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Medicines for Europe's view on the application of statistical methodology for comparability

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WORKSHOP ON DRAFT REFLECTION PAPER ON STATISTICAL METHODOLOGY FOR THE COMPARATIVE ASSESSMENT OF QUALITY ATTRIBUTES IN DRUG DEVELOPMENT

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Importance of reflection paper on statistical methodologies to compare quality attributes

Medicines for Europe welcomes an EMA reflection paper on statistical approaches

- Statistical methods are used for comparing quality attributes today

Benefits of a reflection paper

- Clarify appropriate use of statistics
- Describe statistical assumptions for different approaches
- Clarify the role of statistical approaches within the regulatory decision making process
- Guide for industry of how to use statistics adequately
- Facilitate efficient and consistent regulatory assessments within EU

1 footnote

Scope of the EMA reflection paper

We appreciate the scope to cover both applications of comparability: manufacturing changes and biosimilar development

- Same scientific principles apply
- Same statistical methods apply
- Ensure consistent regulations for all biological medicines
- Follows general principle of consistent regulations in other areas of drug regulation to foster consistently safe and effective biological medicines
- Ensures level playing field for competition
- Note: the US-FDA wrote a biosimilar-only guideline which bares the risk of higher formal requirements for biosimilars than for reference products with potential detrimental effects on competition
  - Greater hurdle to demonstrate formal comparability for biosimilar developers
  - Biosimilar specific requirements which could potentially be misused by reference medicine manufacturers to fend off biosimilar competition
  - FDA mitigates this risk by clarification that statistics do not set pass/fail criteria for final regulatory conclusions

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Key comments on draft reflection paper

- Appropriate use of statistics may support comparability exercises but cannot serve as the decisive method for final regulatory decision making
- Any differences in the comparison of quality attributes need to be assessed for their clinical relevance before making the final regulatory conclusion
- The descriptive and inferential statistical methodologies should be described in a neutral and balanced manner
  - A specific method should only be used when the statistical assumptions are met
- Existing guidelines and requirements for quality need to be considered
  - Detailed proposals were submitted with our comments
- Define “consistent manufacturing” reflecting ICH guidelines
  - State where quality attributes are kept within acceptable limits and ranges
  - Avoids misunderstandings between statisticians and process scientists

Key comments on draft reflection paper

- Equivalence testing of means for quality attributes establishes a new regulatory concept
  - Requires constant mean, an assumption which is not required by existing regulations and which is rarely met in practice
  - Equivalence testing for means is of limited value for setting comparability criteria for manufacturing changes or biosimilar assessments
  - If the statistical assumptions are not met, alternative inferential or descriptive statistical approaches should be used
- Considerations of statistical tools should not establish new regulatory concepts nor conflict with existing well-established processes consistently ensuring quality unless justified by real life data documenting that a given problem can effectively be addressed
- Acknowledge the different role and utility of statistical methodologies in the regulatory decision making process in the comparison of quality attributes and in assessing clinical endpoints

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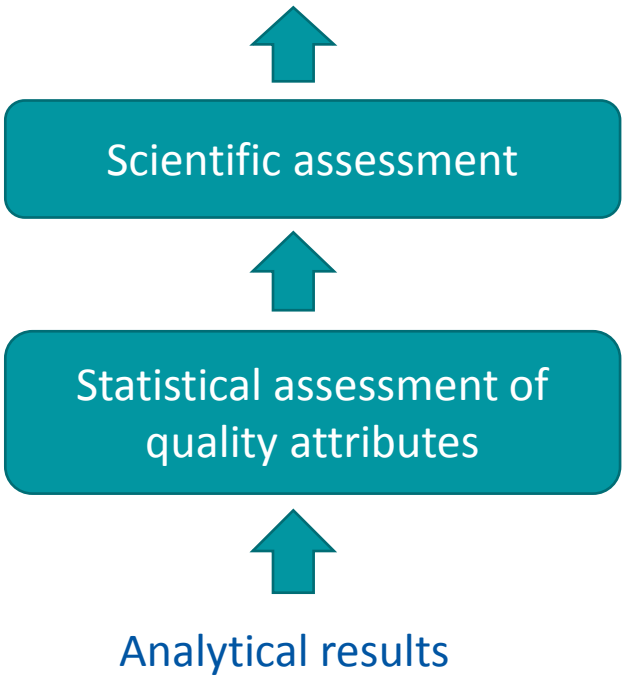
Differences in equivalence testing of clinical endpoints and quality attribute mean

	Equivalence testing for primary endpoint in clinical trials	Equivalence testing of means of quality attributes in comparability exercises
Mean	• Mean response to the medicine is a clinically relevant estimator of the treatment effect • Mean is stable in a defined population	• Mean is clinically irrelevant • Mean may change over time
Variability	• Variability of the physiological processing / patient variability • Stable property of medicine in a defined patient population • Controllable by the sponsor	• Variability of the manufacturing process + analytical variability • Variability may change over time • Reference medicine/pre-change variability (range) represents acceptable quality • Mostly outside the control of the sponsor
Sampling	• Independent stratified random sampling possible	• Independent stratified random sampling impossible. You have to take what is available from campaign production
Relevance of a difference	• A difference resulting in a non-equivalence of the mean may indicate a **clinically relevant** difference in treatment effect	• As long as individual batches are within acceptable quality range (e.g. as defined by reference medicine / historical data of pre-change batches) a difference in the mean is **clinically irrelevant** • Any differences in the quality attributes need to be assessed with regard to their potential impact on safety and efficacy

Role of statistical comparison of quality attributes for the final regulatory decision



Including the totality of all available data

Including product and process understanding

Statistical plan
Descriptive/inferential statistical methods

Appropriate use of statistics may support comparability exercises but cannot serve as the decisive method for final regulatory decision making

- Differences in quality attributes are acceptable if they are clinically meaningless

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Consistent manufacturing

- Defining “consistent manufacturing” would prevent misunderstandings between statisticians and process experts
- “Consistency” in a general linguistic term might be interpreted in the sense of a stationary stochastic process, i.e., the underlying distribution of the data remains stable over time
  - Would be ideal but does not reflect current regulations
- “Consistent manufacturing” is the state when quality attributes are kept within predefined and acceptable ranges or limits
  - Compliant with existing regulations as ICH Q7, ICH Q6A/B, ICH Q8, ICH Q11
  - Other parameters such as mean or batch variability may change over time
- GMP guideline ICH Q7 (2000)
  - “...procedures should be established [...] to.. determine compliance of the intermediate or API with established specifications before a batch is released .”
  - Acceptance criteria for specifications: “... Numerical limits, ranges, or other suitable measures for acceptance of test results”

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Consistent manufacturing

- Specifications for biologicals ICH Q6B (1999)
  - "A specification [...] establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use"
- Product development ICH Q8(R2), (2009)
  - "A CQA [critical quality attribute] is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution[1] to ensure the desired product quality."
  - Design space "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change."

1) Example for distribution given in ICH Q8(R2): particle size distribution for solids

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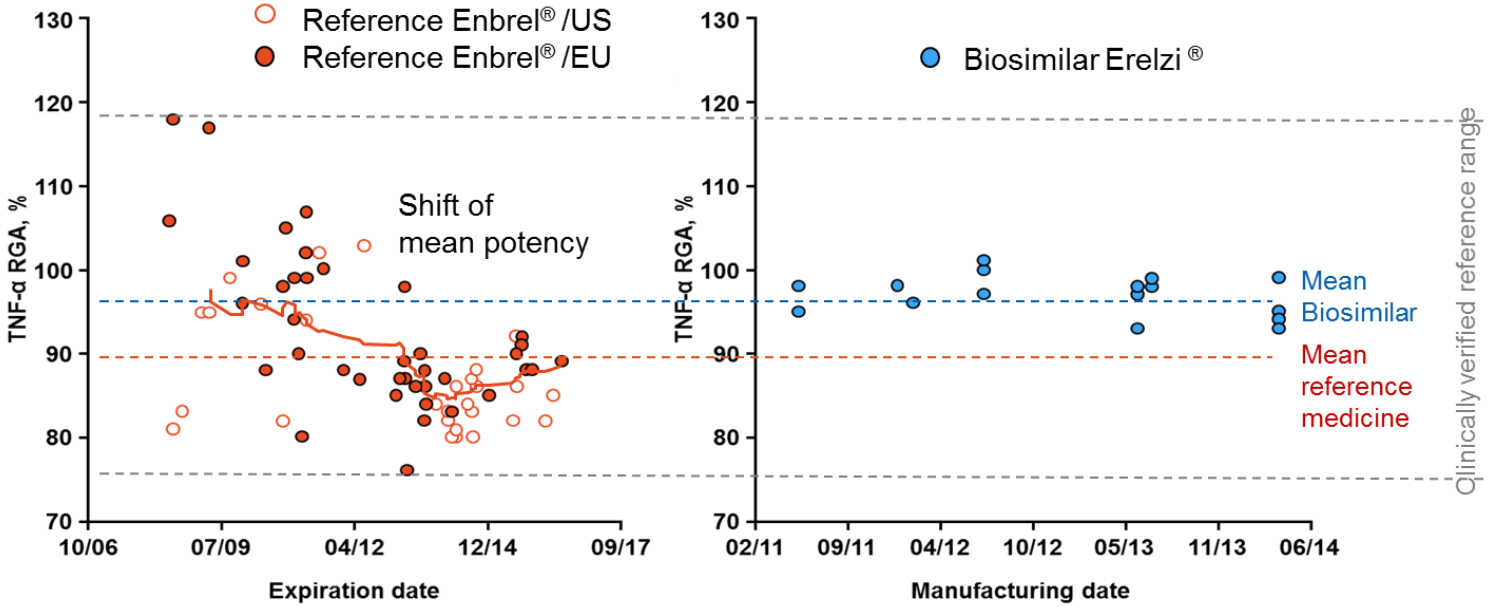
Consistent manufacturing
What do current guidelines tell us?

- "A critical quality attribute should be within an appropriate limit, range, or within-lot-distribution"
- The mean of different batches is not specified as a regulatory expectation
- Consequently, the mean may change over time as long as the critical quality attributes of individual batches remain within appropriate limits

References:
ICH Q6B guideline on specifications for biologicals, 1999
ICH Q7 guideline on GMP, 2000
ICH Q5E guideline on comparability after manufacturing changes, 2004
ICH Q8(R2) guideline on product development, 2009

The mean can change over time – example 1 Etanercept



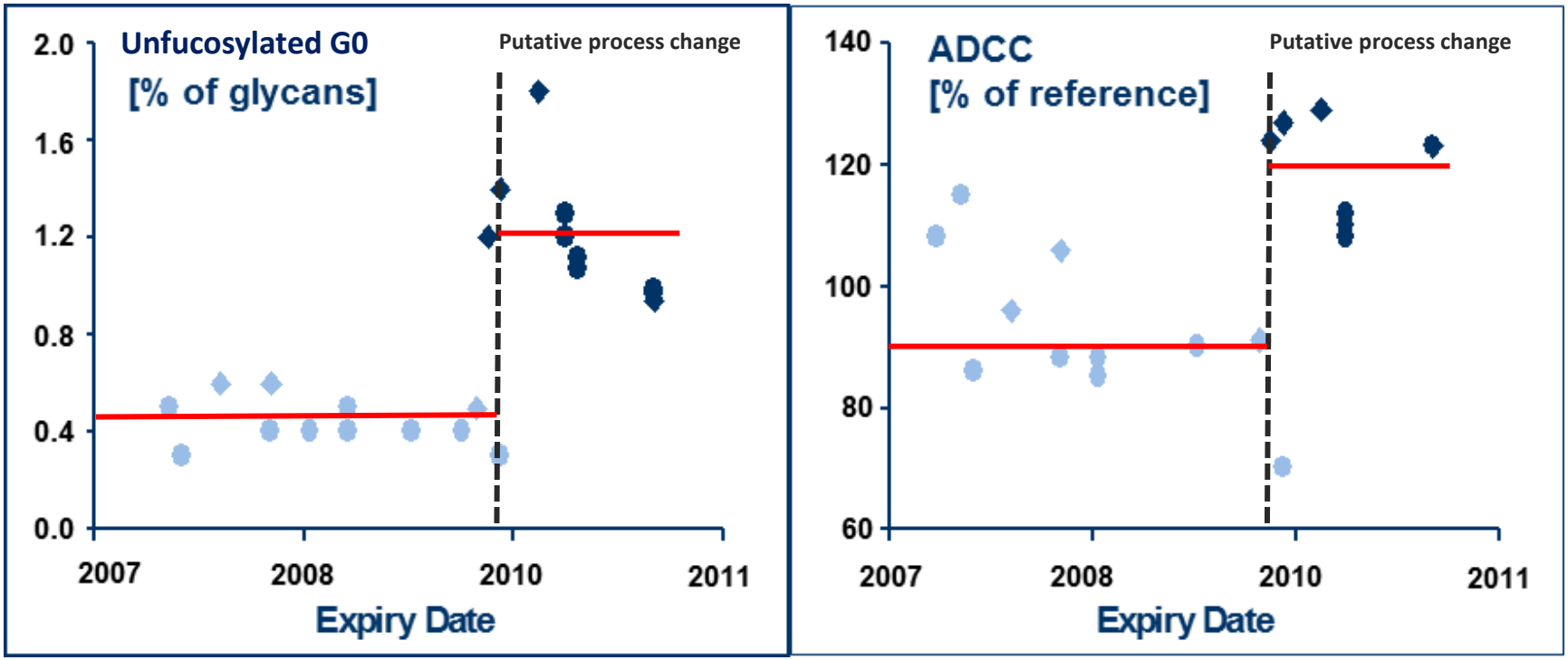
The red line indicates the moving average as calculated by 11 to 21 data points

Example demonstrates that a strict regulatory requirement for equivalent means poses the risk to falsely reject true biosimilars

Reference: derived from Lamanna et al., Scientific Reports, 7: 3951, 2017

Enbrel® is a registered trademark of Amgen Inc.

The mean can change over time – example 2
Rituximab reference medicine

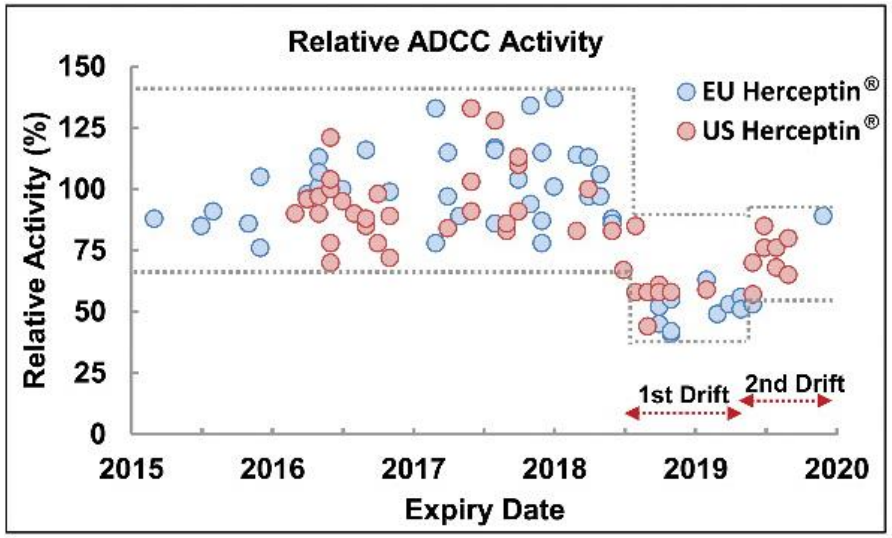


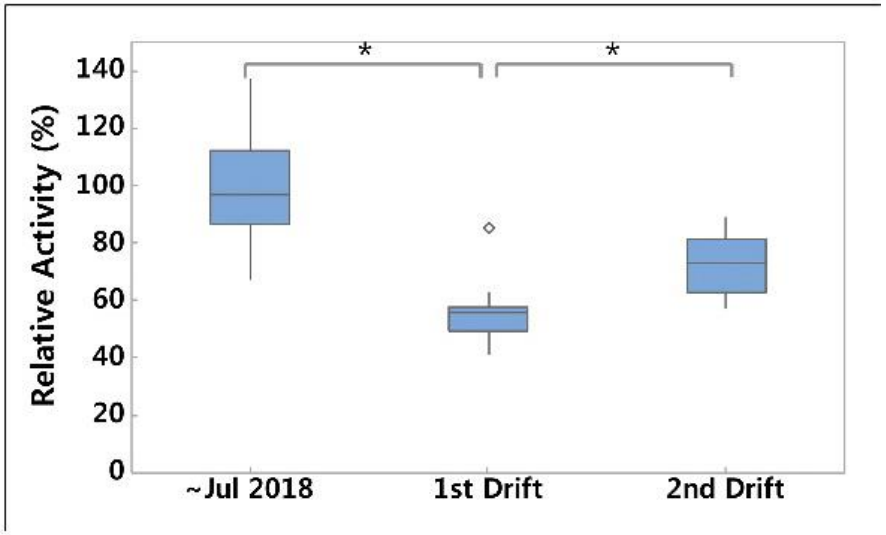
The mean can change over time and still represent acceptable consistent quality

Statistics cannot serve to set pass/fail criteria for comparability

Reference: derived from Schiestl et al. Nat Biotechnol, 2011;29:310-312

The mean can change over time – example 3
Trastuzumab reference medicine





Reference: Kim et al. Mabs, 2017; 9. 704-714

Example demonstrates the possibility that strict requirements for equivalence testing of means would be a moving target which could be misused by reference medicine manufacturer to fend off biosimilar competition

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Conclusions

- A reflection paper is highly desirable
  - Guide for industry of how to use statistics adequately
  - Facilitate efficiency and consistency in regulatory assessments across EU
- The scope should remain to cover manufacturing changes and biosimilar development to ensure consistent regulations for all biological medicines
- Current draft of the EMA reflection paper serves as a starting point
- We recommend further discussion including a second round for public consultation before finalizing the EMA reflection paper
  - Current draft is still at an early state and includes discordant ideas

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Looking forward to contributing to further discussions

THANK YOU!

ANY QUESTION?