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Current challenges in the development of biosimilars

4th Annual Biosimilars Forum
Statistical and Regulatory Perspectives in Biosimilar Development
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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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- Latest numbers
- Challenges at quality level
- Challenges at pre-clinical level
- Challenges at clinical level
  - Questionable biosimilarity in PK?
  - in efficacy?
  - in safety?
- Challenges at pharmacovigilance level
- Challenges for global convergence
- Summary and outlook

Biosimilar products in EU (as of October 2019)

61 products for 15 reference products have been authorised (7 withdrawn) (more to come)

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INN	Name	INN	Name	INN	Name
Somatropin	**Omnitrope**, [Valtropin (W)]	Insulin lispro	**Insulin lispro Sanofi**	Bevacizumab	**Mvasi, Zirabev**
Follitropin	**Ovaleap** **Bemfola**	Insulin glargine	**Abasaglar** **Semglee** [Lusduna (W)]	Infliximab	**Inflectra** **Remsima** **Flixabi** **Zessly**
Filgrastim	**Ratiograstim** **Tevagrastim** **Filgrastim Hexal** **Zarzio** **Nivestim** **Grastofil**, [Biograstim (W)] **Accofil**, [Filgrastim ratioph. (W)]	Adalimumab	**Amgevita** [Solymbic (W)] **Imraldi** [Cyltezo (W)] **Halimatoz, Hyrimoz** **Hefiya, Hulio** **Idacio, Kromeya**	Rituximab	**Truxima** **Rixathon** **Riximyo** **Blitzima** **Ritemvia** [Rituzena (W)]
Pegfilgrastim	**Udenyca** **Pelgraz, Pelmeg** **Fulphila** **Ziextenzo** **Grasustek**	Epoetin alfa Epoetin zeta	**Abseamed** **Binocrit** **Epoetin Alfa Hexal** **Retacrit** **Silapo**	Trastuzumab	**Ontruzant** **Herzuma** **Kanjinti** **Trazimera** **Ogivri**
Etanercept	**Benepali** **Erelzi**	Enoxaparin Na^+	**Inhixa** **Thorinane**	Teriparatide	**Movymia** **Terrosa**

Challenges 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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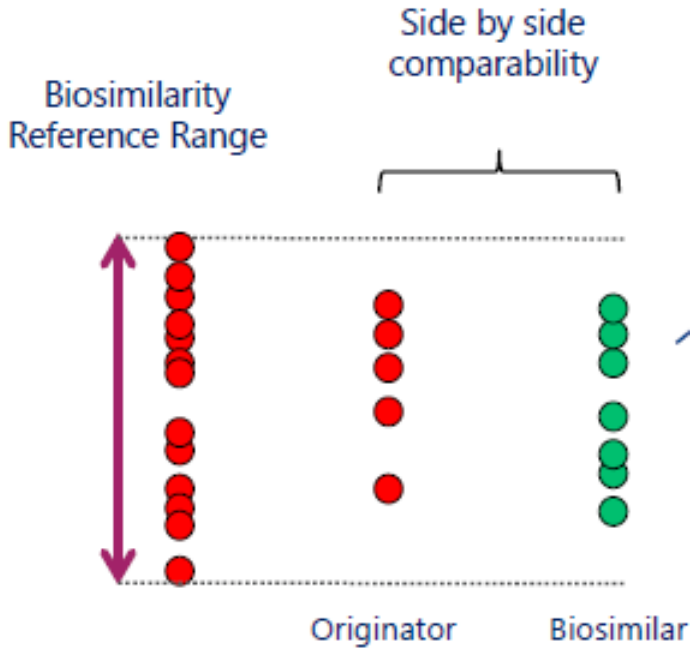
- Reflection paper on **statistics for comparison of quality attributes**
  - Replace the descriptive approaches used until now, e.g. min-max ranges, tolerance intervals, … (see also the biosimilar GL on quality issues EMA/CHMP/BWP/247713/2012) with inferential approaches, e.g. confidence intervals, prediction intervals, …?
- Comparison of (**critical**) **quality attributes**: (C)QA
  - Minimum number of batches to be used in the head-to-head comparison?
  - Sufficient batches of the originator available?
- Understanding of the **association between quality** characteristics **and clinical outcome**
  - Lack of understanding how differences impact the clinical outcome ⇨ decisions taken arbitrary?



Challenges at quality level

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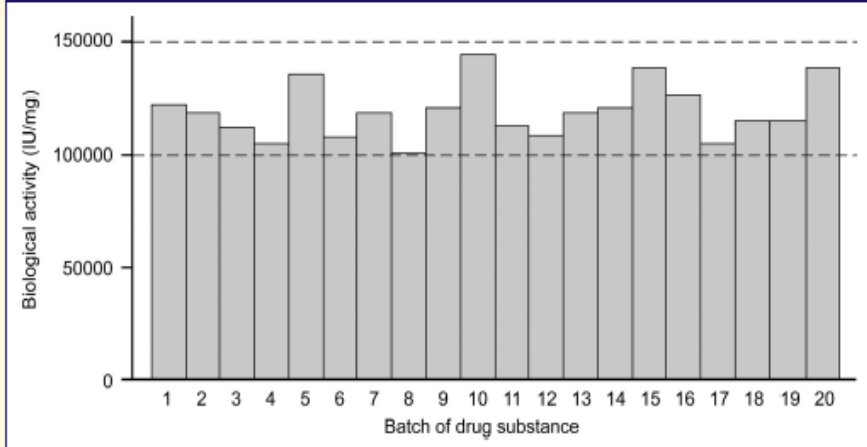
- Development of **non-originator follow-on biologics** that are not biosimilars according to EU standards

EMA-approved true biosimilars

Example: Binocrit®

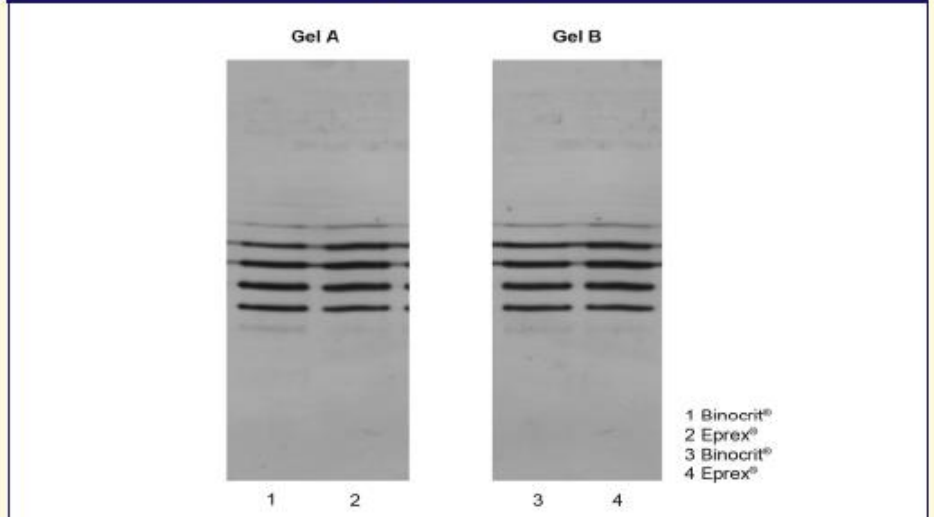
Figure 4: *In vivo* biological activity of 20 consecutive batches of Binocrit



In vivo biological activity of 20 consecutive batches of Binocrit determined with the normocythaemic mouse assay according to the erythropoietin monograph of Ph. Eur. [10]. The method is routinely applied for release of drug substance.

- **High batch consistency** in biological activity

Figure 3b: Comparison of the isoform pattern for Binocrit and comparator product epoetin alfa by isoelectric focusing gel electrophoresis



- **NO difference to originator** in Isoelectric Focussing Gels

Brockmeyer and Seidl et al., Eur J Hosp Pharm Pract 2009; 15: 34-40

Challenges at quality level

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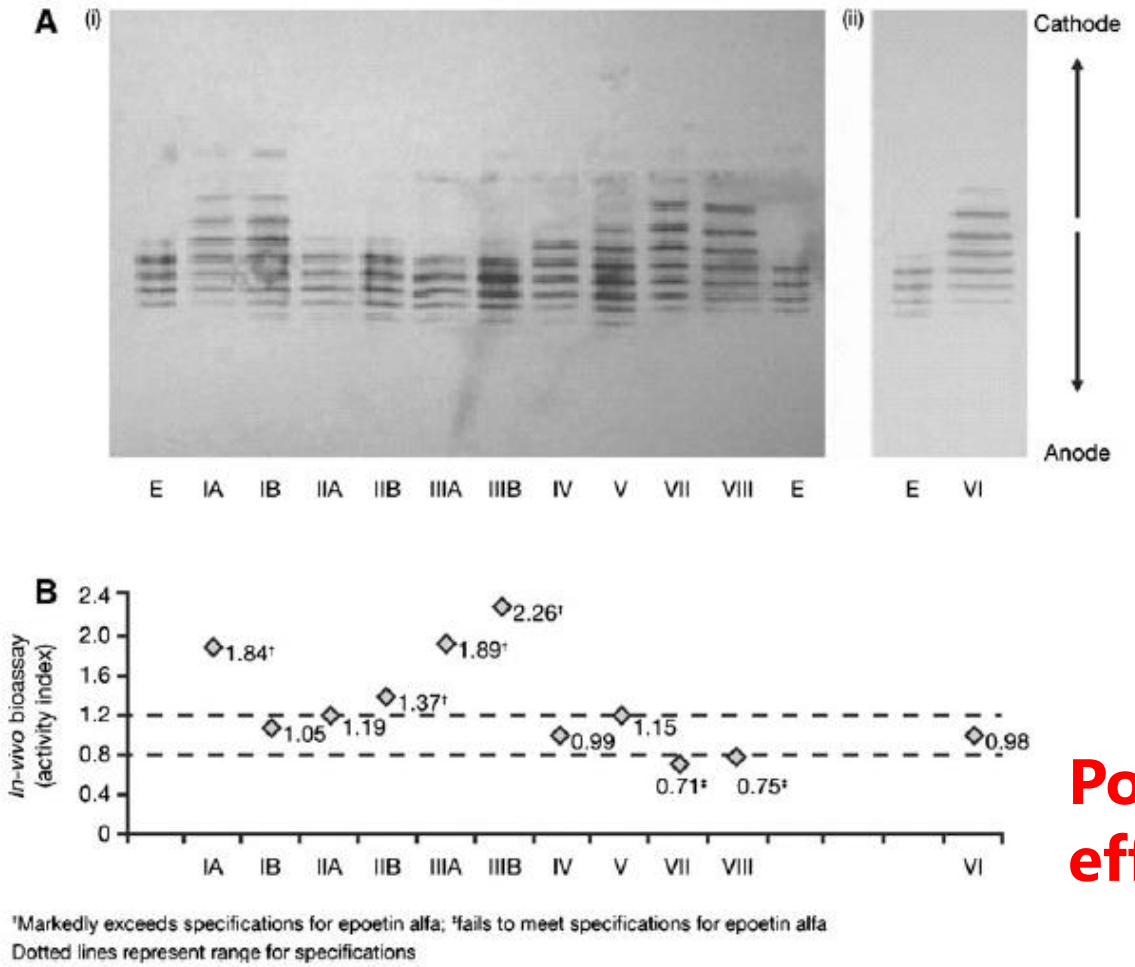
- Development of **non-originator follow-on biologics** that are not biosimilars according to EU standards, may „contaminate" the global market

Isoelectric focussing gels of non-innovator erythropoetins



†Markedly exceeds specifications for epoetin alfa; ‡fails to meet specifications for epoetin alfa
Dotted lines represent range for specifications

Sample	Concentration (IU/mL)	Country
IA	2000	Korea
IB	4000	Korea
IIA	2000	Korea
IIB	10 000	Korea
IIIA	2000	Korea
IIIB	10 000	Korea
IV	2000	Argentina
V	10 000	Argentina
VI	4000	India
VII	10 000	China
VIII	6000	China

Potential impacts on efficacy and safety !

Challenges at quality level

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- **Changes to the manufacturing process**
  - Occur after approval as well as during development
  - For these changes (active substance/finished product) a comparability assessment needs to be performed (ICH Q5E)
  - Strong recommendation to generate quality, safety and efficacy data using **batches of the commercial manufacturing process**
  - Any additional bridging approach necessary during development introduces more uncertainties !
- A biosimilar product has its **own lifecycle**
- Postmarketing no longer comparison to reference product **!**
  - How much will the individual products drift apart over time?

Challenges at non-clinical level

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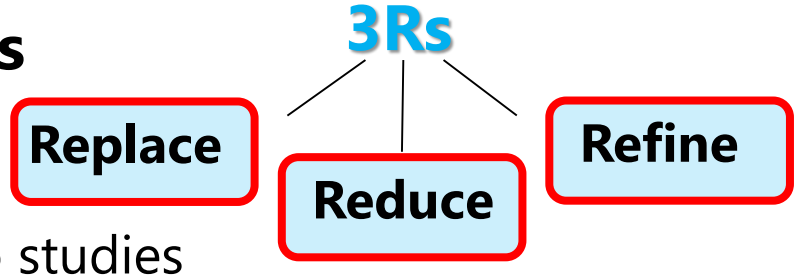
- **In EU very rarely requirement for in vivo studies**
- Other regions still ask for this ⇨
  - Dossiers submitted to EMA often contain results of in vivo studies
  - These data often show heterogenous results



- How to address differences at non-clinical in vivo level ?
  - **Questions** to be asked:
    - Is the animal model relevant?
    - Is there a plausible rationale for differences in non-clinical PK or PD (based on the quality characterisation)?
    - Do the differences concern a major pathway/mode of action?
    - Can further investigations with more sensitive/more physiologic in vitro assays be helpful?
  - **Conclusion** on non-clinical findings to be interpreted in context of results on quality and clinic

Challenges at clinical level – PK

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- **Pegylated molecules can show high variability in PK**
- Importance of the design of the PK study
  - Cross-over design decreases the impact of variability
  - Sample size should be calculated in a conservative way
  - Period- and sequence effects in the cross-over design should be investigated
- Equivalence margins for the 90% confidence interval may need to be adjusted in exceptional cases
  - Potential widening of the CI for such highly variable drugs is currently discussed
  - Biosimilar guideline on filgrastim currently being revised

Challenges at clinical level – efficacy

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- **Improved efficacy is generally not acceptable**
  - Concept of „biobetters“ (superiority) not defined in EU regulation ⇨ requirement of **equivalence**
  - Non-inferiority designs to be discussed in scientific advice
- Occasionally observation of “superior” efficacy
  - E.g. with some recent trastuzumab biosimilars
  - Conclusion that this was most likely due to lower afucosylation of certain originator batches with lower ADCC activity
- Non-similar results of clinical comparison may be accepted in exceptional cases
  - Stringent scrutiny of the results (including subgroup analyses)
  - Adequate rationale to explain the root cause (study power?, variability?, antibody formation?,…)
  - Lack of impact on clinical performance
  - Totality of evidence needs to show similarity in quality, non-clinical, PK and clinical data

Challenges at clinical level – safety

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- Overall the **biosimilar should have the same safety profile as the innovator**
  - Evaluation in descriptive terms only, studies not powered for statistical demonstration of equivalence in safety
  - Improved safety (e.g. lower immunogenicity) may be acceptable
- But can we also accept higher immunogenicity ?
  - Observed recently for an infliximab biosimilar
    - No correlation to minor differences in quality attributes
    - No impact on clinical efficacy or the general safety profile
    - Conclusion that this was most likely a chance finding
  - Potential other reasons could be
    - Difference in impurities, antigenicity
    - Artefact due to assay variability, difference in assay sensitivity

Challenges at pharmacovigilance level

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- **Post-approval commitments for biosimilars**
- AEs of special interest are basically the same for the originator and each biosimilar in the class, but product-specific findings may trigger concern:
  - At the quality level if ⇨
    - Different expression systems, altered mAb structure
    - Differences in glycosylation pattern, impurities, etc.
  - At the clinical level if ⇨
    - Higher immunogenicity (ADA incidence, titres), immune mediated Aes
    - Strikingly different safety profile, previously unreported AEs
- PASS, product- or disease-specific registries may be requested
  - Understanding implications of certain quality aspects/differences might reduce the need for further studies or justify the need for additional ones

Challenges at global level

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- **Substitution and switching in EU**
- The decision for substitution and switching of biosimilars is taken on a national member states' level
  - EMA has no remit in recommending substitution or switching
- However, any biosimilar approved via the centralized procedure at EMA is in principle **considered to be interchangeable**
  - In EU there is no separate concept for biosimilar interchangeability as compared to the US
- Most member states allow switching upon decision of the physician
  - Some also rely on automatic switching rules on the basis of product tenders

Challenges at global level

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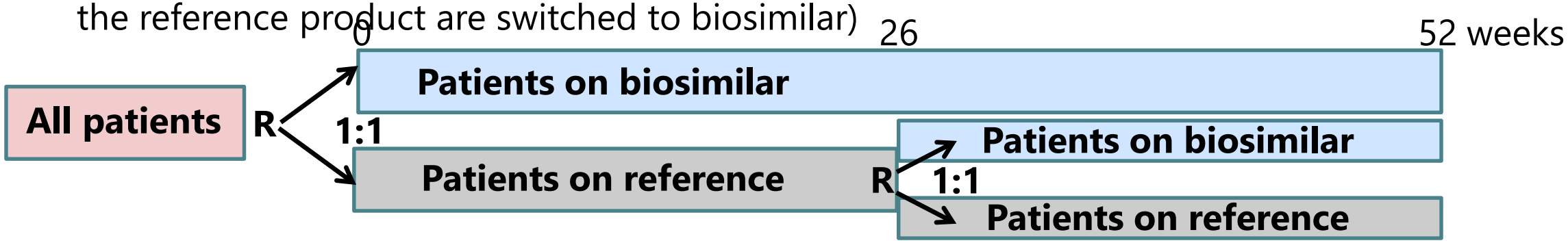
- **Substitution and switching in US**
- Patient Protection and Affordable Care Act defines 2 biosimilar categories
  - **Biosimilars:** considered as new active ingredient, not eligible for substitution or market exclusivity
  - **Biosimilars interchangeable with the reference product:** considered as the same active ingredient, may be substituted, market exclusivity up to 1 year
    - Use of non-US licensed reference product will unlikely provide adaequate data to determine interchangeability with the US reference product (now softened a bit)
    - Clinical studies in global biosimilar developments often conducted with the US reference product and incorporating a **switching design** (e.g. after 6 months half of the patients on the reference product are switched to biosimilar)



Challenges at global level

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- **Huge differences to EU exist in other regions, e.g. in MENA**
- Regulation of biosimilars lags behind those of EMA and FDA
  - Prevalence of counterfeit medicines and so-called intended copies (not „real“ biosimilars)
- Great disparity in regulation in the region, with a multitude of guidelines (mostly adapted to WHO guideline) and several products licensed in some of the countries
  - e.g. in Iran (> 20 products), Jordan and Saudi Arabia (1 product), Lebanon (> 3 products),…
  - Most of the countries have their own guidelines
- Optimal use of biosimilars/access of patients to affordable medicines hampered by
  - Intended copy products and relatively “loose“ pharmacovigilance practices allowed by regulators
  - Physicians‘ preference to prescribe branded biologics (is also incentivised), insufficient education
  - Political and economic difficulties in the region

Summary and outlook

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How to meet those challenges… ?

- Advance the statistical quantification and assessment of biosimilarity in critical quality attributes
- Refine the in vitro and in vivo assessment of non-clinical and clinical biosimilarity
- Take a rational approach to pharmacovigilance measures
- Improve the understanding of the biosimilar concept for our physicians and patients by education and training
- Consider supporting countries/regions where the regulation and clinical use of biosimilars are less advanced
- Attempt further convergence of biosimilar regulation on a global level

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Thank you for your interest and time

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