Extension of the SAEM algorithm and evaluation of Wald and likelihood ratio tests for interaction or bioequivalence studies

A. Dubois [(1)], M. Lavielle [(2)], S. Gsteiger [(3)], E. Pigeolet [(3)] and F. Mentré [(1)]

(1) UMR738 INSERM, University Paris Diderot, Paris, France.
(2) INRIA, Saclay, France.
(3) Novartis Pharma AG, Basel, Switzerland.

Introduction

- Drug interaction studies: are PK of different formulations different ? (interaction test H_0: no difference)
- Bioequivalence studies: are PK of different formulations equivalent ? (bioequivalence test H_0: inequivalence)
- Standard approach (FDA [1,2] and EMEA [3,4])
  - Compute AUC and Cmax by non compartmental analysis
  - Test on log parameters
  - Needs >10 samples per subject
- Nonlinear mixed effects models
  - Joined data analysis for all subjects
  - Few samples per subject → study on patients

Objectives

- Adapt and evaluate the SAEM algorithm in MONOLIX software for the analysis of crossover trials
- Develop the likelihood ratio test (LRT) for bioequivalence
- Evaluate by simulation the type I error of Wald tests and LRT

Methods

- Statistical model
  - Data: individual plasma concentrations under both formulations
  - Estimation
    - Mean PK parameters for the reference formulation
    - Treatment (β_T), period (β_P) and sequence (β_S) effect
    - Between (BSV) and within subject (WSV) variability
- Parameters estimation by maximum likelihood
  - Extension of the SAEM algorithm to estimate WSV (Generalization of [5])
  - Wald test: estimation with the complete model (log likelihood L_{all})
  - LRT: estimation with the complete model, with β_T fixed to log(0.8) and to log(1.25) for the tested parameter (log likelihood $L_{\log(0.8)}$ and $L_{\log(1.25)}$)
- Global test on the treatment effect β_T

	Interaction test	Bioequivalence test [8]
H_0	β_T=log(0.8)	$\beta_T \le \log(0.8)$ or $\beta_T \ge \log(1.25)$
Wald test [6,7] Reject H_0 if	$\log(0.8) \notin CI_{95\%}(\hat{\beta}_T)$	$CI_{90\%}(\hat{\beta}_T) \in [\log(0.8); \log(1.25)]$
LRT Reject H_0 if	$-2\times(L_{\log(0.8)} - L_{all}) \ge \chi^2_1(0.95)$	$\hat{\beta}_T \in [\log(0.8); \log(1.25)]$ $-2\times(L_{\log(0.8)} - L_{all}) \ge \chi^2_1(0.9)$ $-2\times(L_{\log(1.25)} - L_{all}) \ge \chi^2_1(0.9)$

- Simulation study
  - Theophylline PK: one-compartment model with first order absorption and elimination (parameters k_a, Cl/F, V/F)
  - Designs with 40 subjects: 10 (rich) or 3 (sparse) samples per subject
  - Crossover trials with two or four periods
  - Treatment effect on Cl/F and V/F
    - 1000 simulations under $H_{0,80}$: $\beta_{T,Cl/F}$=log(0.8) and $\beta_{T,V/F}$=log(0.8)
    - 1000 simulations under $H_{0,125}$: $\beta_{T,Cl/F}$=log(1.25) and $\beta_{T,V/F}$=log(1.25)
  - Two levels of variability (residual error=10%)

	BSV	WSV
Low	10% for V/F and 20% for k_a and Cl/F	BSV/2
High	50%	15%

- Evaluation of the SAEM algorithm: relative bias and RMSE
- Type I error estimation: proportion of rejected H_0

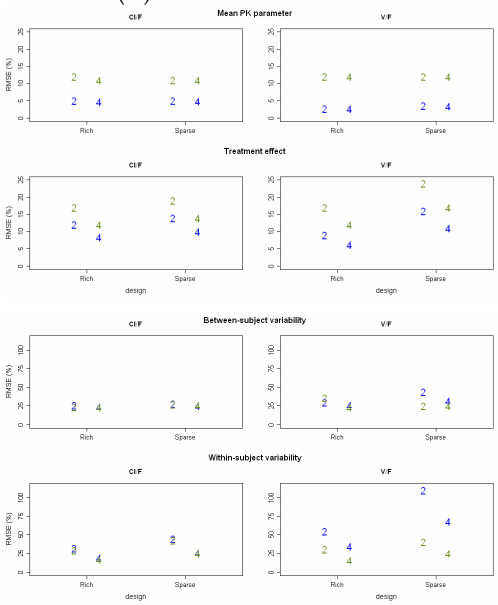
[1] FDA. Guidance on drug interaction studies (2006)
[2] FDA. Guidance on statistical approaches to establishing bioequivalence (2001)

Results

- Evaluation of the SAEM algorithm (crossover trials with 2 or 4 periods)
  - Relative bias (%)

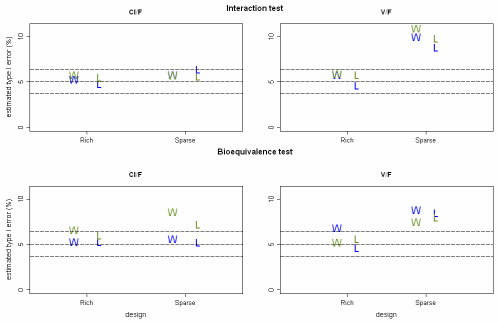
	Rich design	Sparse design
Fixed effect	<2%	<5%
Variance components	<10%	<20%

  - Relative RMSE (%)



Crossover trials with 2 (2) or 4 (4) periods
Low variability
High variability

    - RMSE (rich design) < RMSE (sparse design)
    - RMSE (4 periods) < RMSE (2 periods)
    - RMSE satisfactory except for the WSV on V/F for the low variability and 2 periods
- Type I error (crossover trials with 2 periods)



W: Wald test
L: LRT
Low variability
High variability
Horizontal lines: the nominal level at 5% and its 95% prediction interval for 1000 replicates ([3.7%; 6.4%])

  - Type I error at 5% for the rich design
  - Slight inflation of the type I error for the sparse design
  - Similar results for the Wald test and LRT, and for interaction and bioequivalence tests

Conclusion

- SAEM algorithm in MONOLIX software
  - Accurate extension for estimation of WSV and crossover trials analysis
- Model-based interaction or bioequivalence tests
  - Good tool applicable to rich and sparse design
  - Good statistical properties under asymptotic conditions

[3] EMEA. Guidance on drug interaction studies (1998)
[4] EMEA. Guidance on investigation of bioavailability and bioequivalence (2001)
[5] Panhard X and Samson A. *Biostatistics*. **10**: 121 (2009)
[6] Panhard X and Mentré F. *Statistics in Medicine*. **24**: 1509 (2005)
[7] Panhard X, Taburet AM, Piketti C and Mentré F. *Statistics in Medicine*. **26**: 1268 (2007)
[8] Schuirmann DJ. *Journal of Pharmacokinetics and Biopharmaceutics*. **15**: 657 (1987)