Model-based bioequivalence analysis of pharmacokinetic crossover trials compared to standard non-compartmental analysis

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Context

- Crossover trials with two periods and two sequences
- Standard approach (FDA[1] and EMEA[2])
  - Compute AUC and C_{max} by non compartmental analysis
  - Test on log parameters
    - Using linear mixed effects model with treatment, period, sequence, and subject effects
  - Needs >10 samples per subject
- Nonlinear mixed effects models (NLMEM)[3,4]
  - Simultaneous data analysis for all subjects
  - Few samples per subject → study on patients

Objectives: mimick the standard bioequivalence analysis using NLMEM and Wald test

Methods

- NLMEM bioequivalence analysis mimicking NCA analysis
  - Statistical model
    - Parametric pharmacokinetic (PK) model
    - Between (BSV) and within subject variability (WSV) on all PK parameters
    - Treatment (β), period, and sequence effects on all PK parameters
  - Parameter estimation by maximum likelihood
    - SAEM algorithm implemented in MONOLIX 2.4[5,6]
- Bioequivalence Wald test
  - Schuirmann's test[7] H_0: $\{\beta \leq \log(0.8)$ or $\beta \geq \log(1.25)\}$
    - Rejection of H_0: $CI_{90\%}(\hat{\beta}) \in [\log(0.8); \log(1.25)]$
    - $CI_{90\%}$ computed from the estimated treatment effect and its standard error (SE)
  - Wald test on secondary parameters[8]
    - $\beta_{AUC} = -\beta_{CL/F}$ (linear PK) → $SE(\beta_{AUC}) = SE(\beta_{CL/F})$
    - β_{Cmax}: nonlinear function of fixed effects → estimation of $SE(\beta_{Cmax})$ by delta method[9] or by simulation using the parameter estimates and the Fisher information matrix estimate
- Simulation study
  - One-compartment model (parameters k_a, CL/F, V/F)
  - Crossover trials with two periods and two sequences
  - Designs
    - Rich: N=40, n=10
    - Original: N=12, n=10
    - Intermediate: N=24, n=5
    - Sparse: N=40, n=3
  - Treatment effect on CL/F and V/F
    - 1000 simulations under $H_{0,80}$: $\beta_{CL/F}$=log(0.8) and $\beta_{V/F}$=log(0.8)
    - 1000 simulations under $H_{0,125}$: $\beta_{CL/F}$=log(1.25) and $\beta_{V/F}$=log(1.25)
  - Two levels of variability
    - For the random effects

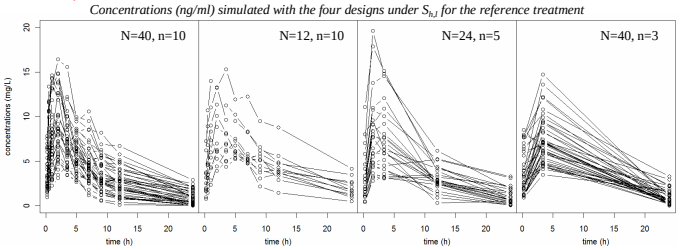
	BSV	WSV
$S_{l,-}$	10% for V/F 20% for k_a and Cl/F	BSV/2
$S_{h,-}$	50%	15%

    - For the error model

	a (mg/l)	b
$S_{-,l}$	0.1	10%
$S_{-,h}$	1	25%

    - $S_{l,l}$ and $S_{h,l}$: simulations with the 4 designs
    - $S_{h,h}$: simulations with the intermediate design

Concentrations (ng/ml) simulated with the four designs under $S_{h,l}$ for the reference treatment



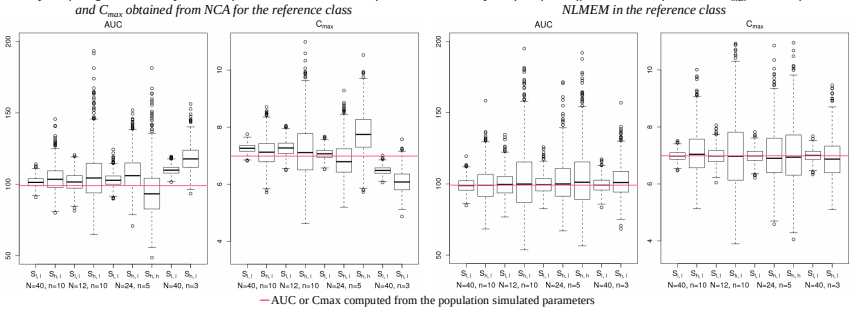
- Evaluation of the estimates for $H_{0,80}$
  - Geometric mean of AUC and C_{max} for the reference treatment compared to the population simulated parameters
  - β_{AUC} and β_{Cmax} compared to the simulated value
  - $SE(\beta_{AUC})$ and $SE(\beta_{Cmax})$ compared to the empirical SE (standard deviation of the 1000 treatment effect estimates)
- Type I error estimation: proportion of rejected H_0
  - Wald test performed with the estimated and empirical SE

Results

- Evaluation of the estimates
  - AUC and C_{max}

Boxplot of the geometric sample mean of the individual estimates of AUC and C_{max} obtained from NCA for the reference class

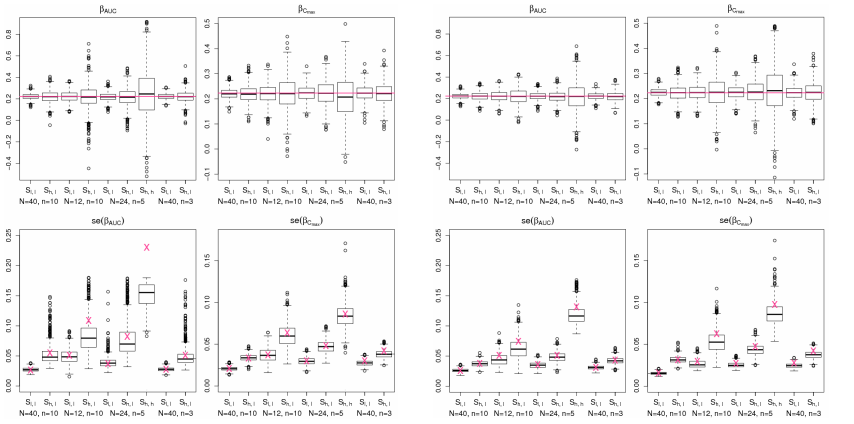
Boxplot of the fixed effect estimates of AUC and C_{max} obtained from NLMEM in the reference class



    - NCA: biased means for sparse design
    - NLMEM: no bias even for sparse design
  - β_{AUC} and β_{Cmax}, $SE(\beta_{AUC})$ and $SE(\beta_{Cmax})$

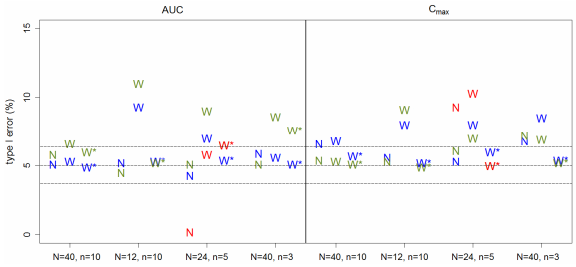
Boxplot of the treatment effect on AUC and C_{max}, and their SE obtained from NCA

Boxplot of the treatment effect on AUC and C_{max}, and their SE obtained from NLMEM (SE estimated by delta method for β_{Cmax})



    - Good estimation of the treatment effect for NCA and NLMEM
    - Underestimation of the SE increasing when large variability
    - NLMEM: similar estimation of SE(β_{Cmax}) by delta method and simulation
- Type I error

Type I error versus the design for AUC and C_{max}



$S_{l,l}$, $S_{h,l}$ and $S_{h,h}$

N: test based on NCA estimates

W: Wald test using estimated SE

W*: Wald test using empirical SE

Horizontal lines: the nominal level at 5% and its 95% prediction interval for 1000 replicates [3.7%; 6.4%]

  - NCA: type I error at 5% except for C_{max} with the sparse design and for $S_{h,h}$
  - NLMEM
    - Type I error at 5% for the rich design but inflation when N or n decreases
    - Correction of the inflation by the use of the empirical SE

Conclusion

- Bioequivalence analysis by NCA
  - Bias in the geometric means of AUC and C_{max} for sparse design
  - Good properties of the test except for high variability
- Bioequivalence analysis by NLMEM
  - Good estimation of the population estimates even for sparse design
  - Good properties of the test for rich design (asymptotic conditions)
    - Correction of the test for small sample size needed (linked to the underestimation of the SE)
  - Applicable to nonlinear pharmacokinetics (biologic drugs) and to sparse design

[1] FDA. Guidance on statistical approaches to establishing bioequivalence (2001)
[2] EMEA. Guidance on investigation of bioavailability and bioequivalence (2001)
[3] Dubois A, Gsteiger S, Pigeolet E and Mentré F. *Pharmaceutical Research*. **27** (2010)
[4] Panhard X, Taburet AM, Piketti C and Mentré F. *Statistics in Medicine*. **26** (2007)
[5] Kuhn E and Lavielle M. *ESAIM Probability and Statistics*. **8** (2004)
[6] www.monolix.org
[7] Schuirmann DJ. *Journal of Pharmacokinetics and Biopharmaceutics*. **15** (1987)
[8] Dubois A, Lavielle M, Gsteiger S, Pigeolet E and Mentré F. *submitted*
[9] Oehlert GW. The American Statistician. **46** (1992)