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International Pharmaceutical Regulators Programme

IPRP Biosimilars Working Group Workshop: “Increasing the Efficiency of Biosimilar Development Programs Re-evaluating the Need for Comparative Clinical Efficacy Studies (CES)”

IPRP Biosimilars Working Group (BWG)

Session 2: Stakeholder perspectives on the need for CES in biosimilar development programs

Wednesday, 13 September 2023

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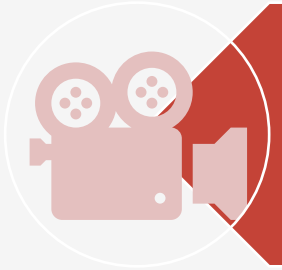
Welcome

Chat, microphone, and video are disabled for attendees

Direct questions to a specific speaker(s) using the Q&A function



The session is being recorded

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Overview of Session

- Welcome (5 min)
  - Brooke Dal Santo, US FDA
- Presentations by Industry Representatives (110 min)
  - Martin Schiestl, Sandoz
  - Elena Guillen, Hospital Clinic de Barcelona
  - Elena Wolff-Holz, Biocon
  - Frank Schneider, Dipl.-Ing., Teva
  - Keith Watson, KRW Bio Reg Solutions
  - Fabrice Romanet, Fresenius-Kabi
  - Gillian Woollett, Samsung
- Break (5 min)
- Q&A Panel with Speakers (50 min)
  - Moderated by Steffen Thirstrup, EMA
- Closing Remarks (10 min)
  - Sarah Yim, US FDA

IPRP Biosimilar Working Group Background

Chair: Sarah Yim, US FDA Co- Chair: Ali Al Homaidan, SFDA

Participants

- ANVISA, Brazil
- COFEPRIS, Mexico
- CPED, Israel
- EAC
- EC, Europe
- EDA, Egypt
- FDA, United States
- GHC
- Health Canada, Canada
- HSA, Singapore
- MFDS, Republic of Korea
- MHLW/PMDA, Japan
- MHRA, UK
- NRA, Iran
- PAHO/PANDRH
- SAHPRA, South Africa
- SFDA, Saudi Arabia
- Swissmedic, Switzerland
- TFDA, Chinese Taipei
- TGA, Australia
- TITCK, Turkey
- WHO

Scope

- To discuss regulatory challenges and potential topics/areas for harmonization or convergence regarding biosimilars
- To consider how regulatory convergence can be achieved and how regulatory information can be exchanged without compromising confidentiality
- To explore work sharing process with other international bodies and to collaborate in terms of training of international regulators

https://www.iprp.global/working-group/biosimilars

Purpose of the Workshop

- Goal: Increase efficiency in Biosimilar development program
- How: Re-evaluate the need for comparative clinical efficacy studies in biosimilar development programs based on the experience accrued from international regulatory experts and external subject matter experts
- Public Sessions:
  - Day 1: Regulator perspectives on how have we been using comparative clinical efficacy studies in biosimilar development programs and what have we learned
  - **Day 2: Stakeholder perspectives on the pros and cons of comparative efficacy studies in biosimilar development programs**
- Regulators Sessions (next week):
  - Discuss regulatory considerations for streamlining biosimilar development programs
  - Discuss considerations around when comparative efficacy studies may or may not be needed

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Moderator

Steffen Thirstrup, MD, PhD, EMA

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Advisory functions | European Medicines Agency (europa.eu)

https://dk.linkedin.com/pub/steffen-thirstrup/5/40/160

- Steffen Thirstrup is a medical doctor and board-certified specialist in clinical pharmacology and therapeutics. He holds a PhD in pharmacology and has a long background in clinical internal medicine with special emphasis on adult respiratory medicine. Dr. Thirstrup serves as **Chief Medical Officer at the European Medicines Agency.**
- From 2004-09 Steffen Thirstrup worked at **Danish Medicines Agency** first as the Danish **member of CHMP** at the European Medicines Agency (EMA) for five years including 10 months as joint CHMP- and **CAT-member**, followed by a short period as head of **Danish Institute for Rational Pharmacotherapy** dealing with HTA and best practice guidelines for primary care. In 2011 Dr. Thirstrup rejoined the licensing division at the Danish Medicines Agency acting as **Head of Division for Medicines Assessment and Clinical Trials**. During this period Prof Thirstrup co-chaired the **European Commission's working group on market access for biosimilars** medicinal products and acted as key scientific contact for the managing entity of the IMI beneficiaries for the PROTECT collaboration (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium).
- In March 2013, Dr. Thirstrup joined the pharmaceutical consultancy company **NDA Group AB** as a full-time medical advisor on NDA's regulatory advisory board. In April 2014 Prof Thirstrup was appointed as director for the Regulatory Advisory Board at NDA Regulatory Services Ltd.
- Dr. Thirstrup was appointed adjunct professor in pharmacotherapy at the Faculty of Health Sciences, University of Copenhagen, in 2012.
- Dr. Thirstrup is author of more than 30 scientific papers, guidelines and text-book chapters as well as co-editor of 5th edition of *Basal og Klinisk Farmakologi* (Medical school pharmacology textbook in Danish).

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Speaker #1

Martin Schiestl, Ph.D., Sandoz

Martin Schiestl received his doctoral degree in chemistry with a specialization in bioanalysis from the University of Innsbruck in Austria in 1996. In the same year, he started his work on Biosimilar medicines at Sandoz where he built up the analytical and pharmaceutical development departments in charge of the biosimilar portfolio and other biological medicines of Sandoz. He moved into the regulatory and policy field in 2009, further fostering regulatory sciences for biosimilar medicines. In his current role, he is responsible for the Global Regulatory Affairs Policy at Sandoz Biopharmaceuticals.

Sandoz Biopharma

Streamlined Clinical Biosimilar Development

Martin Schiestl, Head Regulatory Affairs Policy, Sandoz
IPRP Conference – virtual 12-13 September 2023

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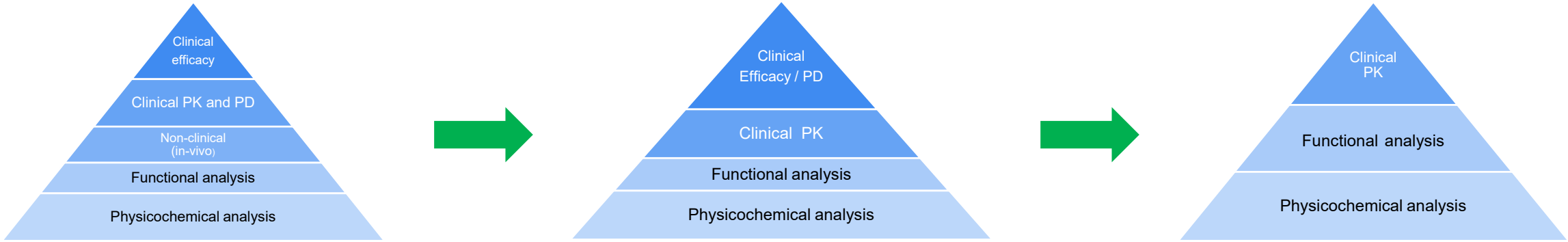
Evolution of the biosimilar pathway



Biosimilar development as setup 2004

Today's accepted regulatory options

Streamlined development (anticipated)

5 steps	4 steps	3 steps
1. Physicochemical analysis	1. Physicochemical analysis	1. Physicochemical analysis
2. Functional analysis	2. Functional analysis	2. Functional analysis
3. Non-clinical (animal testing)	-	-
4. Clinical PK/PD	3. Clinical Pharmacokinetic (PK)	3. Clinical Pharmacokinetic (PK)
5. Comparative clinical efficacy	4. Comparative clinical efficacy (conventional enpoint or qualified PD biomarker)	-

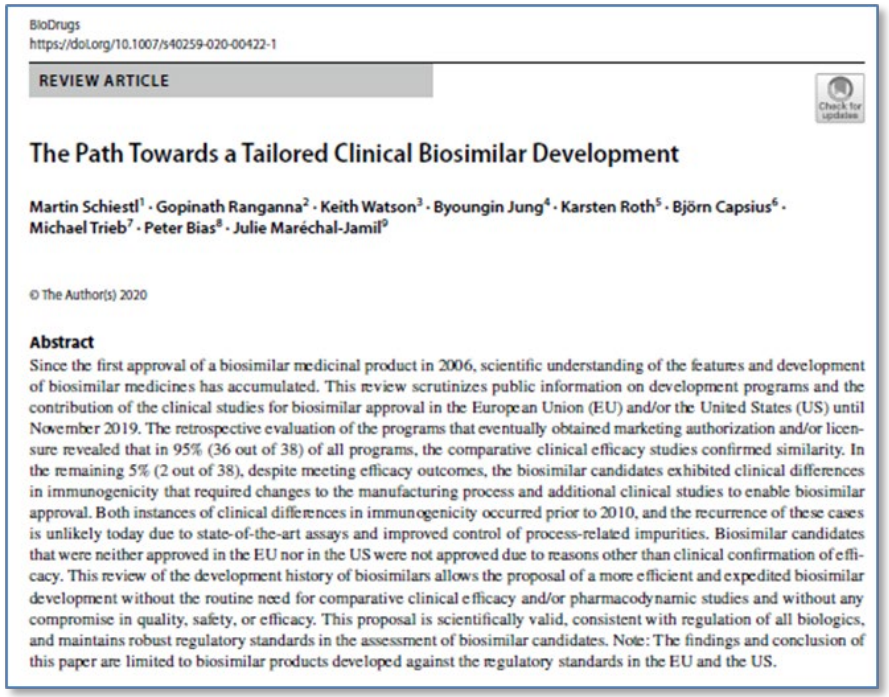
Regulatory science already enables a streamlined clinical development program today

A detailed discussion of the scientific reasoning for streamlined development without comparative clinical efficacy studies can be found in recent peer reviewed publications:

- EU regulators:
  - Guillen et al. Clin Pharmacol Ther, 2023;113, 108-123. https://doi.org/10.1002/cpt.2785
- UK regulators:
  - Bielsky et al. Drug Discov. 2020;25, 1910-1918 doi: https://doi.org/10.1016/j.drudis.2020.09.006
- Biosimilar industry:
  - Schiestl et al. BioDrugs 2020;34, 97–306; https://doi.org/10.1007/s40259-020-00422-1

Learnings from 2006 until 2019: Comparable efficacy was always confirmed in all programs

- IGBA working group reviewed the value of clinical studies of biosimilar development programs in EU and US (data set 2006-2019)
- **Review revealed that comparative clinical efficacy was never a decisive criteria in biosimilar development**
- Successful biosimilar programs despite missing primary endpoints
  - E.g. candidates for trastuzumab biosimilars
- Unsuccessful biosimilar candidates despite successful clinical efficacy trials failed at the analytical and/or clinical PK level
  - E.g. candidates for interferon alfa, insulin biosimilars



BioDrugs
https://doi.org/10.1007/s40259-020-00422-1

REVIEW ARTICLE

The Path Towards a Tailored Clinical Biosimilar Development

Martin Schiestl[1] · Gopinath Ranganna[2] · Keith Watson[3] · Byoungin Jung[4] · Karsten Roth[5] · Björn Capsius[6] · Michael Trieb[7] · Peter Bias[8] · Julie Maréchal-Jamil[9]

Abstract

Since the first approval of a biosimilar medicinal product in 2006, scientific understanding of the features and development of biosimilar medicines has accumulated. This review scrutinizes public information on development programs and the contribution of the clinical studies for biosimilar approval in the European Union (EU) and/or the United States (US) until November 2019. The retrospective evaluation of the programs that eventually obtained marketing authorization and/or licensure revealed that in 95% (36 out of 38) of all programs, the comparative clinical efficacy studies confirmed similarity. In the remaining 5% (2 out of 38), despite meeting efficacy outcomes, the biosimilar candidates exhibited clinical differences in immunogenicity that required changes to the manufacturing process and additional clinical studies to enable biosimilar approval. Both instances of clinical differences in immunogenicity occurred prior to 2010, and the recurrence of these cases is unlikely today due to state-of-the-art assays and improved control of process-related impurities. Biosimilar candidates that were neither approved in the EU nor in the US were not approved due to reasons other than clinical confirmation of efficacy. This review of the development history of biosimilars allows the proposal of a more efficient and expedited biosimilar development without the routine need for comparative clinical efficacy and/or pharmacodynamic studies and without any compromise in quality, safety, or efficacy. This proposal is scientifically valid, consistent with regulation of all biologics, and maintains robust regulatory standards in the assessment of biosimilar candidates. Note: The findings and conclusion of this paper are limited to biosimilar products developed against the regulatory standards in the EU and the US.

1. Schiestl et al. BioDrugs 2020;34, 97–306; https://doi.org/10.1007/s40259-020-00422-1

IGBA: International Generic and Biosimilar Medicines Association

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Sameness of efficacy is ensured at multiple levels

No need for insensitive comparative efficacy study as a 4th safety net when the first three suffice

Physicochemical characterization

Functional characterization

1st safety net

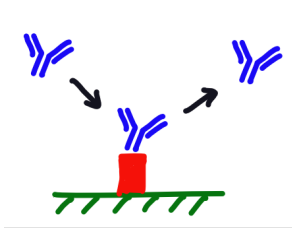
Structural similarity

Function is the result of structure

2nd safety net

Binding assays

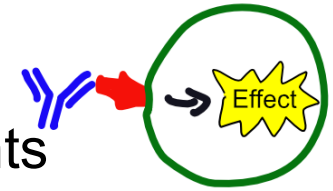
Primary binding events with target and receptors



3rd safety net

Cell-based bioassays

Effect in living cells following primary binding events



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Cell-based bioassays are more sensitive than comparative efficacy trials – Trastuzumab example

- Large difference in ADCC potency of the reference product measured by cell-based bioassay [1-5]

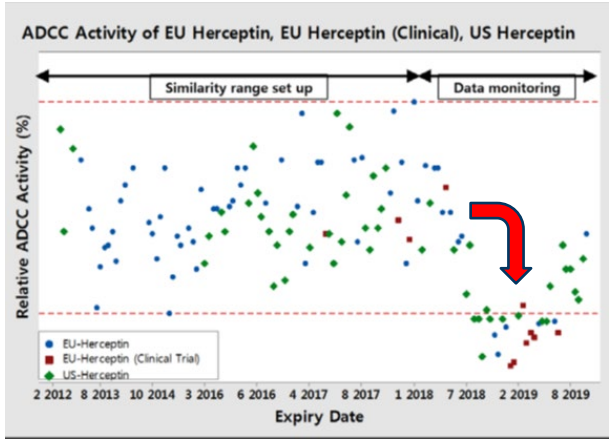
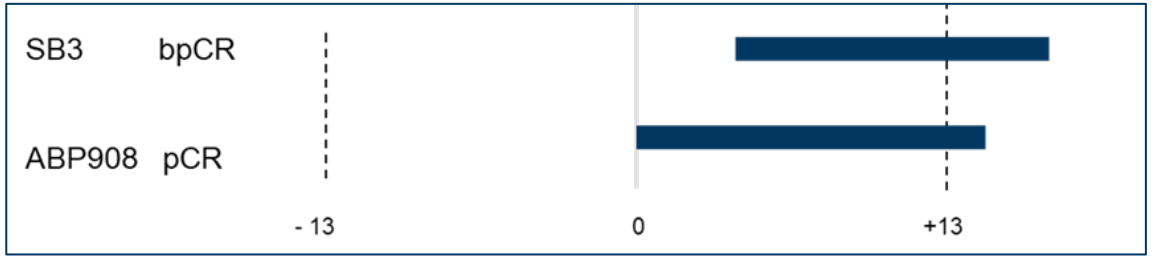


Figure adapted from EPAR for Ontruzant (SB3)

Primary clinical endpoint

- EMA approved equivalence margins were slightly missed for ABP908 and SB3 [1]
- FDA approved margins were slightly missed by ABP908, but SB3 was within margins [4,5]

Primary endpoints of SB3 and ABP908 trastuzumab biosimilar trials for EU filing



Products approved in EU and US

1. EPARs (European Public Asessment Reports) for Ontruzant (SB3), Kanjinti (ABP908), accessed 7 Sep 2022
2. Kim et al. Drifts in ADCC-related quality attributes of Herceptin®: Impact on development of a trastuzumab biosimilar. mAbs, 2017; 9:704-714
3. Lee et al. Biological Characterization of SB3, a Trastuzumab Biosimilar, and the Influence of Changes in Reference Product Characteristics on the Similarity Assessment. BioDrugs 2019; 33:411-422
4. FDA Kanjinti review Application no 761073. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761073Orig1s000TOC.cfm, accessed 7 Sep 2022
5. FDA Ontruzant review Application no 761100. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761100Orig1s000TOC.cfm, accessed 7 Sep 2022

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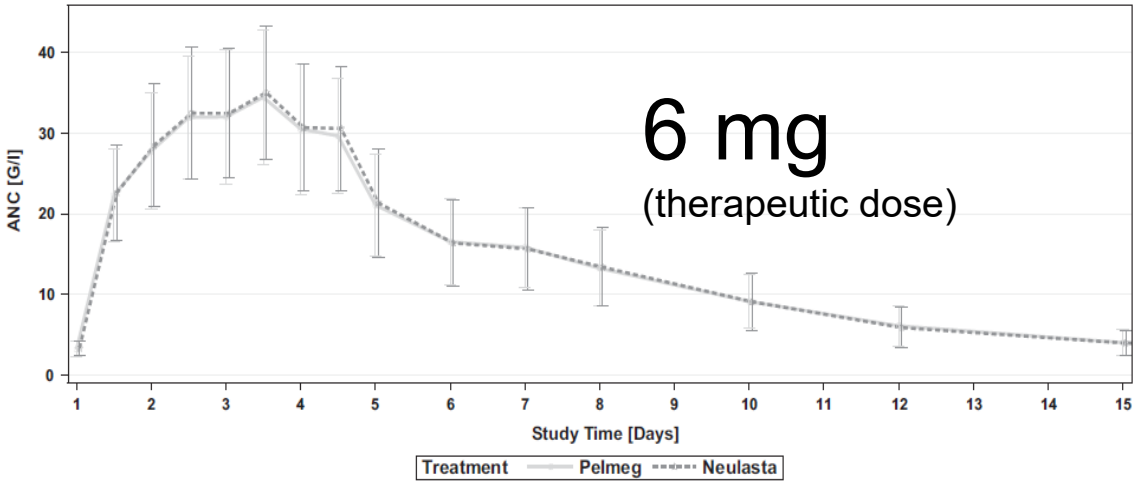
How can we ensure same safety and immunogenicity?

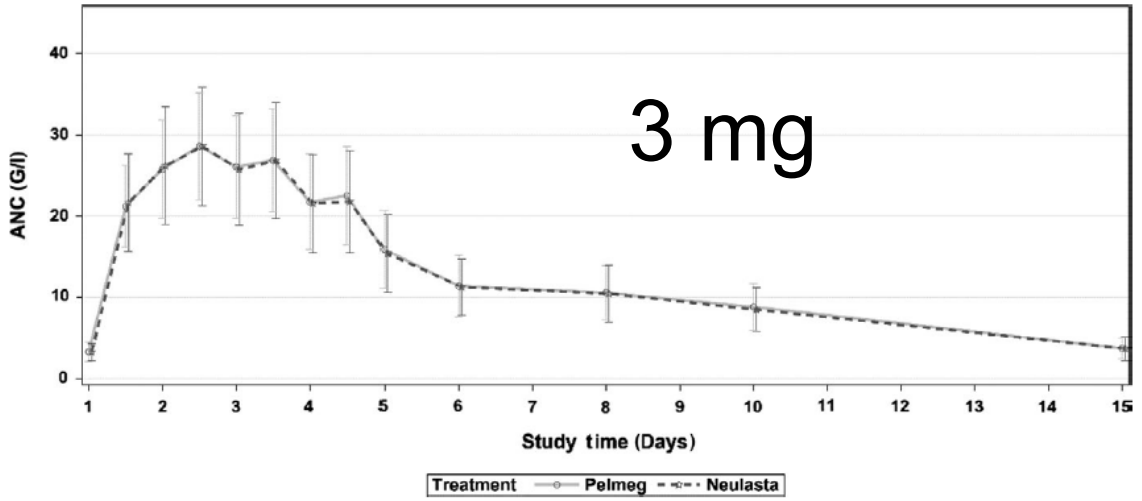
- Comparable safety is the result of:
  - Sameness of structure and functions, which result in same efficacy and same target related safety profile
    - Note: Safety profile of biotherapeutics is largely predicted from on-target effects
  - Control of other safety relevant factors (e.g. contaminants, process impurities) by today's quality standards
- Comparable immunogenicity is the result of:
  - Identicality of the amino acid sequence
    - Same T-cell epitopes, which are linear peptides formed by degradation of a protein
  - Control of risk factors which may potentially increase unwanted product related immunogenicity
    - Keeping impurities low, such as aggregates, non-human glycans etc.
    - Ensured by today's quality standards
- Comparative clinical pharmacokinetic trial delivers confirmatory safety and immunogenicity data

PD biomarker - a blunt tool in biosimilar development

- Example: limited dose sensitivity of neutrophil count, an US-FDA/EMA accepted PD endpoint for pegfilgrastim
- Reduction of dose by 50 % results in only 13 % lower PD response
  - Source: two consecutive PD studies for pegfilgrastim in healthy volunteers
  - Comparing both doses in a controlled parallel design study could potentially meet predefined 80-125 % equivalence margin
  - Same study sites, study population inclusion criteria, and analytical labs used for both studies
  - Product approved in EU 2018

Study [1,2]	Dose	$AUEC_{0\text{-last}}$ Reference product
B12019-101	6 mg	7110.5
B12019-102	3 mg	6170.8
Difference	50 %	13 %





1. Roth et al. Pharmacol Res Perspect. 2019;e00503. https://doi.org/10.1002/prp2.503
2. Wessels et al. Pharmacol Res Perspect. 2019;e00507. https://doi.org/10.1002/prp2.507

AUEC: Area under the effect curve; PD biomarker: Pharmacodynamic biomarker

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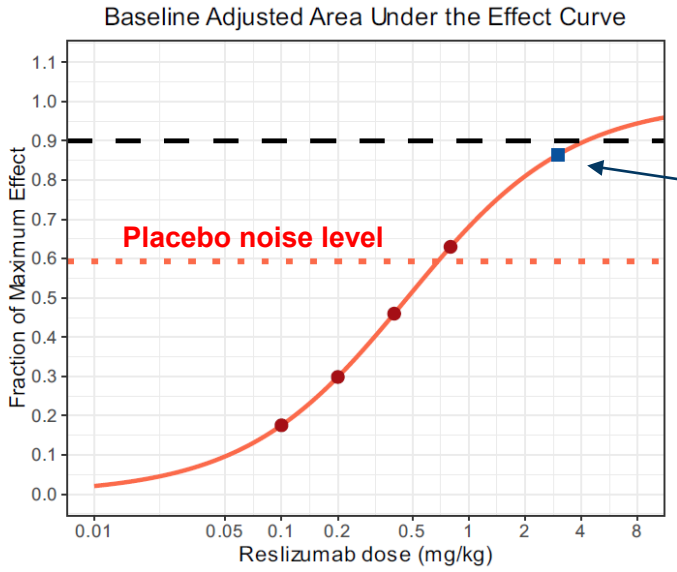
US-FDA sponsored PD pilot studies revealed issues with dose sensitivity and/or high baseline noise

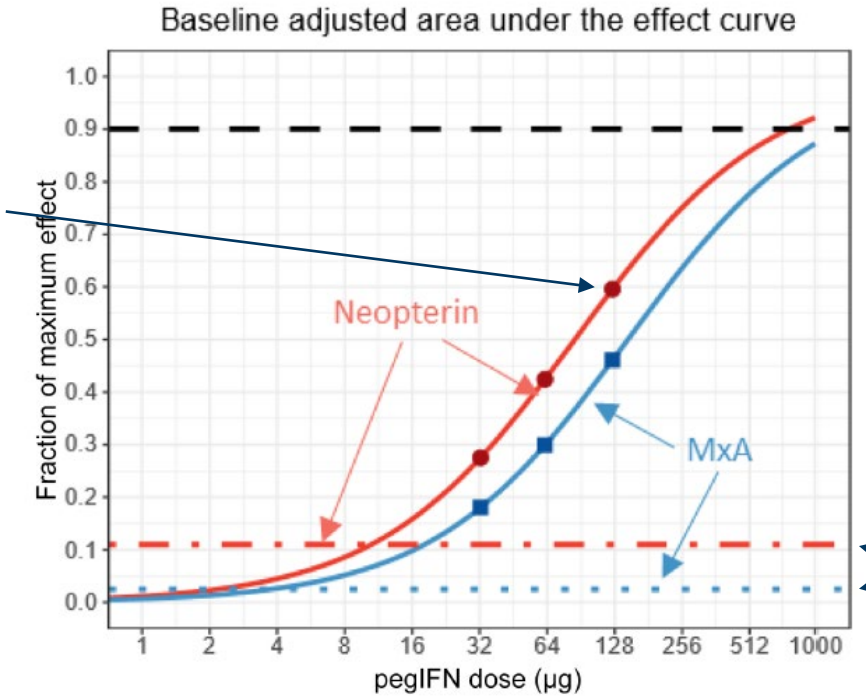
Example for antagonistic therapeutic
Anti-IL5 mAb; PD marker: eosinophils count [1]



Therapeutic dose

Result:
50 % dose reduction results in 32 % lower simulated AUEC eosinophils response

Example for agonistic therapeutic
Peginterferon ß1a [2]



Result:
50 % dose reduction results in 16 % lower measured and 30 % lower simulated AUEC neopterin response

Placebo noise level

- Issues with antagonists: difference between placebo noise and saturation of effect is small, which limits sensitivity for differences
- Issues with agonists: low sensitivity for differences even in best case scenarios

1. Adapted from Gershuny et al. Clin Pharmacol Ther, 113: 80-89. https://doi.org/10.1002/cpt.2760
2. Adapted from Florian et al. Clin Pharmacol Ther, 113: 339-348. https://doi.org/10.1002/cpt.2784

AUEC: Area under the effect curve; PD marker: Pharmacodynamic biomarker; mAb: monoclonal antibody; IL5: Interleukin 5

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Conclusions

- Regulatory science has evolved and keeps doing so
- Any study involving human subjects must take particular care to contribute new knowledge not otherwise obtainable
  - We should only conduct clinical studies that provide decisive information for biosimilar evaluation
  - Non-decisive studies use patients whose time (and accompanying resources) would be better off participating in studies which foster progress of healthcare
- Comparative clinical efficacy was never a decisive criteria in biosimilar development in EU/US
- Pharmacodynamic biomarker studies are a blunt tool in biosimilar development and do not provide additional knowledge on top of what a robust analytical package together with clinical pharmacokinetic study can provide
  - The existence of a PD biomarker does not by itself make it suitable for biosimilar development
- Regulatory science enables streamlined clinical biosimilar development without comparative clinical efficacy studies, based on:
  - A robust analytical package including a comprehensive panel of precise functional assays
  - Comparative clinical pharmacokinetic study

Thank you

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Speaker #2

Elena Guillen Benitez, MD, PhD candidate, Hospital Clinic de Barcelona

- Medical doctor specialized in Clinical Pharmacology currently working in Hospital Clinic (Barcelona, Spain). PhD candidate at Universitat Autonoma Barcelona.
- Experience in biologics, biosimilars, advanced therapies and innovational products.
- Since September 2021, conducting research on biosimilar regulation, as part of EMA´s Collaborating National Expert programe, and englobed in part of a doctoral thesis.

Supporting tailored clinical programs for biosimilar monoclonal antibodies: **the data behind, a quality perspective**

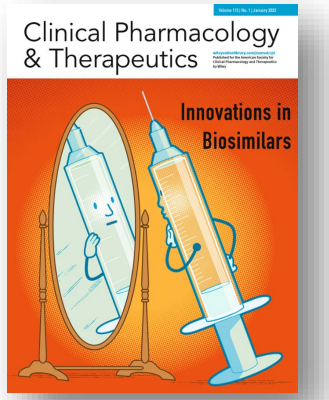
Elena Guillén Benítez

MD, Clinical Pharmacologist. Hospital Clinic (Barcelona)

PhD Candidate. Universitat Autònoma de Barcelona

IPRP Conference – virtual 12-13 September 2023

Disclaimer: The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies with which the authors are affiliated.



A data driven approach to support tailored clinical programmes for biosimilar monoclonal antibodies

How much does the outcome of clinical efficacy trials matter in regulatory decision making for biosimilars?

Accepted for publication (BioDrugs)

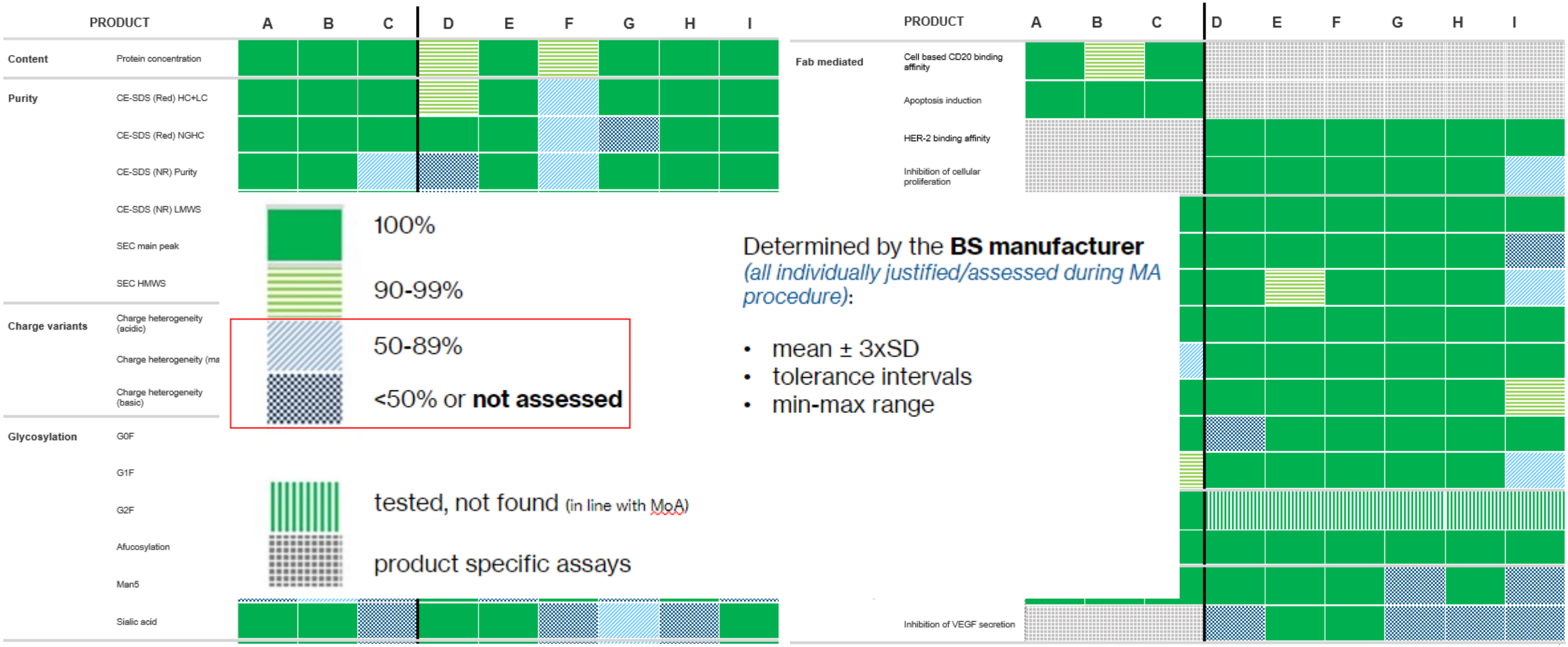
Nadine Kirsch-Stefan, Elena Guillen, Niklas Ekman, Sean Barry, Verena Knippel, Sheila Killalea, Martina Weise, Elena Wolff-Holz

Disclaimer: The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies with which the authors are affiliated.

Focus

- **Quality** results
- Submitted dossiers, EPARs and withdrawal AR to EMA
- Different mAbs: 7 adalimumabs, 5 bevacizumabs, 4 rituximabs and 7 trastuzumabs
- Includes **withdrawn** applications

Can product comparability be based solely on quality considerations?



Kirsch-Stefan N, Guillen E, Ekman N, Barry S, Knippel V, Killalea S, Weise M, Wolff-Holz E. (2023) Does the outcome of clinical efficacy trials matter in regulatory decision making for biosimilars? [Manuscript submitted for publication in BioDrugs]

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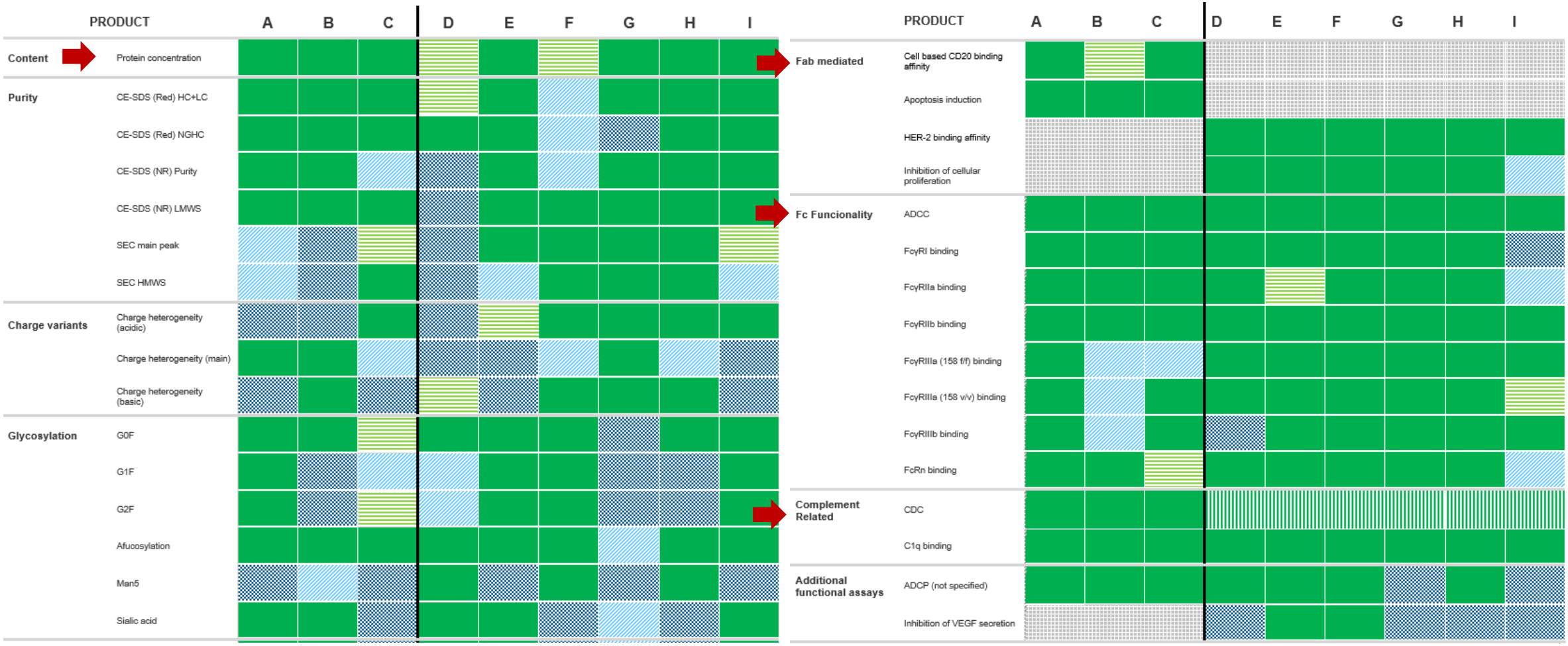

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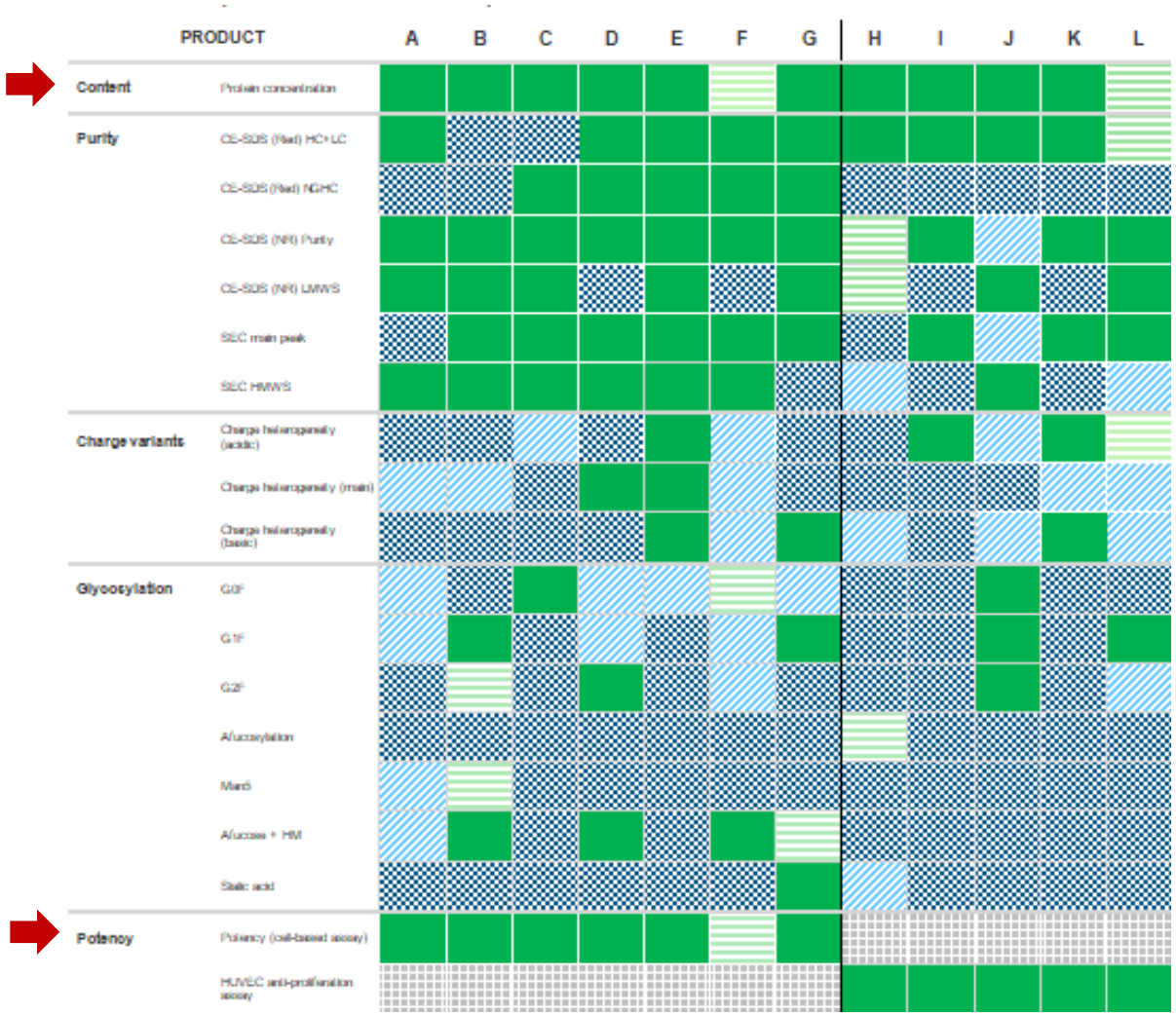

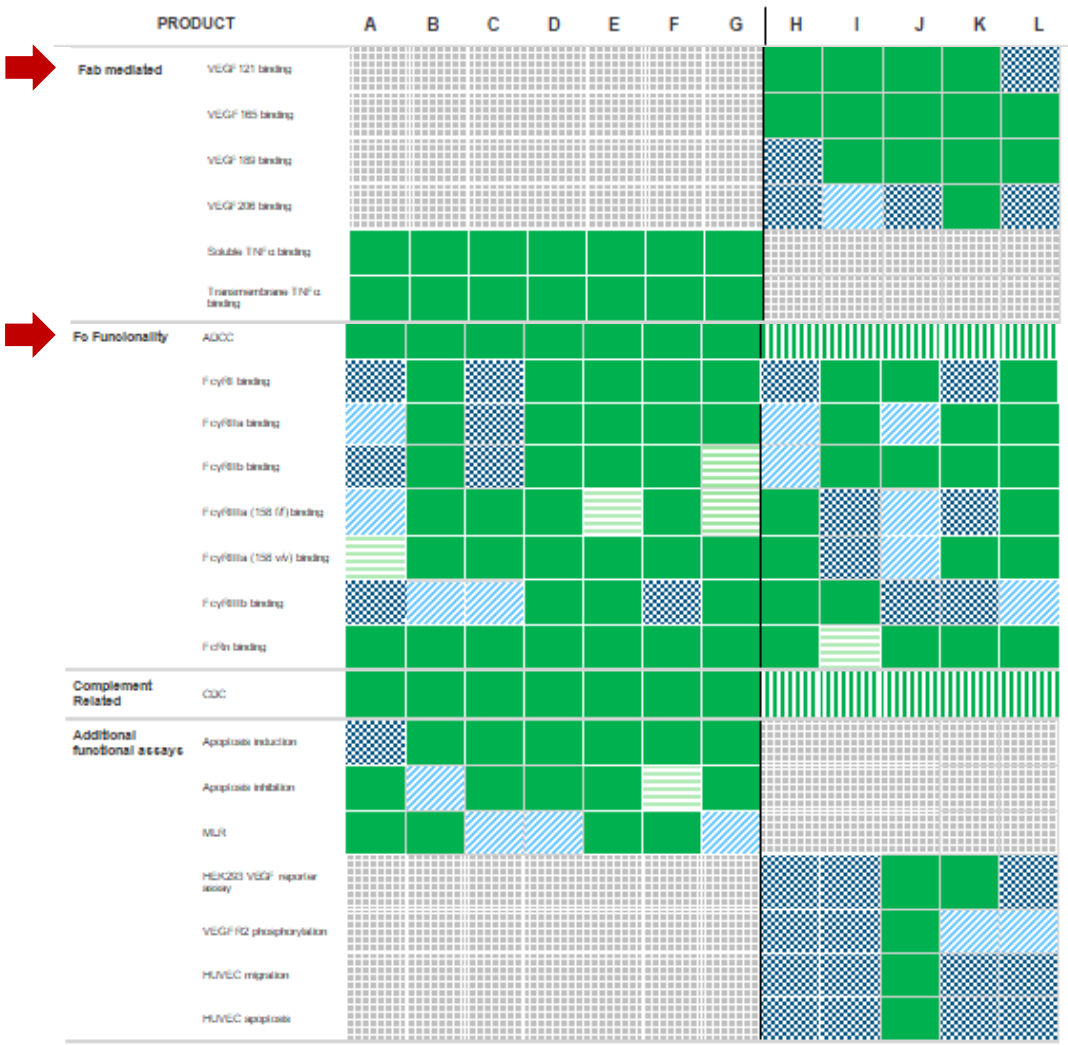

Guillen E, Ekman N, Barry S, Weise M, Wolff-Holz E. A Data Driven Approach to Support Tailored Clinical Programs for Biosimilar Monoclonal Antibodies. Clin Pharmacol Ther. 2023;113:108–23. doi:10.1002/cpt.2785

Can product comparability be based solely on quality considerations?

Content	Protein Content (UV-280)
Primary structure	Molecular weight/intact mass (RPLC-UV/MS)
	Amino acid sequence (Peptide mapping)
	N-terminal sequencing (Peptide mapping, Edman sequencing)
	C-terminal sequencing (Peptide mapping)
	Peptide mapping (Peptide mapping)
	Disulfide bond analyses (Peptide mapping)
	Free thiols (Ellmans test, FLR)
Higher Order Structure	Secondary structure (FTIR)
	Secondary- and tertiary structure (Far and Near UV Circular Dichroism)
	Protein folding (Intrinsic and extrinsic fluorescence)
	Thermal stability (DSC)
	Tertiary structure (1D 1H NMR, 2D 1H-1H NOESY NMR, 2D-NMR, HDX, X-ray crystalography, Antibody conformational array)
Protein modifications	N-term Pyroglutamate (Peptide mapping)
	C-terminal lysine (Peptide mapping, CEX)
	Iso-aspartate (Peptide mapping)
	Deamidation (Peptide mapping)
	Oxidation (Peptide mapping)
	Glycation (BAC)
	Succinimidation (Peptide mapping)
	Isomerisation (Peptide mapping)
	Proline amide (Peptide mapping)
	Thioether (Peptide mapping)
	Cysteinylation (Peptide mapping)
Glycosylation	N-glycan profile (LC-ESI-MS/MS, 2-AB labeling HILIC-UPLC)
	Afucosylation (LC-ESI-MS/MS, 2-AB labeling HILIC-UPLC)
	High mannose (LC-ESI-MS/MS, 2-AB labeling HILIC-UPLC)
	Sialylation (LC-ESI-MS/MS, 2-AB labeling HILIC-UPLC)
	G0F (LC-ESI-MS/MS, 2-AB labeling HILIC-UPLC)
	G1F (LC-ESI-MS/MS, 2-AB labeling HILIC-UPLC)
	G2F (LC-ESI-MS/MS, 2-AB labeling HILIC-UPLC)
	Galactosylation (LC-ESI-MS/MS, 2-AB labeling HILIC-UPLC)
Purity/impurity profile and charged variants	Size heterogeneity (SEC, CE-SDS reducing and non-reducing, SV-AUC, SEC-MALS, DLS, FFF)
	Hydrophobic heterogeneity (HIC)
	N-linked glycosylation site (LC-ESI-MS/MS)
	Charge heterogeneity (CEX-HPLC, iCIEF, iCE, cIEF, IEC-HPLC)
Fab mediated	soluble TNF-binding (ELISA, SPR, FRET)
	membrane TNF-binding (cell-based assay)
	TNF-α neutralisation (NF-kB reporter, viability/cell death)
Fc and complement mediated	ADCC *e.g. for one product, up to 20 assays were performed, including: • NK-PBMC ADCC using healthy and patient blood • Whole blood ADCC using healthy and patient blood • FcγRIIIa ADCC reporter • Addition of serum to these assays • Addition of IgG to these assays
	FcγRI binding (SPR)
	FcγRIIa (131H, 131R) binding (SPR)

Content	Protein Content (UV-280)
Primary structure	Molecular weight (RPLC-UV/MS)
	Intact mass/reduced mass (LC-ESI-MS)
	Isoelectric point (cIEF)
	Amino acid sequence (peptide mapping)
	N-terminal sequencing (Peptide mapping, Edman sequencing)
	C-terminal sequencing (Peptide mapping)
	Amino acid sequence (Peptide mapping)
	Disulfide bond analyses (Peptide mapping)
	Free thiols (Ellmans test)
Higher Order Structure	Secondary structure (FTIR, Far and Near UV Circular Dichroism)
	Tertiary structure (Far and Near UV Circular Dichroism, FL)
	Protein folding (Intrinsic and extrinsic fluorescence)
	Thermal stability (DSC)
	Epitope mapping (HDX-MS)
	Di-sulfide bridging (RP-HPLC-ESI-MS, non-reduced peptide mapping)
Protein modifications	Deamidation (Peptide mapping)
	Oxidation (Peptide mapping)
	Glycation (BAC)
	Aspartate Isomerisation (Peptide mapping)
	Thioether (Peptide mapping)
	Cysteinylation (Peptide mapping)
Glycosylation	N-glycan profile (peptide mapping, LC-ESI-MS/MS, HILIC-UPLC)
	O-glycosylation (peptide mapping)
	Ng-HC and p75 (CE-SDS, reduced)
	Afucosylation (NP-HPLC)
	Fucosylation (NP-HPLC)
	High mannose (NP-HPLC)
	Sialylation (NP-HPLC, UHPLC-FLR)
	G0F (LC-ESI-MS/MS, 2-AB labeling HILIC-UPLC)
	G1F (LC-ESI-MS/MS, 2-AB labeling HILIC-UPLC)
	G2F (LC-ESI-MS/MS, 2-AB labeling HILIC-UPLC)
	Galactosylation (NP-HPLC)
Purity/ impurity profile and charge variants	Size heterogeneity (SEC, CE-SDS non-reduced and reduced, CGE non-reducing and reducing, SV-AUC, SEC-MALS, DLS, FFF)
	Particles (MFI)
	Charge heterogeneity (CEX-HPLC, iCIEF, cIEF)
	Hydrophobic heterogeneity (HIC)
Fab mediated	VEGF121 binding (HUVEC-cell based assay, SPR, ELISA)
	VEGF165 binding (HUVEC-cell based assay, SPR, ELISA)
	VEGF189 binding (HUVEC-cell based assay, SPR, ELISA)
	VEGF206 binding (HUVEC-cell based assay, SPR, ELISA)
	VEGF B, C, D binding (BLI)
	HUVEC neutralisation assay (cell-based assay)
	VEGFR phosphorylaton inhibition (cell-based assay)
	Cell signaling assay (HEK293 RGA)
	KDR/KDR dimerization assay (cell-based assay)

Guillen E, Ekman N, Barry S, Weise M, Wolff-Holz E. A Data Driven Approach to Support Tailored Clinical Programs for Biosimilar Monoclonal Antibodies. Clin Pharmacol Ther. 2023;113:108–23. doi:10.1002/cpt.2785

How were queries resolved?

BEVACIZUMAB	QA	Percentage of batches within the similarity range	How resolved
Product L	Protein content	≥90% of batches	The small difference in protein content was concluded be of no clinical relevance. Batch-to-batch variability of the biosimilar within the expected range.
Product L	Binding to VEGF 121	<50% of batches or not done	High similarity for binding to other VEGF isoforms confirmed using orthogonal methods
Product H	Binding to VEGF 189	<50% of batches or not done	High similarity for binding to other VEGF isoforms confirmed using orthogonal methods
Product H, I, J, L (all except K)	Binding to VEGF 206	Variable, often < 90%, see Table 1	High similarity for binding to other VEGF isoforms confirmed using orthogonal methods VEGF 206 is a less frequent isoform in human tissues (39)
Product I	Binding to FcRn	≥90% of batches	Based on regulatory experience and the results from the comparative PK study, the minor difference was seen as negligible.
Product H – L (all)	Binding to several FcγReceptors	variable, see Table 1	Binding to FcγReceptors are not considered critical for the mode of action of bevacizumab.
Product H – L (all)	Glycosylation (7 attributes)	Variable, often < 90%, see Table 1	Due to the lack of Fc functions for bevacizumab, glycosylation pattern is not critical for bevacizumab. The PK profiles demonstrated similar.
Products H – L (all)	Purity testing	Variable, often < 90%, see Table 1	Based on regulatory experience, the small difference was seen as negligible.
Products H – L (all)	Charge variants	Variable, often < 90%, see Table 1	Acceptable based on product understanding.
Products H,I,K,L (all except J)	Additional functional assays	Variable, often < 90%, see Table 1	The assays are not considered as highly critical, differences accepted based on the totality of evidence presented for similarity.

Guillen E, Ekman N, Barry S, Weise M, Wolff-Holz E. A Data Driven Approach to Support Tailored Clinical Programs for Biosimilar Monoclonal Antibodies. Clin Pharmacol Ther. 2023;113:108–23. doi:10.1002/cpt.2785

How were queries resolved?

RITUXIMAB	QA	Percentage of batches within the similarity range	How resolved
Product B	Cell based CD20 binding assay	≥ 90% of batches	Minor difference not expected to affect the clinical performance of the product. Slight differences explained and justified by the method variability.
Products B and C	Binding to several Fcγ-Receptors (FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa-158 f/f and FcγRIIIb	Variable, see Online Resource 1	Minor differences in binding results, similarity confirmed in cell-based functional assays.
Product B	Binding to FcγRIIIa 158 v/v	80-50% of batches	Viewed as sufficient based on ADCC assay results.
Product C	Binding to FcRn	≥ 90% of batches	Based on regulatory experience and the results from the comparative PK study, the minor difference was seen as negligible.
Product A – C (all)	Glycosylation (6 attributes)	Variable, often < 90%, see Online Resource 1	Similarity confirmed in cell-based functional assays. No clinically significant difference in PK profile.
Product A – C (all)	Purity testing	Variable, often < 90%, see Online Resource 1	Based on regulatory experience, the small difference was seen as negligible. In most cases, purity of biosimilar was marginally increased.
Product A – C (all)	Charge variants	Variable, often < 90%, see Online Resource 1	Acceptable based on product understanding.

Kirsch-Stefan N, Guillen E, Ekman N, Barry S, Knippel V, Killalea S, Weise M, Wolff-Holz E. (2023) Does the outcome of clinical efficacy trials matter in regulatory decision making for biosimilars? [Manuscript submitted for publication in BioDrugs]

What about the withdrawn applications?

Cases			Quality		Clinical	
			biosimilarity	general Q	PK/PD	E/S/I
SCENARIO 1	**IgG type**	**Date of MA**	+	+	+	+
Infliximab 1	IgG1	10/09/2013				
Infliximab 2	IgG1	26/05/2016				
Infliximab 3	IgG1	18/05/2018				
Etanercept 1	Mod. IgG1	13/01/2016				
Etanercept 2	Mod. IgG1	23/06/2017				
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Adalimumab 2	IgG1	24/08/2017				
Adalimumab 3	IgG1	17/09/2018				
Adalimumab 4	IgG1	02/04/2019				
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Adalimumab 7	IgG1	15/11/2021				
Rituximab 1	IgG1	15/06/2017				
Rituximab 2	IgG1	13/07/2017				
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Bevacizumab 5	IgG1	26/03/2021				
Bevacizumab 6	IgG1	21/04/2021				
Bevacizumab 7	IgG1	17/08/2022				
Trastuzumab 1	IgG1	09/02/2018				

Analysis of MAA outcome

Cases			Quality		Clinical	
			biosimilarity	general Q	PK/PD	E/S/I
SCENARIO 2	**IgG type**	**Date of MA**	-	-	+	+
Rituximab 4	IgG1	not approved				
Trastuzumab 5	IgG1	not approved				
SCENARIO 3	**IgG type**	**Date of MA**	+	+	-	+
Adalimumab 8	IgG1	10/11/2017				
Adalimumab 9	IgG1	26/07/2018				
SCENARIO 4	**IgG type**	**Date of MA**	+	+	+	-
Trastuzumab 6	IgG1	15/11/2017				
Trastuzumab 7	IgG1	16/05/2018				
SCENARIO 5	**IgG type**	**Date of MA**	-	-	-	-

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What about the withdrawn applications?

Key quality requirements	Withdrawn Rituximab biosimilar candidate	Withdrawn trastuzumab biosimilar candidate
In-depth knowledge of the RP		
The main MoA is known and demonstrable		
CQA are known		
Sufficient (representative) batches of the RP are analyzed		
Adequately established QTPP		
Attributes of the biosimilar candidate		
The manufacturing process is well controlled. Release and stability specification limits are appropriate		
The quality profile of the batches used to generate clinical biosimilarity data is representative of the quality profile of the proposed commercial batches		
Suitable and appropriately qualified analytical methods used for analytical and functional similarity assessment		
Biosimilarity exercise		
Adequate overall approach for demonstrating biosimilarity		

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Conclusions

Can product comparability be based on quality (plus PK) considerations?

1. Yes, the **extent of Q data that is analysed is considerable**: numerous orthogonal and comprehensive methods are used to analyse multitude of QAs.
2. For **critical QAs** of adalimumab, bevacizumab, trastuzumab and rituximab approved biosimilars >90% (in most cases 100%) of batches were within range
3. Other, less critical QAs have a **varying concordance** with EU-RP similarity range, which **may be viewed as acceptable based on further Q analysis to resolve queries**.
4. Not only is biosimilarity analysed in a Quality level, but also **general Q aspects** are comprehensively looked into.

How are queries resolved?

1. For approved products some **uncertainties (variability) are expected and allowed**.
2. When resolving residual uncertainties regarding Quality data, more Quality data and clinical PK data are important to resolve residual uncertainty. Clinical efficacy data played a **limited or no role** in addressing quality concerns
3. We also have products where unsatisfactory Q packages were seen, **even with good clinical packages, supporting insensitivity of clinical trials.**

From a Q point of view there is sufficient data that **an assessment can be made on a quality level.**

Thank you for your attention

IPRP
International Pharmaceutical Regulators Programme

Speaker #3

Elena Wolff-Holz, MD, Ph.D., Biocon

Dr. Elena Wolf-Holz has recently joined Biocon Biologics Ltd as Global Head Clinical Development. Prior to that, she was a senior regulator at Germany's National Competent Authority Paul-Ehrlich-Institute for 14 years and has extensive knowledge in the development of biologic therapeutics, with a focus on cancer and immunology. Since 2016, she has been the head of the Biosimilar Medicinal Products Working Party (BMWP) within the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP). Elena has also been a member of the Scientific Advice Working Party (SAWP) of the CHMP since 2017. With over 28 years of experience, she has held several leadership positions in clinical development and medical marketing functions at major biotech companies, including Centocor Inc (now Janssen, J&J) and Amgen, in both US and Germany.

As a result of her work, Elena has earned multiple authorships and co-authorships in esteemed scientific journals and delivered numerous presentations at national and international conferences. Elena obtained her M.D. degree from Heidelberg University and completed a postdoctoral fellowship at Harvard Medical School.

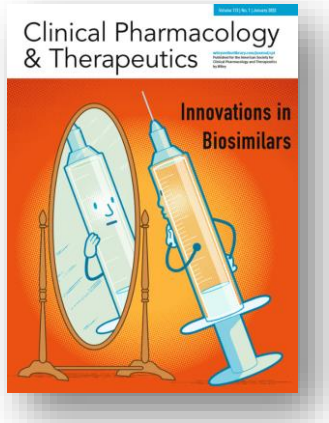
Does the outcome of clinical efficacy trials matter in regulatory decision making for biosimilars?

Elena Wolff-Holz, MD PhD

Biocon Biologics Ltd

IPRP Conference – virtual 12-13 September 2023

Disclaimer: The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies with which the authors are affiliated.



A data driven approach to support tailored clinical programmes for biosimilar monoclonal antibodies

How much does the outcome of clinical efficacy trials matter in regulatory decision making for biosimilars?

Accepted for publication (BioDrugs)

Nadine Kirsch-Stefan, Elena Guillen, Niklas Ekman, Sean Barry, Verena Knippel, Sheila Killalea, Martina Weise, Elena Wolff-Holz

Disclaimer: The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies with which the authors are affiliated.

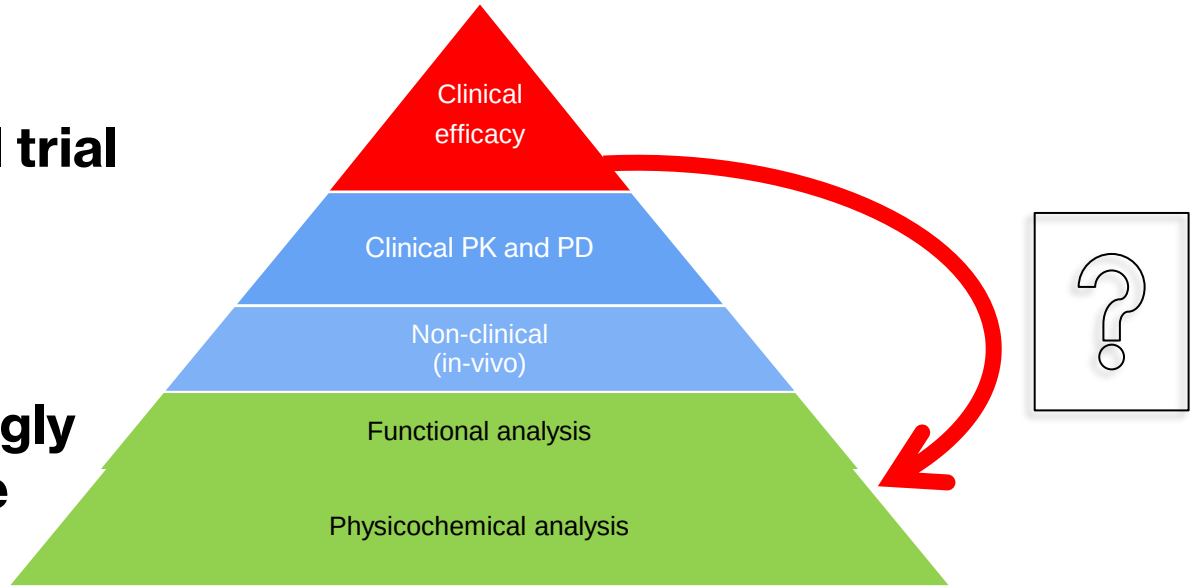
Remaining question and concern:

Could a failed clinical trial

lead regulators to **not approve** a biosimilar candidate

that otherwise would have been erroneously approved because of “seemingly good” Quality data?

Failed clinical trial



Seemingly positive

Remaining question and concern:

Could a failed clinical trial

lead regulators to **not approve** a biosimilar candidate

that otherwise would have been erroneously approved because of “seemingly good” Quality data?

Method

All **assessed** biosimilar mab/fusion proteins

33 mAbs/3 fusion proteins (July 2012-Nov 2022)

Outcome of the MAA

- EPARs
- Categorized: hypothetical scenarios

Number/nature of issues raised in first regulatory assessment

- List of questions (D120 reports)
- ***Anonymized***

23 mAbs: 7 adalimumabs, 5 bevacizumabs, 4 rituximabs and 7 trastuzumabs (includes **withdrawn** applications)

Analytical and functional data

- Product dossiers (raw data)
- Reviewed
- ***Anonymized***
- Categorized: % of BS batches within the **similarity range**

Clinical data

- EPARs
- Analyzed

29 / 36 outcome of MAAs: quality and clinical data viewed as supportive and aligned

Cases			Quality		Clinical	
			biosimilarity	general Q	PK/PD	E/S/I
SCENARIO 1	**IgG type**	**Date of MA**	+	+	+	+
Infliximab 1	IgG1	10/09/2013				
Infliximab 2	IgG1	26/05/2016				
Infliximab 3	IgG1	18/05/2018				
Etanercept 1	Mod. IgG1	13/01/2016				
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Bevacizumab 6	IgG1	21/04/2021				
Bevacizumab 7	IgG1	17/08/2022				
Trastuzumab 1	IgG1	09/02/2018				

Analysis of MAA outcome

Cases			Quality		Clinical	
			biosimilarity	general Q	PK/PD	E/S/I
SCENARIO 2	**IgG type**	**Date of MA**	-	-	+	+
Rituximab 4	IgG1	not approved				
Trastuzumab 5	IgG1	not approved				
SCENARIO 3	**IgG type**	**Date of MA**	+	+	-	+
Adalimumab 8	IgG1	10/11/2017				
Adalimumab 9	IgG1	26/07/2018				
Etanercept 3	Mod. IgG1	20/05/202				
SCENARIO 4	**IgG type**	**Date of MA**	+	+	+	-
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Trastuzumab 7	IgG1	16/05/2018				
SCENARIO 5	**IgG type**	**Date of MA**	-	-	-	-

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2 / 36 outcome of MAAs: quality was unconvincing but clinical trial was successful

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			biosimilarity	general Q	PK/PD	E/S/I
SCENARIO 1	**IgG type**	**Date of MA**	+	+	+	+
Infliximab 1	IgG1	10/09/2013				
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Infliximab 3	IgG1	18/05/2018				
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5 / 36 outcome of MAAs: quality was convincing with uncertainties in clinical which were resolved

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			biosimilarity	general Q	PK/PD	E/S/I
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- Product dossiers (raw data)
- Reviewed
- ***Anonymized***
- Categorized: % of BS batches within the **similarity range**

Clinical data

- EPARs
- Analyzed

Discrepancies in clinical attributes and how the resulting uncertainty during MAA was resolved

ADALIMUMAB	Clinical attribute	Observation	How resolved
Hyrimoz/Halimatoz/ Hefiya; Hulio and Amsparity	PK	Unity was not included in the 90% CI	1.Permissable (44) 2.Relevant QAs (high mannose, sialic acid) showed close similarity.
Hyrimoz/Halimatoz/ Hefiya; and Hulio)	PK	Initial study failed to meet predefined acceptance range	1.Root cause analysis 2.Subsequently, successful PK studies were submitted.

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Discrepancies in clinical attributes and how the resulting uncertainty during MAA was resolved

TRASTUZUMAB	Clinical attribute	Observation	How resolved
Ontruzant	bpCR (RD)	95% CI not fully contained within prespecified equivalence margin	1. Justified by confounding effect of ADCC shift in reference lots 2. Conclusion of biosimilarity based on the overall biosimilarity assessment
Kanjinti	pCR in breast tissue and axilary lymph nodes (RD and RR)	95% CI not fully contained within prespecified equivalence margin	1. Justified by confounding effect of ADCC shift in reference lots 2. Additional functional analysis for ADCC performed 3. Additional analysis adjusting for subjects exposed to IMP with low ADCC 4. Conclusion of biosimilarity based on overall biosimilarity assessment
Kanjinti	pCR (only breast) (RD and RR)-except RD in PP	95% CI not fully contained within prespecified equivalence margin	1. Justified by confounding effect of ADCC shift in reference lots 2. Additional functional analysis for ADCC performed 3. Additional analysis adjusting for subjects exposed to IMP with low ADCC 4. Conclusion of biosimilarity based on overall biosimilarity assessment
Zercepac	DOR, PFS, OS	Seemingly better efficacy (HR<1)	1. Study not designed to demonstrate equivalence for PFS 2. No significant differences found in second interim analysis 3. Conclusion of biosimilarity based overall biosimilarity assessment
Withdrawn rituximab biosimilar candidate	Deaths	Eight patients died in the product arm versus none in the reference arm	1. Chance finding likely 2. Study not designed to evaluate hard clinical endpoints

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Analytical and functional data

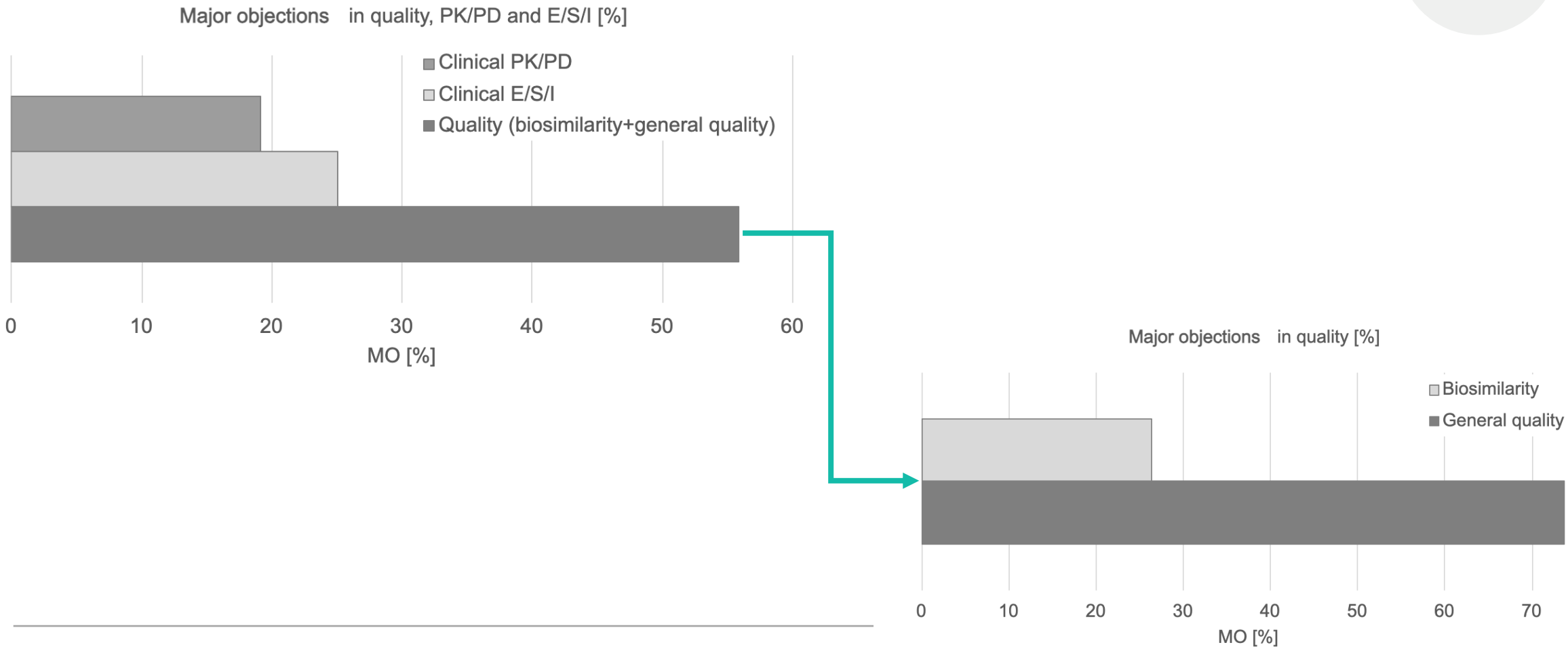
- Product dossiers (raw data)
- Reviewed
- ***Anonymized***
- Categorized: % of BS batches within the **similarity range**

Clinical data

- EPARs
- Analyzed

Analysis of Major objections (MO) raised in the first assessment report D120 of the MAA procedure

Comparison of the percentage of MO raised with regard to quality/CMC or clinical aspects of the MAAs (the sum of MO (quality/CMC, clinical PK/PD and clinical E/S/I) was calculated and normalised to the number of all MO)



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Most frequent Major Objections

	MO REGARDING	MOST FREQUENT QUESTIONS FOR MO
QUALITY	**Formal aspects**	• GMP certificate missing • EU GMP inspection pending, • provision of a risk evaluation concerning the presence of nitrosamine impurities (EMA/369136/2020, EMA/409815/2020).
QUALITY	**Biosimilarity**	• difference in critical quality attributes • insufficiency of ADCC assays used to conclude on biosimilarity • insufficient number of batches used for biosimilarity exercise, testing panel incomplete.
QUALITY	**General quality**	• manufacturing process, • in-process controls, • comparability of clinical versus commercial batches of the biosimilar candidate, • consistency of the manufacturing process, • missing information or data to assess quality and comparability of the biosimilar candidate.
CLINICAL	**PK/PD**	• investigation of observed PK differences/difference in biosimilarity regarding PK • clinical justification of the pre-specified margins of PK comparability • PD analysis in second therapeutic area in case of extrapolation to all indications of RP • submission of individual patient data
CLINICAL	**E/S/I – formal aspects**	• confirmation of compliance with ethical requirements (Directive 2001/20/EC) or with the principles of GCP and of the Declaration of Helsinki, • pending GCP inspections • one-year safety and immunogenicity data not yet submitted at timepoint of initial submission in line with EMA Guideline (EMEA/CHMP/BMWP/42832/2005 Rev. 1)
CLINICAL	**E**	• failed primary endpoint analysis • differences observed for RP compared to published data.
CLINICAL	**S/I**	• additional safety and immunogenicity data in case of observed ADAs, • insufficient submitted data with respect to i.e. ADA and occurrence of neutralizing antibodies, • justification for observed differences in safety profile.

Kirsch-Stefan N, Guillen E, Ekman N, Barry S, Knippel V, Killalea S, Weise M, Wolff-Holz E. (2023) Does the outcome of clinical efficacy trials matter in regulatory decision making for biosimilars? [Manuscript submitted for publication in BioDrugs]

In 67% of cases, First Assessment (D120) quality plus clinical was aligned

Analysis of questions raised in the first assessment report of the MAA procedure: categorization of Bs candidates into six different cases with no MO (green) or at least one MO (red) in the respective area.

Case	Quality MO	Clinical MO		% of biosimilar candidates applicable to each case*
		PK/PD	E/S/I	
1				42
2				11
3				22
4				25

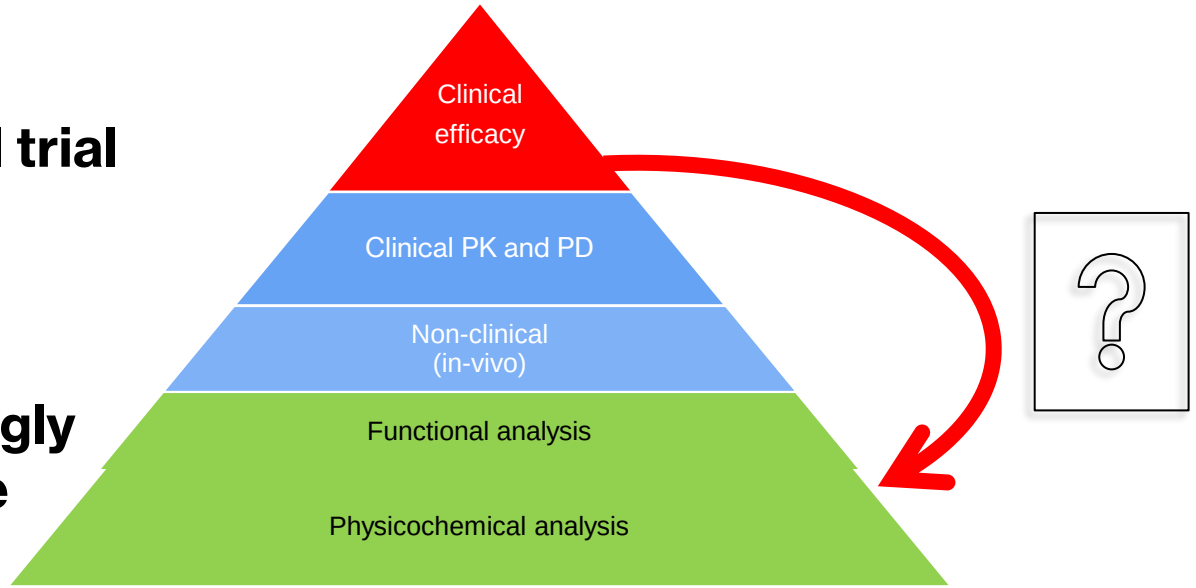
Kirsch-Stefan N, Guillen E, Ekman N, Barry S, Knippel V, Killalea S, Weise M, Wolff-Holz E. (2023) Does the outcome of clinical efficacy trials matter in regulatory decision making for biosimilars? [Manuscript submitted for publication in BioDrugs]

In 11% of cases, First Assessment (D120) identified MO for quality part but not clinical

Case	Quality MO	Clinical MO		% of biosimilar candidates applicable to each case*
		PK/PD	E/S/I	
1				42
2				11
3				22
4				25

Kirsch-Stefan N, Guillen E, Ekman N, Barry S, Knippel V, Killalea S, Weise M, Wolff-Holz E. (2023) Does the outcome of clinical efficacy trials matter in regulatory decision making for biosimilars? [Manuscript submitted for publication in BioDrugs]

Failed clinical trial



Seemingly positive

Remaining question and concern:

Could a failed clinical trial

lead regulators to **not approve** a biosimilar candidate

that otherwise would have been erroneously approved because of “seemingly good” Quality data?

In 22% of cases, First Assessment (D120) identified MO for clinical part but not quality

Case	Quality MO	Clinical MO		% of biosimilar candidates applicable to each case*
		PK/PD	E/S/I	
1				42
2				11
3				22
4				25

Kirsch-Stefan N, Guillen E, Ekman N, Barry S, Knippel V, Killalea S, Weise M, Wolff-Holz E. (2023) Does the outcome of clinical efficacy trials matter in regulatory decision making for biosimilars? [Manuscript submitted for publication in BioDrugs]

For the **22%** of cases where MOs were raised for clinical part but not for quality:

Identified issues (MOs) for clinical were eventually accepted because of

1. Imbalances in trial arms
2. Immaturity of secondary endpoint data at the time of MAA submission
3. Changes in the QA of the RP
4. Chance findings
5. In some cases, a further in-depth sensitivity analysis improved the understanding of the clinical data and facilitated a positive conclusion.

Analytical/functional characterisation is most critical for decision making and regulatory approval

Kirsch-Stefan N, Guillen E, Ekman N, Barry S, Knippel V, Killalea S, Weise M, Wolff-Holz E. (2023) Does the outcome of clinical efficacy trials matter in regulatory decision making for biosimilars? [Manuscript submitted for publication in BioDrugs]

Conclusions

The concern, that in the **absence of comparative efficacy data**
a biosimilar candidate might be inappropriately approved
based on a "seemingly good" quality package only
is **not supported by data**

Why?

→"Seemingly good quality" will be ascertained to be truly good quality

→ Clinical data are viewed to be less sensitive and less conclusive

Conclusions

1. In the First Assessment (D120) of **33 mAbs and 3 fusion proteins** evaluated by EMA, we **found no instance where MO/queries of clinical data, including failed efficacy trials**, led to a negative overall decision.

2. In the analysis of quality and clinical packages of all 23 mAb biosimilar candidates **in no case were clinical trial data necessary to resolve residual uncertainties** regarding the quality part.

3. **The quality/CMC part of the dossier appears to be predictive for the marketing authorisation of a biosimilar candidate**, irrespective of the outcome of the clinical trial.

4. A **revision of the respective regulatory biosimilars guidelines in Europe should be considered** in order to allow a more rational use of clinical resources and improve the access to innovative and affordable medicines for patients.

Thank you !

IPRP International Pharmaceutical Regulators Programme

Speaker #4

Frank Schneider, PhD, Dipl.-Ing., Teva

- Frank Schneider is a biotechnologist with extensive experience in drug research and development from concept to authorization working at ratiopharm GmbH (Teva Pharmaceutical Industries Ltd.).
- Following completion of the PhD thesis in cancer research Frank worked for more than 20 years in the life sciences, 4 years thereof in biotech and pharmaceutical start-ups.
- As Chief Scientific Officer of a small pharmaceutical company that was specialized in selective modification/improvement of existing drugs he was responsible for drug development projects in all phases including patent issues, chemical, pharmaceutical, nonclinical and clinical development as well as regulatory affairs.
- At Teva Frank leads clinical pharmacology and biosimilar PK/PD studies and supports scientific advice meetings and submissions at different regulatory agencies.

The Role of Clinical Pharmacology Data for Waiving Clinical Efficacy Studies

Frank Schneider, PhD

Associate Director, Clinical Development

ratiopharm GmbH

ratiopharm belongs to Teva Pharmaceutical Industries Ltd.

Disclaimer

This presentation reflects the views of the author. All errors and omissions are ultimately and entirely my own.

Presentation Contents

Pharmacokinetics of Therapeutic Biologics

- **Extensive knowledge is available about PK of biologics, which are complex and depend on diverse factors** such as route of administration, physicochemical properties and binding
- Biologics are usually administered via parenteral route
  - Pathways for systemic drug absorption are affected by transport through extracellular matrix and pre-systemic elimination following sc administration
  - Distribution from blood to peripheral tissue is slow and limited
- Elimination occurs via non-specific catabolism, target mediated clearance and formation of immune complexes
- Differences in quality attributes between biosimilar and reference can have impact on absorption, distribution, metabolism and elimination (ADME)

Sensitivity of PK versus Efficacy

- **Advances in analytical techniques for structural and functional characterization allow a thorough investigation of features affecting the potency of a biosimilar**
- But, **exposure** that also determines the effect of the biosimilar is more difficult to predict from analytical data because of the nonspecific factors that can affect ADME
- **A PK study can investigate the overall effect of differences in quality on exposure**
- PK of many biosimilars can be tested in the most sensitive population of healthy subjects
  - Most biologics are target specific and have a large therapeutic window and limited off-target toxicity
  - Lower variability of PK endpoints due to less confounding factors
  - Higher sampling frequency possible
- PK equivalence testing requires usually a lower sample size compared to efficacy
- Maximum effect is often reached at doses below the recommended dose and efficacy endpoints are not sensitive to small changes in exposure

Use of PD Measures?

- **Pharmacodynamic (PD) measures are not optimal endpoints for similarity testing and should be used according to their relevance**
  - Qualified biomarkers are rarely available for biosimilar development
  - Available PD data from the reference product are often not sufficient to establish a meaningful equivalence margin for formal equivalence testing
  - High variability of PD measures and low expression levels in healthy participants lead to low sensitivity
- PD may contribute to similarity assessment and interpretation of PK results if the measured molecules have a direct impact on PK
  - Concentrations and variability of target molecules can affect PK of the drug in case of relevant target mediated drug exposure

Additional Gain from Clinical Pharmacology Studies

- **In addition to PK, clinical pharmacology studies can assess safety, local tolerability and immunogenicity**
- Safety and tolerability can be assessed blinded and more frequently
  - Also transient changes of safety parameters can be discovered
- Innate acute humoral immune responses can be assessed after single dose
  - Comparison of anti-drug antibody (ADA) in healthy participants in contrast to patients is not biased by the presence of other drugs or immune complexes
  - New technologies and assays and revised guidances improved assessment of ADA and neutralizing potential leading to higher sensitivity and better drug tolerance
- The need to evaluate formation of ADA after repeated dosing should be determined in a risk based assessment
- Extensive sampling in a clinical pharmacology study allows assessment of drug concentrations, ADA and PD (where required) over time and evaluation of possible correlations

Conclusion

> Following structural and functional analytical comparison of a biosimilar candidate and the reference product, pharmacokinetics provide the most sensitive measure to evaluate residual uncertainties.

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Speaker #5

Keith Watson, Ph.D., KRW Bio Reg Solutions

- Keith Watson is an independent regulatory consultant, owner & managing director of KRW BioReg Solutions Ltd, based in the UK
- He has > 25 years of experience working with biologics/biosimilars in pharmaceutical, consultancy, regulatory and manufacturing environments.
- A former Senior Quality assessor at the MHRA
- I has extensive experience in CMC, regulatory and policy work with respect to biosimilars
- Been involved in the development, regulatory activities and approvals of numerous biosimilars, including Remsima, the first biosimilar mAb approved in Europe.
- Via Industry positions, he was a previous Chair of IFPMA bio-therapeutics Group, and previous member of Medicine for Europe biosimilars WG, Europabio Biosimilars WG and various EFPIA sub-groups

JOINT IPRP/FDA WEBINAR

Increasing the Efficiency of Biosimilar Development Programs-- Reevaluating the Need for Comparative Clinical Efficacy Studies

Date: 12th-13th September 2023

Presentation: Comparability and Biosimilarity: Time to apply the same regulatory standard

Keith Watson Ph.D.

Owner & Managing Director

KRW BioReg Solutions Ltd

Registered in England No. 14231732

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The Science of Advice

DISCLAIMER

I am an independent regulatory consultant.

I have no conflicts of interest with any trade association, regulatory agency, non-governmental organisation or Biopharmaceutical Industry.

The views I express in this presentation are my own.

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BIOSIMILAR DEVELOPMENT

There are few if any unknowns when developing and manufacturing a biosimilar of a recombinant protein.

- The production cell line of the reference product is usually known, the fermentation and purification technologies that are used are well-established. There is lots of prior knowledge to call on (experience, literature, regulatory approvals, EPAR's)

- The manufacturing processes, because of the need for consistency, is often conservative and the core unit operations for a particular class of product is often similar and been used for years. This allows "platform approaches"[1] to be used so rarely is there a need to consider completely new configurations or unit operations.

- Strategies for assessing each quality attribute and their effect on PK, safety and efficacy are mature and lots of publicly available information including guidelines are available.

- There are a multitude of analytical tools that allow a biological to be comprehensively characterized, to the level of individual amino acids, and the same tools could discriminate minor differences in quality attributes.

- The binding and functional responses of a reference product or biosimilar to its soluble antigen or membrane receptor are quantified by a range of solid-phase and cell-based assays.

- **Importantly, regulators have extensive experience of both comparability assessments and biosimilar development**

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COMPARABILITY AND BIOSIMILARITY

- The same scientific and technical principles of comparability should also apply to the development and regulatory approval of biosimilars.

- The principles of comparability are described in ICH Q5E[2], whose cornerstone is how to assess differences in quality attributes, for this it recommends a risk-based approach, based on the intended manufacturing change. For biosimilarity the risk is automatically deemed high, mandating, in the absence of a validated PD marker, both a PK and efficacy study.

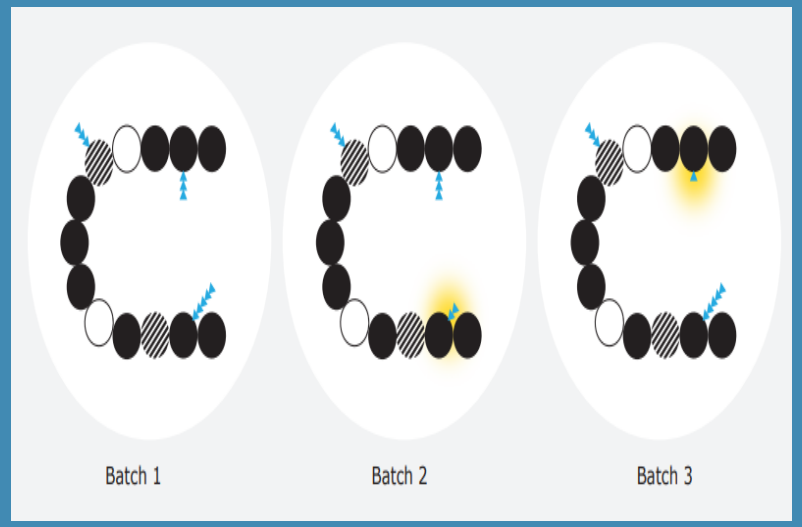
- ICHQ5E recognises the first step in assessing comparability is using a range of analytical and functional assays, if that is insufficient then non-clinical or clinical data may be required. Although biosimilars are moving away from non-clinical models, clinical data including efficacy data is demanded irrespective of the similarity of the quality attribute profile.

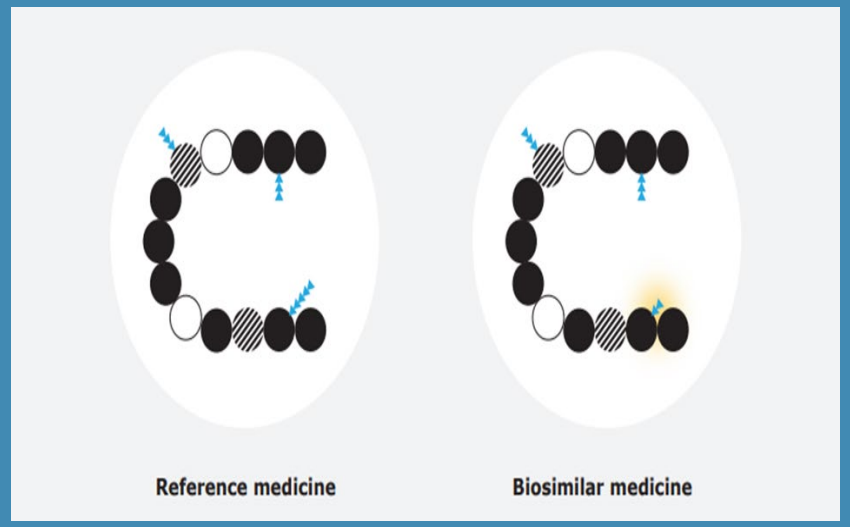
- The principles of comparability as described in ICH Q5E[2], have been used successfully for over 20 years[3,4] and rarely is additional non-clinical or clinical data required from the originator manufacturer. There are very few examples where clinical data was needed, including Aranesp® (darbepoetin alfa)[5] following a process change to a serum-free bioreactor to reduce the risk of contamination, and Humira® (adalimumab), a change in formulation and concentration to improve patient convenience[5]

REGULATORS ARE TAKING A DIFFERENT APPROACH WHEN MANAGING SIMILAR TYPES OF VARIABILITY

Consecutive batches of the same biological medicine may show a small degree of variability (yellow shadow) within the accepted ranges, for example in glycosylation (sugar molecules attached to the protein. Similarly, variability (yellow shadow) between a BS and the RP is comparable to what may occur between different batches of the same biological medicine. Minor variability, e.g. in glycosylation (represented by small blue triangles) may be allowed, while the protein's amino acid sequence (circles) and biological activity are the same.

Taken from[6] https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf





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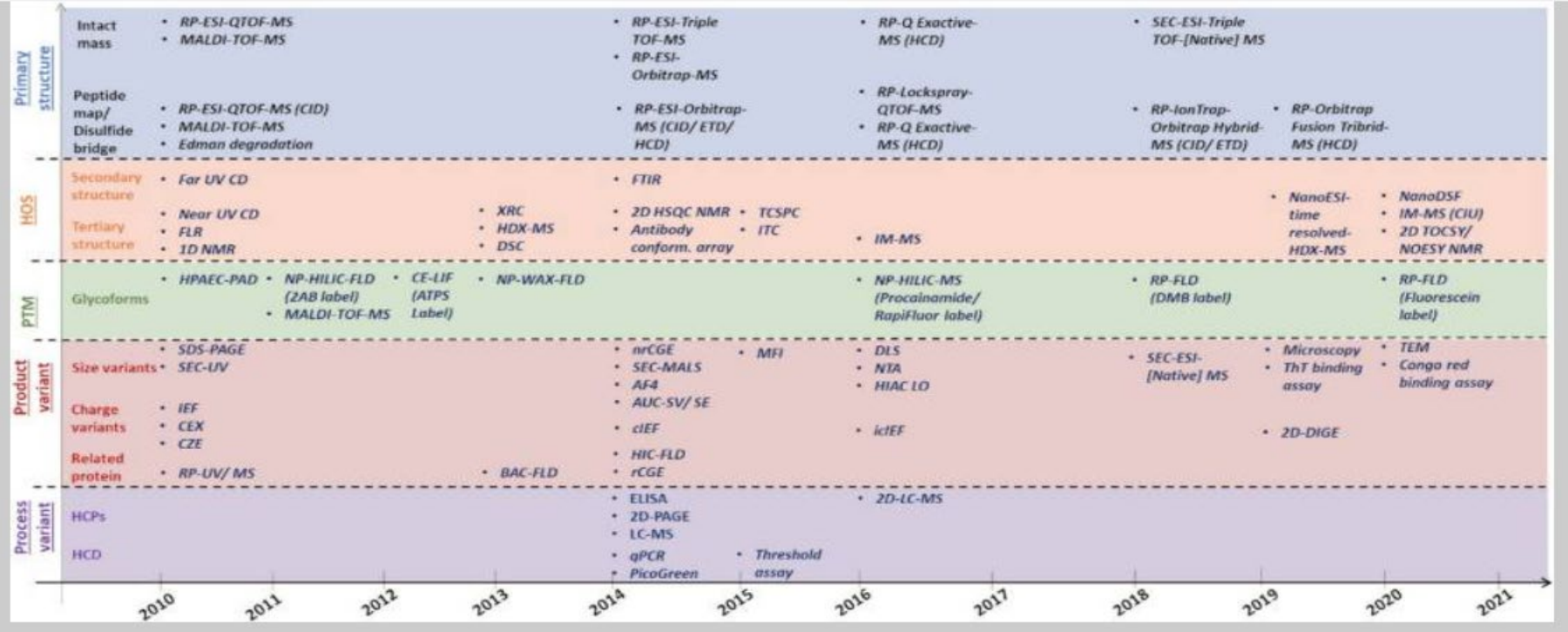
SINCE THE ONSET OF BIOSIMILAR DEVELOPMENT THERE HAS BEEN AN EVOLUTION IN ANALYTICAL PLATFORMS[7]

- Most of this has been driven by biosimilar manufacturers due to the requirement of regulators to understand, to the greatest extent possible, minor differences in attributes between the biosimilar and reference product.



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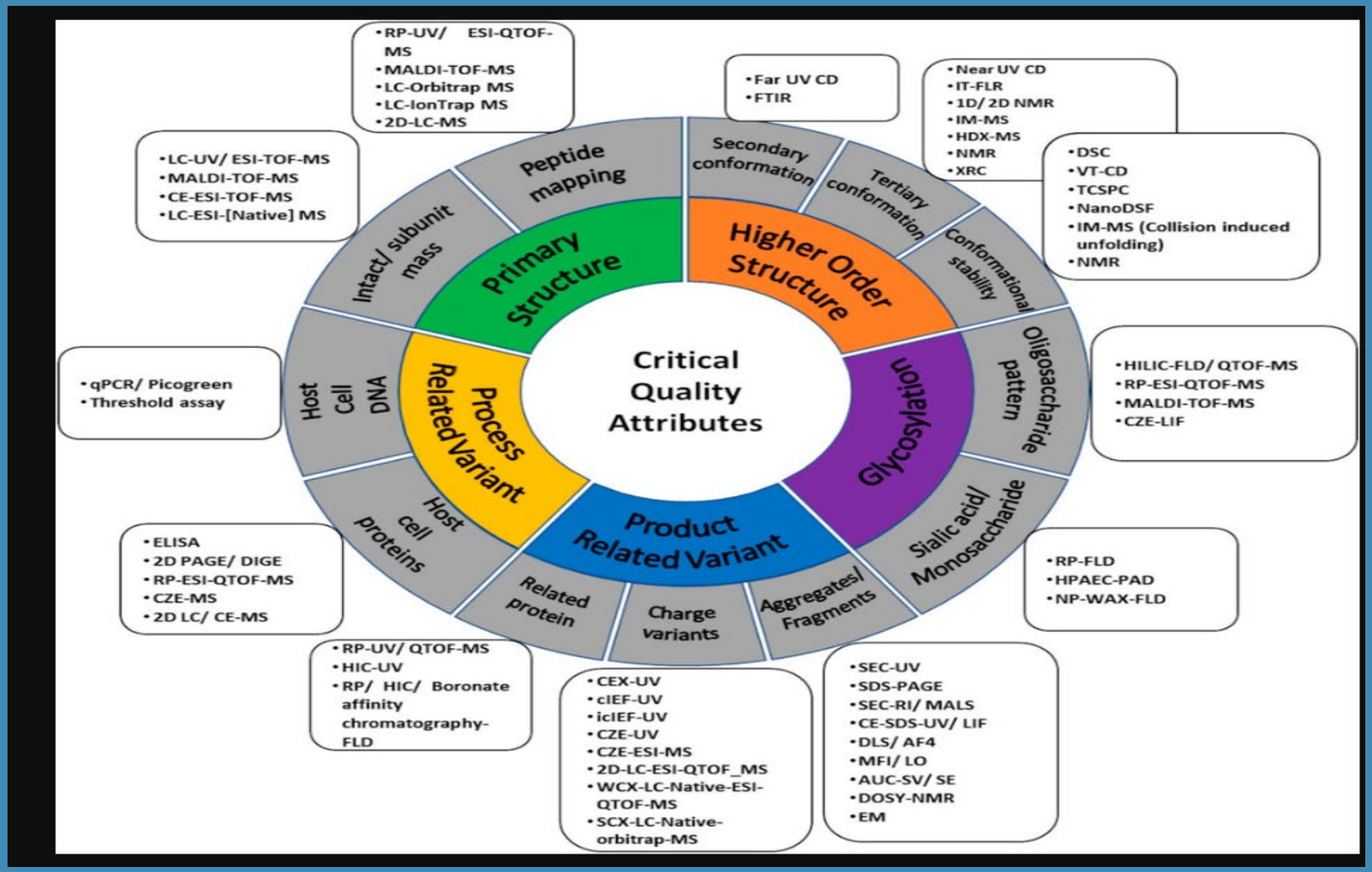
THERE IS NOW A COMPREHENSIVE MAP OF ORTHOGONAL ANALYTICAL PLATFORMS FOR DIFFERENT CRITICAL QUALITY ATTRIBUTES (CQAS)[7]



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COMPARABILITY= BIOSIMILARITY

- Using anti-TNF molecules as exemplars, Alsamil et al.[3] classified post-approval changes made by originator and biosimilar manufacturers between January 1999 and May 2020 according to European Commission regulation 1234/2008[8] and them ranked them as low, medium or high risk. There were 801 implemented manufacturing changes.

- High risk changes related to drug substance site, process change and control strategy and drug product composition. The majority of the 801 implemented changes for originators and biosimilars were classified as low (62.5%) or medium (25.6%) risk, while a small fraction were considered high-risk (11.9%)[3]

- The frequency of HIGH-RISK manufacturing change is similar between originator and biosimilar manufacturers. It occurs at all stages of the lifecycle but most importantly, there is NO EVIDENCE OF SAFETY OR EFFICACY CONCERNS for any reported change, irrespective of risk.

- Virtually all changes were managed by analytical and functional evaluation. Humira® (adalimumab), a change in formulation and concentration to improve patient convenience required comparative PK studies[5] which for this change is mandated by Regulatory authorities.

- Since a clinical efficacy study is insensitive to discriminate minor differences in quality attributes, it is incongruous that an efficacy study is needed to support approval of a biosimilar yet another high-risk change made immediately after aproval, assessed using same analytical tools etc, does not.

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CONCLUSIONS

The scientific principles behind comparability and biosimilarity are the same - the foundation of both being the reliance on analytical and functional testing. This is shown by:

1. Analytical and functional assays used to determine comparability and biosimilarity are often the same
2. For >20 years high risk changes e.g., site, process changes, formulation, device have all been managed using principles of ICHQ5E. Rarely, if at all, have additional clinical efficacy studies been required. For formulation changes PK studies are usually mandated by the regulator
3. The requirement for a PK study to support biosimilar development is accepted; just as a well-designed comparative PK study for the combination of multiple high-risk changes for a currently-approved biologic

In conclusion, data from 20 years of comparability assessments and 15 years of biosimilarity approvals demonstrate that efficacy studies are not needed to support approval of biosimilar.

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2) ICHQ5E guideline. Comparability of Biotechnological/Biological products subject to changes in their manufacturing process (2004) https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-e-comparability-biotechnological/biological- products-step-5_en.pdf

3) Nature and timing of post-approval manufacturing changes of tumour necrosis factor α inhibitor products: A 20-year follow-up study of originators and biosimilars (2022).
Ali M. Alsamil, Thijs J. Giezen, Toine C. Egberts, Erik Doevendans, Hubert G. Leufkens, , Helga Gardarsdottir https://doi.org/10.1016/j.ejps.2022.106227

4) Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. (2016). Balázs Vezér, Zsuzsanna Buzás, Miklós Sebeszta & Zsombor Zrubka https://doi.org/10.1185/03007995.2016.1145579

5) Extrapolation: Experience gained from original biologics (2021).
Luisa-Fernanda Rojas-Chavarro, Fernando de Mora https://doi.org/10.1016/j.drudis.2021.05.006

6) EMA Biosimilars for healklthcare professionals
https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf

7) Analytical Similarity Assessment of Biosimilars: Global Regulatory Landscape, Recent Studies and Major Advancements in Orthogonal Platforms (2022). Neh Nupur, Davy Gulliarme, Anurag S. Rathore https://doi.org/10.3389/fbioe.2022.832059

8) European Commission Regulation 1234/2008
https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:334:0007:0024:en:PDF

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SCIENCE AND EXPERIENCE SHOULD LEAD THE WAY. HISTORY AND DATA HAS SHOWN THAT EFFICACY STUDIES ARE NOT NEEDED WHEN DETERMINING BIOSIMILARITY OR COMPARABILITY

Streamlined approval of biosimilars: moving on from the confirmatory efficacy trial

Marie-Christine Bielsky, Anne Cook, Andrea Wallington, Andrew Exley, Shahin Kauser, Justin L. Hay, Leonard Both, David Brown

BioDrugs. 2022; 36(3): 359–371. PMCID: PMC9148871
Published online 2022 May 21. doi: 10.1007/s40259-022-00533-x PMID: 35596890

Regulatory Evaluation of Biosimilars: Refinement of Principles Based on the Scientific Evidence and Clinical Experience

Pekka Kurki, Hye-Na Kang, Niklas Ekman, Ivana Knezevic, Martina Weise, and Elena Wolff-Holz

Review › BioDrugs. 2020 Jun;34(3):297-306. doi: 10.1007/s40259-020-00422-1.

The Path Towards a Tailored Clinical Biosimilar Development

Martin Schiestl, Gopinath Ranganna, Keith Watson, Byoungin Jung, Karsten Roth, Björn Capsius, Michael Trieb, Peter Bias, Julie Maréchal-Jamil

Medicines & Healthcare products Regulatory Agency

Confirmatory efficacy trial
MHRA….It is considered that, in most cases, a comparative efficacy trial may not be necessary if sound scientific rationale supports this approach….

Guidance

Guidance on the licensing of biosimilar products

Updated 7 November 2022

VIRTUAL

Increasing the Efficiency of Biosimilar Development Programs--Reevaluating the Need for Comparative Clinical Efficacy Studies

SEPTEMBER 12 - 13, 2023

A Data Driven Approach to Support Tailored Clinical Programs for Biosimilar Monoclonal Antibodies

Elena Guillen, Niklas Ekman, Sean Barry, Martina Weise and Elena Wolff-Holz

https://doi.org/10.1002/cpt.2785

World Health Organization

FINAL POST-ECBS version
ENGLISH ONLY

Guidelines on evaluation of biosimilars

Replacement of Annex 2 of WHO Technical Report Series, No. 977

Adopted by the Seventy-fifth meeting of the World Health Organization Expert Committee on Biological Standardization, 4–8 April 2022. This is the final edited version which will be published in the WHO Technical Report Series.

WHO….An adequately powered comparative efficacy and safety trial will not be necessary if sufficient evidence of biosimilarity can be drawn …….

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IPRP International Pharmaceutical Regulators Programme

Speaker #6

Fabrice Romanet, SVP, Head of Program Leadership, Regulatory and Governmental Affairs, Fresenius-Kabi

- Fabrice Romanet is biologist by training and has worked in R&D within the pharmaceutical industry for over 17 years.
- Fabrice is now Senior Vice President responsible for heading up the global departments of Program Leadership, Regulatory Affairs and Healthcare Policy at Fresenius Kabi Biopharmaceuticals Business Unit
- As an end-to-end developer, Fabrice is especially interested in delivering high quality, affordable biologics to healthcare systems around the world and has extensive experience in liaising with leading health agencies such as EMA, FDA, Health Canada, TGA and MHRA.
- As an active member of the US associations AAM, Biosimilar Forum and Medicine For Europe, Fabrice has a keen interest in pursuing science-led evolution of regulatory development biosimilar guidelines.

How to give more access at a lower cost to biologics patients in the future

IPRP workshop

Fabrice Romanet

SVP, Head of Program Leadership, Regulatory Affairs and Policy Biosimilars
Fresenius Kabi Biopharmaceuticals

In an ideal world, everyone should have access to affordable biologics. This is not the case today.

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70%

of deaths worldwide from NCDs*

80%

Access to medicines/biologics in US, Canada, Europe

vs

20%

Access to medicines/biologics in ROW

2 billion

without access to essential medicines according to WHO

$1.9 trillion

Global medicine spending by 2027 (3-6% increase/yr)

* Non-Communicable Diseases: Heart disease, stroke, cancer, diabetes, chronic lung disease etc.

Non-communicable diseases. The Kings Fund. https://www.kingsfund.org.uk/time-to-think-differently/trends/disease-and-disability/non-communicable-diseases.
Expanding access to monoclonal antibodies | Wellcome
The Global Use of Medicines 2023 – IQVIA

In their 2014 resolution the WHO clearly stated their commitment to making biologics more affordable.

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caring for life

World Health Organization

SDG target 3.8: ***achieve universal health coverage, including financial risk protection, access to quality essential health care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.***

A clear call to action from WHO to utilize biosimilars !

"The **World Health Assembly in 2014** adopted a resolution that mandates both Member States and the WHO Secretariat to facilitate access to biotherapeutic products in a way that ensures their quality, safety and efficacy. The availability of biosimilars is expected to increase access to biotherapeutic products by providing more treatment options triggering competition which would lead to a consistent reduction in the average price of treatment."

WHO members have biosimilar action plans

Majority of countries fully recognize the importance of biosimilars to healthcare systems and have policy frameworks e.g. **FDA BsUFA & EMA BMWP**

Hye-Na Kang et al. Biologicals. 2020 May; 65: 1–9. The regulatory landscape of biosimilars: WHO efforts and progress made from 2009 to 2019

Biosimilars are already reducing health costs, increasing patient access and have already gained trust of the medical community

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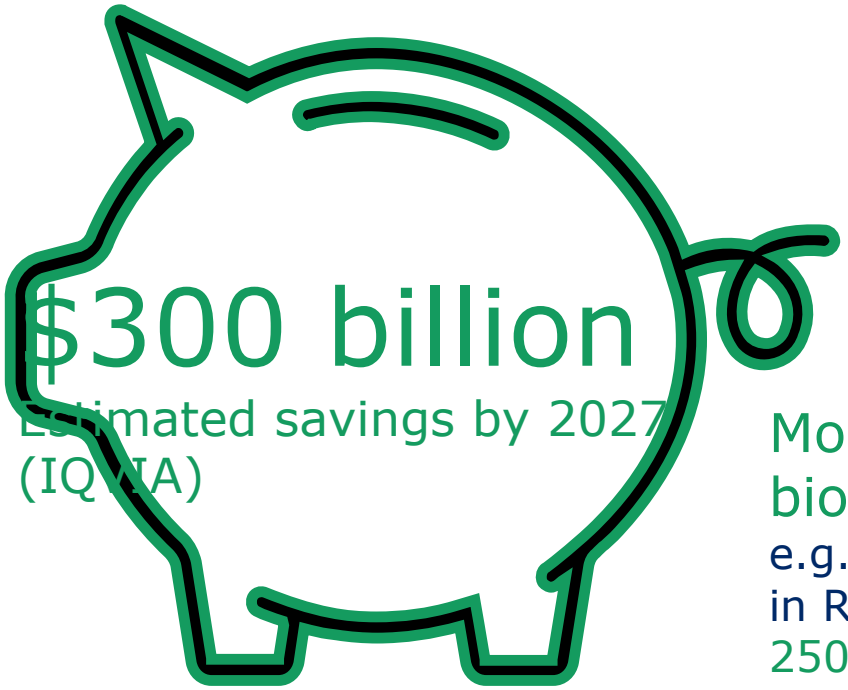
Nearly 5 billion patient-days of experience
with biosimilars have been accrued to date across the EU and US



More patient access through biosimilars
e.g. UK NICE broadening TNF usage in Rheumatoid Arthritis benefiting 25000 more patients.

- Medicines for Europe. Billions more euros to re-invest in better healthcare thanks to biosimilar medicines. 2022. https://www.medicinesforeurope.com/wp-content/uploads/2022/12/20221213-Press-Release-Bios-stakeholder-workshop.pdf#:~:text=Biosimilar%20medicines%20have%20now%20generated%20over%2030%20billion,4.5%20billion%20patient%20treatment%20days%20of%20positive%20experience
- Biosimilars Council. Biosimilars are a prescription for better health. 2022. https://biosimilarscouncil.org/.
- The Global Use of Medicines 2023 – IQVIA
- Overview | Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed | Guidance | NICE

Unfortunately, global biosimilars development requires significant investment as it is negatively impacted by several factors:

IP dictates LOE, elongated by patent thickets

Global revenue of originator, reimbursement, pricing dynamics

Technical risk & development complexity

Because of the current challenges, many biologics are not expected to have any biosimilars competition by 2027 = limited potential for negotiation on pricing

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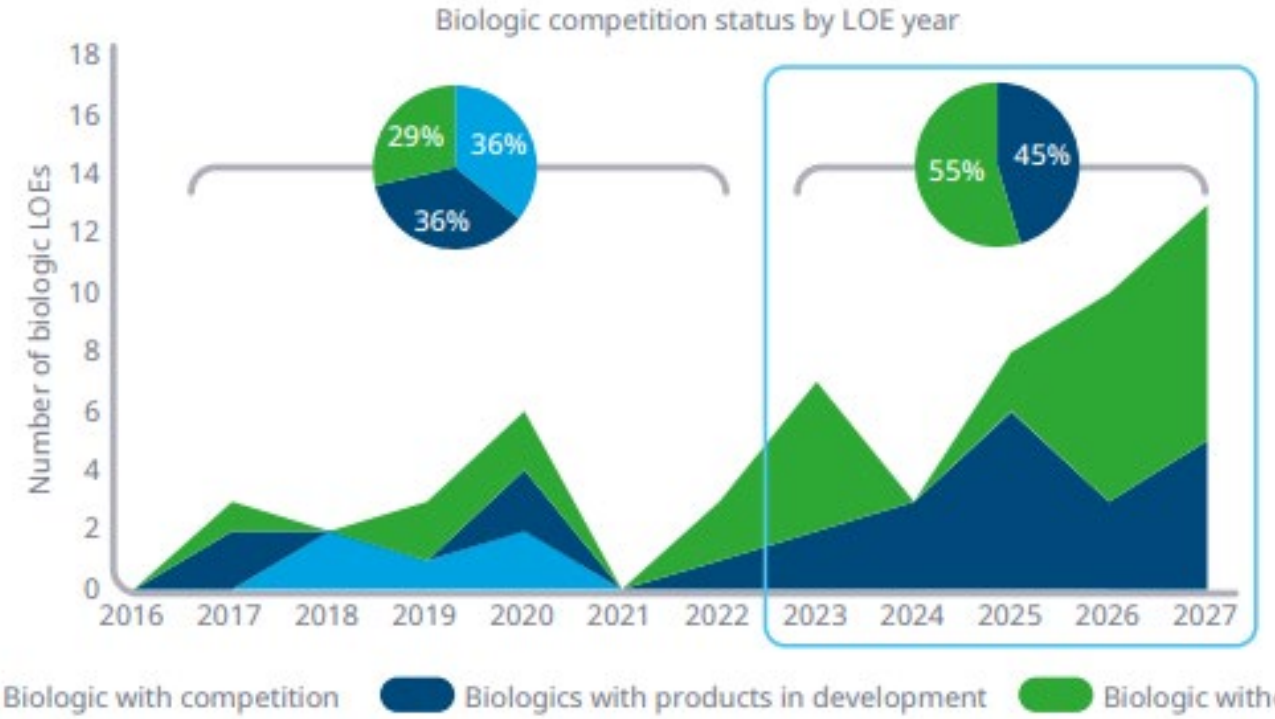
Exhibit 13: Forecast number molecules losing exclusivity in Europe and respective pipeline



No competition from biosimilars for

55%

of biologics market in 2027

Source: IQVIA Patent Intelligence, Pipeline Intelligence, and IQVIA Forecast Link analysis (November 2022); Historic analysis sourced from IQVIA Institute report, Protection expiry and Journey into the Market (2022)

Note: The intellectual property for biologicals can involve multiple patents, patent timelines, data exclusivity, and litigation for each individual product and therefore it is difficult to give an exact date for protection expiry for biologicals. It should be noted that these results are estimates as determined from IQVIA MIDAS® and ARK Patent Intelligence where available, and historical products are cross-referenced to public sources

IQVIA

For oncology the development barriers to entry are even higher

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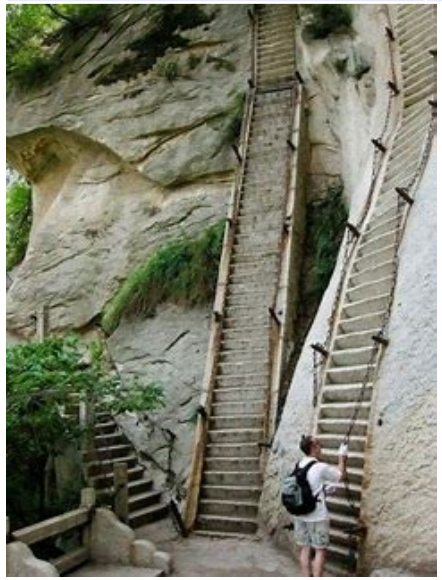
Product	Comedication	Endpoint	Margin	Standard-deviation	Total sample size
Pembrolizumab	Chemotherapy	ORR	8.6 %	0.499	1424
Pertuzumab	Trastuzumab Chemotherapy	ORR	1.8 %	0.398	21554
		pCR	4.5 %	0.49	4986



- Clinical efficacy trial high sample size
- Cost of oncology trials 3 to 4 times cost of non-oncology biosimilar
- High cost of RMP
- Phase 3 competition for patients intense
- Costly and technically challenging manufacturing requirements for ADCs
- IP challenges higher (oncology combinations with additional IP; ADC linker technology IP)

Although the cost of investment is much higher and they face additional IP barriers, oncology products face the same rate of price erosion as the rest of the market

Orphan drugs face even greater hurdles

Challenges to biosimilar developers :

- Phase 3 patient recruitment extremely challenging & lengthy
- Extreme high cost for RMP
- IP challenges
- Unknown market access challenges including reference product reimbursement is highly variable

*

Product	Approx cost per annum	Product	Approx cost per annum
Soliris	$500k	Zynteglo	$2.8 mil
Strensiq	$1.2 mil	Hemgenix	$3.5 mil

Although the number of orphan drugs is increasing with personalized medicine (e.g. oncology genomics), inequitable access is amplified due to the high development cost

*Net prices stated are illustrative and may vary country to country due to differing pricing policies. They also do not take into account confidential rebates/ discounts and thus could be considerably lower than this illustration

Biosimilar guidelines not defined for new ATMPs bringing further uncertainty

Beyond Monoclonals

- Gene therapies
- CAR-T
- mRNA technology

Health Authorities will play a vital role in providing opportunities to make regulatory efficiencies and encourage biosimilar development

International Convergence Global Development

Convergence of requirements (vs local data requirements)

Acceptance of **Global Reference Product**

Clinical Development Streamlining

Optimized **regulatory processes and timelines**

Global health agencies to provide consistent biosimilar education on websites and clear positioning on switching

Generate new guidance for future biosimilars including mRNA vaccines and advanced therapy medicinal products

International Reliance

Expand the WHO PQ program to include more biologics

Increase coordination and leveraging **Mutual Recognition of facility inspections**

More patient access at a lower cost is only possible if current barriers to biosimilars development are significantly reduced.

- Biosimilars have delivered on their promise so far, but the future is far from certain.
- Not all biologics may be copied for multiple reasons, but primarily due to the cost of development vs ROI
- Evolution in biosimilar development guidance is needed urgently where science permits, including phase 3 waivers for Mabs. We call for immediate action !
- Global guidelines with convergence between regulatory agencies are required for current biosimilars and new waves

Thank you for listening!

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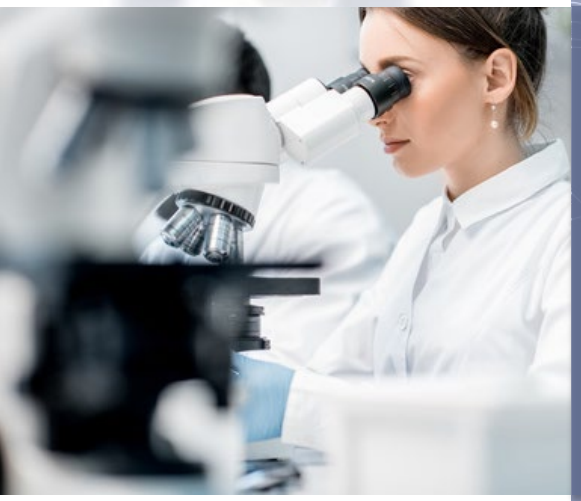
Speaker #7

Gillian Woollett, M.A., D.Phil., Samsung Bioepis

- Dr. Gillian Woollett joined Samsung Bioepis in 2021 to stand up a US presence for science-based regulatory strategy and policy in the leading global market for biologics, including biosimilars.
- She is currently Chair of the International Generics and Biosimilars Association (IGBA) Biosimilars Committee with a similar focus on efficient development.
- Dr. Woollett has represented the biopharma industry in the media as the industries' voice on international, as well as US, regulatory and scientific issues.
  - Federal Advisory Committees and testified before the US Congress.
- She also provides a point of scientific interface with academic and professional organizations.
  - She is an appointee to the Nomenclature and Labeling Expert Committee of the United States Pharmacopeia (USP), was on the Board for the Foundation for The Accreditation of Cellular Therapy (FACT) for almost a decade and served on the Science Board of the Pharmaceutical Education Research Institute (PERI).
- Dr. Woollett earned her B.A., M.A. in Biochemistry from the University of Cambridge, and her D.Phil. In Immunology from the University of Oxford in the UK. She is well published in the peer reviewed literature
- Past work experience includes SVP and Principal Regulatory Scientist at Avalere Health, Chief Scientist, and Administrator, at the law firm of Engel & Novitt, LLP – a boutique food and drug law firm. VP, Science and Regulatory Affairs at BIO, AVP at PhRMA.



Gillian Woollett, MA, DPhil, Chair IGBA Biosimilars Committee
13 September 2023

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Disclaimers

- I am an employee of Samsung Bioepis
- Samsung Bioepis is a member of Biosimilars Forum (BSF) and Medicines for Europe (MfE)
- I am Co-Chair of International Generics and Biosimilars Association (IGBA) Biosimilars Cmte, along with Giuseppe Randazzo of Alliance for Accessible Medicines (AAM)

However, all errors and omissions are, ultimately, entirely my own

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OUR ASPIRATION – one science, one quality supports global access

As you have heard from the earlier speakers:

1. **Biologics offer promise** for treatment and cures for a broad range of unmet medical needs, and, when IP expires, biosimilars can enable affordable access worldwide

2. **The cost to approval** for a biosimilar is ~100 times that of a small molecule generic drug, and the time for development is 7-10 years, so to have biosimilars available to less commercially successful biologics depends upon improving the efficiency of their development by reducing unnecessary comparative efficacy studies (CES)

3. **Efficient development** relies upon predictable, science-based regulatory approaches that themselves are kept current and consistent across jurisdictions (regulatory reliance). This increases confidence in regulators as it is independent of any business model

4. **Sustainable markets** with fair competition will ultimately decide how broad access can be, but biosimilar development and approval is the essential first step

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Consistent use of established regulatory science gives confidence in all biologics and in all regulators everywhere

1. FDA's Comparability Protocol 1996[1], became **ICH Q5E[2]**, enabling biologics to evolve (e.g. new manufacturing sites, replace equipment and suppliers):

   Determinations of product comparability can be based solely on quality considerations if the manufacturer can provide assurance of comparability through analytical studies as suggested in this document . Additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish comparability[3]

2. Comparability established **critical quality attributes (CQAs)** as the basis for sameness, and are prioritized for potential clinical significance, and used in a head-to-head comparative manner
3. This regulatory science led the way for biosimilarity also based on analytics, with limited CES. In the US, CES are already waivable as a matter of law[4]

Review consistency is a priority within and across regulators[5]: You either believe in CQAs or you don't, and if you do they must apply independent of business model

One Science, One World – regulatory reliance shares the work by enabling efficiency everywhere

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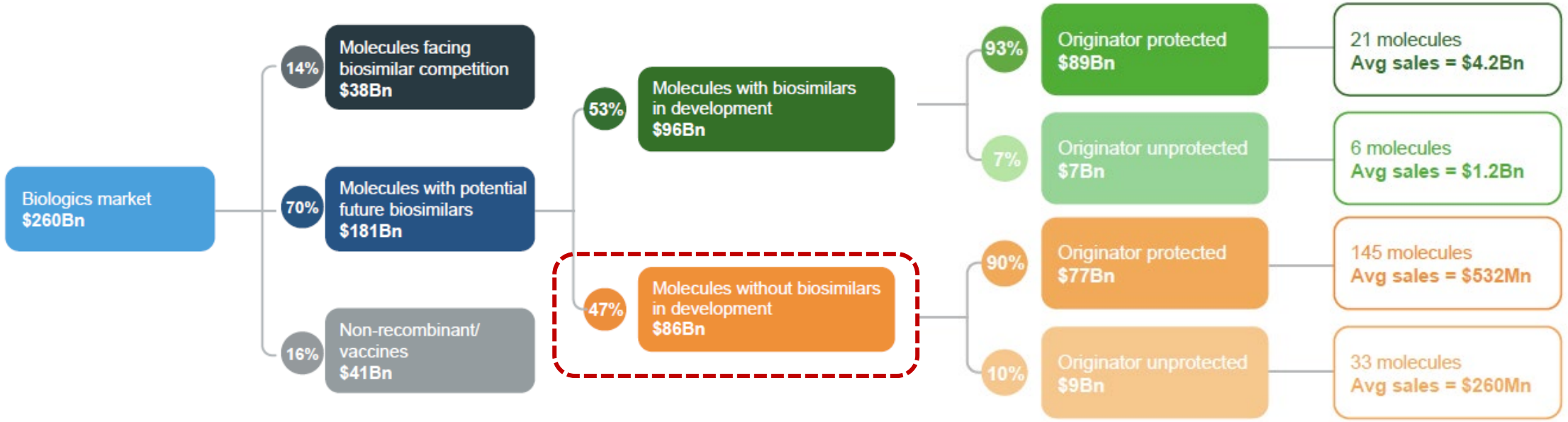
CES = Comparative Efficacy Studies

1. Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products here; 2. ICH Q5E here; 3. FDA Guidance - Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations 2019 here; 4. BPCIA here; 5. FDA BsUFA III Commitment letter here

Hiccups in the pipeline for future biosimilars are already visible

Nearly half of the biologics facing LOE <10 years have no biosimilars in development



- Science-based regulatory streamlining may increase the number of originator biologics to which biosimilars are developed – hence increasingly critical NOW
- Regulatory reliance can increase patient access in additional markets for those biosimilars that are developed for EU/ US

That this is without risk to patients suggests it would be a wise approach to follow

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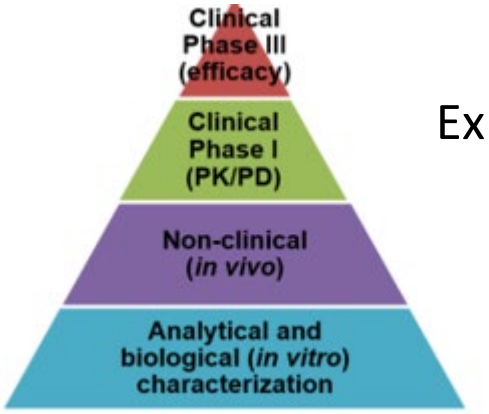
LOE = Loss of Exclusivity

IQVIA. 2023. Biosimilars in the United States 2023–2027: Competition, Savings, and Sustainability
https://www.iqvia.com/insights/the-iqvia-institute/reports/biosimilars-in-the-united-states-2023-2027

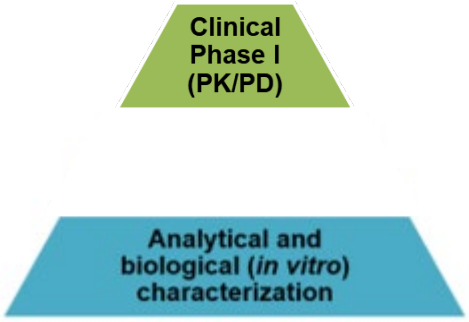
Experience supports global streamlined biosimilar development

The science is asked and answered, there is an urgent need for regulations to catch up



Old Model

Experience shown no regulatory value to animal studies or routine comparative efficacy studies



New Model

- Enables a substantial reduction in data burden for no net change in regulatory confidence
- The reduction in time and cost can impact the feasibility of biosimilar development, especially to non-blockbuster reference biologics

Regulatory streamlining can make more biosimilars feasible

Reliance expands access & affordability, with no change in quality, safety or efficacy

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The Path Towards a Tailored Clinical Biosimilar Development. BioDrugs **34**, 297–306 (2020). https://doi.org/10.1007/s40259-020-00422-1;. ***An Efficient Development Paradigm for Biosimilars***. BioDrugs **33**, 603–611 (2019). https://doi.org/10.1007/s40259-019-00371-4; ***The Role of PD Biomarkers in Biosimilar Development - To Get the Right Answer One Must First Ask*** **the Right Question CPT 23Sep22** https://doi.org/10.1002/cpt.2753

Single Global Development for Originators & Biosimilars is Efficient

The originator product is the same globally, so it must be feasible for the biosimilar to be as well

Biologic	Trade name	Sponsor	Countries in which 1st approvals were based on the same studies	Studies submitted for 1st approvals in > 1 country	Indications studied
Infliximab	Remicade	Janssen	US, EU, Canada, Australia	T16, T21	Crohn's disease
Etanercept	Enbrel	Amgen	US, EU, Canada, Australia	16.009, 16.014	Rheumatoid arthritis
Adalimumab	Humira	AbbVie	US, EU, Canada, Australia	DE009, DE011, DE019, DE031	Rheumatoid arthritis
Pegfilgrastim	Neulasta	Amgen	US, EU, Canada, Australia	980226, 990749	Febrile neutropenia in treatment of non-myeloid cancers
Bevacizumab	Avastin	Genentech/ Roche	US, EU, Canada, Australia	AVF2107g, AVF0780g	Metastatic colon cancer
Ranibizumab	Lucentis	Genentech	US, EU, Canada, Australia	FVF2598g, FVF2587g, FVF3192g	Age-related macular degeneration

*This is not necessarily a comprehensive list of the countries in which these studies were submitted for licensure of the product

1. The reference product is global when pivotal clinical data are the same across jurisdictions, likewise for additional indications – often this is public information[1]
2. No unnecessary bridging studies, especially PK and CES, supports more efficient development and enables earlier access in more jurisdictions[2]

CES = Comparative Efficacy Studies

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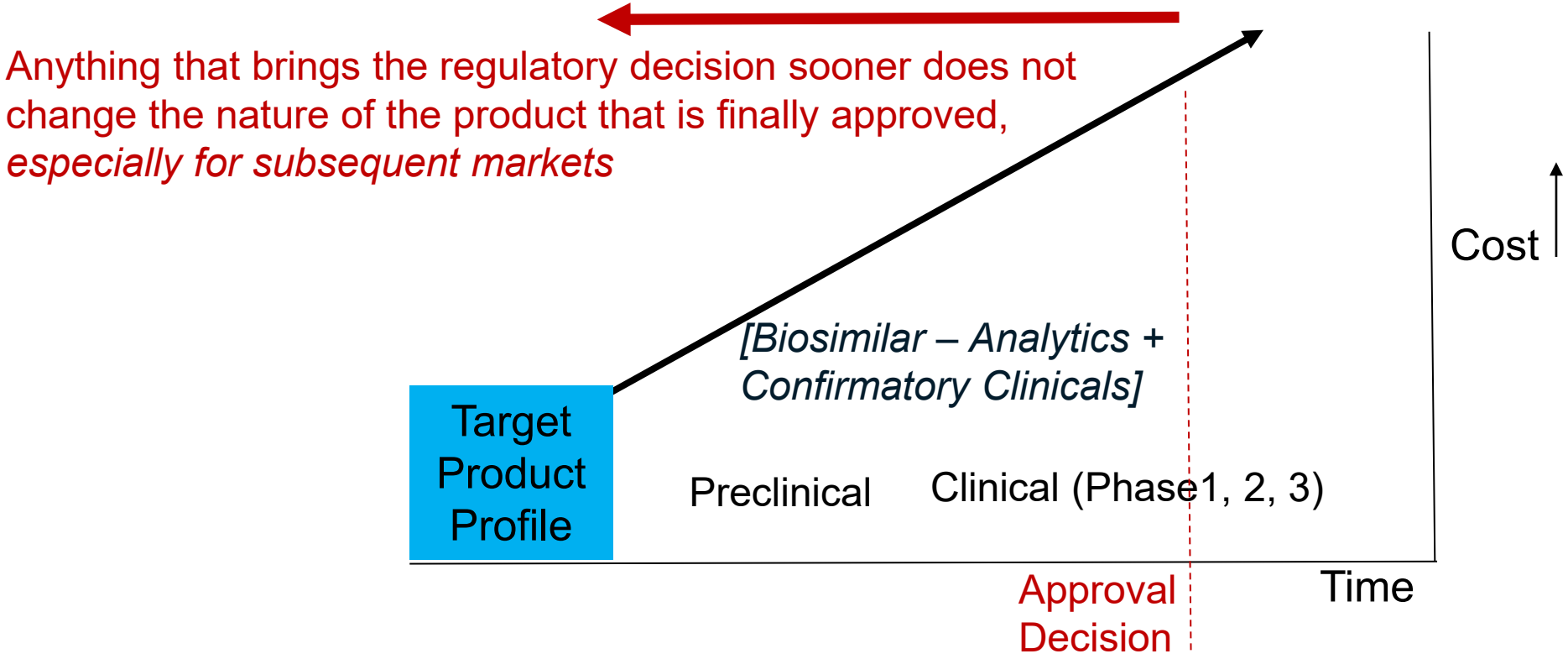
1. FDA *Q&A on Biosimilar Development and the BPCI Act Guidance for Industry 2021* https://www.fda.gov/media/119258/download
2. Webster, C.J., Woollett, G.R. *A 'Global Reference' Comparator for Biosimilar Development*. BioDrugs (2017) https://doi.org/10.1007/s40259-017-0227-4

Regulatory predictability is key to efficient feasible development



1. Getting biosimilars to market more quickly and more efficiently with no compromise in quality matters for each & every jurisdiction, i.e. one product for all markets globally
2. What can the regulator in the "next market" ask for that the previous one hasn't considered?

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Webster, C.J., George, K.L. & Woollett, G.R. *Comparability of Biologics: Global Principles, Evidentiary Consistency and Unrealized Reliance*. BioDrugs (2021). https://doi.org/10.1007/s40259-021-00488-5

CONCLUSIONS – The time is NOW

Global access to biologics, including biosimilars, depends on the following:

- **Streamlining biosimilar development,** with no unnecessary CES, is essential to their expanded availability for more originator biologics
- **Regulatory certainty/predictability** is key to meaningful reform and confidence in science-based regulation
- **Immediate regulatory changes** - Investment decisions are being made today based on current costs and development times, so a reduction in expectations for CES today may help restore known pipeline gaps.
- **Efficient global development** depends on regulatory reliance (which includes harmonization/ convergence) to support fit-for-purpose standards of safety, quality and efficacy for all biologics, for all markets, for all patients

Consistent and immediate elimination of expectations for comparative clinical efficacy studies are urgently needed if biosimilars are to be feasible and sustainable globally

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5 Minute Break

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Panel Discussion

- Stakeholders Experience and Considerations to Date (110 min) Moderated by Steffen Thirstrup, EMA

- Panelists

1. Martin Schiestl
2. Elena Guillen Benitez
3. Elena Wolff-Holz
4. Frank Schneider
5. Keith Watson
6. Fabrice Romanet
7. Gillian Woollett

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Panel

Possible Questions

- How should we address the timing mismatch, i.e., when developers ask about CES early, before residual uncertainties arising from the comparative analytical assessment may be known?

- If you believe CES are unnecessary most of the time, are there any scenarios where you think they might be useful?

- What are the considerations for and impacts on the developer and the marketplace when a CES is recommended?

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Closing Remarks

Sarah Yim, MD, US FDA

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Speaker #3

Elena Wolff-Holz, MD, Ph.D., Biocon

Dr. Elena Wolf-Holz has recently joined Biocon Biologics Ltd as Global Head Clinical Development. Prior to that, she was a senior regulator at Germany's National Competent Authority Paul-Ehrlich-Institute for 14 years and has extensive knowledge in the development of biologic therapeutics, with a focus on cancer and immunology. Since 2016, she has been the head of the Biosimilar Medicinal Products Working Party (BMWP) within the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP). Elena has also been a member of the Scientific Advice Working Party (SAWP) of the CHMP since 2017. With over 28 years of experience, she has held several leadership positions in clinical development and medical marketing functions at major biotech companies, including Centocor Inc (now Janssen, J&J) and Amgen, in both US and Germany.

As a result of her work, Elena has earned multiple authorships and co-authorships in esteemed scientific journals and delivered numerous presentations at national and international conferences. Elena obtained her M.D. degree from Heidelberg University and completed a postdoctoral fellowship at Harvard Medical School.