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Upside Down

Biosimilar world changing at lightspeed

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Biosimilar Medicinal Products Working Party

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New Start 09/23

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

BMWP Tasks in a nutshell:

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

A scary void

The Biosimilar Pathway has become unattractive

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

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

Reflection Paper on a tailored approach in biosimilar development

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2025
EMA/CHMP/BMWP/60916/2025
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on a tailored clinical approach in biosimilar development

Draft for internal consultation agreed by Biosimilar Medicines Working Party[1]	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>[2]
End of consultation (deadline for comments)	<DD Month 2025>[3]
Agreed by <Working Party>[3]	<Month YYYY>
Adopted by <Committee>	<DD Month YYYY>

Comments should be provided using this EUSurvey form *(add the link to the form)*. For any technical issues, please contact the EUSurvey Support.

Keywords	Reflection Paper, Biosimilar, Comparative Efficacy Study, Tailored clinical approach [4]

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.

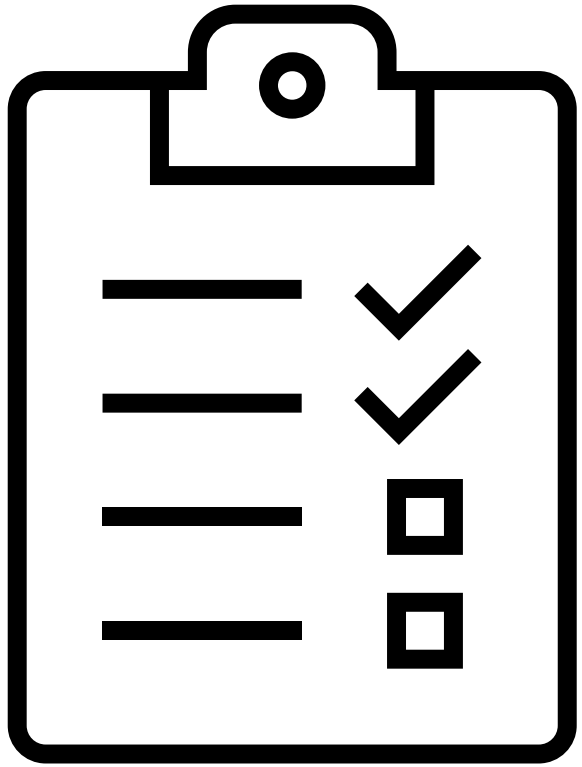
This Reflection Paper is **not intended to replace current guidance** or current practice with regard to analytical comparability exercises.

Steps and Timelines

- **Q2 2025 -** RP published for public consultation (Sept 30th)
- **Q3 2025** - Workshop to discuss with external stakeholders (Sept 22nd at EMA, Amsterdam)
- Final Adoption taking Feedback into account

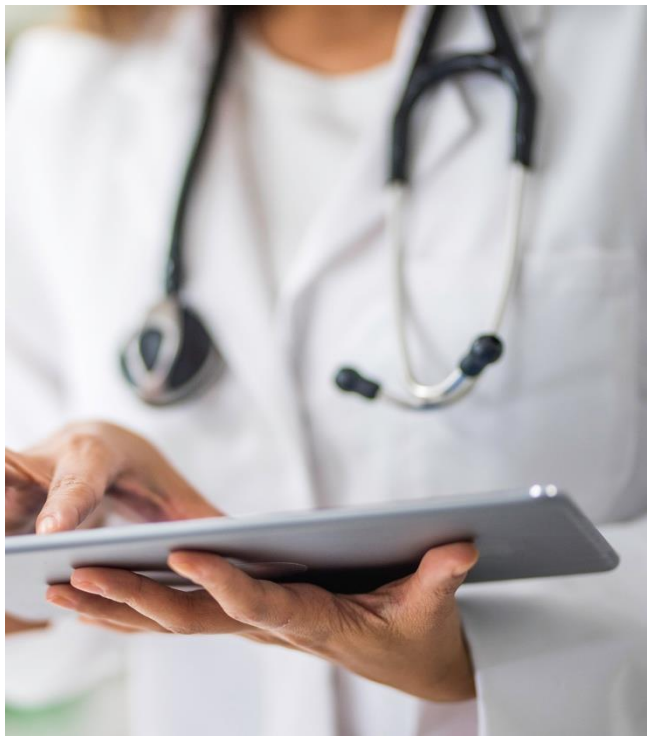
The conditions of ‚Tailoring‘

- 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?

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

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

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

Initial Immunogenicity thoughts

But might still play a role in data requirements

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- 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 may still be possible**

Recent developments

Why data beyond healthy volunteer PK studies aren't needed

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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 senstitivity 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

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- 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 …

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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…

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- GCSF
- Insulin
- LMWH
- …

- Relevant PD markers for mABs mainly lacking
- (Exception: Maybe BMD for denosumab)

The role of PD is heavily discussed…

A first approach

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Hardly any biologic has validated biomarkers in place

Qualification long process

Only more simple biosimilars have been auhorised in the past based on PD

PD should not be a default when evaluating a reduction of clinical data

Most Biosimilar Developments will not require primary PD Endpoints

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- 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 strenghen similarity exercise

Example Romiplostim

Thrombopoietin Receptor Agonist

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- **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**

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Learnings from the Industry Workshop

(Un)Surprising Concerns

The Biosimilar industry

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- Tailoring should not be an exception, but the clear default
- If efficacy trial, you should justify which question it answers
- Delete Reference to the EMA „Statistics in Quality“ reference
- PD insensitive and unnecessary
- PK trial solves it all

The „Quality Statistics“ Reflection Paper

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

Industry provided Case studies, showing that nearly all Biosimilars would have failed if principles would have been applied „literally“ and in the strictest manner

Statistics in quality remains difficult topic.

Any prescriptive Guidance to date has failed

How about the rest of the world?

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After pioneering with our RP:

Health Canada has issued their guidance: no specific mention of statiscal considerations

US FDA: some guiding principles on quality level – request for a „comparability plan“ very much sticking to established comparability principles – no new statistical plans requested.

The Originator Industry

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Agreement, that tailoring will be possible in most cases

Wish for simple Decision trees

Impurity assessment should be stricter

Wish for global harmonisation

Product specific guidances

Originator Industry P2

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- PK not sufficient for immunogenicity in some cases
- Specific Safety Studies necessary
- Stronger Pharmacovigilance
- Transparancy in EPAR and SmPC

Safety Studies and Pharmacovigilance

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Powered Studies are simply unfeasible and unreasonable

What is the clinical relevance of ADA?

Pharmacovigilance in Europe very solid

Products switched back and forth – meaningful?

Impurities

Should their assessment change?

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- Impurities are characterised and quantified
- How should a strict comparability for Impurities look like?
- Would that be meaningful?
- How to factor in novel impurities?
- Dont forget that other strong drivers as AS sequence, glycosilation etc, are also controlled

Is the risk of immunogenicity overrated?

A subliminal fear since the 2000s

Eprex and the Pure Red Cell Aplasia

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In the mid-90s, case reports from PRCA appear under Eprex treatment

This is followed by an "epidemic" of more than 60 cases/year (46/100000 patient years)

Serum albumin against polysorbates 80 in formulation (because of prions)

Interaction with stoppers of syringes – immunogenic aggregates
exchanged for Teflon – cases disappear

Changes in biologics are very dangerous

Consequences

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The biosimilar concept starts with a bag of uncertainty

Immunogenicity, Immunogenicity, Immunogenicity

At that time, no one thought about the benefits of clinical trials

Without it, the concept would never be accepted

Clinical Studies on Biosimilar Interchangeability

Kurki et al, 2021

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- **Key Switching Study Data:**
  - Multiple clinical trials show no loss of efficacy or increase in immunogenicity after switching.
  - NOR-SWITCH study (infliximab) confirmed no significant differences in disease activity or safety.
  - EGALITY trial (etanercept) demonstrated stable efficacy and immunogenicity after multiple switches

- **Immunogenicity and adverse event rates remain consistent across switches.**

Real-World Evidence on Biosimilar Safety and Effectiveness

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Post-Marketing Pharmacovigilance Data:

Large-scale real-world studies confirm comparable safety and effectiveness profiles.

No increased immunogenicity or loss of efficacy observed in clinical practice.

Regulatory and Clinical Confidence:

No safety signals identified in millions of patient-treatment years.

Conclusion

Scientific evidence supports multiple switches between biosimilars and reference biologics without impact on safety or efficacy.

So we do clinical trials for immunogenicity

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Hm, really?

Studies not powered on antidrug antibodies

Recorded purely numerically/descriptively. For example, 10% against 12%

Would we have seen the EPREX PRCA in a clinical biosimilar trial?

BUT BUT BUT

Thank God for Quality

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BUT – would definitely be noticed in modern quality assessment

Aggregates/impurities form a major focus in the quality assessment and are precisely detected.

Would have been an absolute "show stopper"

The little stone became an Avalanche

Its now a global topic

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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

EC delegates will be BMWP chair and vice-chair

In conclusion

Things are moving fast

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- Where will we end up in quality comparability? Stricter or same requirements in statistics? (might trigger revision in ICH Q5e)
- It’s now global
- Nobody cares/defends efficacy – its all about immunogenicity. Overrated?
- Recent data suggests: Immunogenicity can be captured equally good (or bad) in a PK trial
- First tailored biosimilar mAbs already filed for MAA