Pharmacokinetic Bioequivalence Analysis of Biologics Using Nonlinear Mixed Effects Modeling

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Background

- Standard bioequivalence analysis (FDA[1] and EMEA[2]) for chemical drugs
  - Compute AUC and C_{max} by non compartmental analysis (NCA)
  - Test on log parameters using linear mixed effects model
- Biologic drug: complex structure → biosimilarity rather than bioequivalence
  - Biosimilarity analysis: pharmacokinetics (PK), efficacy, toxicity…
- Nonlinear mixed effects models (NLMEM)
  - Simultaneous data analysis for all subjects

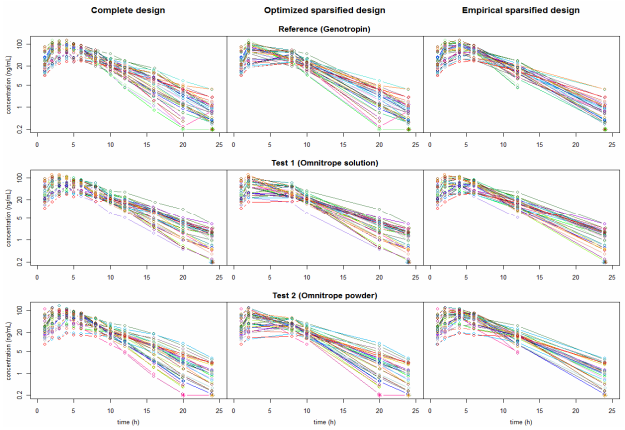
Objective: illustrate how to perform a NLMEM-based PK bioequivalence analysis using data of two biosimilary trials

NLMEM-based bioequivalence

- NLMEM bioequivalence analysis[3,4]
  - Statistical model
    - PK model (determined using reference formulation data)
    - Between (BSV) and within subject (WSV) variability if data from crossover trial
    - Treatment (β), period, and sequence effects
  - Parameter estimation by maximum likelihood
    - SAEM algorithm implemented in MONOLIX 3.2[5,6]
- Bioequivalence Wald test
  - H_0: { $\beta \le \log(0.8)$ or $\beta \ge \log(1.25)$ }
    - Rejection of H_0: $CI_{90\%}(\beta) \in [\log(0.8); \log(1.25)]$
    - $CI_{90\%}$ computed from the estimated β and its standard error (SE)
  - Wald test on secondary parameters[4]
    - Estimation of β and its SE by delta method or simulations

Somatropin (growth hormone)

- Single dose, crossover trial on 35 healthy volunteers[7]
  - 3 formulations, 3 periods, 6 sequences
    - Genotropin® by Pfizer: 5 mg/ml powder formulation (reference)
    - Omnitrope® by Sandoz: 3.3 mg/ml solution (T_1) and 5mg/ml powder (T_2)
  - Single subcutaneous dose of 5 mg at each treatment period
    - 12 samples per period
- Sparse datasets with 6 samples per period
  - Optimized design (OD): sampling times optimized using PFIM 3.1[8]
    - NLMEM parameter estimates of Genotropin® data
    - Fedorov-Wynn algorithm
  - Empirical design (ED): sampling times determined by a PK modeller



Individual plots of the three somatropin datasets for each formulation (LOQ=0.2 ng/mL)

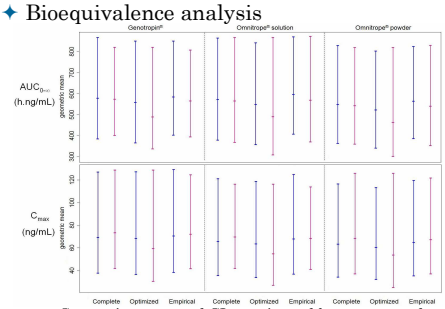
- PK modeling: one-compartment with linear elimination

	t_{lag} (h)	k_a (h^{-1})	V/F (L)	CL/F (L/h)	$corr_{CL\text{-}V}$
μ_R	0.49 (0.07)	0.32 (0.07)	26.22 (0.1)	8.63 (0.03)	
β_{T1}	-0.22 (0.07)	-0.2 (0.07)	-0.12 (0.1)	0.01 (0.03)	
β_{T2}	-0.07 (0.06)	-0.06 (0.08)	0.07 (0.11)	0.05 (0.03)	
BSV	0.33 (0.05)	0.18 (0.04)	0.44 (0.04)	0.23 (0.02)	0.81
WSV	0.09 (0.04)	0.19 (0.03)	0.26 (0.03)	0.1 (0.01)	0.49
a (ng/mL)	0.11 (0.02)				
b	0.14 (0.004)				

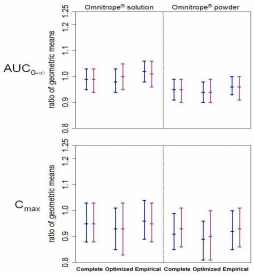
Parameter estimates (SE) obtained by MONOLIX 3.2 for the complete data
(μ_R: mean PK parameters for Genotropin®, period and sequence effects not reported)

[1] FDA. Ucm070244. (2001)
[2] EMA. CPMP/EWP/QWP/1401/98 Rev. 1. (2010)
[3] Dubois A et al. *Pharm Res* (2010)
[4] Dubois A et al. *Stat Med (in press)*
[5] Panhard X and Samson A. *Biostatistics* (2009)
[6] www.monolix.org
[7] Fuhr U et al. *Eur J Endocrinol* (2010)
[8] www.pfim.biostat.fr
[9] Sorgel F et al. *BMC Clin Pharmacol* (2009)

- Bioequivalence analysis



Geometric means and $CI_{95\%}$ estimated by NLMEM and NCA for each dataset and somatropin formulation



Geometric mean ratios (test/reference) and $CI_{90\%}$ estimated by NLMEM and NCA for each dataset

  - Geometric mean estimates
    - Difference in NCA estimation for ED and OD datasets → importance of the design
    - Stable NLMEM estimation
  - Bioequivalence test: Omnitrope® powder and solution bioequivalent to Genotropin® by NLMEM and NCA

Erythropoetin alpha (EPO)

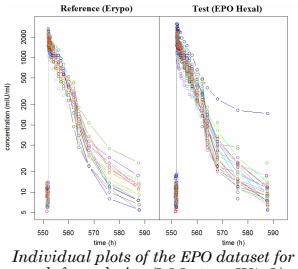
- Multiple dose, parallel group trial on 75 healthy volunteers[9]
  - Two formulations
    - Erypo® by Johnson & Johnson (reference, 38 subjects)
    - EPO Hexal® by Sandoz (test, 37 subjects)
  - 11 IV doses of 100 IU/kg on 4 weeks
    - Baseline (day 1) and trough (day 8, 15, 19, 22 and 24) concentrations
    - Complete PK with 19 sampling times after the 11th dose
- PK modeling: two-compartment with linear and Michaelis-Menten elimination
  - Approximation of a target drug mediated disposition model

$$\frac{dC_c(t)}{dt} = \frac{Q}{V_C}C_p(t) - \frac{Q}{V_C}C_c(t) - \frac{CL_{lin}}{V_C}C_c(t) - \frac{V_{max}C_c(t)}{V_c(K_m + C_c(t))}$$
$$\frac{dC_p(t)}{dt} = \frac{Q}{V_p}C_c(t) - \frac{Q}{V_p}C_p(t)$$

with $C_c(0) = C_p(0) = 0$
for each time dose $C_c(t^+) = C_c(t^-) + \frac{Dose}{V_c}$

    - Measured concentration: $C_0 + C_c(t)$ with C_0 the endogenous baseline concentration
    - Proportion of the dose nonlinearly eliminated (PDNE)

$$Dose = CL_{lin} \times AUC + \int \frac{V_{max}(t)}{K_m + C_c(t)} \times C_c(t)dt \Rightarrow PDNE = 1 - \frac{CL_{lin} \times AUC}{Dose}$$

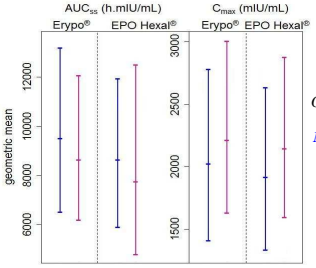


Individual plots of the EPO dataset for each formulation (LOQ=2.5 mIU/mL)

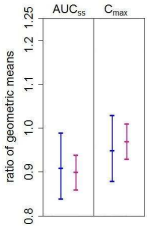
	V_c (L)	V_p (L)	CL_{lin} (L/h)	Q (L/h)	V_{max} (IU/h)	K_m (IU/L)	C_0 (IU/L)	$corr_{CL_{lin}\text{-}V_c}$
μ_R	4.05 (0.14)	2.58 (0.46)	0.36 (0.06)	0.34 (0.06)	341.22 (38.09)	90.83 (17.74)	8.26 (0.34)	
B	0.06 (0.05)	0.17 (0.23)	0.17 (0.23)	0.20 (0.21)	-0.07 (0.16)	-0.16 (0.28)	0.06 (0.06)	
BSV	0.21 (0.01)	0.16 (0.04)	0.34 (0.02)	0.13 (0.05)	0.13 (0.03)	0.39 (0.05)	0.25 (0.02)	0.9 (/)
b	0.15 (0.003)							

Parameter estimates (SE) obtained by MONOLIX 3.2
(μ_R: mean PK parameter for Erypo®)

- Bioequivalence analysis



Geometric means and $CI_{95\%}$ estimated by NLMEM and NCA for EPO formulation



Geometric mean ratios (test/reference) and $CI_{90\%}$ estimated by NLMEM and NCA

  - PDNE ratio estimated to 0.95 with $CI_{90\%}$ [0.72; 1.24]
  - EPO Hexal® bioequivalent to Genotropin® by NLMEM and NCA

Conclusion

- Similar bioequivalence test results using NLMEM and NCA (both examples)
- NLMEM-based bioequivalence analysis
  - Good estimation of the NLMEM parameters even for sparse design
    - Stable estimation of the geometric means (contrary to NCA)
  - Analysis of specific PK parameters not available by NCA
  - Taking into account data below LOQ