Is it possible to perform equivalent simulations with NONMEM and TS2?

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INTRODUCTION

Context

✓Simulations are more and more performed in order to evaluate the impact of variability and to compare different trial designs as well as to challenge model assumptions and to qualify models.

✓NONMEM (NM)[1]: input datasets are tricky to build and NM does not provide statistical analysis on its output.

✓Trial Simulator 2 (TS2)[2]: abilities to create trial designs (parallel, cross-over and latin-square), outputs can be directly evaluated using a special release of S-PLUS 6.2.

Objective

✓Assessment of the equivalence of the simulations performed with NM and TS2 using principally a graphical comparison (visual predictive check).

MATERIALS AND METHODS

✓Two types of model tested:

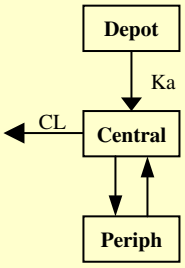
Two-compartment model

Design

✓12 subjects.

✓Single dose.

✓11 sampling times.



Drug-Metabolite model

Design

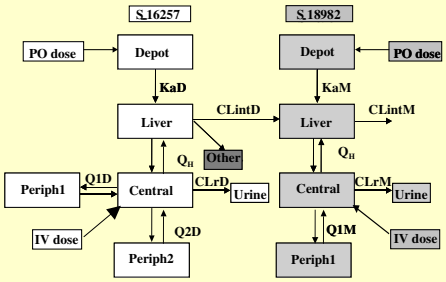
✓83 subjects:

➢47 subjects (drug).

➢36 subjects (drug+ketoconazole).

✓Single dose.

✓9 sampling times.



✓Designs are simulated 1000 times twice with NM and TS2 (2 replicates of 1000 simulations for each software).

✓Evaluation of intra-software and inter-software relative difference is performed at two different chosen times corresponding to peak and trough of the concentrations.

✓Intra-software relative difference: $$\frac{|MEDIAN_{replicate1} - MEDIAN_{replicate2}|}{MEDIAN_{replicate1\ /\ replicate2}}$$

✓Inter-software relative difference: $$\frac{|MEDIAN_{NM} - MEDIAN_{TS2}|}{MEDIAN_{NM\ /\ TS2}}$$

✓Graphical comparison: representation on the same graph of median, P5 and P95 of the data simulated with both software.

RESULTS

✓Problems occurred during simulation step:

➢NM: need of a code to truncate etas distribution.

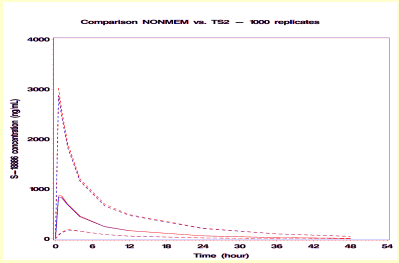
➢TS2: difficulties to implement complex models (drug-drug interaction).

✓Intra-software relative difference and Inter-software relative difference are lower than 4%.

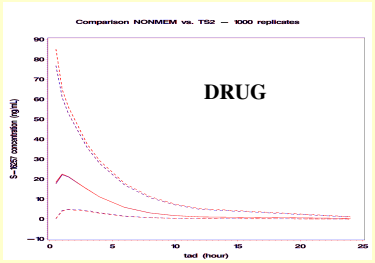
Two-compartment model	Peak	Trough
NM Intra-software relative difference (%)	0.88	3.15
TS2 Intra-software relative difference (%)	1.32	1.48
Inter-software relative difference (%)	3.74	2.34

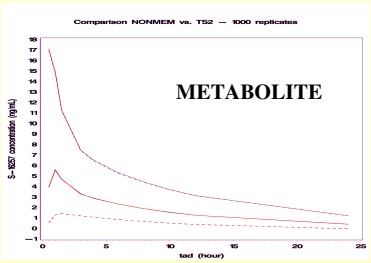
Drug-Metabolite model	Peak (Drug/Metabolite)	Trough (Drug/Metabolite)
NM Intra-software relative difference (%)	0.73/0.89	0.46/1.80
TS2 Intra-software relative difference (%)	0.80/0.22	1.26/0.55
Inter-software relative difference (%)	0.37/0.12	1.55/3.11

✓Graphical comparison: simulated curves are well superposed.



NM/TS2 comparison for the two-compartment model. Graph represents median (full line), P5 and P95 (dotted lines) of the data simulated with NM (blue) and TS2 (red).





NM/TS2 comparison for the drug-metabolite model without drug-drug interaction. Graphs represent median (full line), P5 and P95 (dotted lines) of the data simulated with NM (blue) and TS2 (red).

CONCLUSION

✓NM and TS2 simulations are judged graphically equivalent.

✓Structural model and error model can be checked by simulating without and with variability.

✓Models implemented in TS2 can be used to simulate new trial designs or reference groups.

References :

1. Beal SL, Sheiner LB. NONMEM users guides. San Francisco : NONMEM Project Group, University of California; 1992.
2. Pharsight Trial Simulator user's guide version 2.2. Pharsight Corporation.