Revised EMA Reflection Paper:

'**Similarity Condition**' and '**Similarity Criterion**' as two separate aspects for the comparison of Quality Attributes data

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Disclaimer

I attend this meeting/conference to represent the AGES. The views expressed here in no way shall be binding for the AGES. My remarks do not necessarily reflect the official view of AGES, BASG, EMA or EC.

Seven years from Concept to Reflection Paper (RP)

Concept Paper :	16/01/2014
CHMP-adoption of Draft RP:	31/03/2017
Public Consultation end:	31/03/2018
EMA Workshop:	03+04/05/2018
Kick-off Revision:	24/08/2018
CHMP-adoption of revised RP:	22/07/2021

Focus on sections containing revised content

Table of contents

What is the ‘similarity condition’?

Can be agreed before data collection based on theoretical grounds

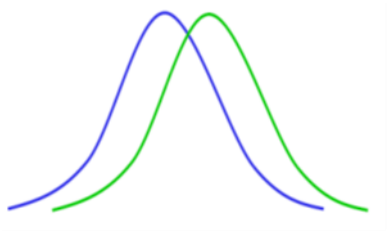


Figure 1

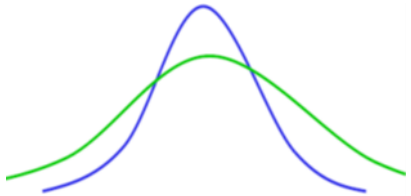


Figure 2

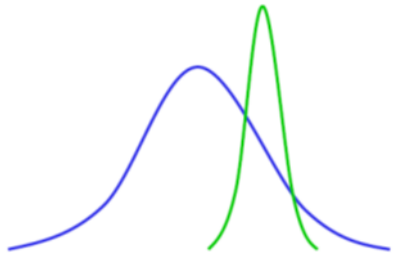


Figure 3

??

Figure x

Reference Medicinal Product
Biosimilar Candidate

or

Before manufacturing change
After manufacturing change

A two-step approach is required

"... it needs to be noted that for most comparisons of QAs there is no general agreement yet regarding what constitutes an agreeable **similarity condition** based on the underlying distributions. However, as long as this question remains open, any subsequent discussions regarding the adequacy of a certain **similarity criterion** [...] aiming to support a similarity claim based on samples falls short. In particular, operating characteristics of a similarity criterion such as the probability of correctly/falsely concluding similarity cannot be quantified when there is a lack of consensus and pre-specification of the similarity condition. **Hence, the selection of the applied 'similarity criterion' needs to be preceded by the definition of the 'similarity condition' at all times.**

Rethink inferential framework

<u>Fundamental need:</u>

Whenever regulatory decision making would heavily rely on QA data comparisons for best possible understanding is needed how the risk for a false positive (similarity) decision is controlled

→ Differentiate: similarity condition and similarity criterion!

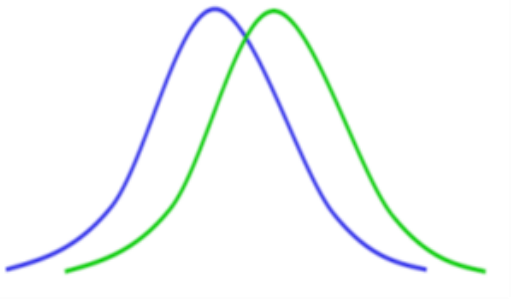
1) Decide upon similarity condition
2) Chose similarity criterion to be used based on expected operating characteristics

→ Check if similarity condition can be assumed to hold

Decide upon similarity condition

To be clarified before data collection, e.g. in a biosimilar setting

Reference Medicinal Product
Biosimilar Candidate



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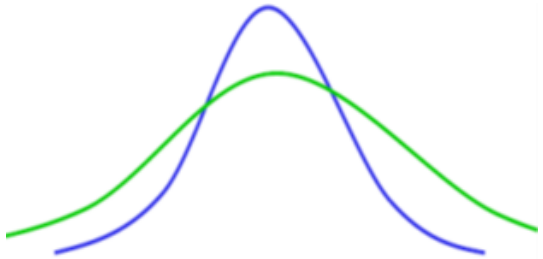

Figure 2

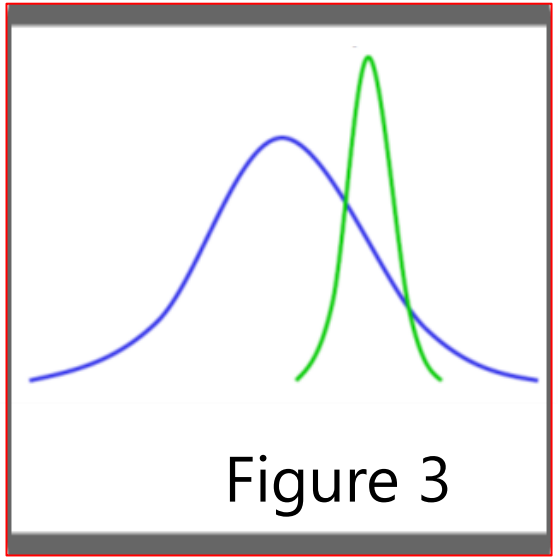

Figure 3

??

Figure x

Example:
Test distribution “entirely contained” within reference distribution, regardless of differences in means and spread (variability);

Choose Similarity criterion

Based on operating characteristics, to be applied to empirical data

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Frequently seen:

e.g.:

- Min-Max-Range of Test entirely contained in mean ± 3SD of Reference
- Min-Max-Range of Test entirely contained in mean ± 2SD of Reference
- Testing equivalence of means
- ...

Operating characteristics of applied criterion

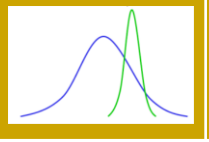
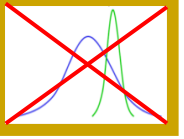
Probabilities to come to the “right” decision regarding similarity

Similarity Condition:
e.g. Test distribution “entirely contained” within reference distribution, regardless of differences in means and spread;

Similarity Criterion

e.g. Min-Max-Range of Test entirely contained in mean ± 3SD of Reference

(use of sample data)

	similarity condition holds 	similarity condition does not hold 
similarity criterion says → “similar”	true positive	false positive
similarity criterion says → “not similar”	false negative	true negative

Estimation of Operating characteristics

Parameters to be controlled in a systematic investigation

- Parameters describing shape and location of underlying distributions (i.e. means, variability, skewness)
- Input parameters to define the similarity criterion, e.g. “p” and “q” in tolerance interval TI(p,q), or “k” in ± k x SD interval criteria
- Sample size for reference/pre-change condition (i.e. # batches)
- Sample size for biosimilar candidate/post-change condition (i.e. # batches)

→ Search for optimum, maximizing probability for correct decision

→ Simulation

Overall conclusion on similarity

Usually involves more than one critical QA

- Methodological approach to be applied per CQA (-grouping)
- Possibly different assumptions for similarity condition for different CQA
- Possibly different similarity criteria to be applied for different CQA
- ‘One-size-fits-all’ approach rather unlikely to cover whole range of CQA

Further changes after revision

- Scope categories as defined in the draft version of the RP: ‘pre/post-manufacturing changes', 'biosimilars' and 'small molecules', now presented less dominantly.
- Former Appendix containing “check-list” replaced by proposal for QA data comparison protocol

QA data comparison protocol

A recommendation to pre-plan

- Description of comparative evaluation of QA data in prospective manner
- Context of QA-comparison in whole development /life cycle
  → Statement on importance to show similarity at quality level
  → Consequences of not showing similarity
- Identification of CQAs to be analysed
- Similarity condition(s)
- Justification of choice of similarity criteria (OC-evaluation)
- Sampling strategy

Unchanged /further elaborated

- No methodological discussion of criticality assessment
- No focus on process control-methodology
- Definition of consistency during manufacturing further elaborated
  (→ key issue for question: “What gets actually compared?”)

Implications /Expectations

RP – a milestone on a longer journey

- contains problem description
- illustrates actual complexity of the (inferential) comparison task
- introduces terminology to improve exchange/discussion
- offers a 2-step framework to “rethink” the QA-data comparison task
- can be expected to provoke more methodologically sound comparison approaches
- may lead to changes in existing regulatory guidance documents
- can be expected to increase the potential to give more weight to QA similarity evidence

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