Round Table Discussion

2nd Annual Biosimilars Forum

06 Oct 2017

Topics

- Comparison of Quality Attributes
  - Some examples
  - Easy Wins
  - Harder Nuts to Crack
- PK considerations in biosimilarity assessment
  - Statistically Significant Differences
- Real-world Evidence
- Adaptive Designs
- Interchangeability
- Estimands in therapeutic equivalence studies

Overarching Guideline

CHMP/437/04 Rev 1

- Scientific principles based on ICH Q5E; **impact of changes in manufacturing process**
  - Quality attributes have to be highly similar
  - existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product

- Ultimate goal: **exclude any relevant differences** between biosimilar and reference medicinal product.

- Therefore, studies should be **sensitive** enough with regard to design, conduct, endpoints and/or population to detect such differences.

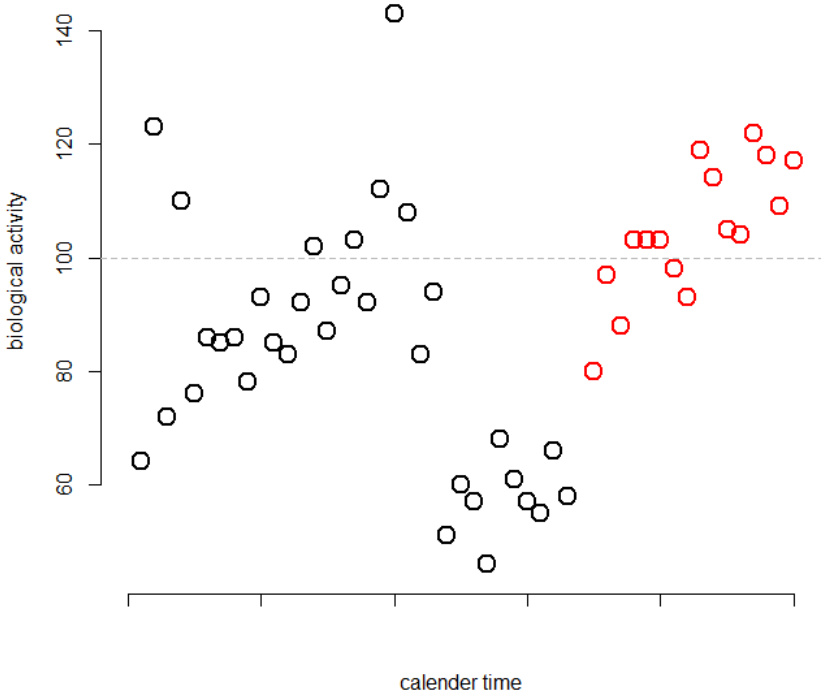
Overarching Guideline on Quality

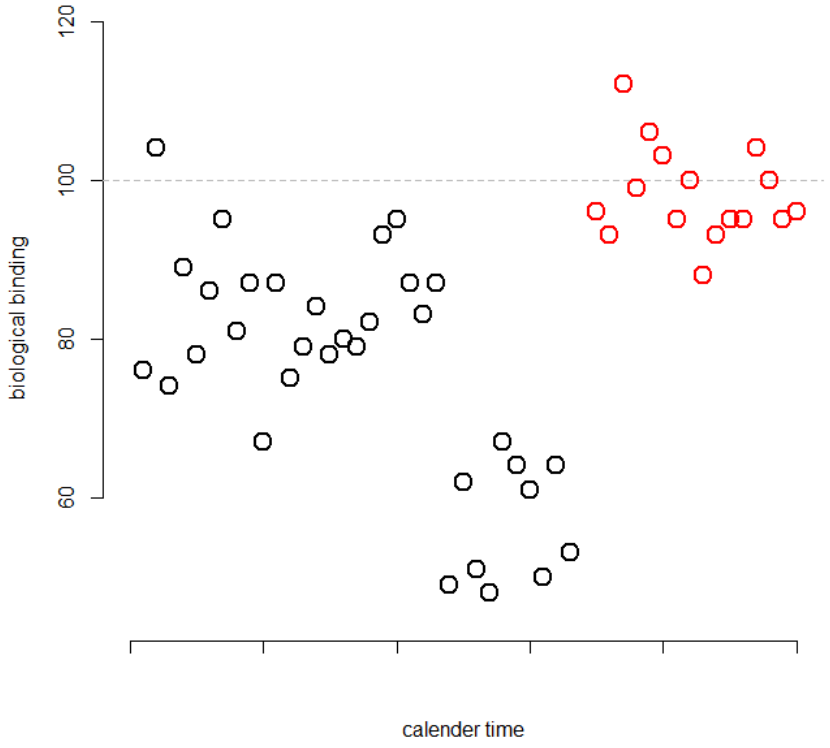
EMA/CHMP/BWP/247713/2012

- **Multiple different batches** of reference …
- … using sensitive and **orthogonal** methods …
- … differences should be justified and **demonstrated to have no impact on clinical performance**
- **Quantitative ranges** should be established … based primarily on reference … should not be wider than **range of variability of representative reference batches**, unless otherwise justified … A **descriptive statistical approach** to establish ranges for quality attributes could be used, if appropriately justified.

Example – shifts and drifts

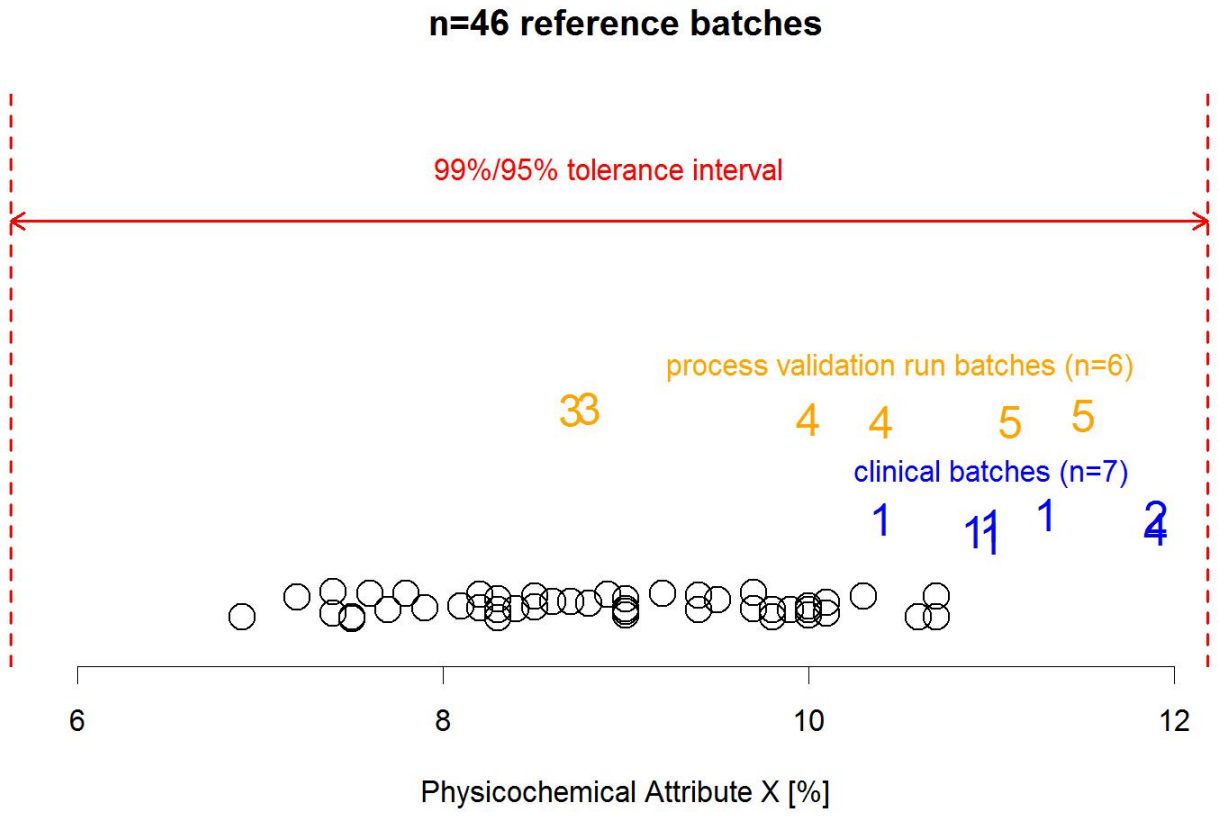
Manufacturing changes …





Example – acceptance ranges

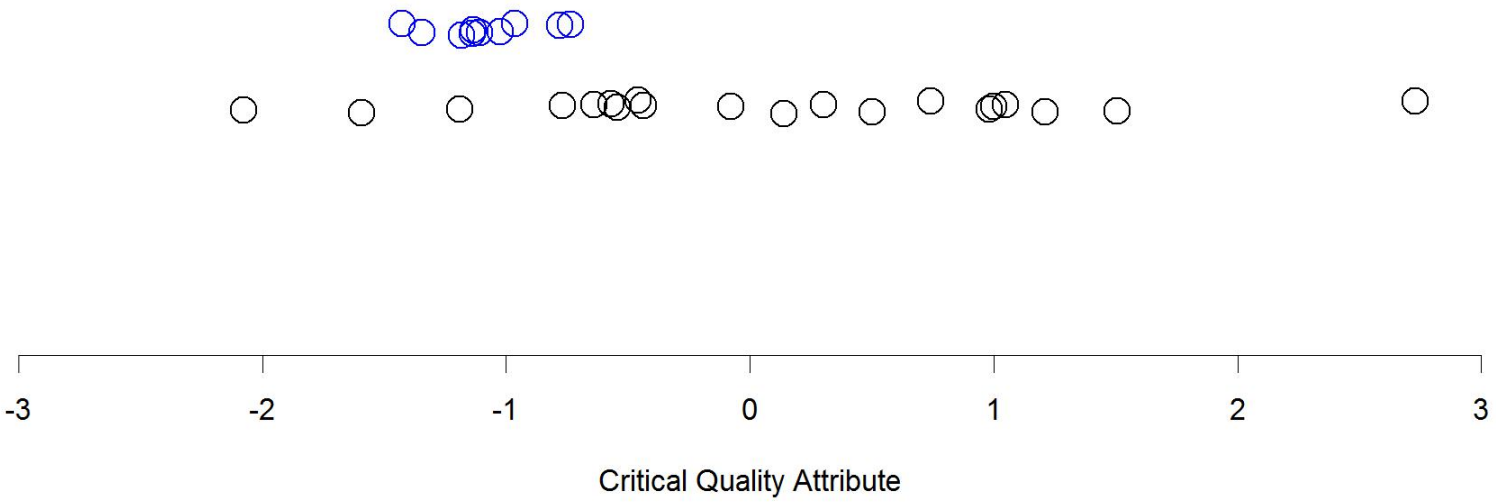
Do we understand their properties?



Example – FDA's Tier 1 analysis

Is it all about the means?

$\delta = 1.5\ \sigma_R = 1.73$
mean difference [90% CI] = 1.17 [0.54;1.80]
mean difference [90% CI] = 1.17 [0.71;1.63], allowing σ_is to differ



Comparison of Quality Attributes

Digesting EMA's draft reflection paper

- FDA's tiered approach ⇔ EMA's draft reflection paper
- Easy Wins
  - Objectives of comparison
  - Prospective planning of sampling strategy
  - Understanding the sources of variability
  - Prospective planning with pre-specification of methods
  - Reporting: raw data, descriptive statistics, graphs

Comparison of Quality Attributes

Digesting EMA'S draft reflection paper

- Harder Nuts to Crack
  - Choice of parameters and the method to describe distance between parameters
  - Definition of acceptance range, relevant difference as a starting point?
  - Can (inferential) statistical methods be already derived from the above (conclusions on the basis of acceptance range, equivalence testing)?
  - If yes, do we (need to) understand their properties (e.g. probability of false positive conclusion)?

PK considerations

Statistically Significant Differences

EMA Guideline on non-clinical and clinical issues

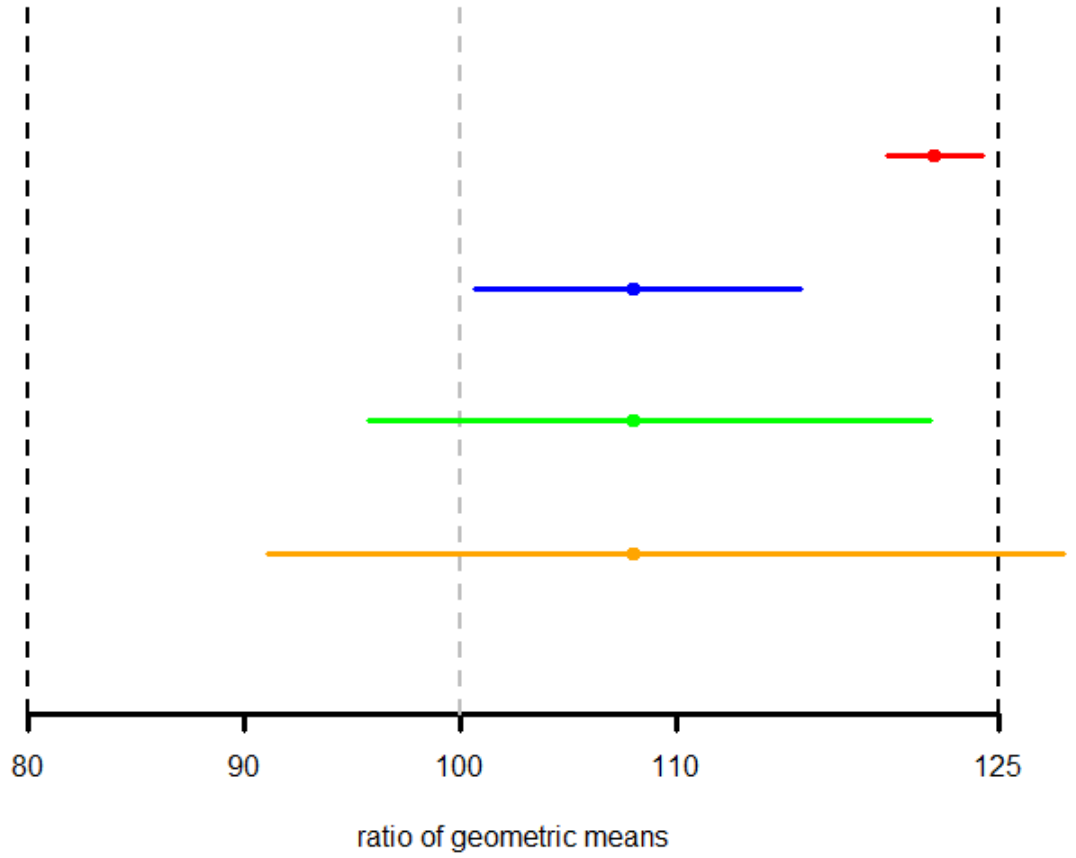
(EMEA/CHMP/BMWP/42832/2005 Rev1)

- interpretation of BE studies less straightforward than for small molecules: PK is used to detect possible differences in the interaction with the body
- 90% CIs within a pre-specified, justified acceptance range may not, by itself, be sufficient, location and the width CI should also be considered

- **“For example, statistically significant differences in 90% CIs within the justified acceptance range regarding relevant PK parameters would need to be explained and justified as not to preclude biosimilarity“**

PK considerations

Statistically Significant Differences



Real World Evidence

- Available evidence of originator product (including observational studies) should inform study design, equivalence margin, PK/PD models, immunogenicity measures, …
- The NOR-SWITCH study
  - Government –funded RCT to address switching from originator to Biosimilar infliximab
  - Primary endpoint: disease worsening during 1-year follow-up
  - Switching was shown to be non-inferior
- Vid's thoughts

Sequential/Adaptive Designs

- Acceptable approaches in two-stage designs

Interchangeability

CHMP/437/04 Rev 1:

- Evaluation of biosimilar medicines for authorisation purposes by the EMA does not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine
- Substitution policies are within the remit of the EU member states

- Andrea will give deeper insight