

Martin Schiestl
Global Head Regulatory Policy, Sandoz

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Industry perspective and scientific background for current similarity comparison

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Analytical data form the foundation for biosimilar evaluations

- The comparative analytical assessment combined with the process quality controls support the evaluation of biosimilars
- Structure defines function defines clinical performance

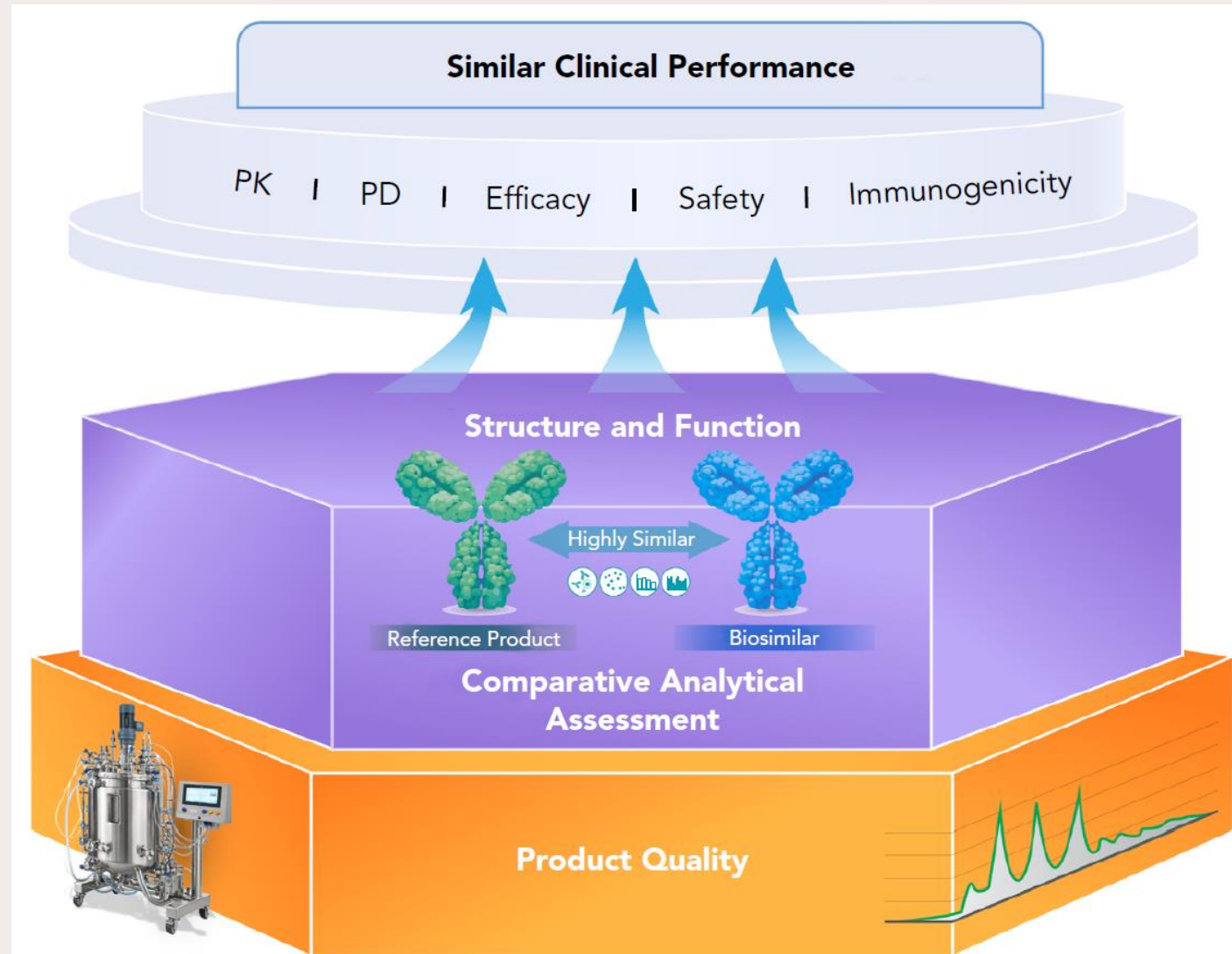
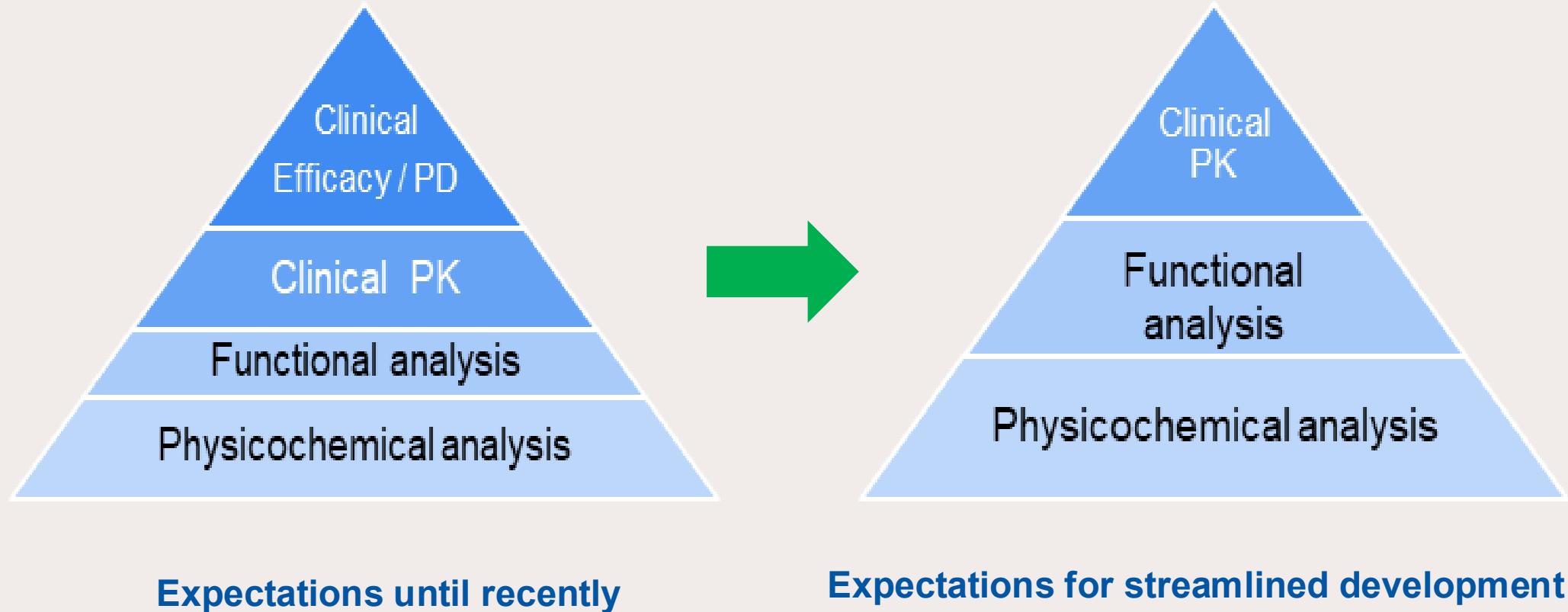


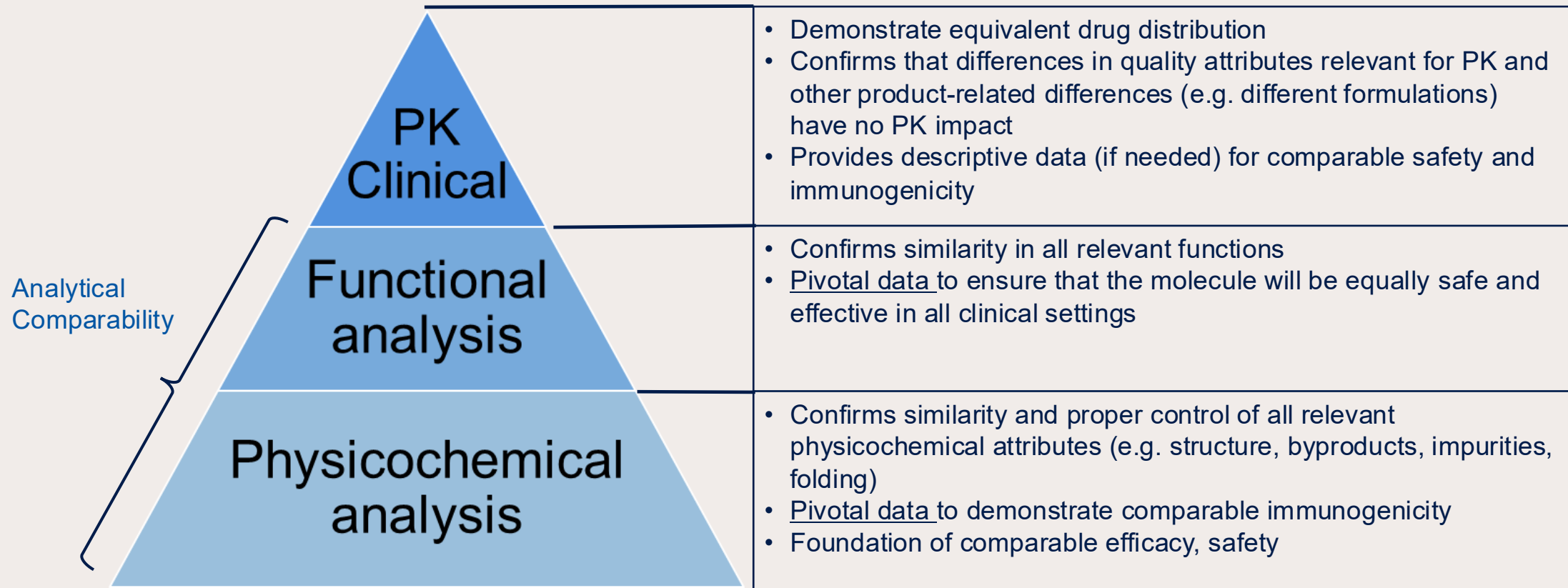
Illustration by Herndon et al. Blood 2026; 148 (7): 807–817. doi: <https://doi.org/10.1182/blood.2025031673>

PK: Pharmacokinetic, PD: Pharmacodynamic

The evolution of the comparative data package in the regulatory biosimilar pathway



Elements and role of comparability data in the regulatory assessment of biosimilar candidates



The scientific basis for streamlined biosimilar development is well established

- The scientific validity of biosimilar development based on comparative analytical and clinical pharmacokinetic data alone is supported by the fact that comparative efficacy studies are the least sensitive tool to detect differences between a biosimilar and its reference product
- Hence, in most cases, the comparative efficacy study does not provide useful information for the evaluation of biosimilars.
- This argument is supported by multiple studies from regulators and industry showing that the analytical and PK data alone were sufficient to demonstrate biosimilarity (references see next slide).

Streamlined biosimilar development is based on sound science:

- **EU regulators**

- Guillen et al. Drugs 2025;85(5), 601-608. <https://doi.org/10.1007/s40265-025-02168-y>
- Kirsch-Stefan et al. BioDrugs 2023;37, 855–871. <https://doi.org/10.1007/s40259-023-00631-4>
- Guillen et al. Clin Pharmacol Ther, 2023;113, 108-123. <https://doi.org/10.1002/cpt.2785>

- **US regulators**

- Herndon et al. Blood 2026; 148 (7): 807–817. doi: <https://doi.org/10.1182/blood.2025031673>
- Ji et al., J. Clin. Pharmacol. 2025;65(4) 499–507. <https://doi.org/10.1002/jcph.6165>
- Cavazzoni P, Yim S. JAMA. 2024;332(15):1235–1236. <https://doi.org/10.1001/jama.2024.15225>

- **Japan regulators**

- Goto et al. PharmMed 19 Sep 2025; <https://doi.org/10.1007/s40290-025-00583-w>
- Kuribayashi et al. PharmMed 2024;38:225–239. <https://doi.org/10.1007/s40290-024-00525-y>

- **UK regulators**

- Bielsky et al. Drug Discov. 2020;25, 1910-1918. <https://doi.org/10.1016/j.drudis.2020.09.006>

- **Industry**

- Schiestl et al, BioDrugs 2025;39;769-776. <https://doi.org/10.1007/s40259-025-00733-1>
- Schiestl et al. BioDrugs 2020;34, 97–306. <https://doi.org/10.1007/s40259-020-00422-1>

- **IPRP (International Pharmaceutical Regulators Programme)**

- IPRP, Workshop Summary Report: Increasing the Efficiency of Biosimilar Development Programs — Reevaluating the Need for Comparative Clinical Efficacy Studies, May 2024. https://admin.iprp.global/sites/default/files/2024-07/IPRP_BWG_Final%20IPRP%20Scientific%20Workshop%20Summary%20Report_2024_0506.pdf
- IPRP Regulatory Perspectives on the Utility of Comparative Efficacy Studies in Biosimilar Development Programs 20 Feb 2026, https://admin.iprp.global/sites/default/files/files/2026-02/IPRP_BWG_Reg_Perspectives_CES_2026_0220.pdf

Kirsch-Stefan et al.

Study authored by EU regulators

- Review of marketing applications for 36 monoclonal antibodies and antibody derived fusion proteins evaluated by EMA (July 2012 until November 2022)
 - Data source included public EPARs and confidential Day 120 assessment reports
 - Detailed analysis of analytical biosimilarity data and clinical comparability data of 4 rituximab and 7 trastuzumab biosimilars
- Conclusions:
 - “The results further support the argument that sufficient evidence for biosimilarity can be obtained from a combination of analytical and functional testing and pharmacokinetic studies which may also generate immunogenicity data.”
 - “In the analysis of quality and clinical packages of trastuzumab and rituximab biosimilar candidates, in no case were clinical trial data necessary to resolve residual uncertainties regarding the quality part.”
 - “The analytical and biological results can be considered predictive for the clinical performance of the biosimilar candidates.”

BioDrugs (2023) 37:855–871
<https://doi.org/10.1007/s40259-023-00631-4>

ORIGINAL RESEARCH ARTICLE



Do the Outcomes of Clinical Efficacy Trials Matter in Regulatory Decision-Making for Biosimilars?

Nadine Kirsch-Stefan¹ · Elena Guillen² · Niklas Ekman^{3,7,8} · Sean Barry^{4,8} · Verena Knippel¹ · Sheila Killalea^{4,9} · Martina Weise^{5,7,10} · Elena Wolff-Holz⁶

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Abstract

Background There is an increasing body of evidence supporting a more flexible approach in clinical data requirements for the approval of more complex biosimilar substances such as monoclonal antibodies (mAbs).

Objective The aim of this paper is to further analyse the role of quality/chemistry, manufacturing and controls (CMC) and clinical data for the conclusion on biosimilarity and the decision on marketing authorisation (MA).

Methods In the present study, we analysed the MA applications (MAAs) of all 33 mAbs and three fusion proteins evaluated by the European Medicines Agency (EMA) between July 2012 and November 2022 with special emphasis on all submitted rituximab (four products) and trastuzumab (seven products) biosimilar candidates, including withdrawn applications. For the two withdrawn applications, the comparative efficacy trials suggested biosimilarity, but the quality/CMC package was not accepted by EMA. We therefore investigated whether a negative MAA outcome could have been predicted based on the evidence generated in the quality/CMC packages, regardless of clinical trial data. For this purpose, we reviewed the respective European Public Assessment Reports (EPARs) or withdrawal assessment reports, and the first regulatory assessments for all these 36 MAAs (i.e. day 120 of the centralized procedure), which are not publicly available. During EMA review, where significant issues are identified which would preclude a marketing authorisation, these issues are raised as questions to the applicant and are classified as major objections (MO).

Why is streamlined development coming now?

- The scientific validity would be reason enough to implement streamlined biosimilar development as soon as possible
 - Aim to prevent clinical studies which are not needed for regulatory decision making
- The fact that the biosimilar void, i.e. the number of biologicals not attracting biosimilar competition, is increasing helped to accelerate regulatory initiatives
 - Countering the biosimilar void demands utilization of all science-based means to make biosimilar development more efficient

Streamlining may help to fill biosimilar void

Biosimilar void, i.e. the number of biologicals without biosimilar competition is increasing ¹⁻⁴

The later the study, the larger the estimated biosimilar void ranging from 55 %^{1,2} and 70 %³ to 90 %⁴.

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

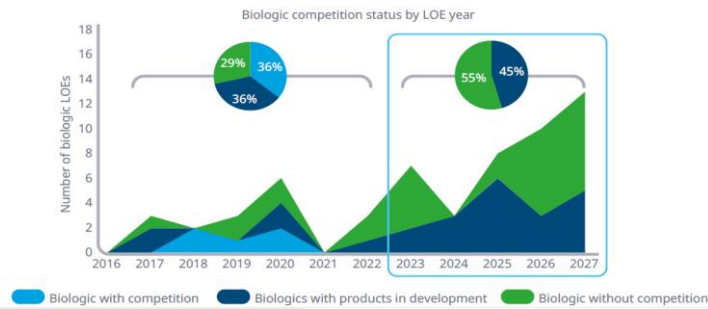
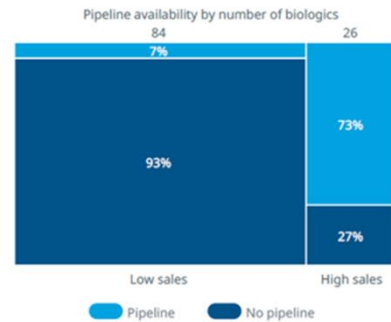
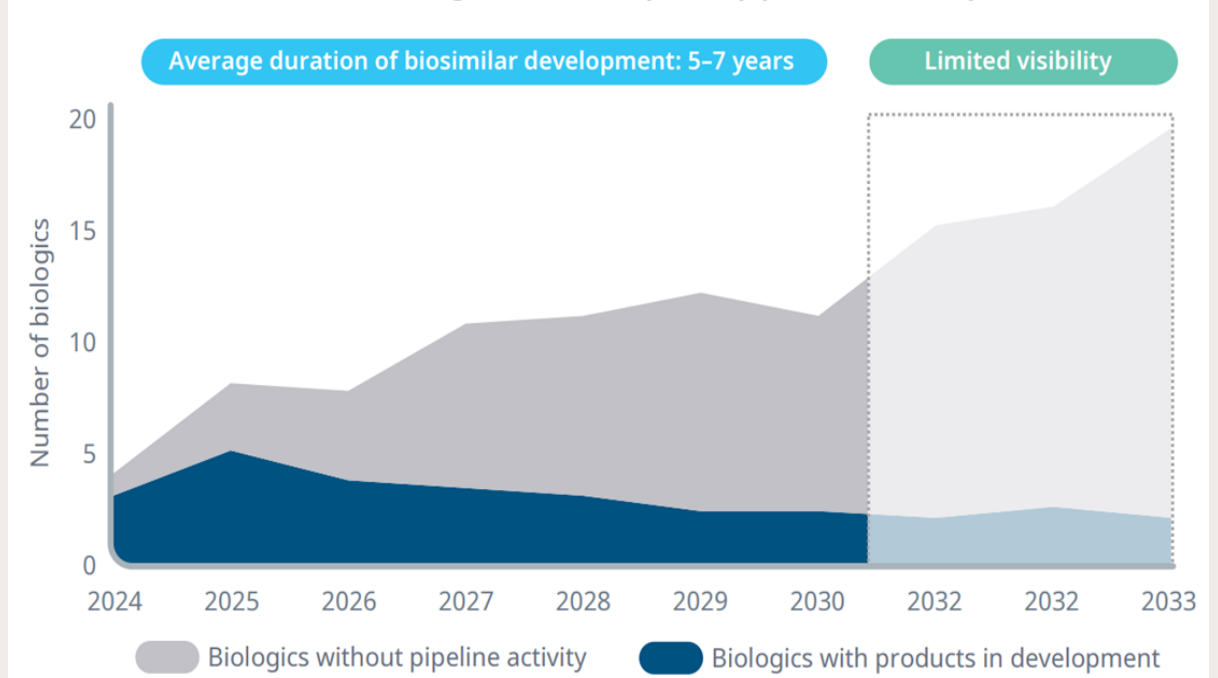


Exhibit 6: Biosimilar pipeline for low- vs. high-sales biologics based on European forecast sales



Future biologic LOEs in Europe and pipeline availability



1. IQVIA, The Impact of Biosimilar Competition in Europe 2022, <https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2022.pdf>
2. IQVIA, Assessing the biosimilar void, Oct 2023, <https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/assessing-the-biosimilar-void>
3. IQVIA, The Impact of Biosimilar Competition in Europe 2024, <https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2024.pdf>
4. IQVIA, Assessing the Biosimilar Void in the U.S. 2025, <https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/assessing-the-biosimilar-void-in-the-us>

Status at regulatory agencies – September 2026

Health Authority	Streamlining implemented in guideline	Streamlining Guideline status	Comment
MHRA (UK)	Yes	Final since 2021 Latest update 2025 ¹	Pioneering guideline stating that a CES may not be necessary in most cases
FDA (US)	Yes	Draft 2025 ²	Strong encouragement to sponsors to consider streamlining
EMA (EU)	Yes	Final 2026 ³ (Reflection paper)	Reflection paper enables streamlining as the new default in EU in most cases
Health Canada	Yes	Final 2026 ⁴	Most progressive guideline as it reverses the burden of proof from justifying why a CES is not needed to why a CES is needed for regulatory decision making. Health Canada guidance may serve as the role model for other Health Authorities.
PMDA (Japan)	No	-	PMDA is interested in implementing streamlining

1. MHRA 2025, <https://www.gov.uk/government/publications/guidance-on-the-licensing-of-biosimilar-products/guidance-on-the-licensing-of-biosimilar-products>

2. FDA 2025, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/scientific-considerations-demonstrating-biosimilarity-reference-product-updated-recommendations>

3. EMA 2026, https://www.ema.europa.eu/en/documents/other/reflection-paper-tailored-clinical-approach-biosimilar-development_en.pdf-0

4. Health Canada 2026, <https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/information-submission-requirements-biosimilar-biologic-drugs.html>

ICH M18 guideline will facilitate global harmonization

- ICH M18 guideline on “Framework for Determining Utility of Comparative Efficacy Studies [CES] in Biosimilar Development Programs” ¹
- Issues to be Resolved:
 - Factors that are relevant to consider for the context of determining the utility of CES, or other clinical studies, in biosimilar development programs.
 - In a framework where there is no CES in a biosimilar development program, how efficacy, safety, and an acceptable immunogenicity profile are assured.
- ICH M18 will enable fast alignment on regulatory requirements for streamlining globally
 - M18 working group joined by regulators of 22 jurisdictions ², covering 3.2 billion of the world population
- **Timeline**
 - Nov 2025: First Meeting of the M18 Expert Working Group
 - Finalization of M18 expected by 2028

1. ICH M18 concept paper, 2025, https://database.ich.org/sites/default/files/ICH_M18_Final_Concept_Paper_MCEndorsed_2025_1119.pdf

2. Working group list of M18 Expert Working Group at <https://ich.org/page/multidisciplinary-guidelines>

How to ensure same clinical properties in a streamlined biosimilar development?

Sameness of efficacy is ensured by analytical data

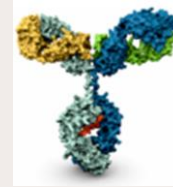
Three “safety nets” in place to ensure that biosimilar works the same as the reference product

Physicochemical
characterization

1st safety net

Structural similarity

Function is the result of structure

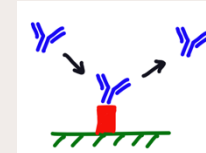


Functional
characterization

2nd safety net

Binding assays

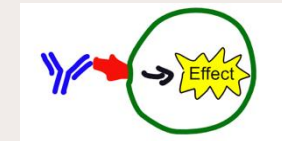
Primary binding events with target and receptors



3rd safety net

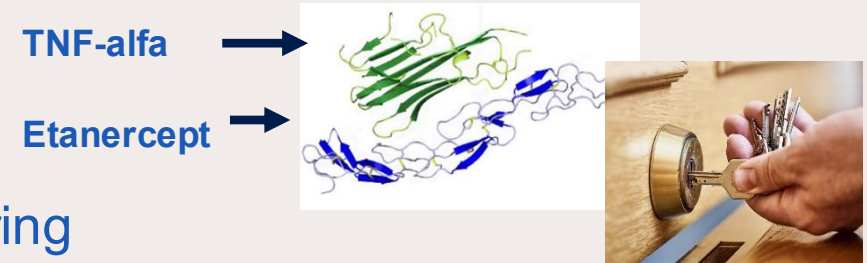
Cell-based bioassays

Effect in living cells following primary binding events



Sameness of safety is ensured by analytical data

1. Product related adverse events of a recombinant biotherapeutic are the consequence of its on-target effects
 - In other words: If the efficacy is the same, the product related safety will be the same
 - Caused by the high specificity of how proteins react with their targets
 - This specificity is in analogy of a security key that fits to its dedicated lock
2. Safety relevant impurities are controlled in manufacturing by today's quality standards
3. If needed, the clinical pharmacokinetic study may deliver supportive safety data



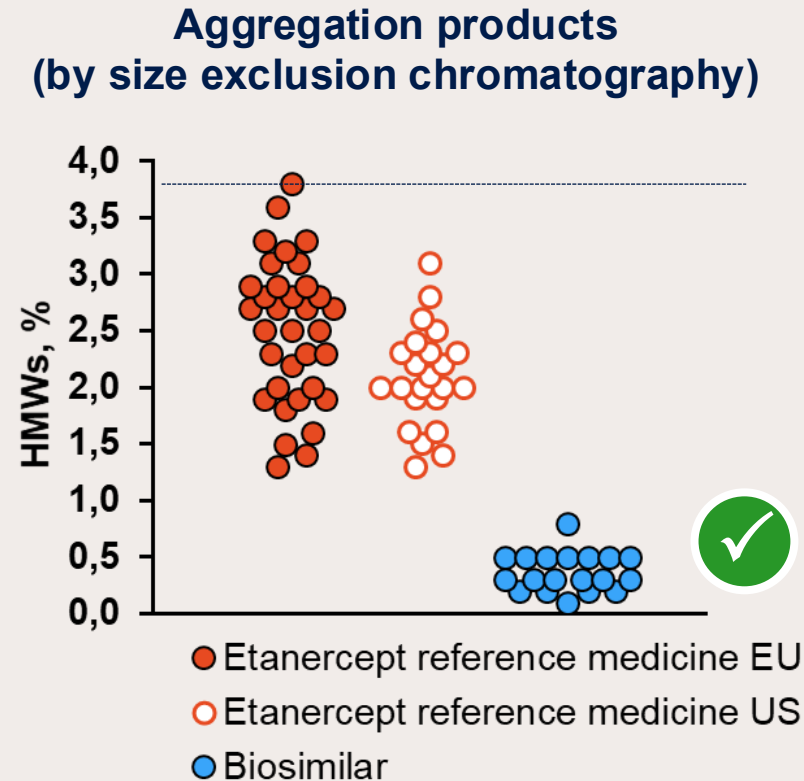
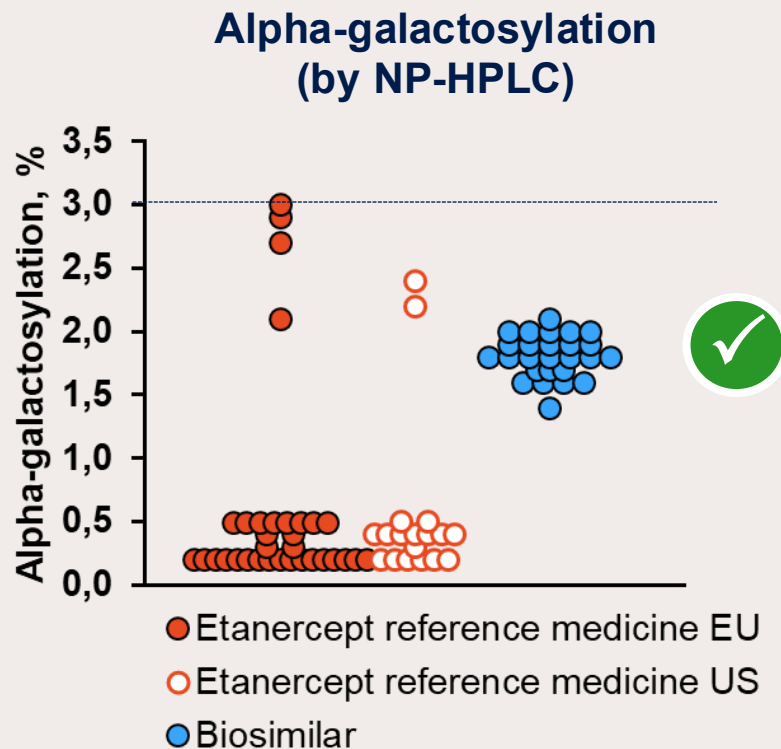
Sameness of immunogenicity is ensured by analytical data

1. High analytical similarity results in comparable immunogenicity ^{1,2}
 - The identity of the amino acid sequence ensures that the biosimilar has the identical antigen structures which could be recognized by our immune system
 - Impurities which could potentially increase unwanted immunogenicity are either compared to be comparable with the reference product or controlled in manufacturing by today's quality standards
 - E.g. Non-human glycans, aggregates, host cell proteins
2. If needed, the clinical pharmacokinetic trial may deliver supportive immunogenicity data ^{2, 3, 4}

1. Kurki et al. BioDrugs 31, 83–91 (2017). <https://doi.org/10.1007/s40259-017-0210-0>
2. Kurki et al. Drugs 81, 1881–1896 (2021). <https://doi.org/10.1007/s40265-021-01601-2>
3. Ji et al., J. Clin. Pharmacol. 2025;65(4) 499–507. <https://doi.org/10.1002/jcph.6165>
4. Schiestl et al, BioDrugs 2025;39;769-776. <https://doi.org/10.1007/s40259-025-00733-1>

Comparable immunogenicity is expected when relevant impurities of biosimilar are below the upper level of the reference product

Example of how to control impurities which are considered as potential risk factor for immunogenicity



NP-HPLC: Normal phase high performance liquid chromatography; HMW: High molecular weight variants

Adapted from slides from FDA Arthritis Advisory Committee, July 13, 2016,
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM513088.pdf>, accessed 22.9.26

**Clinical pharmacokinetic studies
may provide supportive data for
safety and immunogenicity**

-

if needed

Ji et al. 2025

Study authored by FDA regulators

- Reference: Ji P, Schrieber SJ, Glaser R, Chen J, Shukla C, Doddapaneni S, Chandrahas S
A Meta-Analysis of the Safety and Immunogenicity of Pharmacokinetic Similarity Studies and Comparative Clinical Studies
J. Clin. Pharmacol. 2025;65(4) 499–507. <https://doi.org/10.1002/jcph.6165>
- Scope: 35 US-licensed biosimilar mAbs and fusion proteins
- Objective
 - “[...] comparative efficacy trials are not powered to detect differences in safety outcomes, the question at hand is whether pharmacokinetic studies could provide useful safety information in the absence of a comparative efficacy study.”

Comparison of descriptive safety data between PK and CES studies

Adverse Events

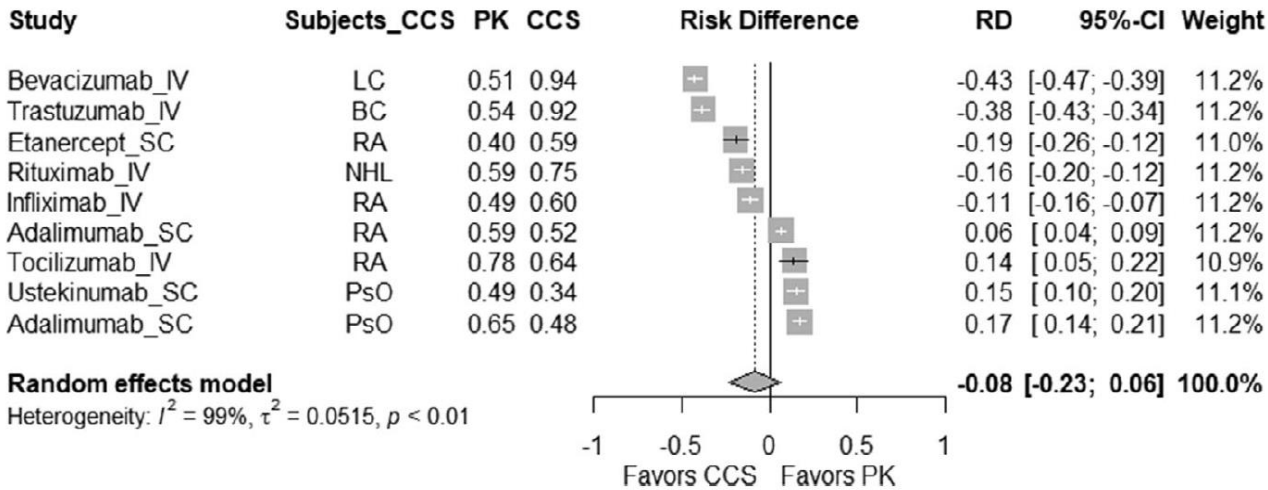
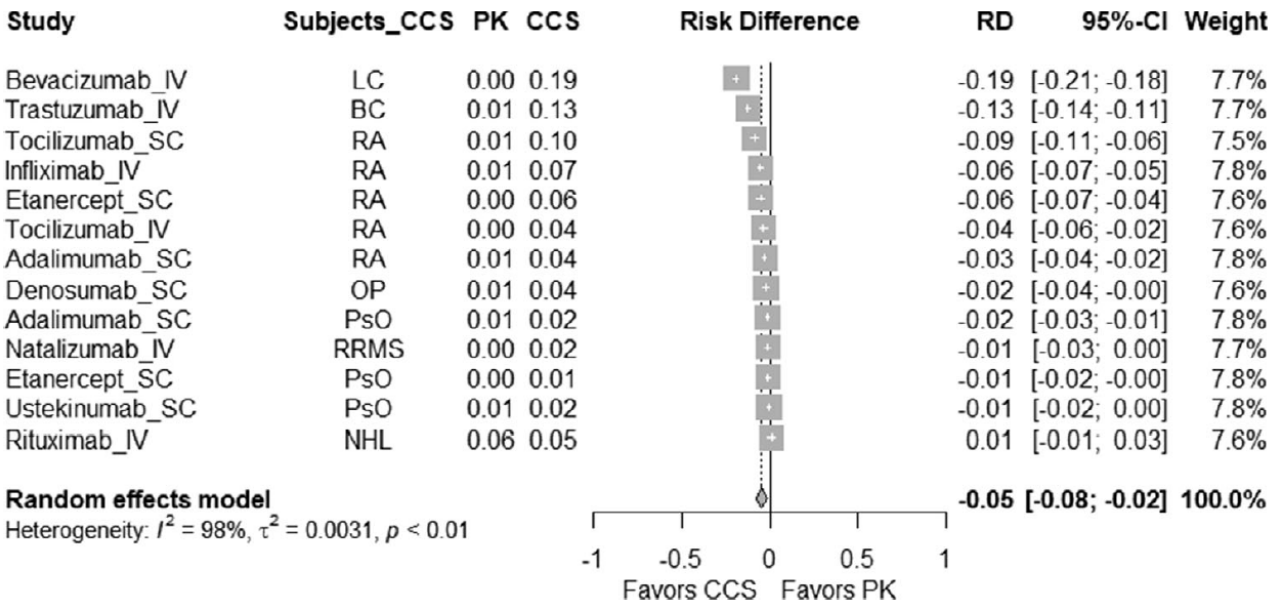


Illustration of risk differences in proportion of subjects between pharmacokinetic studies (PK) and comparative clinical [efficacy] studies (CCS).

Serious Adverse Events

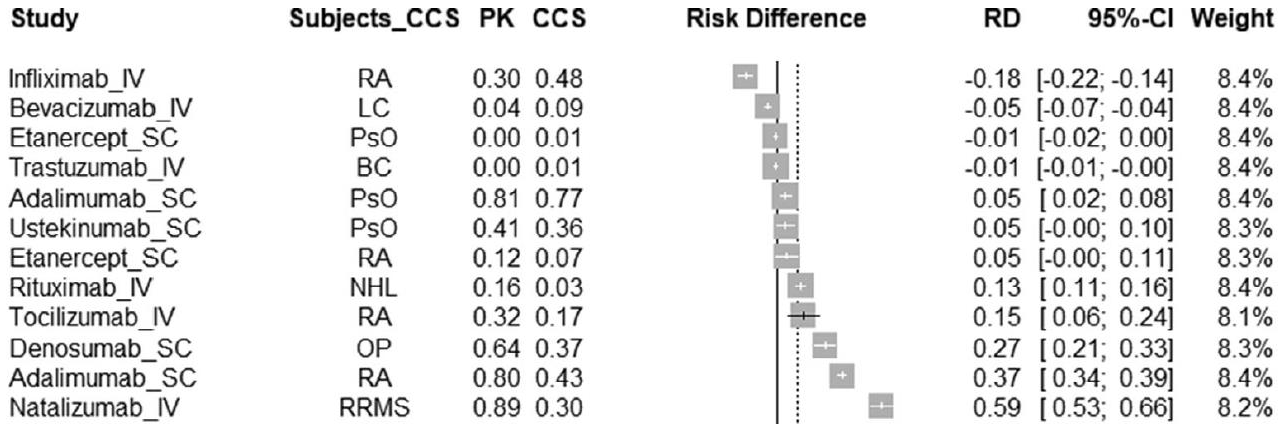


“While there were numerical differences in the average risk difference for AEs, serious AEs, AEs leading to discontinuation, and deaths, the trend is consistent, indicating fewer subjects experienced these AEs across all categories in the PK studies compared to the CCS.”

1. Ji et al 2025, J. Clin. Pharmacol. 2025;65(4) 499–507. <https://doi.org/10.1002/jcph.6165>

Comparison of descriptive immunogenicity data between PK and CES studies

Anti-drug antibody incidence



Neutralizing antibody incidence

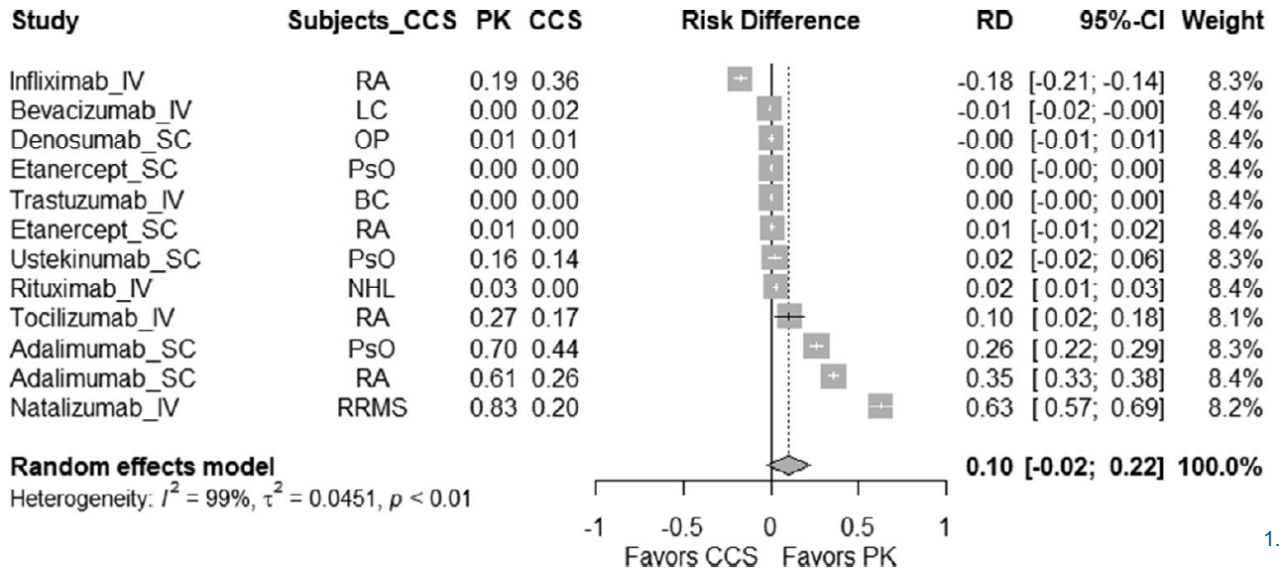


Illustration of risk differences in proportion of subjects between pharmacokinetic studies (PK) and comparative clinical [efficacy] studies (CCS).

“The overall risk difference (95% CI) for ADA incidence is 0.12 [-0.01,0.25], indicating that ADA development in pharmacokinetic similarity studies is not less compared to CCS.”

Ji et al 2025, J. Clin. Pharmacol. 2025;65(4) 499–507 . <https://doi.org/10.1002/jcph.6165>

“Pharmacokinetic similarity studies, as currently designed, provide useful information to descriptively evaluate immunogenicity and safety, and comparative clinical [efficacy] studies do not appear to be more definitive“

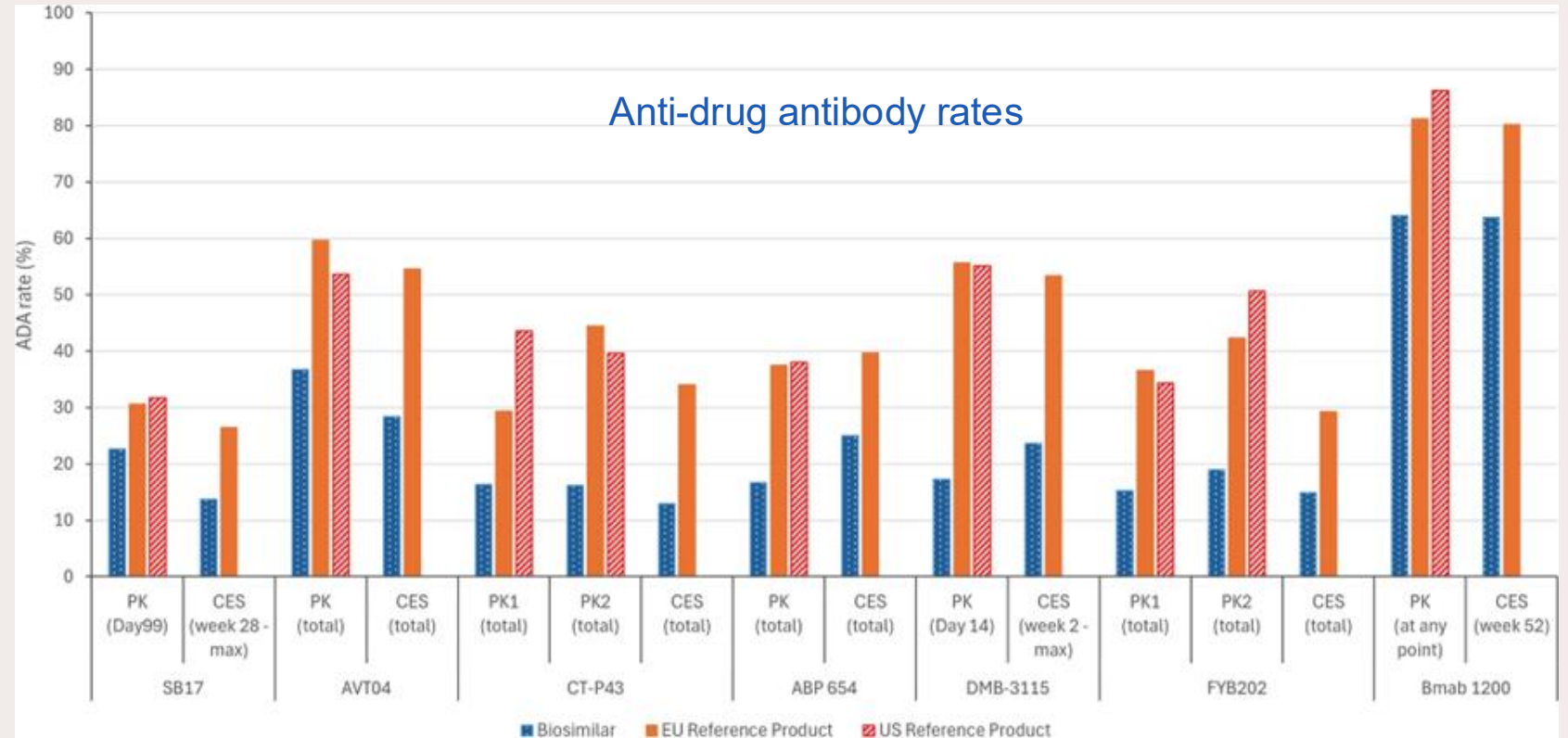
Schiestl et al. 2025

Ustekinumab case study

- Reference: Schiestl M, Roy N, Trieb M, Park JP, Guillen E, Woollett G, Wolff-Holz E
Analytical Data and Single-Dose PK are Sufficient to Conclude Comparable Immunogenicity for Biosimilars: An Ustekinumab Case Study
BioDrugs 2025;39;769-776. <https://doi.org/10.1007/s40259-025-00733-1>
- Scope: 7 EU and US-licensed ustekinumab biosimilar medicines
- Data source: EPARs and FDA assessment reports
- Objective
 - Review the role of analytical, clinical pharmacokinetic and comparative clinical efficacy study data in the assessment of comparable immunogenicity between the biosimilar medicines and the reference product

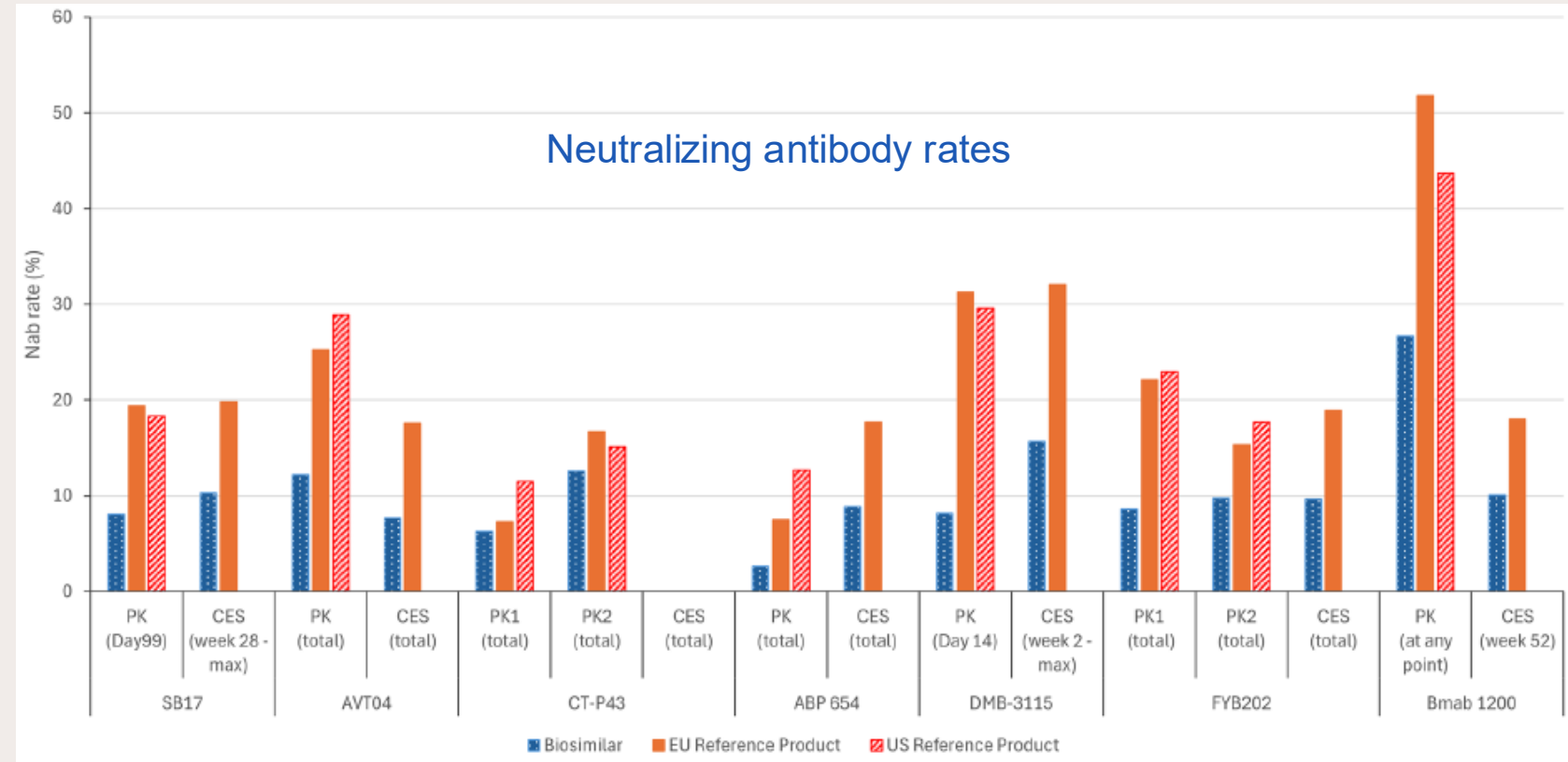
Ustekinumab case study

- Single dose PK studies in healthy volunteers revealed a numerically lower immunogenicity of Ustekinumab biosimilar medicines compared to the reference product
- Anti-drug antibody values depend on the assay sensitivity of the respective study
- The Anti-drug antibody incidences found in the PK study were reproduced in the CES studies. CES did not provide further insights.



Ustekinumab case study

- Single dose PK studies in healthy volunteers revealed a numerically lower immunogenicity of Ustekinumab biosimilar medicines compared to the reference product
- Neutralizing antibody values depend on the assay sensitivity of the respective study
- Neutralizing antibody incidences found in the PK study were reproduced in the CES studies. CES did not provide further insights.



Non-human glycans are known risk-factors for immunogenicity

- Non-human glycans: α -1,3-gal and N-glycolylneuraminic acid (NGNA)
- Ustekinumab biosimilar medicines contain less non-human glycans (see next slide)
- Impact of manufacturing cell-line:
 - SP2/0 cell lines produce typically higher amounts of non-human glycans than CHO cell lines ¹
- Immunogenicity risk of α -1,3-gal structures is supported by evidence
 - α -1,3-gal present on the Fab portion of cetuximab is associated with causing anaphylaxis in some patients ^{1, 2}
 - α -1,3-gal Fc glycans (especially when bivalent) can also bind to anti- α -1,3-gal antibodies and should be therefore considered as a critical quality attribute ²
 - Immunogenicity against α -1,3-gal is associated with allergy against red meat ³
 - Risk factor are bites from the lone star tick which cause high-titer IgE Ab to α -1,3-gal

1. Hatfield et al., mAbs 2023; 15:1, <https://doi.org/10.1080/19420862.2023.2239405>
2. Chung et al., N Engl J Med 2008; 358:1109-1117
3. Berg et al., Ann Allergy Asthma Immunol 2014; 112:97-101

Biosimilar Ustekinumabs contain less non-human glycans

Public data show lower levels of non-human glycans in the Ustekinumab biosimilar medicines compared with the reference product ^{1,2,3}

- Other risk factors for unwanted immunogenicity are comparable
- Lower Non-human glycan contents correlate with lower ADA levels in PK study

Table 1 Content of non-human glycans, terminal α -1,3 gal, and NGNA in comparison to the RP					
Biosimilar	Cell line	α -1,3 gal content in biosimilar	α -1,3 gal content in RP	NGNA content in biosimilar	NGNA content in RP
SB17	CHO	Not detected Lower than RP	1.8–2.6% Higher than biosimilar	Not detected	Detected
AVT04	SP2/0	Much lower than RP	Much higher than biosimilar	Similar	Similar
CT-P43	CHO	NA	NA	NA	NA
ABP 654	CHO	Not detected	1.7–4.9%	Not detected	Detected
DMB-3115	SP2/0	Lower than RP	Higher than biosimilar	Lower than RP	Higher than biosimilar
FYB202	CHO	Lower than RP	Higher than biosimilar	Lower than RP	Higher than biosimilar
Bmab 1200	SP2/0	Lower than RP	Higher than biosimilar	Lower than RP	Higher than biosimilar

All data are from the EPARs, with the exception of SB17, which stems from the US FDA action package data [25–33]

α -1,3 gal α -1,3 galactose, *CHO* Chinese Hamster Ovary, *EPAR* European Public Assessment Report, *FDA* Food and Drug Administration, *NGNA* N-glycolylneuraminic acid, *RP* reference product, *NA* not available

Three biosimilar medicines are, like the reference product, produced in SP2/0 cells, which have higher propensity for non-human glycans. Still, all biosimilar medicines showed lower levels of non-human glycans and lower numerical immunogenicity.

Ustekinumab case-study

Conclusions

1. **Single-dose clinical PK studies were sensitive in detecting ADA and Nab rates**, and the comparative efficacy studies confirmed the findings of the single-dose PK studies without providing more insights on immunogenicity
2. The numerically lower immunogenicity rates of the biosimilar medicines correlate with lower levels of non-human glycans, which has been shown to have the potential to increase immunogenicity. **This finding corroborates the predictive nature of the analytical assessment for comparable immunogenicity**, a principle that has been successfully applied in the regulation of process manufacturing changes of biologics for over 3 decades.
3. This study suggests that, if needed, **immunogenicity data from a single-dose clinical PK study, together with the comparative analytical assessment with a focus on quality attributes with potential immunogenic relevance**, are sufficient for evaluating the comparable immunogenicity of a proposed biosimilar.

Conclusions

- Streamlined biosimilar development is based on comparative analytical and clinical pharmacokinetic data, without a Phase III-type comparative efficacy study (CES)
 - The scientific basis is well established
 - Comparative efficacy, safety, immunogenicity is ensured by pivotal comparative analytical data and process controls
- Streamlined development may counter the increasing biosimilar void
- Regulatory harmonization is ongoing
 - The ICH M18 will greatly facilitate global harmonization

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Single-dose PK studies suffice

- There are concerns that a single-dose study may not be as sensitive for assessing immunogenic response as a multiple-dose study
 - Ji et al 2025:
 - “This concern regarding low sensitivity after single-dose administration likely originated from vaccination practices, where multiple doses are often required to enhance the immune response and achieve long-lasting protective immunity.”
 - “However, unlike vaccinations, which typically have a very short half-life, the half-life of monoclonal antibodies and fusion proteins is generally long, ranging from weeks to months. As a result, these products tend to remain in the body long enough to generate ADA, suggesting that an assessment following single-dose administration may be sufficient to evaluate the product’s immunogenicity.”
 - Experience in biosimilar development confirm high sensitivity of single-dose studies
 - Schiestl et al: Ustekinumab case study: all PK studies were single-dose studies
 - Kurki et al, Li et al: Single-dose PK studies delivered sensitive immunogenicity response, which were replicated in the CES studies
- Conclusion
- Single-dose PK studies suffice to provide sensitive supportive immunogenicity data in a Streamlined development, if needed
- A multi-dose PK study would not be more definitive for regulatory decision making

1. Ji et al 2025, J. Clin. Pharmacol. 2025;65(4) 499–507. <https://doi.org/10.1002/jcph.6165>
2. Schiestl, M., Roy, N., Trieb, M. et al. BioDrugs (2025). <https://doi.org/10.1007/s40259-025-00733-1>
3. Kurki et al. Drugs 81, 1881–1896 (2021). <https://doi.org/10.1007/s40265-021-01601-2>