow** reaction, occurring after extended treatment ▪ Production of binding antibodies ▪ Disappears after treatment cessation
Cause	▪ Antigenic epitopes • Mainly non-human epitopes	▪ Impurities ▪ Glycosylation variants ▪ **Aggregates**

Astier A. SFPO Nice, Oct 2007
Astier A. Conf Osijek, Mar 2007

Biopharmaceutical manufacturing is complex and variable

- While biopharmaceuticals are produced under controlled conditions, variations can still arise
  - Differences in glycosylation
  - Degradation variants
- Foreign proteins may be released from cells during extraction of the biopharmaceutical
- Manufacturers highly purify bulk material and very efficiently characterize residual levels of foreign protein contaminants



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Hot air or hot topic?

Join the biosimilar debate!

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Questions

Let's vote again!

- Which of the topics below do you regard as the most important barrier to use of biosimilars?

A. The analytical techniques used to establish similarity
B. The regulatory pathway for biosimilars
C. The concept of extrapolation
D. Immunogenicity concerns with biosimilars

Vote Now

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Hot air or hot topic?

Join the biosimilar debate!

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Hot air or hot topic?

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Balloon debate: round 2

Issue 2

Variability

–

Biosimilars are not identical?!

Martin Schiestl

SANDOZ A Novartis Division

How similar are biosimilars and their reference products in biochemical structure?

Amino acid sequence **Primary sequence**	**Identical**
Folding Secondary, tertiary, quaternary structure	**Indistinguishable**
Glycosylation and related substances	**Identical structures in comparable amounts** Differences are only acceptable if they are clinically not relevant

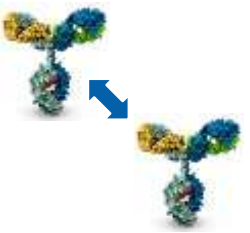

Figure adapted from McCamish M & Woollet G. Mabs 2011;3(2):209–17.
Adapted from: Food and Drug Administration (FDA). Guidance on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry (April 2015). Available at: http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed 2017 March 15.

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Variability is in the nature of biologicals

Batch-to-batch

- Non-identicality is a normal principle in glycosylated proteins
- No batch of any biologic is 'identical' to the other batches
- Variability is natural even in the human body

Variability of major glycan variant in commercial mAb

Manufacturing changes

- Manufacturing changes are made frequently
- Differences in attributes can be larger than batch-to-batch variability
- Such changes are stringently controlled by regulators and approved only if they do NOT lead to clinically meaningful differences

Variability of rituximab reference product

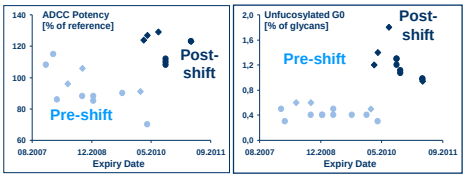

Figure developed by Thomas Stangler, Sandoz Biopharmaceuticals.
ADCC = antibody-dependent cellular cytotoxicity; mAb = monoclonal antibody.
Schiestl M, et al. Nat Biotechnol 2011;29(4):310–12; Windisch J. EGA's perspective on the draft quality guideline, 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500154191.pdf. Accessed 2016 March 18.

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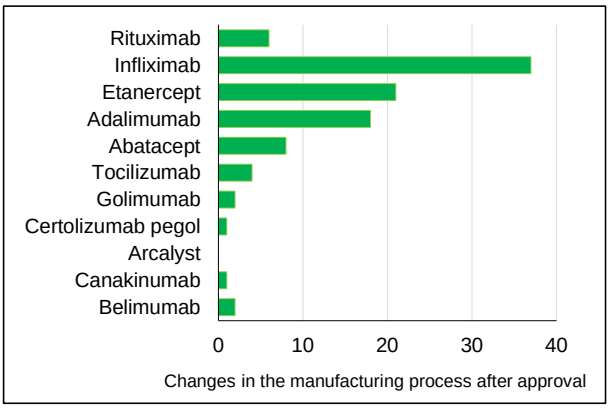
Biosimilar regulation is based on experience with manufacturing process changes of originator products

Originators may change manufacturing processes multiple times after approval



Changes include e.g.

- New raw material supplier
- New manufacturing site
- New cell line

Such changes are well understood today and tightly controlled by regulators (ICH Q5E)

Number of changes in the manufacturing process after approval for monoclonal antibodies/cepts authorised in rheumatological indications. Products in order of date of approval in Europe (from rituximab, authorised on 2 June 1998 for the initial authorisation in oncology, to belimumab, licensed on 13 July 2011).
Schneider CK. Ann Rheum Dis 2013;72:315–8.

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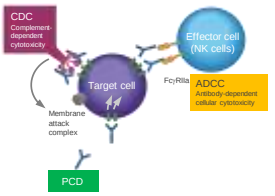
Potency – biosimilar rituximab

- Functional cell culture bioassays

	CD20 binding	ADCC	CDC	Apoptosis
GP2013	97%–108%	86%–105%	99%–111%	88%–103%
Originator	96%–110%	70%–132%	95%–127%	88%–102%

- Fc receptor binding assays (surface plasmon resonance assays)

Receptor	Affinity constants (K_D), µM	
	Originator	GP2013
FcRn	0.55–0.58	0.54–0.58
FcγRIa	10.4–11.8 nM	10.9–12.4 nM
FcγRIIa	2.4–2.7	2.4–2.7
FcγRIIb	11.4–12.8	11.0–12.7
FcγRIIIa F158	7.4–10.3	8.5–10.9
FcγRIIIa V158	3.5–4.9	4.2–5.0
FcγRIIIb	9.2–11.7	9.9–12.4



Routine ADCC assay uses Raji B cells and immortalised human NK cell line

Figure adapted from Taylor RP, et al. Nat Clin Pract Rheumatol. 2007;3:86-95.
ADCC = Antibody dependent cell cytotoxicity; CDC = Complement dependent cytotoxicity; NK cells = Natural killer cells.
Visser J, et al. BioDrugs. 2013;27:495-507.

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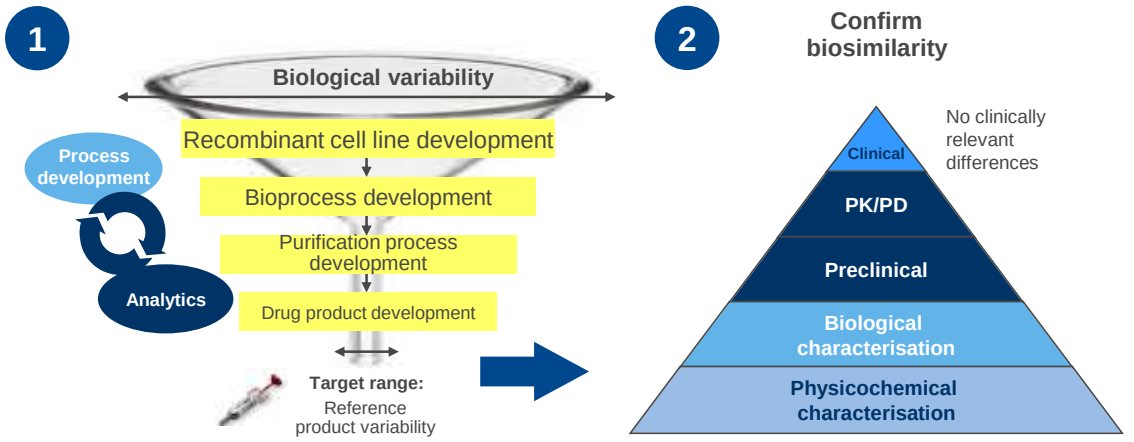
Issue 2

TOTALITY OF EVIDENCE

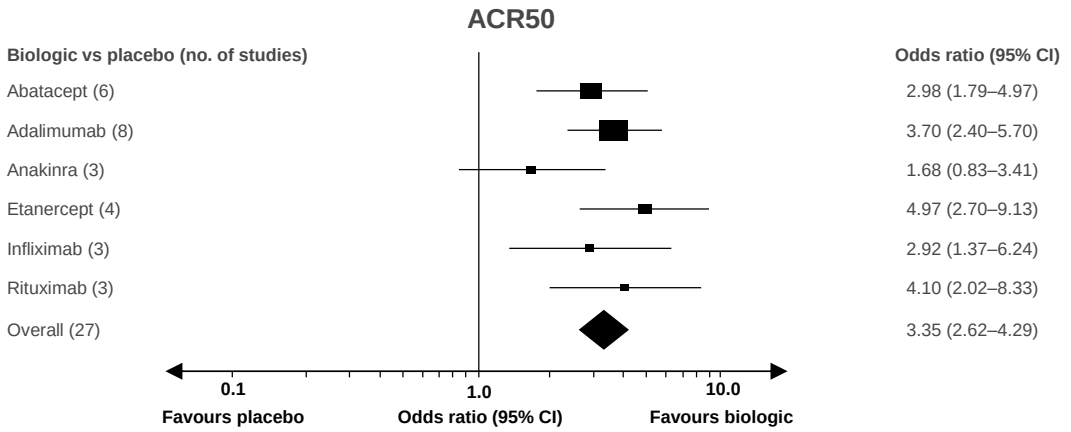
Steffen Thirstrup

Biosimilars are systematically developed to match the reference product



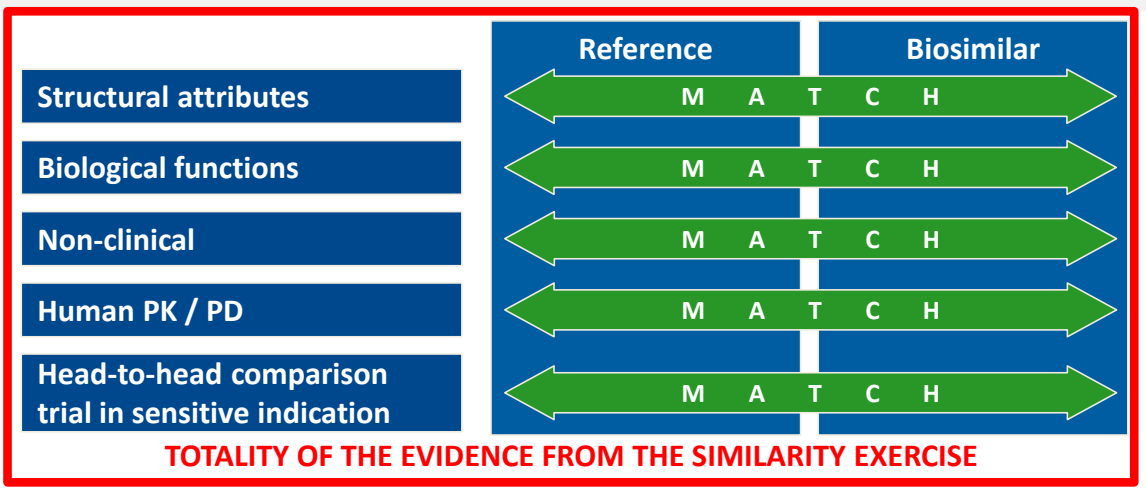
Jörg Windish/Sandoz Biopharmaceuticals©
Adapted from McCamish M & Woollett G. MAbs 2011;3:209–17.

Are clinical endpoints sensitive enough?



Singh JA, et al. Cochrane Database Syst Rev 2009; Oct 7:CD007848. doi: 10.1002/14651858.CD007848.pub2

Totality of evidence

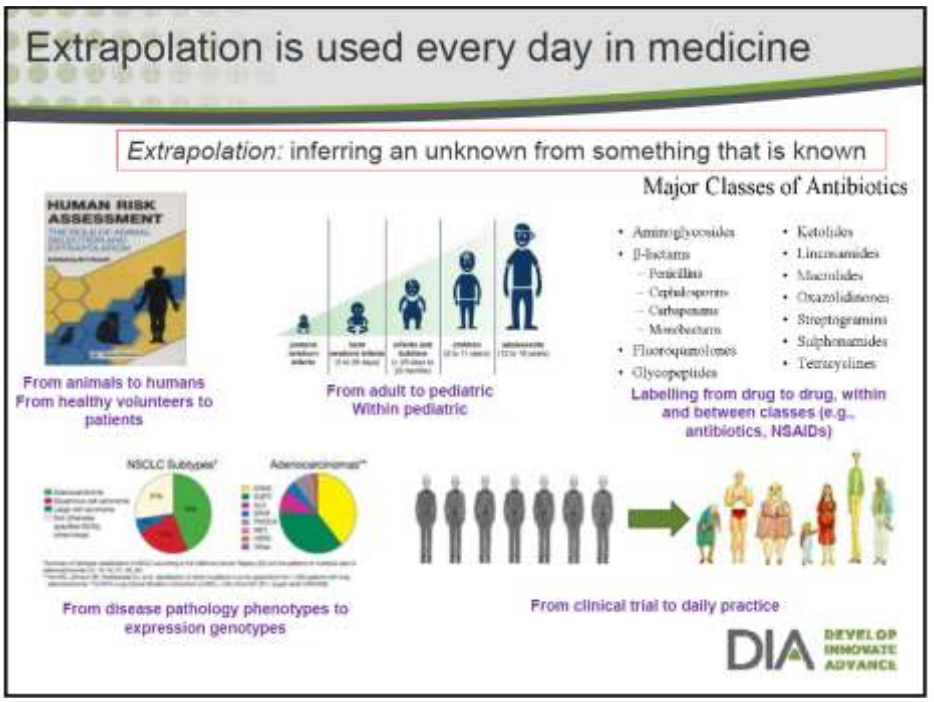


Ebbers HC. J Crohns Colitis 2014;8(5):431–5; Weise M, et al. Blood 2014;124(22):3191–6; Weise M, et al. Blood 2012;120(26):5111–17.

Erasmus MC
University Medical Center Rotterdam

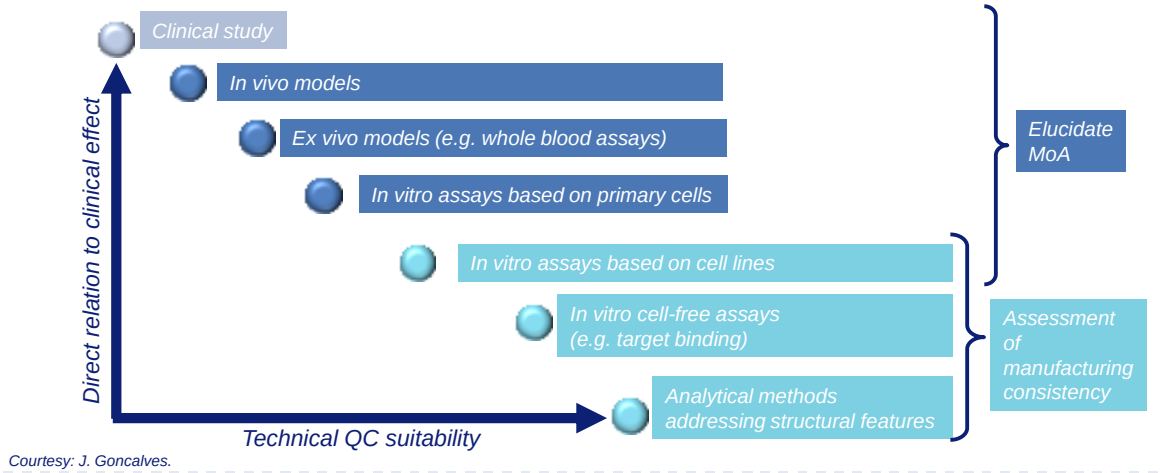
Issue 2: Extrapolation is a widely accepted concept in medicine

Arnold G. Vulto



In vitro and in vivo models are more sensitive to elucidate mode of action than clinical studies

Erasmus MC



Courtesy: J. Goncalves.

Conflicting acceptance

- Why do physicians have a lack of confidence in fully licensed medicines, once they are coined “biosimilar”?
- The SC forms of trastuzumab and rituximab with completely overhauled formulations and different route of administration were assessed and licensed with a “biosimilar-like” abbreviated pathway (ICH Q5E) and found rapid acceptance by clinicians with all the extrapolated indications

If the molecule is the same, it will do the same, in all indications of the reference product

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Hot air or hot topic?

Join the biosimilar debate!

Immunogenicity concerns with biosimilars

ISSUE 2

Alain Astier

Role of aggregates in immunogenicity

- Strongly dependent on size
  - More immunogenic: 1–2 µm
- Sub-micron oligomers are a sign of possible further harmful aggregation
- Major implication of aggregate formation is the induction of antibodies, which can lead to:
  - Loss of efficacy (neutralizing Abs)
  - Toxicity/immunogenicity (antigenic Abs)

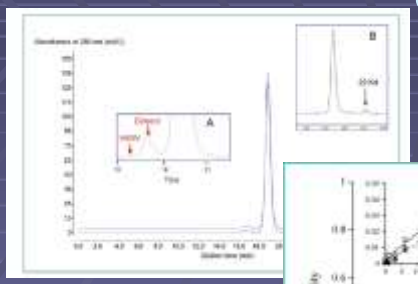
Wang W, et al. Int J Pharm 2012;431:1–11

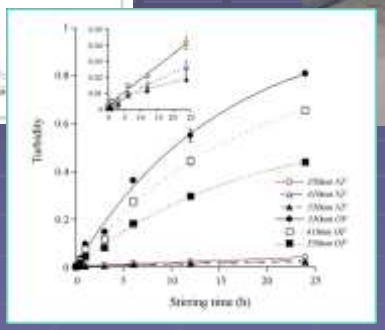
Aggregation of proteins

- Principal physical instability
- Non-classical degradation
- A general response of proteins to mechanical and thermal stresses
- Occurrence is underestimated
  - Aggregates can be soluble, sub-visible or insoluble
- One of the most underestimated causes of protein aggregation is mechanical stress
  - Shaking or stirring
  - Shearing (rapid extraction by syringe)
  - Exposure to hydrophobic gas interface

93

Aggregation depends on specific mAbs and conditions





Long-term stability of bevacizumab repackaged in 1 mL polypropylene syringes for intravitreal administration

Mechanically-induced aggregation of the monoclonal antibody cetuximab

Paul M, et al. Ann Pharm Fr 2012;70:139–54.
Lahlou A, et al. Ann Pharm Fr 2009;67:340–52.

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Questions

Let's vote again!

- Which of the topics below do you regard as the most important barrier to use of biosimilars?
  - A. The analytical techniques used to establish similarity
  - B. The regulatory pathway for biosimilars
  - C. The concept of extrapolation
  - D. Immunogenicity concerns with biosimilars

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Hot air or hot topic?

Join the biosimilar debate!

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Hot air or hot topic?

Join the biosimilar debate!

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Balloon debate: round 3

Issue 3

How to control so many quality attributes?

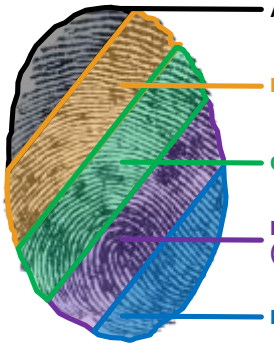
–

How to deliver a consistent medicine?

Martin Schiestl

SANDOZ A Novartis Division

Biosimilar and reference medicine must match in all relevant attributes



- Characterisation using over 40 different analytical methods
- Approximately 100 different quality attributes
- Attributes often analysed with multiple methods (redundancy)

Sandoz-generated/owned slide.
Windisch J. EGA's perspective on the draft quality guideline, 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500154191.pdf. Accessed 2016 March 18.

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Which quality attributes matter clinically? Criticality assessment

Quality attributes related to:
- **Molecule**
- **Process materials**
- **Excipients**

Assessment of clinical relevance

- **Immunogenicity**
- **Safety/Toxicity**
- **Pharmacokinetics**
- **Efficacy**

Criticality	Criticality score
Very high	121–140
High	86–120
Moderate	56–85
Low	31–55
Very low	2–30

Existing product knowledge
- **Literature**
- **In-house studies**
- **Related molecules**

FDA Arthritis Advisory Committee, 13 July 2016. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM513088.pdf. Accessed 2017 March 15; ICH Q8(R2) Guideline. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf. Accessed 2017 March 15.

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Clinical relevance of quality attributes is well understood

Potentially clinically relevant attributes

Efficacy

- Amino acid sequence
- Folding, disulphide bridges, free cysteines
- Degradation
- Deamidation
- Glycation
- Glycosylation: fucosylation, mannose X, sialylation, galactose

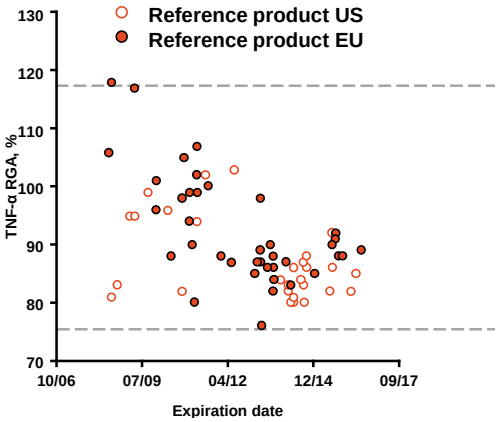
Immunogenicity

- Amino acid sequence
- Aggregates
- Folding, disulphide bridges, free cysteines
- Degradation
- Host cell proteins
- Leachables / extractables
- Glycosylation
- Galactose-α1,3-Galactose

- **Quality attributes are assessed systematically and for each indication separately**

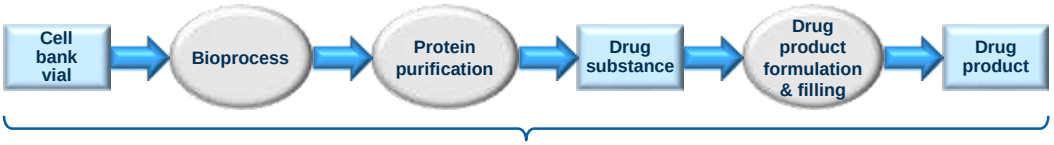
Brocchini S, et al. Adv Drug Deliv Rev 2008;60(1):3–12; Chung CH, et al. N Engl J Med 2008;358:1109–17; Dashivets T, et al. PLoS One 2015;10:e0143520; Goetze AM, et al. MAbs 2010;2(5):500–7; Kennedy DM, et al. Clin Exp Immunol 1994;98:245–51; Liu H, May K. Mabs 2012;4:17–23; Markovic I. Expert Opin Drug Saf 2007;6:487–91; Rathore N, Rajan RS. Biotechnol Prog 2008;24(3):504–14; Ripple DC, Dimitrova MN. J Pharm Sci 2012;101:3568–79; Wang X, et al. Biotechnol Bioeng 2009;103:446–58; Weber CA, et al. Adv Drug Deliv Rev 2009;61:965–76; Wright A, et al. EMBO J 1991;10:2717–23.

TNF-α neutralisation activity of biosimilar etanercept within reference product range of variability



FDA Arthritis Advisory Committee, 13 July 2016. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM513088.pdf Accessed 2017 March 15.

Manufacturing process designed to deliver a consistent biosimilar product



Manufacturing process controlled by

- Raw material controls
- Process design
- In-process testing and control of process parameters
- Release testing of harvest, drug substance, and final dosage form

Quality System governed by Quality Assurance functions
Compliance with Good Manufacturing Practices (GMP)
Inspected by health authorities

FDA Arthritis Advisory Committee, 13 July 2016. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM513088.pdf. Accessed 2017 March 15.

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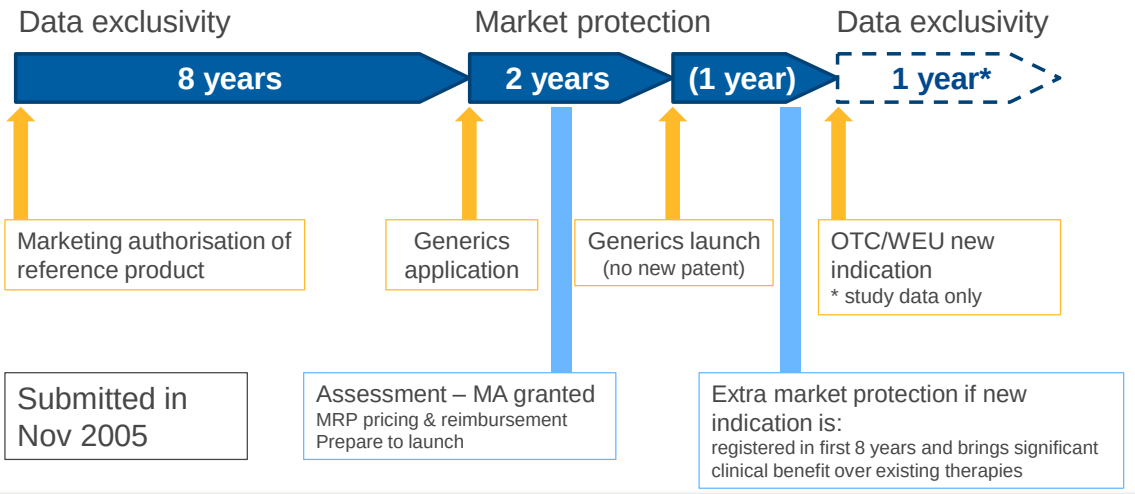
6 Public

Issue 3

PRECAUTIONARY PRINCIPLE

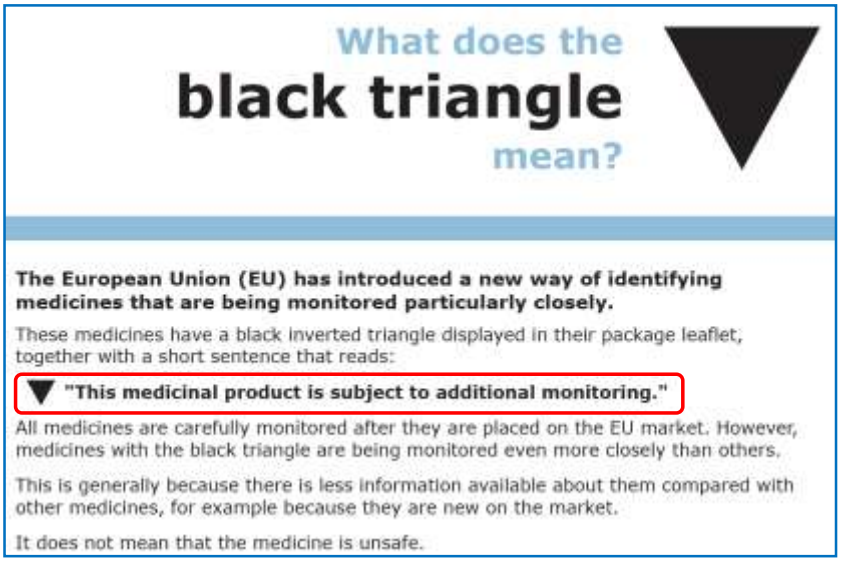
Steffen Thirstrup

10 years of market experience with the reference product



Medicines subject to 'Additional Monitoring'

- Contains a new active substance authorised in the EU after 1 January 2011
- **Biological medicine, such as a vaccine or a medicine derived from plasma, for which there is limited post-marketing experience, including biosimilars**
- Conditionally approved or approved under exceptional circumstances
- The company that markets the medicine is required to carry out additional studies; for instance, to provide more data on long-term use of the medicine or on a rare side effect seen during clinical trials



Erasmus MC
University Medical Center Rotterdam

Issue 3: Extrapolation for biosimilars has significant and widespread support

Arnold G. Vulto

The extrapolation concept is widely supported

After a time of reluctance, all experts and medical specialist-organisations now support the concept of indication extrapolation

eular
fighting rheumatic & musculoskeletal diseases together

ECCO European Crohn's and Colitis Organisation

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ECCO position statement on biosimilars

ECCO Position Statement

ECCO Position Statement on the Use of Biosimilars for Inflammatory Bowel Disease—An Update

Silvio Danese,[a,b] Gionata Fiorino,[c] Tim Raine,[d] Marc Ferrante,[e] Karen Kemp,[f] Jaroslaw Kierkus,[g] Peter L. Lakatos,[h] Gerassimos Mantzaris,[i] Janneke van der Woude,[j] Julian Panes,[k] Laurent Peyrin-Biroulet[l]

ECCO, European Crohn's and Colitis Organisation
Silvio D, et al. J Crohns Colitis 2017;11(1):26-34.

ECCO statements on biosimilars

6. Ecco Statements

A consensus meeting was held on October 15, 2016 in Vienna. Based on the current regulatory guidance form the European Medicines Agency and the evidence about efficacy and safety of biosimilars in IBD patients, the attendees agreed on the following statements:

1. Biosimilarity is more sensitively characterised by performing suitable *in vitro* assays than clinical studies.
2. Clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation. Therefore data for the usage of biosimilars in IBD can be extrapolated from another sensitive indication.
3. When a biosimilar product is registered in the EU, it is considered to be as efficacious as the reference product when used in accordance with the information provided in the Summary of Product Characteristics.
4. Demonstration of safety of biosimilars requires large observational studies with long-term follow-up in IBD patients. This should be supplemented by registries supported by all involved stakeholders (manufacturers, healthcare professionals and patients' associations).
5. Adverse events and loss of response due to immunogenicity to a biologic drug cannot be expected to be overcome with a biosimilar of the same molecule.
6. As for all biologics, traceability should be based on a robust pharmacovigilance system and the manufacturing risk management plan.
7. Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients.
8. Switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists, and patients, and according to national recommendation. The IBD nurse can play a key role in communicating the importance and equivalence of biosimilar therapy.

Silvio D, et al. J Crohns Colitis 2017;11(1):26-34.

ECCO statements on biosimilars – extrapolation

6. Ecco Statements

A consensus meeting was held on October 15, 2016 in Vienna. Based

1. Biosimilarity is more sensitively characterised by performing suitable *in vitro* assays than clinical studies.
2. Clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation. Therefore data for the usage of biosimilars in IBD can be extrapolated from another sensitive indication.

tional studies with long-term follow-up in IBD patients. This should be supplemented by registries supported by all involved stakeholders (manufacturers, healthcare professionals and patients' associations).

recommendation. The IBD nurse can play a key role in communicating the importance and equivalence of biosimilar therapy.

Silvio D, et al. J Crohns Colitis 2017;11(1):26-34.

ESMO position on biosimilars

Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers

Josep Tabernero,[1] Malvika Vyas,[2] Rosa Giuliani,[3] Dirk Arnold,[4] Fatima Cardoso,[5] Paolo G Casali,[6] Andres Cervantes,[7] Alexander MM Eggermont,[8] Alexandru Eniu,[9] Jacek Jassem,[10] George Pentheroudakis,[11] Solange Peters,[12] Stefan Rauh,[13] Christoph C Zielinski,[14] Rolf A Stahel,[15] Emile Voest,[16] Jean-Yves Douillard,[2] Keith McGregor,[2] Fortunato Ciardiello[17]

Tabernero J, et al. ESMO Open 2017;1(6):e000142.

ESMO position on biosimilars – extrapolation

As biosimilars are complex products that undergo new clinical studies in line with those of their reference products, extrapolation of the indications should be permitted if verified scientifically. Analytical, preclinical, pharmacokinetics, pharmacodynamics and clinical data, along with immunogenicity, should be collected if the biosimilar is to be correctly extrapolated to all indications of its reference product.

Thus, extrapolation to all clinical indications may be acceptable in the EU,[13] and globally, if there are enough relevant data related to the safety and efficacy of the biosimilar, any differences in the data are appropriately justified.[10]

Tabernero J, et al. ESMO Open 2017;1(6):e000142.

If the molecule is the same, it will do the same, in all indications of the reference product

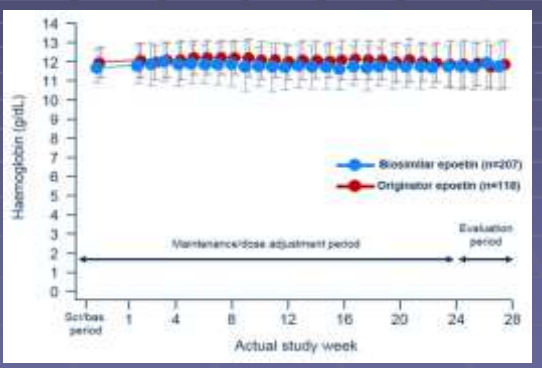
Immunogenicity concerns with biosimilars

ISSUE 3

Alain Astier

Demonstrate clinical similarity in Phase III trials: biosimilar epoetin

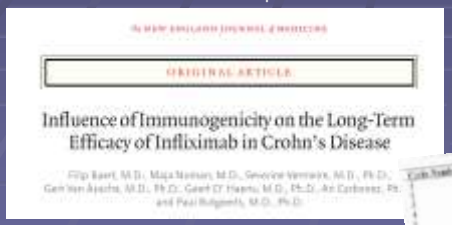
- Patients were treated with a biosimilar erythropoiesis-stimulating agent or epoetin alfa (the reference product)
  - Biosimilar ESA was as efficacious as the reference product, with a similar safety profile



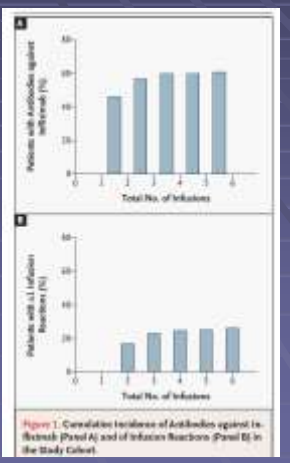
Haag-Weber M, et al. Clin Nephrol 2009; 72:380–90.

Immunogenicity and clinical trials

- Short term clinical trials cannot give relevant answers on immunogenicity
- Originator mAbs are immunogenic
  - After infliximab use:
    - 61% of patients developed neutralizing Abs
    - 27% of patient exhibited infusion reactions


ORIGINAL ARTICLE

Influence of Immunogenicity on the Long-Term Efficacy of Infliximab in Crohn's Disease



Baert F, et al. N Engl J Med 2003;348:601–8.

Safety in other indications


AGA Abstracts


Gastroenterology

515 Biosimilar Infliximab Is Effective and Safe in Inflammatory Bowel Disease Patients Naive to Anti-TNF Therapy: A Tertiary Center Experience


Efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: A retrospective multicenter study.

How to evaluate the immunogenic profile?

- Progressive appearance of immunological reactions
- Surveillance in real-life use (pharmacovigilance plan) is mandatory
- Comparison with the originator alone has relevance to ensure avoidance of bias

SANDOZ A Novartis Division

Questions

SANDOZ A Novartis Division

Hot air or hot topic?

Join the biosimilar debate!

SANDOZ

Summary

The final vote!

- Which of the topics below do you regard as the most important barrier to use of biosimilars?
  - A. The analytical techniques used to establish similarity
  - B. The regulatory pathway for biosimilars
  - C. The concept of extrapolation
  - D. Immunogenicity concerns with biosimilars

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Conclusions

Your feedback is important

- Please complete the evaluation form in the event app
- Don’t forget to hand in your iPad


SANDOZ
Hot air or hot topic?
Join the biosimilar debate!