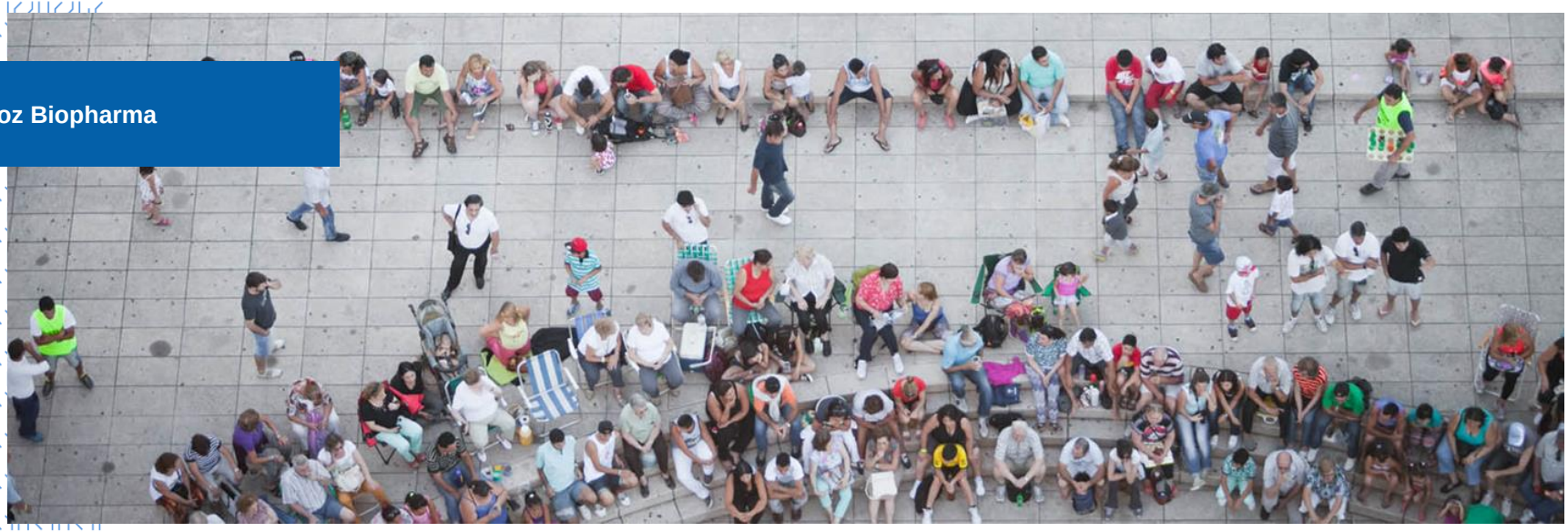
Sandoz Biopharma



A critical review of the final EMA reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

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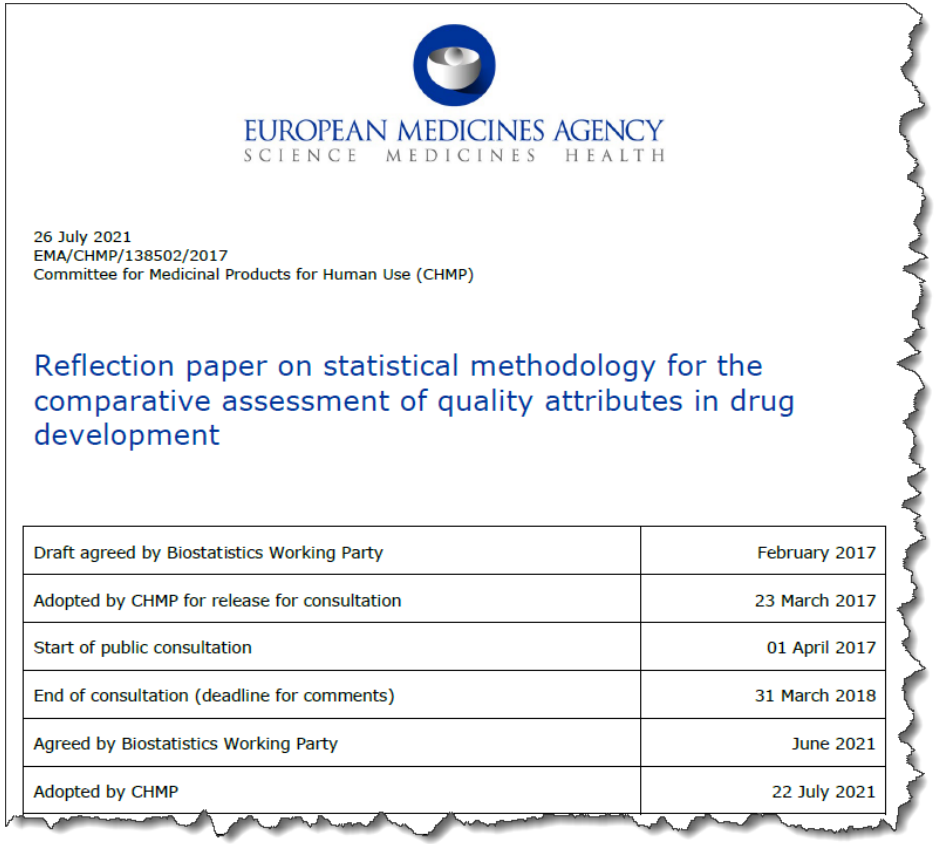
CMC Strategy Forum Europe, 18-21 October 2021

SANDOZ A Novartis Division

In scope

- Manufacturing changes of biologicals
- Biosimilar evaluation
- Generic medicines (abridged/hybrid applications)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 July 2021
EMA/CHMP/138502/2017
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

Draft agreed by Biostatistics Working Party	February 2017
Adopted by CHMP for release for consultation	23 March 2017
Start of public consultation	01 April 2017
End of consultation (deadline for comments)	31 March 2018
Agreed by Biostatistics Working Party	June 2021
Adopted by CHMP	22 July 2021

https://www.ema.europa.eu/en/statistical-methodology-comparative-assessment-quality-attributes-drug-development, accessed on 13 Oct 2021

What is an EMA reflection paper?

- EMA definition of a Reflection Paper (RP)
  "*A document outlining the view of the European Medicines Agency or one of its committees, working parties or other groups on a particular issue*." [1]
- EMA definition of a Guideline
  "*A document providing guidance on the scientific or regulatory aspects of the development of medicines and applications for marketing authorisation. Although guidelines are not legally binding, applicants need to provide justification for any deviations.*" [2]
- Because the Reflection Paper is NOT a Scientific Guideline, it should not be treated as a Guideline

1. https://www.ema.europa.eu/en/glossary/reflection-paper, accessed on 13 Oct 2021
2. https://www.ema.europa.eu/en/glossary/guideline, accessed on 14 Oct 2021

Objectives of the reflection paper on statistical methodologies

- Identification of specific areas where the quantitative comparative evaluation of quality characteristics plays an important role from the regulatory perspective
- It raises open issues from a statistical perspective, and addresses questions related to comparison objectives, sampling strategies, sources of variability and options (or limitations) for statistical inference
- It provides more detailed guidance of how to actually carry out the comparison task based on empirical sample data
- Establish a common language and to improve understanding among all experts
- Trigger further discussion of realistic requirements to demonstrate ‘similarity at the quality level’
- Discusses likely limitations hampering statistical inference, pointing towards meaningful, but expectedly less stringent, alternatives

https://www.ema.europa.eu/en/statistical-methodology-comparative-assessment-quality-attributes-drug-development, accessed on 13 Oct 2021

RP proposes new regulatory requirements which seem inspired by clinical statistics

New requirements for QAs in RP	Corresponds with
Similarity condition	**Margin** for clinical endpoint (to show, e.g. superiority, equivalence)
Similarity criteria	**Statistical tests** including prespecified criteria for clinical endpoints
Statistical **operating characteristics** to justify similarity criteria	**Test size justification** (α, the maximum probability of committing a Type I error)

Problem: " *... analysis approach applied to clinical data cannot be easily transferred to quality data comparison. Distinct differences exist between the two settings ...*" [1]

1. https://www.ema.europa.eu/en/statistical-methodology-comparative-assessment-quality-attributes-drug-development, accessed on 13 Oct 2021

Reflection paper contains relevant considerations …

- Different statistical approaches may be used for different quality attributes
- Discussion of different statistical methods and their limitations
- Underlying assumptions, i.e. process consistency
- Issues with sampling of reference and test product batches
- Role of control strategy to ensure product consistency
- Each released batch of the reference product defines acceptable quality
- *"... the question in how far dissimilarity in QA data can be seen compliant with a biosimilarity claim may not be based on the outcome of a single statistical test, but rather taking the entire biosimilar data package as a whole*."

https://www.ema.europa.eu/en/statistical-methodology-comparative-assessment-quality-attributes-drug-development, accessed on 13 Oct 2021

… acknowledges the limitations …

- “ *… identifying the similarity condition may be challenging …”*
- “ *… no universally applicable/agreeable similarity condition exists*.”
- “ *… there is no specific minimum number of required batches/units (e.g. 3 batches, as frequently suggested in practice for manufacturing changes) which could guarantee to capture the true underlying variability*.”
- “*… sample size constraints (e.g. low batch numbers) and associated risk for a false negative conclusion may lead to the need to use approaches other than inferential statistical comparison of QAs*.”
- “*… as the underlying truth is not observable, it will never be known whether a specific decision on the fulfilment of a similarity condition based on a similarity criterion is right or wrong.”*

https://www.ema.europa.eu/en/statistical-methodology-comparative-assessment-quality-attributes-drug-development, accessed on 13 Oct 2021

… but contains also idealistic expectations.

- "*… the selection of the applied 'similarity criterion' (see Section 4.3) needs to be preceded by the definition of the 'similarity condition' at all time*s."
  - What if no consensus can be achieved on similarity conditions for the CQAs?
- "*Any post-hoc justifications that observed (unexpectedly large) differences in one or more of the analysed QAs would have no or only minor impact on clinical outcome might eventually be seen to contradict preceding criticality assessment of QAs and/or an adequate definition of the similarity condition*."
  - Could be interpreted that post-hoc justification based on updated process and product knowledge is not acceptable by definition
- Example on probability for a false positive decision on see next slide

https://www.ema.europa.eu/en/statistical-methodology-comparative-assessment-quality-attributes-drug-development, accessed on 13 Oct 2021

Example: Acceptable probability of incorrectly concluding comparability when such is not the case

- "*Currently, only limited guidance can be given regarding the adequate choice of acceptable probability for a false positive decision for the comparison of QAs' data. The 5%-significance level established in the context of clinical trials can serve as an obvious first threshold for orientation*." [1]
- However
  - 5 % error rate requires very wide similarity conditions
  - A practical evaluation suggests an error rate of 10 to 20 % or more as more reasonable, when using a quality range approach (+/- X standard deviation) [2]
- Consequence: either we accept high error rates with tight similarity conditions or small error rates with wide similarity conditions

1. https://www.ema.europa.eu/en/statistical-methodology-comparative-assessment-quality-attributes-drug-development, accessed on 13 Oct 2021
2. Richard K. Burdick (2021) Statistical Considerations for Comparative Assessment of Quality Attributes, Statistics in Biopharmaceutical Research, 13:3, 297-302, DOI:10.1080/19466315.2020.1767194

What does FDA and MHRA require in their biosimilar guidances for comparing quality attributes?

FDA [1]

- FDA requests justification of similarity criteria (e.g. justification of multiplier X when using quality ranges , i.e. sample mean +/- X standard deviation), but does not require definition of similarity conditions

MHRA [2]

- Quantitative ranges should be established, where possible
- These ranges should not be wider than the range of variability of the Reference Product batches, unless otherwise justified
- Wide similarity ranges using inappropriate statistical methods should not be used

1. FDA draft guidance on Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations, 2019 https://www.fda.gov/media/125484/download, accessed 14 Oct 2021
2. MHRA Guidance on the licensing of biosimilar products,2021 https://www.gov.uk/government/publications/guidance-on-the-licensing-of-biosimilar-products, accessed 14 Oct 2021

Conclusions

- The EMA Reflection Paper (RP) is a great collection of theoretical and practical considerations regarding the application of statistical methodologies
  - However, it tends to treat quality attributes the same way as clinical endpoints
  - It underestimates role of Control Strategy, process characterization and product knowledge
- The EMA RP is no Scientific Guideline and should not be used as such
  - Challenge remains to translate RP into meaningful and efficient regulatory requirements which facilitate product development and lifecycle
  - Idealistic requirements on similarity conditions and similarity criteria may require substantial resources at industry and regulatory agencies without a patient benefit and may potentially even hamper execution of manufacturing changes and biosimilar development
- FDA and MHRA established pragmatic and efficient guidance
  - EMA RP suggests different regulatory expectations than FDA and MHRA
  - Disadvantage for global development programs
- Personal recommendations
  - Read RP in its entirety and consider limitations to avoid misinterpretations
  - Apply the RP in a pragmatic manner to best utilize its benefits