Federal Institute
for Drugs
and Medical Devices

Quality issues in biosimilars
Some thoughts

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Statistical issues in quality assessments

- **Comparison of empirical data from quality attributes**
  - pre-and post-manufacturing change
  - comparison of a candidate biosimilar product to a reference medicinal product
  - comparison of a candidate generic product to the reference medicinal product
- **Highly relevant in the development of biosimilars**
  - approval based on a successful comparability exercise
  - clinical studies using therapeutic equivalence, PK and PD comparisons insufficient to conclude on biosimilarity
  - therapeutic equivalence trial often lack sensitivity
- **Common/standardized requirements for all applicant needed**

Statistical issues in quality assessments

- **EMA Draft Reflection Paper on**
  - *statistical methodology for the comparative assessment of quality attributes in drug development*
  - to be issued soon (2016)
  - reflection paper =
    - presenting issues
    - considerations on a proper statistical framework
    - streamlining terminology

Quality assessments of biosimilars

- **CHMP *Guideline on Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues, rev.1* (EMA/CHMP/BWP/247713/ 2012)**
  - "… analytical data submitted should be such that firm conclusions on the physicochemical and biological similarity between the reference medicinal product and the biosimilar can be made."
  - quality target product profile (QTPP) for biosimilar manufacturing
    - QTPP, corresponding to a set of quantitative ranges for key QA of the referecne to guide the comparability exercise.
- **demonstrate equivalence in contrast to non-inferiority**
  - exemptions could be potential improvements in specific QAs (e.g. impurities) which might translate to safety advantages
- **similarity on the quality level as the first important milestone in the stepwise development approach**
  - followed by PK/PD and therapeutic equivalence
  - further aspect: bridging from non-EU reference

Statistical issues in quality assessments of biosimilars

- **No agreed criteria or metric to compare test with reference**
  - should be based on theoretical distributions not on samples
- **Sampling issues**
  - limited samples available from reference product
  - no pre-specification of sampling
    - no control on the selection of samples
- **Statistical analysis issues**
  - no pre-specification of the analysis yet (“study protocol”)
  - no agreed criteria for similarity regarding the underlying distributions
  - no use of proper inferential methods
    - assessment often based on descriptive analyses only
    - not accounting for uncertainty and different sources of variability
  - usual sample sizes often do not allow for a powerful analysis

Statistical issues in quality assessments of biosimilars

- **QA distribution of the reference as the basis of the comparability exercise**
  - specification limits not known to the applicant
  - QA may change during the lifetime of the reference product
    - ranges may get narrower
  - limited number of reference samples available

- **Proposals made by applicants**
  - test samples within min and max of the reference
  - test samples within reference tolerance intervals
  - average equivalence
    - but using equivalence limits from (actual) reference data
  - x-sigma approaches
  - descriptive graphical approaches

Statistical issues in quality assessments of biosimilars

- **Possible criteria**
  - 1-α of test values within specification limits of the reference products
    - specification limits of the originator only known to regulator
    - limited information on the reference distribution
  - bioequivalence like criteria based on the average equivalence testing of H_0: $\mu_T/\mu_T \leq c$ or $\mu_T/\mu_T \geq 1/c$ for some $0 < c < 1$
    - specification of equivalence limit c crucial
    - consider reference variability ?
      - interest rather on the comparison of distributions
  - population equivalence ?
    - comparing test and reference distribution
      - e.g. based on mean and variance
      - see e.g. draft FDA guideline on individual and population be (2000)
        - parametric approaches sensitive to distributional assumptions
      - current sample sizes insufficient (especially for non-parametric approaches)
      - narrower distributions acceptable ?

Some issues related to the current proposals

- **test samples within min and max of the reference product**
  - min and max refer to a (limited) sample
  - assuming a (normal) distribution there is no theoretical min and max
    - conservative approach of approximating specification limits?
  - chances of success decrease with the number of test samples
- **test samples within reference tolerance intervals**
  - wider tolerance intervals with smaller sample sizes
  - conservative approach would rather use
    - lower limit of the (1-α)-quantile
    - upper limit of the α-quantile
  - tolerance interval does the contrary:
    - upper limit of the (1-α)-quantile
    - lower limit of the α-quantile

Some issues related to the current proposals

- **x-sigma approaches**
  - estimating reference intervals of the reference product
    - 2 σ = (allegedly) 95% reference interval
  - highly sensitive to distributional assumptions
  - does not account for sample uncertainty
- **average equivalence using equivalence limits derived from (actual) reference data**
  - not properly accounting for reference variability
  - no clear definition of the hypothesis to be rejected

Proper statistical solutions in quality assessments would involve

- **Agreement on criteria related to the reference and test distributions**
  - criteria to be based on theoretical distributions or distributional parameters
    - not on random samples
  - common understanding between statisticians and quality experts
- **Development of statistical methods/hypothesis tests**
  - inferential statistics to test hypotheses related to the agreed criteria
  - proper modelling of the different sources of variability
- **Control of the sampling**
  - how to deal with non-random sampling ?
  - how to control for sample selection ?
- **Concepts may differentiate**
  - categorise QAs according to their criticality (“k-tier approach”)