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The biosimilar concept revisited - is there a need for change?

3rd Annual Biosimilars Forum
Statistical and Regulatory Perspectives in Bio- and Nanosimilar Development
25 – 27 October 2018, Budapest

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Disclaimer

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- I attend this conference as an individual expert, and do not represent the CHMP or the Austrian Medicines Agency

- The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the CHMP or reflecting the position of the CHMP or the Austrian Medicines Agency

Overview

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- Biosimilar concept in Europe
- Approaches to biosimilarity conclusion at quality level
- Decision making at clinical level – some difficult examples
  - Enoxaparin
  - Monoclonal antibodies
    - Infliximab
    - Etanercept
    - Trastuzumab
- Convergence of a global biosimilar concept
- Summary and outlook

Biosimilar products in EU (as of July 2018)

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47 products for 15 reference products are **on the market** (50 authorised)

INN	Name	INN	Name	INN	Name
Somatropin	Omnitrope Valtropin (withdrawn)	**Etanercept**	Benepali Erelzi	**Bevacizumab**	Mvasi
Epoetin alfa **Epoetin zeta**	Abseamed Binocrit Epoetin Alfa Hexal Retacrit Silapo	**Trastuzumab**	Ontruzant Herzuma Kanjinti Trazimera	**Infliximab**	Inflectra Remsima Flixabi Zessly
Filgrastim	Ratiograstim Tevagrastim Filgrastim Hexal Zarzio Nivestim Grastofil Accofil	**Rituximab**	Truxima Rixathon Riximyo Blitzima Ritemvia Rituzena	**Adalimumab**	Amgevita Solymbic Imraldi Cyltezo Halimatoz Hefiya Hyrimoz
(Filgrastim Withdrawn)	Biograstim Filgrastim ratiopharm	**Teriparatide**	Movymia Terrosa	**Enoxaparin Na^+**	Inhixa Thorinane
Insulin glargine	Abasaglar Lusduna Semglee	**Insulin lispro**	Insulin lispro	**Follitropin**	Ovaleap Bemfola

Biosimilar products in EU (as of October 2018)

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Next biosimilars to be approved

- Positive opinions were recently granted by the CHMP for
  - **Adalimumab**: Hulio
  - **Pegfilgrastim**: Pelgraz, Udenyca, Fulphila, Pelmeg, Ziextenzo
  - **Trastuzumab**: Ogivri
    - To be confirmed by the European Commission
    - ⇨ 54 products for 16 reference products and more to come

Development of biosimilars in EU

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Progression of the biosimilar concept

Past

- Implementation of a stringent **comparability exercise at all levels**
- Definition of the equivalence paradigm
- Step-wise comparative approach from quality over non-clinical to PK/PD and then clinical efficacy and safety data

Present

- More focus on quality level (analytical and functional comparison) with proposals for **statistical approach**
- Non-clinical in vivo data strongly repressed
- Role of clinical data mainly to confirm comparable clinical performance

Future ?

- Further strengthening of the **quality comparison**?
- Acceptance of the concept of statistical testing for similar quality?
- Largely reduced need for clinical data?
- PK/PD comparison only (if at all) for all products?
- Global convergence?

Biosimilarity at quality level

EMA/CHMP/138502/2017
Committee for Human Medicinal Products (CHMP)

Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

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Reflection paper on statistics for comparison of quality attributes

- General agreement that the comparability exercise at quality level (physico-chemical and functional characteristics) is **more sensitive** than comparison at clinical level
- Comparison of (critical) **quality attributes**: (C)QA
  - Until now descriptive approaches have been used, e.g. min-max ranges, tolerance intervals, … (see also the biosimilar GL on quality issues EMA/CHMP/BWP/247713/2012)
  - What about an inferential approach?
    - On the basis of confidence intervals, prediction intervals, …
    - But how to define an equivalence margin, similarity criterion, acceptance range?
    - Lack of understanding of the impact of differences on clinical outcome ⇨ largely arbitrary decisions?

Biosimilarity at quality level

16 December 2016
EMA/756854/2016
Human Medicines Research and Development Support Division

Tailored scientific advice to support step-by-step development of new biosimilars

Pilot project to commence in February 2017

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Reflection paper on statistics for comparison of quality attributes

- …The acceptability of **future 'abbreviated' biosimilar programmes** with a scientific comparative focus on the quality data will not only be influenced by the degree of understanding of the association between quality characteristics and clinical outcome, but will also strongly depend on how the risk for a false positive conclusion on similarity can be controlled.
- **Pilot project on tailored scientific advice for biosimilars**
  - Based on mature analytical and functional data related to the comparability exercise
  - Reluctance on this initiative?
    - Further process changes in manufacturing may require later bridging approaches
    - Clinical studies often started in parallel

Biosimilarity at clinical level: difficult decisions

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Enoxaparin – Inhixa: lack of clinical safety data

- Clinical comparability exercise incuded only one comparative PD study
  - Conventional PK comparison not possible due to large heterogeneity of LMWHs
  - 20 HVs tested in a 2-way cross-over comparison for anti-FXa- and anti-FIIa-activity
  - No single AEs occurred in the study
- How to judge the **risk for rare AEs like HITT** ?
  - Non-clinical in vitro assays on Heparin-PF4 complex binding considered most important
  - Were too limited in the initial submission
  - Request for a number of additional comparative in vitro tests
    - TFPI released into HUVEC cell culture medium, structural changes of PF4 measured by CD spectroscopy after addition of enoxaparin, SPR analysis of PF4 binding, PF4/LMWH particle size
- In vitro data provided **reassurance that safety profile is similar**

The concept of extrapolation

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General considerations on extrapolation

- For biosimilars extrapolation is the **most important feature**
  - Relevant aspect for abridged development with potential savings
- However, it is also the **most contentious** issue
- Laid down in a number of biosimilar guidelines
  - Overarching GL, general GLs, product-specific and monoclonal antibodies GLs
- Is a well-established scientific and regulatory principle frequently applied, e.g.
  - Generics and biosimilars, paediatric indications and other populations
  - Changes in the manufacturing process of biological medicines
- Implemented in all biosimilar product approvals until now

Biosimilarity at clinical level: difficult decisions

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Infliximab: extrapolation from rheumatological disorder (RA) to inflammatory bowel disease (IBD)

- Binds 2 different receptors/ligands on immune cells with 2 different modes of action
  - **sTNFα**: transduces the major part of the activity, is modulated via the Fab part of the antibody
  - **mTNFα**: may be responsible for additional mechanism of action (like ADCC and CDC), is modulated via the Fc part of the antibody
- According to the guideline on biosimilar monoclonal antibodies ANY mechanism of action that could potentially be involved in claimed indications should be studied
  - **In vitro assays** should broadly cover all functional aspects of the mAb
  - Even though some may not be considered essential for the therapeutic mode of action

Biosimilarity at clinical level: difficult decisions

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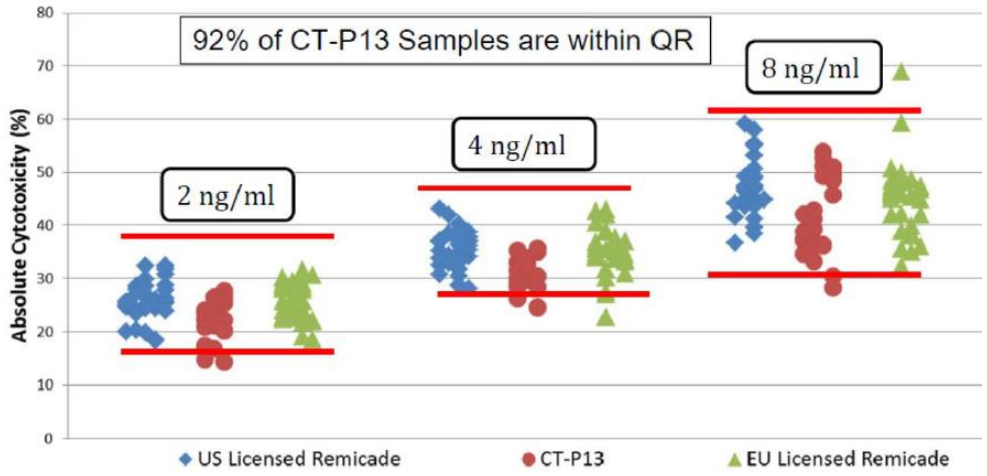
Infliximab – Remsima: extrapolation from RA to IBD

- **Extensive battery of in vitro tests** showed comparable activities except
  - Lower percentage of afucosylated glycoforms ⇨ this led to
    - Lower binding to FcγRIIIa/b ⇨ and in consequence to
      - Lower ADCC
- This **20% lower ADCC activity** was observed in most sensitive and artificial in vitro test system
  - Jurkat cells as target cells (expressing abnormally high levels of tmTNFα) and NK cells as effector cells
  - Is this relevant for the clinical situation?

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

Biosimilarity at clinical level: difficult decisions

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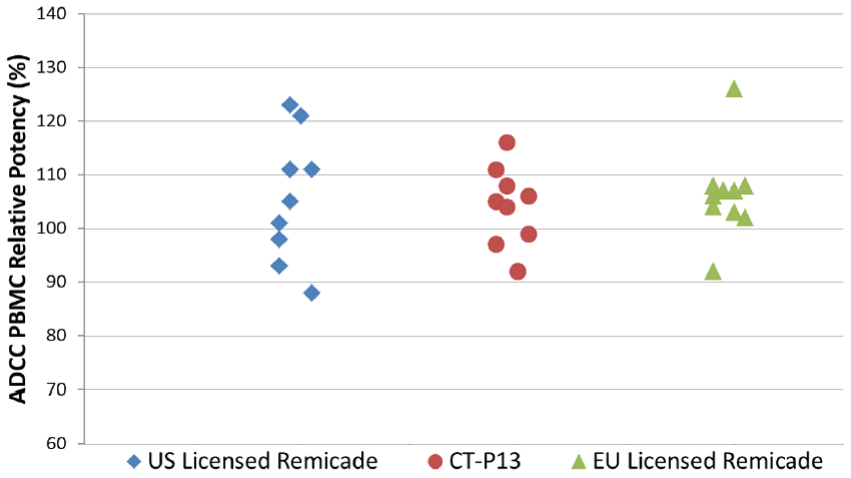
Infliximab – Remsima: extrapolation from RA to IBD

- **In physiologic conditions** difference in afucosylated glycoforms **not clinically relevant**
  - In the NK cell assay with use of serum or whole blood or with PBMCs as target cells ⇨ no differences in binding/ADCC observed
  - In LPS-stimulated monocytes as target cells ⇨ no ADCC response with either product (role of ADCC in inflammation seems limited!)
  - No difference in induction of regulatory macrophages by PBMCs, in suppression of T cell proliferation and promotion of wound healing in cultured colorectal epithelial cells
  - Comparable dose-dependent inhibition of apoptosis and IL-6 & IL-8 secretion in inflammatory model of human intestinal epithelial cell line (Caco-2)

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

Biosimilarity at clinical level: difficult decisions

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Infliximab – Remsima: extrapolation from RA to IBD

- **Conclusion:** based on the totality of evidence the CHMP agreed to extrapolation with approval of all indications
  - Biosimilarity established on the level of quality (**comparable structure**), non-clinical (**comparable function**) and clinical (PK & PD: **comparable PK and PD** profiles in 250 patients with ankylosing spondylitis; efficacy, safety and immunogenicity: **comparable results** in 606 patients with rheumatoid arthritis)
  - Functional tests including transmembrane binding, reverse signalling and apoptosis were comparable
  - Similar induction of regulatory macrophages and inhibition of direct TNFα effects on epithelial cells (play important role in Crohn's disease)
- ⇨ Observed difference in afucosylated species was considered **not clinically relevant**

Biosimilarity at clinical level: difficult decisions

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Infliximab – Flixabi: similarity conclusion for immunogenicity

- **PK equivalence** shown in healthy volunteers; **similar efficacy** shown in RA trial
- Overall safety profile comparable between treatment groups
  - But slightly higher ADA incidence observed in Flixabi arm
  - In both arms high ADA levels due to increased assay sensitivity
  - Methotrexate treatment in RA population did not blunt ADA formation
  - No correlation to minor differences in quality attributes (e.g. slightly higher amount of HMW species)

Diff = 9%

Table 13. Incidence of Anti-drug antibodies and neutralising antibodies to infliximab, in Study SB2-G31-RA (safety set)

		SB2 N=290			Remicade® N=293		
Timepoint	Parameter	n'	n	(%)	n'	n	(%)
Week 0	ADA	290	5	(1.7)	293	7	(2.4)
	Nab	5	0	(0.0)	7	0	(0.0)
Week 30	ADA	251	133	(53.0)	264	116	(43.9)
	Nab	133	129	(97.0)	116	109	(94.0)
Week 54	ADA	223	118	(52.9)	222	89	(40.1)
	Nab	118	99	(83.9)	89	78	(87.6)

ADA = anti-drug antibody, NAb = neutralising antibody; n': number of subjects with available ADA/NAb results against SB2 at each timepoint
ADA was determined as positive if at least 1 ADA positive result was obtained up to the timepoint regardless of the ADA result at Week 0.
Percentages were based on n'.

Diff = 13% → persistent ADA

- Imbalance in ADAs did **not translate into meaningful clinical differences** in efficacy (no higher rate of dose increases) and safety

Biosimilarity at clinical level: difficult decisions

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Etanercept – Benepali: extrapolation in rheumatological disorders

- **Comparable quality/non-clinical data** on
  - Various binding assays, TNFα neutralisation assay, ADCC and CDC assay, apoptosis activity assay
- Benepali has slightly higher afucosylated glycan content (~2-fold) and slightly higher affinities to FcγRIIIa/b
  - In relation to infliximab (set at 100%) ADCC in RMP Etanercept is <5% and in Benepali <5-10%
    ⇨ not considered clinically relevant
- ADCC even less important (compared with infliximab) for the mode of action of etanercept in both arthritic and psoriatic indications ⇨
  - Primary mode of action: competitive inhibition of TNFα binding to cell surface TNF-receptors
- **No clinically relevant differences**, extrapolation granted to all indications

Biosimilarity at clinical level: difficult decisions

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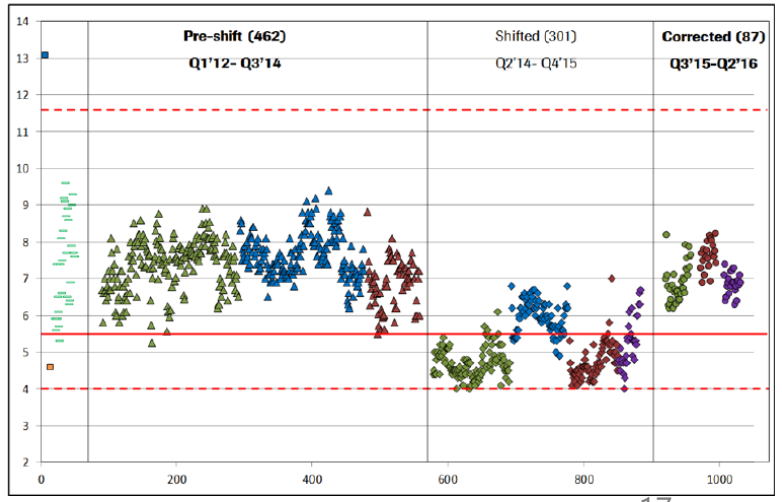
Trastuzumab – Ontruzant: similarity conclusion for efficacy

- Phase III study in women (n = 875 randomised) with newly diagnosed HER2-positive early or locally advanced breast cancer in the neoadjuvant setting
  - Primary efficacy endpoint: **bpCR** in PP set, showing apparent superiority of Ontruzant
    - Upper limit of the confidence interval for the difference in pCR rate slightly exceeded the pre-specified equivalence margins (95% CI: **4.13%, 17.26%**; equivalence margins: -13%, 13%)
  - Secondary endpoints: OS and EFS at 1 yr, no statistical difference
  - No clinically meaningful differences in safety profile
- In recent batches of EU Herceptin (starting from lots with expiry dates of Oct 2018) **apparent shifts in ADCC activity** were found ⇨
  - Lower afucosylation after manufacturing change of originator
  - ~ 40% of patients exposed to Herceptin lot with lower ADCC

Figure S.4.5-2 %aFuc of Historical Commercial Trastuzumab Batches



Biosimilarity at clinical level: difficult decisions

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Trastuzumab – Ontruzant: similarity conclusion for efficacy

- **Conclusion:** although the difference in bpCR was slightly outside the pre-specified equivalence range in the upper bound limit, this was considered at least in part confounded by a small shift in ADCC activity in a number of the EU Herceptin batches used in the pivotal trial
  - The small shift is not considered having significant impact on the clinical outcome, although numerically it is thought to have contributed to a more extreme location of the point estimate and upper bound of the confidence interval, shifting the latter beyond the pre-specified equivalence margin
  - Based on evidence of similarity in quality, non-clinical, PK, clinical efficacy and safety, **biosimilarity has been sufficiently shown** for Ontruzant compared to the reference product Herceptin

Biosimilarity at clinical level: difficult decisions

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Trastuzumab – Kanjinti: similarity conclusion for efficacy

- Pivotal phase III clinical trial in patients with early HER2-positive breast cancer
  - Primary efficacy endpoint: pCR rate in breast and axillary nodes regardless of DCIS,
    - Risk difference in pCR was 7.3% (95% CI: **0.0%, 14.6%**; equivalence margins: -13%, 13%)
    - Lower limit of the CI was within the pre-specified equivalence margin of ±13%, thereby ruling out non-inferiority, the upper limit was not
  - Secondary endpoints: OS and EFS were similar
- Shifts in ADCC activity of some Herceptin lots could have contributed to these results
  - **Further analyses for ADCC activity** with PBMCs as effector cells were conducted
    - Activity, glycan structure and expiration date justified cut-off value of 65% for further analyses
  - After additional histological grading of tumours, tumour stage and central laboratory assessments the primary endpoint was met
- Considering **totality of data**, the residual uncertainty **does not question biosimilarity**

Global convergence of biosimilar concepts

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IPRP – International Pharmaceutical Regulators Programme

- **Biosimilars Working Group**
  - Chair: Korea, Co-chair: Canada
  - Members: 11 countries (Brazil, Canada, Chinese Taipeh, EU/EMA, Korea, Japan, Mexico, Saudi FDA, Singapore, Switzerland, US) and 3 organizations (EAC, PANDRH, WHO)
- **Activities**
  - PASIBs (Public Assessment Summary Information for Biosimilars) – templates for translation from local language into English
  - Reflection Paper on Extrapolation of Indications of Biosimilars
  - Training Manual: The Basics of Analytical Comparability of Biosimilar Monoclonal Antibody for Regulatory Reviewers
  - Several global workshops, meetings, Regulatory Information Sharing IT Platform

Summary and outlook

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What the future may hold … ?

- Assessment of biosimilarity in **critical quality attributes** should be strengthened
  ⇨ new (statistical) approaches under discussion
- **Tailoring** of clinical evidence is needed (to which extent are clinical studies necessary?)
- <u>Extrapolation is essential for the success of biosimilars</u>
  - Most important aspect of biosimilars for reducing costs in health care system
  - To be done on the basis of the totality of data
- **Global convergence** of biosimilar regulation is expected due to a number of ongoing activities

Thank you for your interest and time