Validation of non-compartmental analysis (NCA) and bioequivalence results of PKanalix with respect to Phoenix WinNonLin

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INTRODUCTION

Need

Non-compartmental analysis (NCA) is used at all stages of drug development and is a key method to understand the pharmacokinetic properties of a compound. Bioequivalence analysis of the NCA parameters is a critical step to investigate generic formulations, food effects or drug-drug interactions.

Solution

PKanalix belongs to the MonolixSuite applications, and performs NCA and CA (compartmental analysis) and includes a bioequivalence module starting from the 2021 version.

Validation

As NCA and bioequivalence are commonly part of filings to the regulatory agencies, tools implementing these methods must be appropriately validated. For historical reasons, Phoenix WinNonLin is considered as the standard. In this work, we rigorously compare the results of PKanalix with those of WinNonLin.

ALGORITHMS

λ_z CALCULATION

Selection of admissible points to be checked in the calculation

- Bolus: $adm_{pts} = \{p_i : concentration(t_i) > 0 \; and \; t_i \geq T_{max}\}$
- IV: $adm_{pts} = \{p_i : concentration(t_i) > 0 \; and \; t_i > T_{max} \; and \; t_i \geq T_{endInf}\}$
- Oral: $adm_{pts} = \{p_i : concentration(t_i) > 0 \; and \; t_i > T_{max}\}$

Selection of points to calculate λ_z

If (there are at least 3 admissible points: $Nadm_{pts} \geq 3$) then:

- ❑ For all last consecutive admissible points: n = 3, 4, 5, … , $Nadm_{pts}$
  - Calculate adjusted R^2 coefficient $adjR^2(n)$ and lambda-z value $\lambda_z(n)$
  - Find: N_{max} = number of last consecutive admissible points corresponding to the maximal value of the $adjR^2$ and $\lambda_z < 0$
- ❑ Add more admissible points: n = N_{max} , $N_{max} + 1, \dots$, $Nadm_{pts}$ if $\lambda_z(n) < 0 \quad and \quad (adjR^2(N_{max}) - adjR^2(n) \leq 0.0001)$

BIOEQUIVALENCE (BE)

The bioequivalence analysis relies on the comparison of the geometric least squares mean ratio and its confidence interval (CI) to predefined BE limits. To construct the CI, the individual NCA parameter values are fitted to a general linear model with fixed effects (typically sequence, subject nested in sequence, period and treatment for a 2-2-2 crossover).
PKanalix uses QR factorization to solve the linear model. ANOVA tables and coefficients of variations (i.e intra-subject variability) are also calculated.

Available settings in PKanalix

- ❑ Factors included in the linear model (fixed effects only). Default factors are proposed based on the detected design (parallel or (repeated) crossover)
- ❑ Log-transformation or not of the NCA parameters
- ❑ Level for the confidence interval
- ❑ Bioequivalence limits
- ❑ Degrees of freedom: residuals or Welch-Satterthwaite (unequal variance)

METHODS AND RESULTS 1: NCA

The NCA validation with respect to Phoenix WinNonLin is based on comparing the results of real datasets to test realistic scenarios, specific datasets to detect possible differences in the algorithms, and simulated datasets to identify possibly unpredicted cases. All NCA parameters were calculated with PKanalix and compared with the results of Phoenix WinNonLin.

Real datasets

Datasets:

- Test drugs "M2000" and "MTX-HSA" (book "Applied statistics in the pharmaceutical industry" by Millard S., Krause A.)
- Carbamazepin and Theophylline (book "Bioequivalence studies in drug development" by Hauschke D. et al.)
- Erythromycin (article "The bioavailability of erythromycin stearate versus enteric-coated erythromycin base when taken immediately before and after food" by Clayton D., Leslie A.)

The above datasets were used in the original and modified forms with multiple combinations of NCA settings:

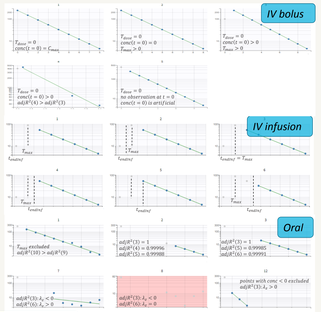
Dose type	Dosing	Weighting	AUC cal. method	BLQ
IV bolus	Single dose	Uniform	LinTrapLin	Missing
IV infusion	Steady state	1/Y	LinLogTrap	Zero
Extravascular		1/Y*Y	LinUpLogDown	LOQ
			LinTrapLin/Log	LOQ/2

Results

This test considered 63 scenarios with a total of 754 individual PK profiles. In all cases, the relative differences between the values of NCA parameters obtained from PKanalix and WinNonLin were less than 10^{-6} .

Specific datasets

Datasets: Manually generated to check rules for inclusion of points in λ_z calculation.



Results

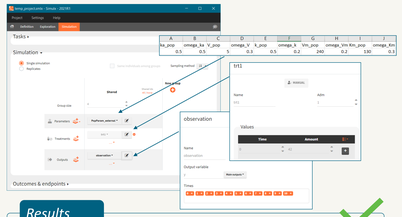
This test considered a total of 35 individual PK profiles. In all cases, the points selected for the λ_z calculation were identical in PKanalix and WinNonLin.

Simulated datasets

Datasets are combinations of:

- 1, 2 or 3 compartment
- Administration: oral or iv bolus
- Linear or non-linear elimination
- Proportional residual error: 4%, 10% or 20%

Datasets were simulated in Simulx, where a population of individuals was simulated for each combination of the above scenario elements.



Results

This test considered 36 scenarios with a total of 3600 individual PK profiles. In all cases, the relative differences between the values of NCA parameters obtained from PKanalix and WinNonLin were less than 10^{-6}.

METHODS AND RESULTS 2: BIOEQUIVALENCE

The validation of the BE results is based on the comparison of the PKanalix results with published benchmarks which were designed to validate bioequivalence softwares. Reference values for the ratio and its confidence interval for parallel, crossover and repeated crossover designs are available. In addition, the other PKanalix outputs (coefficient of variance (CV), ANOVA table) were compared to WinNonLin.

Parallel design

Publication: Fuglsang, A., Schütz, H. and Labes, D. (2015) **'Reference Datasets for Bioequivalence Trials in a Two-Group Parallel Design'**, *The AAPS Journal*, 17(2), pp. 400–404.

Datasets are combinations of:

- Small (N=9), medium (N=26) and large (N=1000) number of individuals
- Balanced and imbalanced number of individuals per group
- With and without outliers (i.e extreme value)
- Homo- and heteroscedasticity (i.e equal or unequal variance)
- Standard or extreme numeric range and geometric means ratio

Main bioequivalence settings:

- Linear model with treatment as fixed effect
- Log-transformation of the NCA parameter
- Degrees of freedom: both residual and Satterthwaite tested

Results

This test considered 11 datasets. In all cases, the ratio and confidence interval were identical to the reference values (given as a percentage with 2 digits). For CV and ANOVA tables, the relative difference with WinNonLin results were less than 10^{-6}.

Crossover design

Publication: Schütz, H., Labes, D. and Fuglsang, A. (2014) **'Reference Datasets for 2-Treatment , 2-Sequence , 2-Period Bioequivalence Studies'**, 16(6), pp. 1292–1297

Datasets are combinations of:

- Small (N=13), medium (N=100) and large (N=1000) number of individuals
- Balanced and imbalance between sequences
- With and without outliers (i.e. extreme value)
- Standard or extreme numeric range and geometric means ratio
- Residual normally distributed or simulation from sine function

Main bioequivalence settings:

- Linear model with sequence, subject nested in sequence, period and treatment as fixed effects.
- Log-transformation of the NCA parameter

Results

This test considered 8 datasets. In all cases, the ratio and confidence interval were identical to the reference values (given as a percentage with 2 digits). For CV and ANOVA tables, the relative difference with WinNonLin results were less than 10^{-6}.

Repeated crossover design

Publication: Schütz, H. *et al.* (2020) **'Reference Datasets for Studies in a Replicate Design Intended for Average Bioequivalence with Expanding Limits'**, *AAPS Journal*. The AAPS Journal, 22(2), pp. 1–7.
Publication: EMA (2015) **'Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP)'**

Datasets are combinations of:

- Designs: four-period full-replicate, three-period full replicate, three-period partial replicate, two-period full-replicate
- Small (N=12) or medium (N=222) number of individuals
- Balanced and imbalance between sequences
- With and without outliers (i.e extreme value)
- Standard or extreme numeric range and geo. means ratio
- Homo- and heteroscedasticity (i.e equal or unequal variance)
- Complete or incomplete (periods missing)

Main bioequivalence settings:

- Linear model with sequence, subject nested in sequence, period and treatment as fixed effects (i.e EMA method A)
- Log-transformation of the NCA parameter

Results

This test considered 31 datasets. In all cases, the ratio and confidence interval were identical to the reference values (given as a percentage with 2 digits). For CV and ANOVA tables, the relative difference with WinNonLin results were less than 10^{-6}.