Evaluation of Model-Based Bioequivalence approach for one single sample pharmacokinetic studies

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Introduction

- Bioequivalence (BE) studies are key to the development and approval of generic drugs
- Traditionally, BE studies with pharmacokinetic (PK) endpoints are conducted using a two-way crossover study design and the two one-sided test (TOST) is performed using estimates of area under the concentration-time curve (AUC) and maximal concentration (Cmax) obtained by non-compartmental analysis (NCA).
- In a typical PK BE studies for ophthalmic drug products, only one sample of aqueous humor is collected from one eye per patient.
- Parallel (P) design studies
  - subjects assigned to one pre-specified sampling times t_j with $j = 1, \ldots, J$
  - C_{ij} the concentration of subject $i = 1, \ldots, N_j$ at t_j
  - total number of samples $(n_{tot}) = \sum_{j=1}^{J} N_j$ = study sample size (N)
- Crossover (C) design studies
  - subject with bilateral cataracts randomly assigned one of two treatments to one of two eyes and one sample collected from each eye at the same t_j
  - C_{ijk} the concentration of subject $i = 1, \ldots, N_{kj}$ at each period/in each eye $k = 1, 2$
  - $n_{tot} = \sum_{k=1}^{2} \sum_{j=1}^{J} N_{kj}$ and $N = n_{tot}/2$

Methods

TOST[1]

- β^T = the treatment effect, i.e., the difference in μ_T and μ_R, which are the average means of the test and reference products for $\log(AUC)$ or $\log(C_{max})$
- $\mathbf{H_0}$: $\beta^{\mathbf{T}} = \mu_{\mathbf{T}} - \mu_{\mathbf{R}} \geq \delta$ or $\beta^{\mathbf{T}} = \mu_{\mathbf{T}} - \mu_{\mathbf{R}} \leq -\delta$ with δ a pre-specified BE margin.

$$\frac{\hat{\beta}^T + \delta}{SE(\hat{\beta}^T)} \geq u_{1-\alpha} \quad \text{and} \quad \frac{\hat{\beta}^T - \delta}{SE(\hat{\beta}^T)} \leq -u_{1-\alpha}$$

  where $\hat{\beta}^T$ and $SE(\hat{\beta}^T)$ are the β^T estimate and its standard error and $u_{1-\alpha}$ is the $1-\alpha$ quantile of a reference distribution.
- $\delta = \mathbf{\log(1.25) = -\log(0.8)}$ and the significance level $\alpha = 0.05$ according to regulation authorities → The typical BE acceptance criteria is for the 90% confidence interval (CI) around the geometric mean ratio (GMR) of AUC or Cmax to be included in the [80; 125]% interval.

Model-based (MB) TOST[2]

- Based on a nonlinear mixed effect model (NLMEM) analysis of the data
- Crossover (C) design studies

$$C_{ijk} = f(t_j, \phi_{ijk}) + g(t_j, \phi_{ijk})\epsilon_{ijk}$$
$$\log(\phi_{ijkl}) = \log(\lambda_l) + \beta_l^T T_{ijk} + \beta_l^{P'} P_k + \beta_l^{S'} S_{ij} + \eta_{ijl} + \kappa_{ijkl}$$

  - $f(.)$ the structural model and $g = a + bf(.)$ the error model
  - ϕ_{ijkl} is the l^{th} element of the PK parameter n_p-vector of individual i at time t_j and occasion k
  - λ_l the l^{th} element of the fixed effect n_p-vector for the covariate reference class
  - T_{ijk}, P_k and S_{ij} the treatment, period and sequence covariate vectors
  - β_l^T, β_l^P and β_l^S the coefficients of treatment, period and sequence effect vectorfor the l^{th} individual parameter
  - η_{ijl} the l^{th} element of the random effect vector η_{ij} for subject i at time t_j capturing the between subject variability (BSV)
  - κ_{ijkl} the l^{th} element of the vector of random effects κ_{ijk} for subject i at time t_j and period k, capturing the within subject variability (WSV)
  - $\eta_{ij} \sim N(0, \Omega)$ and $\kappa_{ijk} \sim N(0, \Gamma)$ independent with ω_l^2 and γ_l^2 the l^{th} diagonal element of Ω and Γ
  - $\epsilon_{ijk} \sim N(0, \sigma^2)$ the independent residual errors

- Parallel (P) design studies

$$C_{ij} = f(t_j, \phi_{ij}) + g(t_j, \phi_{ij})\epsilon_{ij}$$
$$\log(\phi_{ijl}) = \log(\lambda_l) + \beta_l^T T_{ij} + \eta_{ijl},$$

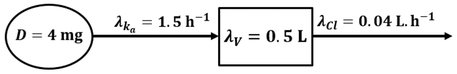
- β^T_{AUC} and $\beta^T_{C_{max}}$ derived from functions of the λ and β^{T2}
- $VAR(\beta^T_{AUC})$ and $VAR(\beta^T_{C_{max}})$ are derived using the delta-method using the inverse of the observed Fisher Information Matrix (FIM) with 90% CI $= \pm u_{1-\alpha} SE$
- NLME modeling was performed using Monolix 2018R2

Objective

To evaluate MB-TOST, by clinical trial simulation, for the analysis of BE crossover (C) and parallel (P) design 1 single point pharmacokinetic studies

Simulation study

- PK model of concentrations of the anti-asthmatic drug theophylline, a narrow therapeutic index, however conventional BE limits are used for the analysis



  - Limit of Quantification at 0.2 mg/L
- Designs
  - each of the N subjects provides one sample in one (parallel, P) or both (crossover, C) eyes at one sampling time chosen among a set of 10 or 5 possible sampling times:

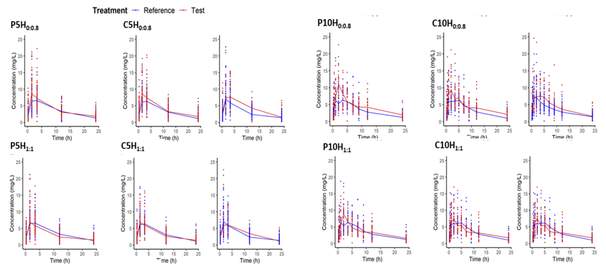
Design	N	Total sample size	Sampling times (h)	Subjects per sampling time
Parallel	500	500	$\{0.25, 0.5, 1, 2, 3.5, 5, 7, 9, 12, 24\}$	50
	500	500	$\{0.25, 1.5, 3.35, 12, 24\}$	100
Crossover	500	1 000	$\{0.25, 0.5, 1, 2, 3.5, 5, 7, 9, 12, 24\}$	50
	500	1 000	$\{0.25, 1.5, 3.35, 12, 24\}$	100

	BSV			WSV			Error model	
	ω_{k_a} (%)	$\omega_{V/F}$ (%)	$\omega_{Cl/F}$ (%)	γ_{k_a} (%)	$\gamma_{V/F}$ (%)	$\gamma_{Cl/F}$ (%)	a (mg/L)	b (%)
Parallel	52	52	52	-	-	-	0.1	10
Cross-over	50	50	50	15	15	15	0.1	10

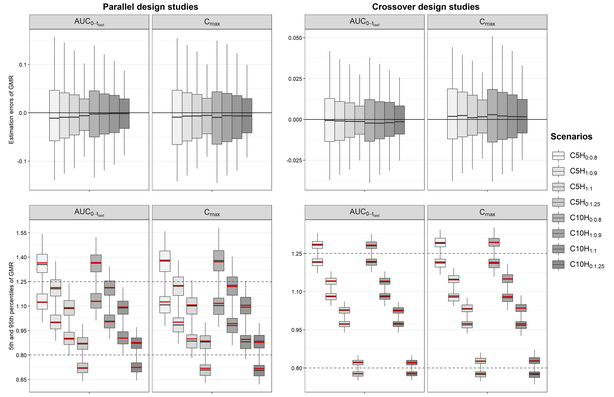
- Under H_0 : $\beta^T = log(0.8)$ and $\beta^T = log(1.25)$ to assess type I error
- Under H_1 : $\beta^T = log(0.9)$ and $\beta^T = log(1)$ to assess the power
- 16 scenarios evaluated with 500 simulated data sets for each scenario → 95% prediction interval around 0.05 = [0.033-0.073]

Results

SIMULATED DATA SET

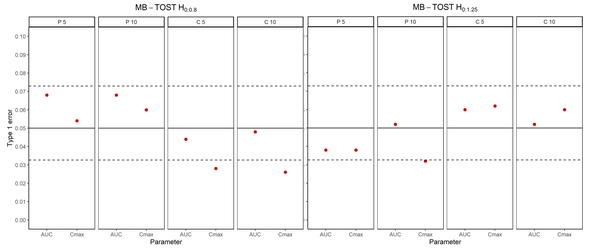


ESTIMATION



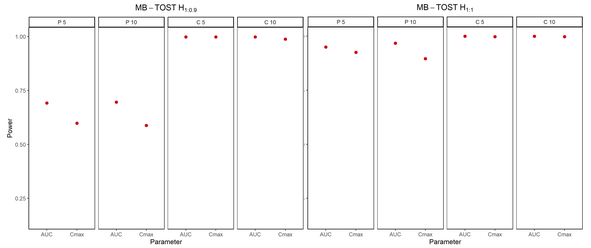
- Model-based GMR for $AUC_{0-t_{last}}$ and C_{max} were unbiased and precise
→ validation of the parameter estimation step
- Overestimation of 90% CI for C_{max}
- Crossover studies, as expected, resulted in smaller 90% CI

TYPE I ERROR



- Controlled type 1 errors for AUC under 0.07 on parallel (P) and crossover (C) study designs
- Significantly conservative type 1 errors for C_{max} for scenarios $C5H_{0:0.8}$ and $C10H_{0:0.8}$

POWER



- High power estimates close to 100% on crossover studies
  - rather low simulated WSV → small 90% CIs

Conclusion

Simulation study shows that MB approaches, when the PK model is accurately specified, can be a good alternative approach for BE studies with only one-time point measured drug concentration.

References

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