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STREAMLINING BIOSIMILARS DEVELOPMENT

ANALYTICAL SIMILARITY – FOUNDATION STONE OF THE TOTALITY OF EVIDENCE PYRAMID

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Agenda

- Analytical Similarity Studies
- Analytical similarity - guidance comparison
- Key factors for successful analytical similarity
- Addressing CQA differences

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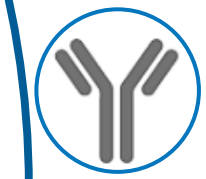
ANALYTICAL SIMILARITY STUDIES

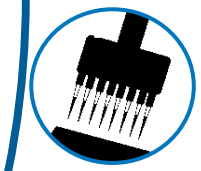
- ***Purpose:*** demonstrate high similarity of biosimilar to RP structure & function
- ***Principle:*** based on ICH Q5E comparability
- ***Methodology:*** Comparative characterization of CQAs with suitable analytical methods
- ***Significance:*** Foundation stone of totality of evidence for biosimilar development / approval
- ***Regulatory Impact:*** Provides high confidence on biosimilar safety and efficacy, enabling a streamlined development program

Reference Product (RP) selection, extensive characterization, CQAs, MoA, QTPP

Establishment of relationship of CQAs with clinical outcomes (efficacy, immunogenicity, PK), Analytical similarity criteria



CQAs - Primary and higher-order structure, Glycosylation and PTMs, Purity / impurities, Biological activity



Analytical methodologies - state-of-the-art, sensitive, specific orthogonal & discriminatory methods to analyze each CQA

Evaluation – statistical approaches (equivalence, quality ranges, qualitative comparison etc.)

Analytical differences should not impact clinical outcomes (justification other CQA data, platform knowledge, additional in vitro studies etc.)

CQA=Critical Quality Attribute, MoA=Mechanism of Action, QTPP=Qualtiy Target Product Profile, PK=Pharmacokinetics, PTM=Post Translational modifications

ANALYTICAL SIMILARITY – GUIDANCE COMPARISON

Regulatory Agency Relevant Guidelines	Summary of Analytical Similarity principle	Analytical differences	Methods and Similarity Evaluation	RP selection / bridging studies
WHO, Global WHO Guidelines on Evaluation of Biosimilars Annex 3 - April 2022	similarity of a biosimilar to an RP in terms of structural and functional aspects is a prerequisite..	any differences should be investigated, explained and justified in terms of lack of clinical impact	state-of-the-art, scientifically sound, sensitive & specific methods	Number of RPs – depends on CQA
			similarity ranges. mean ± x SD, min-max range, tolerance intervals. Equivalence testing	Non-local RP needs analytical bridging
FDA, USA Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Quality-Related Considerations – Sept 2025	analytical studies to demonstrate high similarity to reference product not withstanding minor differences in clinically inactive components…	analytical differences should be further assessed and justified not to impact clinical performance	state-of-the-art, sensitive, discriminatory, specific, orthogonal. Method limitations to be understood	Number of RPs – depends on CQA Minimum 10 lots recommended
			quality ranges. mean ± x SD, equivalence testing, tolerance intervals – not recommended	Non-local RP needs analytical and PK bridging
EMA, Europe Guideline on similar biological medicinal products -quality issues (rev1) – Dec 2014. Reflection paper on a tailored clinical approach in biosimilar development – April 2025	extensive analytical studies to confirm physicochemical and biological similarities…	differences must not compromise the clinical performance	State-of the art, sensitive discriminatory orthogonal methods	Number of RPs – depends on CQA. 15-30 batches based on experience
			similarity ranges based on the RP data	Non-local RP may be used with justification. Needs analytical bridging for clinical use
MHRA, UK Guidance on the licensing of biosimilar products - February 2025	similarity between the biosimilar and the RMP based on a comprehensive comparability exercise…	must be duly justified with regard to their potential impact on safety and efficacy.	State-of the art, sensitive, qualified suitable, discriminatory orthogonal methods	Number of RPs – depends on CQA Minimum 10 lots recommended
			similarity ranges based on the RP data	Non-UK RP may be used with justification
HC, Canada Guidance document: Information and submission requirements for biosimilar biologic drugs – June 2025	extensive comparative quality studies to demonstrate a high degree of similarity including physicochemical functional properties and stability profile..	sufficient evidence and/or scientific justification to be provided to show no impact on safety and/or efficacy.	Suitable, orthogonal scientifically sound, discriminatory methods. Method Limitations to be understood	Number of RPs depend on product and process method variability and statistical methodology
			quantitative analysis, considering the risk ranking of the quality attributes	Non-Canada RP may be used with justification

ANALYTICAL SIMILARITY – GUIDANCE COMPARISON

Convergences and opportunity for resolving divergences

GLOBAL ALIGNMENT:

Strong convergence already exists among global regulatory agencies on several aspects:

- ✓ *Principle of analytical similarity which is based on ICH Q5E*
- ✓ *Analytical differences in CQAs should not impact clinical outcome*
- ✓ *State of the art methods with discriminatory power to measure CQA differences*
- ✓ *Statistical approach for similarity evaluation*

STREAMLINING DEVELOPMENT:

This convergence underscores the discriminatory power and pivotal role of Analytical Similarity supporting streamlining biosimilar development

REFERENCE PRODUCT:

Opportunities for establishing consensus on a few aspects (eg:)

- Foreign RP selection & acceptability
- Need for analytical and / PK bridging studies requirements

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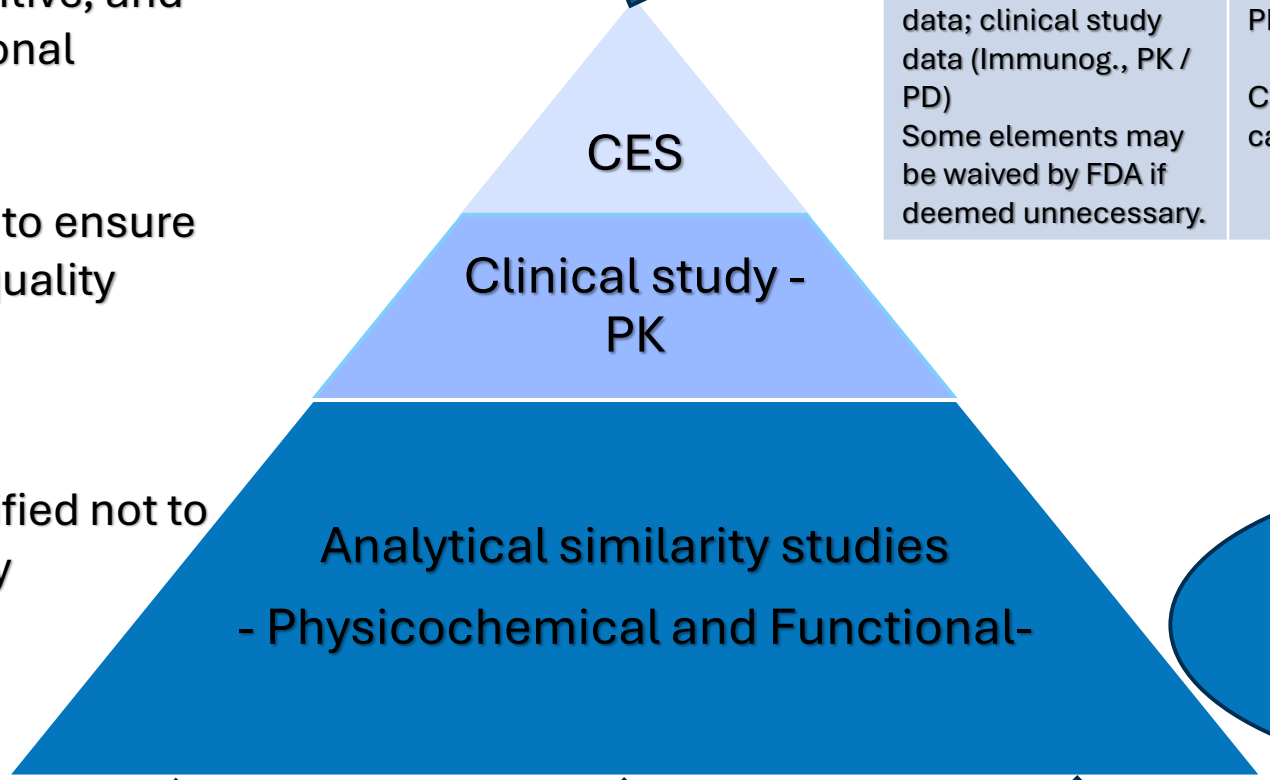
KEY FACTORS FOR SUCCESSFUL ANALYTICAL SIMILARITY

- Enhanced understanding of CQAs and their clinical impact
- Use of advanced, sensitive, and discriminatory, orthogonal analytical methods
- Robust manufacturing to ensure consistent biosimilar quality within RP ranges
- CQA differences fully characterized and justified not to affect safety or efficacy

CES waiver based on robust analytical similarity and PK study

FDA	EMA	Health Canada
Analytical similarity Toxicity assessment / data; clinical study data (Immunog., PK / PD) Some elements may be waived by FDA if deemed unnecessary.	**Analytical similarity** In vitro pharmacology PK study CES – only in some cases as needed	**Analytical similarity** In vitro pharmacology PK study CES – if deemed necessary to be rationalized by sponsor



CQA differences not justifiable….adaptation / changes to manufacturing process may be needed

Enhanced CQAs understanding

Advanced Analytical Science

Advanced Manufacturing science

CES=comparative clinical efficacy study

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ADDRESSING CQA DIFFERENCES

Totality-of-Evidence Approach

- Streamlined development relies heavily on a robust analytical similarity, justification of any CQA differences along with tailored clinical studies to predict equivalent clinical performance of the biosimilar

- **Strong Alignment across regulations on addressing CQA differences:**

  - CQA Differences should be investigated, risk assessed and demonstrated to be not impacting clinical outcomes (safety, efficacy, immunogenicity)

  - Criticality of CQA and extent of difference will drive the level of additional supporting data that may be needed for justification

  - Other quality data, in vitro functional testing data, existing platform knowledge, available literature and if needed additional in vitro studies and Clinical PK data may be used for justification

  - In the case of major differences or differences that cannot be justified to impact clinical outcomes – biosimilar manufacturing changes may be needed to resolve the differences

REFERENCES

WHO - Guidelines on Evaluation of Biosimilars Annex 3 - April 2022

FDA - Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Quality-Related Considerations Guidance for Industry– Sept 2025

EMA - Guideline on similar biological medicinal products -quality issues (rev1) – Dec 2014

EMA - Reflection paper on a tailored clinical approach in biosimilar development – April 2025

MHRA - Guidance on the licensing of biosimilar products - February 2025

Health Canada - Guidance document: Information and submission requirements for biosimilar biologic drugs – June 2025

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