Sandoz Biopharmaceuticals

Quality comparability
Future role of statistical approaches?

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Current guideline developments

- FDA issued draft guidance
  - Statistical approaches to evaluate analytical similarity, September 2017 [1]
  - Scope: biosimilars only
- EMA issued draft reflection paper
  - Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development, March 2017 [2]
  - Scope: manufacturing changes, biosimilar Medicines, generics
  - EMA Workshop 3-4 May 2018
- Guidance or considerations on how to compare quality attributes of multiple batches over time

1. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM576786.pdf , accessed Sept 2017
2. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/03/WC500224995.pdf , accessed April 2018

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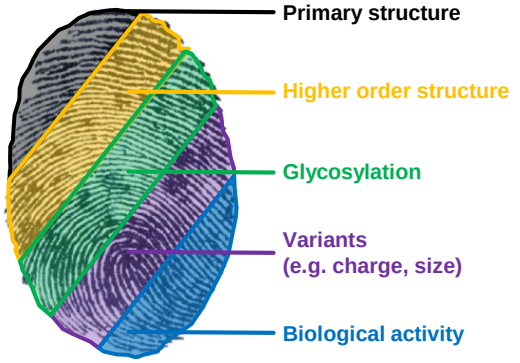
The biosimilar must match the reference medicine in all relevant structural and functional attributes



- Typically more than 40 different methodologies applied
- Analyzing more than 100 different quality attributes

- Derived from Windisch J. EGA's perspective on the draft quality guideline, 2013 [online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500154191.pdf [Accessed 2016 March 18] Sandoz-generated/owned slide (November 18 2014).

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How to compare quality attributes of multiple batches over time?

- Descriptive visual statistics
  - Plot the data and compare visually
- Comparison of ranges
  - Compare against measured or estimated acceptable ranges or limits
- Comparison of means
  - Equivalence test for comparable mean

Variability of major glycan variant in commercial mAb

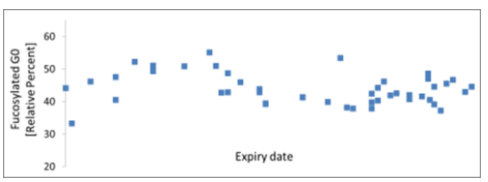

Figure developed by Thomas Stangler, Sandoz data

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Role of statistical approaches for comparing quality attributes

- Every statistical approach requires prerequisites, i.e. statistical assumptions need to be met
- Statistical approaches help to flag differences in quality attributes
- Minor differences in quality attributes can be acceptable if they are found to be clinically meaningless

Appropriate use of statistics may support comparability exercises but cannot serve to set pass/fail criteria for the regulatory conclusion of biosimilarity or comparability following a manufacturing change

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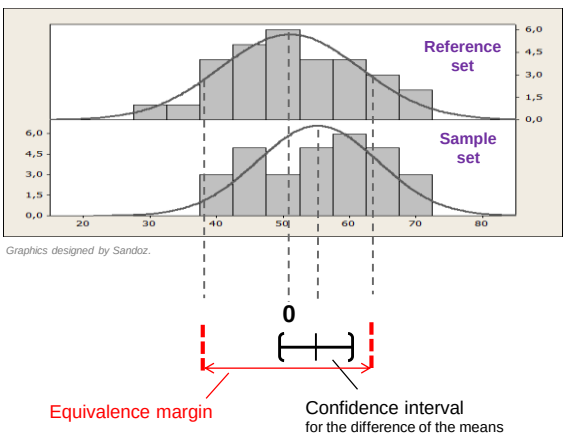
Problem for biosimilar manufacturers: Statistical test for equivalence of means

- Well established statistical approach for clinical studies
- New concept for regulating quality attributes proposed by recent FDA and EMA draft guidelines
- Key prerequisites are often not met for quality attributes
  - Independent data
  - Identically distributed
  - Stable mean



Graphics designed by Sandoz.

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Equivalence of means
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

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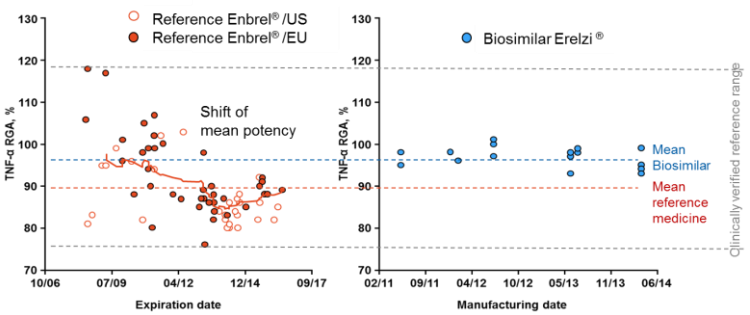
The mean can change over time – example 1
Etanercept reference medicine



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

Example shows that strict regulatory requirement for equivalent mean pose the risk to falsely reject true biosimilars by regulators

Reference: derived from Lamanna et al., Scientific Reports, 7: 3951, 2017
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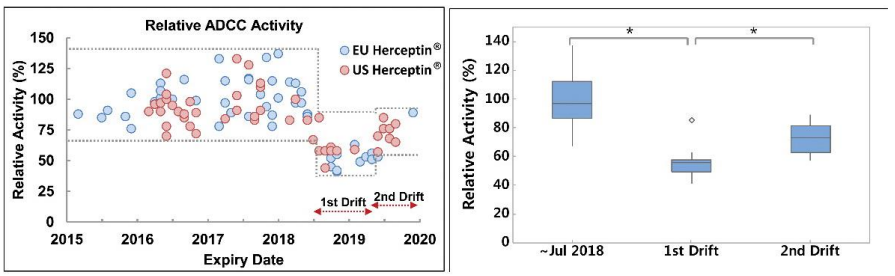
The mean can change over time – example 2 Trastuzumab reference medicine



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

Example demonstrates the possibility that strict requirements for equivalence testing of mean could be misused by reference medicine manufacturer to fend off biosimilar competition

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Conclusion

- Appropriate use of statistics may support comparability exercises but cannot serve to set pass/fail criteria for biosimilarity
- Equivalence testing for means is of limited value in biosimilar assessments
  - The mean can change over time
- Risks of strict requirements for equivalence test of means for biosimilars
  - True biosimilars could be falsely rejected by regulators
  - Potential misuse by reference medicine manufacturers to fend off biosimilar competition
- Upcoming statistical guidelines should be consistent for all biologicals
  - Follows general principle of consistent regulations in all other areas of drug regulation to ensure consistently safe and effective biological medicines
  - Same statistical principles for manufacturing changes and biosimilar development
  - Ensures level playing field for competition

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Thank you

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Equivalence testing is well established for clinical trials

	Equivalence testing for primary endpoint in clinical trials	Equivalence testing of quality attributes in biosimilar evaluation
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 drug in a defined patient population • Controllable by the sponsor	• Variability of the manufacturing process + analytical variability • Variability of reference may change over time • Reference medicine variability (range) represents acceptable quality • Reference medicine variability is outside the control of the sponsor
Relevance of a difference	• A difference resulting in a non-equivalence of the mean will 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) 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

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