

Upside Down

Biosimilar in vitro principles adapting at lightspeed

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Biosimilar Medicinal Products Working Party

New Start 09/23

- 10 Members (5 Quality, 5 Clinical)
- Located in Quality Domain (with QWP and BWP)

Chairperson Re-Election in 2026

BMWP Tasks in a nutshell:

- Provide Guidance
- Scientific Advice/Marketing Authorisation
- International Cooperation
- Interested Parties

Reflection paper on a tailored clinical approach in biosimilar development

Draft for internal consultation agreed by Biosimilar Medicines Working Party ²	21 October 2024
Consultation with MWP, BWP and SAWP	17 January 2025
Adopted by CHMP for release for consultation	<DD Month 2025>

Draft agreed by Biosimilar Medicines Working Party ³	12 February 2025
Adopted by CHMP for release for consultation	<DD Month 2025>
Start of public consultation	<DD Month 2025> ⁴
End of consultation (deadline for comments)	<DD Month 2025> ⁴
Agreed by <Working Party> ³	<Month YYYY>
Adopted by <Committee>	<DD Month YYYY>

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Keywords	Reflection Paper, Biosimilar, Comparative Efficacy Study, Tailored clinical approach ⁴
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Reflection Paper on a tailored approach in biosimilar development

Scope: This Reflection Paper discusses the **necessity of CES for demonstration of biosimilarity**. In order to place those reflections into context, the Reflection Paper first considers the current practice with respect to analytical comparability exercises, including *in vitro* pharmacology, and consider their predictive value.

Subsequently, some reflections will be provided with regard to the contribution of CES, and other human in vivo studies, especially PK/PD studies, and to the assessment of immunogenicity.

This Reflection Paper is **not intended to replace current guidance** or current practice with regard to analytical comparability exercises.

A scary void

The Biosimilar Pathway has become unattractive

Most recent numbers: 90% of Biologics do not have candidate in Pipeline

- Smaller indications
- Add on therapeutics
- Orphans
- High costs

Final Reflection Paper adopted

EMA/CHMP/BMWP/60916/2025 – adopted 16 March 2026



Core scientific principle

“Structure determines function” – the same structure results in the same biological activity.

Builds on 20 years of EU biosimilar experience and on the ICH Q5E comparability paradigm used for manufacturing changes.

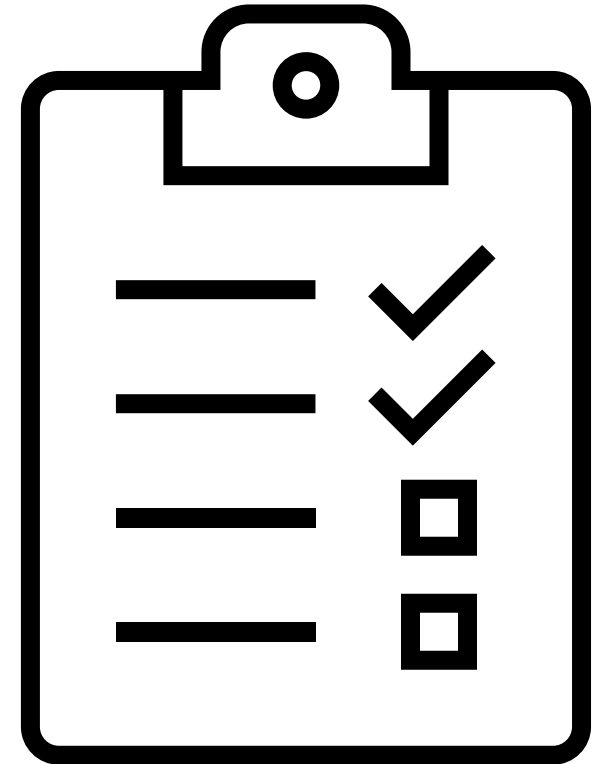
Central conclusion

CES are no longer expected for biosimilars that can be thoroughly characterised with state-of-the-art analytics and show physicochemical and functional similarity.

Applies to the majority of biosimilar candidates: analytics + comparative PK can suffice.

The conditions of ,Tailoring'

- Strong focus on the **potential to characterise the molecule**
- **Mode of action well understood** and characteriseable
- Clinical performance of originator does not inform the potential for tailoring



When Are Clinical Efficacy Studies Still Needed?

- In most cases, comparative CES studies may not be necessary, but specific scenarios require clinical E/S/I data:
 - **Biologicals with an unknown or poorly characterized MoA**
 - Some biologics (e.g. ATMPs) have complex structures and mechanisms
 - Limited understanding or lack of in vitro tests may necessitate CES
 - **Products with high intrinsic heterogeneity or insufficient structural**
- **characterization**
 - Some complex biologics have significant variability
 - If analytical methods do not provide sufficient characterization, CES may be needed
- **Situations where PK studies are not relevant**
 - Locally administered products (e.g., intraocular, intrathecal, intraspinal) may not reach systemic circulation



Does Quality need to become better?

The scope of the RP was an **evaluation whether CES are necessary** (in many cases they are not)

- no relevant additional evidence
- could even lead to „false security“

Quality Comparability (as done) is capable to determine whether a product lies within the range of the originator.

Immunogenic Potential

might still play a role in data requirements

- Some reference products exhibit clinically relevant safety or immunogenicity concerns:
 - High levels of anti-drug antibodies (ADAs) leading to reduced efficacy
 - Immunogenicity-related safety issues (e.g., severe infusion reactions)
- Additional clinical evidence may be required in such cases
- **However, a CES waiver is possible**

The current thinking

Why data beyond healthy volunteer PK studies aren't needed

Healthy volunteer PK studies capture essential immunogenicity concerns

ADA formation readily detectable. These studies offer **controlled conditions**—minimal concomitant medications, monotherapy exposures, and defined sampling windows—enabling detection and characterization of immunogenic responses.

Requiring patient immunogenicity trials adds limited incremental value

In some settings accompanied by immunomodulatory treatments. Recent publications suggest – repeated dosing not needed to evoke ADA answer

Recent publication highlighting sensitivity of HV PK trials for immunogenicity testing.

EMA BMWP supports **comprehensive immunogenicity risk assessment**, focused on **analytical/functional characterisation and ADA incidence and characteristics captured in healthy volunteer studies**.

PK Studies for Biosimilar Evaluation

- Adaptation of PK study design possible depending on the safety and immunogenicity profile of the reference product
- Aspects of adaptation:
 - Dosing schedule
 - Study duration
- Importance of multiple dosing and sufficient study duration to capture delayed antibody responses
- Comparative PK studies often provide sufficient information on safety and immunogenicity

Necessary considerations for PK going forward ...

What is the goal of the remaining clinical data?

- What evidence is expected from the PK-study as the only clinical study
 - PK comparability
 - Immunogenicity
 - Biomarker response (PD)
- The information requested will affect the study design
 - Study size
 - Single dose vs multiple dose
 - Parallel vs cross-over design
 - Healthy volunteers vs patients
- Methods for PK characterisation and statistical comparison
 - ANOVA, population PK (M&S), ...

What about PD?

Mainly for non mAB biologics

Formerly...

- GCSF
 - Insulin
 - LMWH
 - ...
-
- Relevant PD markers for mABs mainly lacking
 - (Exception: Maybe BMD for denosumab)

Most Biosimilar Developments will not require primary PD Endpoints

- Tailored approaches will rapidly become routine in Biosimilar assessment
- For most, classical “BE” PK plus immunogenicity testing will suffice
- PD will remain crucial in exceptional cases
 - Mainly if PK is not sensitive
 - And Marker is available
- If Marker is available but PK is sensitive, not mandatory as primary EP but should be measured to strengthen similarity exercise

Example Romiplostim

Thrombopoietin Receptor Agonist

- **Complex structure**

- Peptibody with non-linear pharmacokinetics

- **Target-mediated drug disposition (TMDD)**

- Binding to TPreceptors on megakaryocytes
- Clearance depends on receptor availability

- **Low systemic exposure**

- Sometimes below LLOQ

- **Non-linear clearance**

- Saturable receptor binding → dose-exposure not proportional

→ **PK comparison difficult; PD markers (platelet response) often more informative**

The Remaining Clinical Package

Comparative PK as the only clinical study

PK

Essential – not waivable

- Primary aim: equivalent exposure; secondary: supportive safety & immunogenicity
- Standard: single-dose study in healthy volunteers
- Multiple doses / longer duration if ADA develop late or are clinically relevant – HV or patients
- PK batch must match RMP protein content

PD

Generally not expected

- For well-characterised molecules PD adds no relevant information
- If measured: no formal equivalence testing needed – results should support similarity
- Only if PK is not feasible: comparative PD with pre-defined margins and sample size
- PD markers may not be interpretable in healthy volunteers

Immunogenicity

Captured in the PK study

- ADA data from comparative PK analysed descriptively
- Regulatory experience: ADA in PK studies correspond well with CES
- Single dose insufficient if neutralising ADA, serious safety events or delayed ADA are expected
- Assess RMP immunogenic risk and ADA timeframe upfront to set study duration

The little stone became an Avalanche

Its now a global topic

ICH M18

Goal: Harmonized framework on need/design of efficacy studies in biosimilars

- **Principle:** *Totality of evidence* — analytical + PK/PD usually sufficient
- **Efficacy Study Required When:** Residual uncertainty remains on safety/efficacy
- **Impact:** Streamlines biosimilar development, reduces unnecessary trials

Start: first meeting at November 25 ICH

Currently: Working on the first Draft. Next Meeting, Prague.

Prerequisites for waiving CES

All five conditions need to be fulfilled

1

Mechanism of action

Comprehensive knowledge of the molecule's MoA is available

2

Analytical characterisation

Structure and functionally relevant QAs (incl. stability-indicating QAs) characterisable with orthogonal, state-of-the-art methods

3

Functional assays

Potency, receptor-binding etc. – assess function directly and serve as surrogate for higher-order structure

4

Validated process & control strategy

Manufacturing process and specifications assure future consistency

5

Pre-established similarity assessment plan

Defined before testing – not a post-hoc justification

CES may still be needed

- Molecule cannot be well characterised
- MoA unknown or poorly understood
- Analytical methods not sufficiently sensitive; structure–function relationship incomplete
- Meaningful PK not feasible, e.g. locally applied products without relevant systemic exposure

Batch Strategy

How many batches are needed?

≥ 6

biosimilar batches

from independent drug substance batches

≥ 10

reference product batches

general minimum for the similarity assessment

15–30

RMP batches

optimal in many cases

The right number of RMP batches depends on

Batch independence

Criticality and variability of
the QA

Sensitivity of the analytical
procedure

Chosen similarity approach

Sample the RMP continuously over time to capture potential shifts or drifts.

Similarity Assessment Plan

Planning is the backbone of comparability

1

Sampling

RMP sampling strategy and selection of biosimilar batches

2

Criticality

Ranking of QAs, justified by their link to PK, efficacy, safety and immunogenicity

3

Methods

Orthogonal, state-of-the-art analytical methods and their validation

4

Statistics

Pre-defined approach for evaluating similarity

Agree upfront

- Present the plan to CHMP via EMA Scientific Advice
- A pre-established plan avoids post-hoc justifications

Side-by-side testing

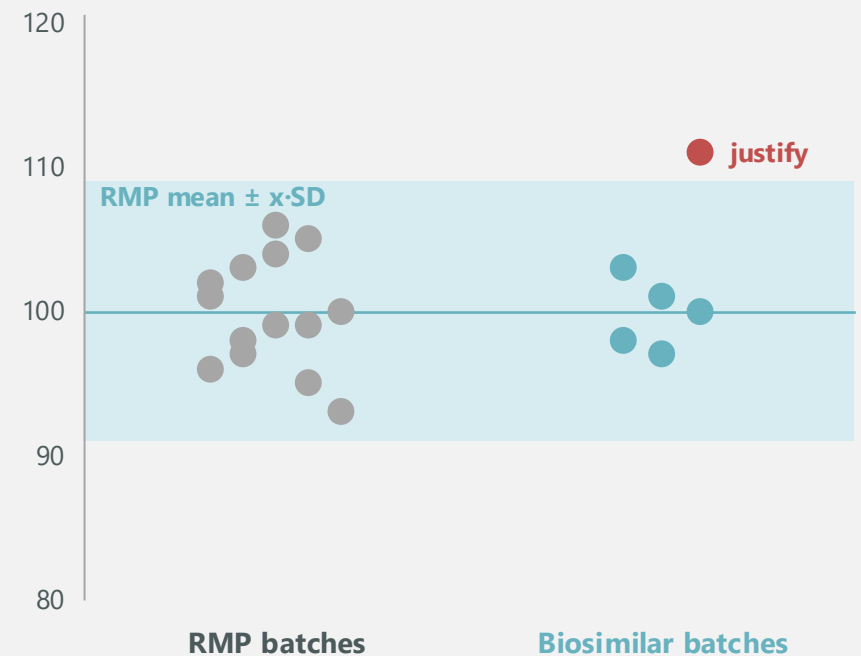
- Largely obsolete – modern methods show little between-run variability
- Still meaningful if between-run variability is high

Similarity Ranges

Graded by the criticality of the quality attribute

- **Similarity range:** Mean $\pm$ x·SD of the RMP batches (x-sigma interval)
- Multiplier x **scientifically justified** and proportionate to criticality – smaller x for high-criticality QAs
- Biosimilar batches within the batch-to-batch variability of the RMP are expected to show the same clinical performance
- **However, this is just ONE WAY, principles of Quality in Statistics Paper should be followed.**

Illustration: potency (% of RMP mean)



Some valid criticism

"This looks like statistics, but it doesn't give you the protection a real statistical test gives."

- 1. The range is built on guesses, not true values.** The mean and sigma come from a small sample of reference batches, often only 10 to 20, so they are estimates. With so few batches, sigma can easily be too small or too large.
- 2. Nobody knows the error risk.** A proper test tells you how likely you are to wrongly call two products similar, for example "at most 5%.."
- 3. The multiplier "x" is arbitrary.** Why 2? Why 3? T
- 4. The result depends on the number of batches.** With few test batches, even a somewhat different product can pass by luck.
- 5. "Inside the range" can hide real differences.**

X-Sigma criticism 2/2

- 6. The batches may not be truly independent.** Several final batches may come from the same starting material
- 7. The reference product changes over time.** Originator products can drift, for example after their own manufacturing changes. Mixing old and new reference batches can make sigma larger and the range too wide.
- 8. Measurement error is mixed in.** Sigma includes both real product variation and noise from the lab method. A noisy method creates a wider range and makes passing easier.
- 9. Many attributes, many chances.** Biosimilar programs check dozens of attributes. Doing many simple checks without any overall plan makes the total error risk even less clear.

The „Quality Statistics“ Reflection Paper

Provides Reflections on how inferential statistics could be implemented in quality comparability

Statistics in quality remains difficult topic.

Any too prescriptive Guidance to date has failed

Interpreting Similarity Results

Not every out-of-range value is a show-stopper

Within range

All biosimilar batches inside the RMP similarity range

→ **Supports biosimilarity**

Physicochemical QA outside range

No automatic failure – but uncertainty increases

→ **Justify with further characterisation; weigh in the overall conclusion**

Biological activity outside range

Batches fail the similarity range for biological activity

→ **Conclusion of biosimilarity unlikely**

Presentation of results

- Tabulated per batch – separately for biosimilar and RMP
- Graphical display of spread and ranges: dot plots, box plots

Critical Quality Attributes (1/2)

Structure, content and function

Primary & higher-order structure

- Amino-acid sequence must be identical – any difference contradicts biosimilarity
- Low-level sequence variants only as controlled product-related substances
- PTM differences (terminal variants, oxidation, deamidation): orthogonal data showing no impact on binding or Fc regions

Protein content

- Do not rely on the RMP label claim
- Determine protein concentration accurately across several RMP batches
- Select biosimilar batch(es) for the PK study to match the RMP protein content

Biological activity

- Relevant and discriminatory functional assays: receptor binding, cell-based potency
- Support criticality assessment of physicochemical QAs
- **Failing the similarity range here makes biosimilarity unlikely**

Critical Quality Attributes (2/2)

Variants, glycans and impurities

Charge variants

- Differences acceptable if thoroughly understood
- Peak fractionation with physicochemical and biological testing
- Enzyme treatment, e.g. carboxypeptidase for C-terminal lysine variants

Glycosylation

- Afucosylation and high mannose are critical for mAbs with Fc effector function
- Data on FcγRIIa/FcγRIIIa variants and ADCC in several assay formats
- **Clear differences in ADCC, ADCP or CDC may preclude approval**

Impurities

- Characterise differences: fractionation, impact at detected levels, comparative stability
- **Reduce impurities – especially those absent in the RMP – as low as technically reasonable**
- Preferred over immunological characterisation

Impurities

Should their assessment change?

- Impurities are characterised and quantified
- How should a strict comparability for Impurities look like?
- Would that be meaningful?
- How to factor in novel impurities?
- Don't forget that other strong drivers as AS sequence, glycosilation etc, are also controlled

Learnings from Scientific Advice

Tailoring in practice – monoclonal antibodies

Monoclonal antibodies

We hardly ever say “no” to tailoring

Why mAbs usually qualify

- Well-understood MoA and well-characterisable molecules
- Mature orthogonal analytics and functional assays, incl. Fc effector functions
- Discussion shifts from “whether” to “how”: similarity assessment plan, batches, PK design

Open question

Should the acceptability of tailoring be captured in a Scientific Advice?

- **For:** planning certainty for developers; documented agreement on the similarity assessment plan
- **Against:** tailoring is meant to be the default – a formal confirmation could turn SA into a de-facto prerequisite

Are ADCs Eligible for Tailoring?

In principle yes – but with careful evaluation

Antibody

- Classical mAb characterisation
- Target binding, Fc functions

+

Linker

- Conjugation sites & chemistry
- Linker stability / payload release

+

Payload

- Identity & purity of the small molecule
- Free payload and related impurities

Additional points for careful evaluation

DAR

Drug-to-antibody ratio and its distribution

Function

Assays covering both binding and payload-mediated cytotoxicity

PK

Several analytes: total antibody, conjugated ADC, free payload

Bottom line: ADCs are not excluded from tailoring – the prerequisites apply to every component.

Towards Bioidenticality?

A very recent discussion

Complex / poorly characterisable

Analytics + PK + CES

Well characterisable (majority)

Analytics + PK

Simple molecules?

Analytics only – PK waived?

decreasing molecular complexity → decreasing clinical data

The idea

- For some molecules in vitro comparability is already so good that differences are practically undetectable
- Especially simple molecules that can also be produced synthetically – e.g. teriparatide, semaglutide
- **Could even the PK study be waived?**

Open points

- Where is the line between “highly similar” and “identical”?
- Immunogenicity then assessed without any human data
- Formulation, impurities and aggregates remain decisive

Status Quo: Overarching Guideline

Concept paper for revision open for consultation



Concept paper EMA/CHMP/BMWP/153523/2026

- Revision of the overarching guideline – unchanged since 2015
- Integrates the Reflection Paper on tailoring and ICH M18
- Aligns with the new EU pharmaceutical legislation

Open for public consultation

until 31 October 2026

Comments via EUSurvey on the EMA guideline page

Link: <https://www.ema.europa.eu/en/similar-biological-medicinal-products-scientific-guideline>

Next Steps: Updating the Guidelines

Quality and non-clinical/clinical biosimilar guidance

Quality guideline

EMA/CHMP/BWP/247713/2012 – effective since Dec 2014

- Embed similarity assessment plan, batch numbers and similarity ranges
- Reflect state-of-the-art analytics

→ [Guideline page](#)

Non-clinical & clinical guideline

EMA/CHMP/BMWP/42832/2005 Rev1 – effective since Jul 2015

- Replace CES default by tailored clinical approach
- PK as core clinical study; new role of PD and immunogenicity

→ [Guideline page](#)

Until revised: a disclaimer on the EMA website points to the adopted Reflection Paper, which reflects the current thinking on clinical data requirements.

Triage of Product-Specific Guidances

Every PSG goes into one of three categories

Keep

Guidance still reflects current thinking

Update

Adapt to the tailored approach

Withdraw

Content covered by overarching
guidance

Current product-specific biosimilar guidances

Monoclonal antibodies

Erythropoietins

G-CSF

Insulins & analogues

Low-molecular-weight heparins

Somatropin

Follitropin (FSH)

Interferon beta

Interferon alpha / peg-IFN alpha

Link: [EMA biosimilar guidelines incl. product-specific guidances](#)

In conclusion

Things are moving fast

- First tailored approaches already in assessment
- BMWP accompanies the first 10
- Things are moving incredibly fast
- Tailoring default? Guideline Updates
- It's now global (ICH M18)
- Nobody cares/defends efficacy
- No clinical data Biosimilars on the horizon?