

OBJECTIVES

The aim of this work is to compare model predictions from PhysPK biosimulation software for a previously published semi-mechanistic model against those obtained by NONMEM, using exposure metrics (AUC and $C_{\max}$ values) for each type of analyte: parent drug (PD), primary- (PM) and secondary-metabolite (SM).

METHODS

A set of 16 scenarios with 24 IDs each previously generated by Monte Carlo simulations in NONMEM 7.3 [1] was introduced in a parametric experiment wrote in EL language in PhysPK biosimulation software [2]. **Figure 1** shows the workflow followed in this analysis.

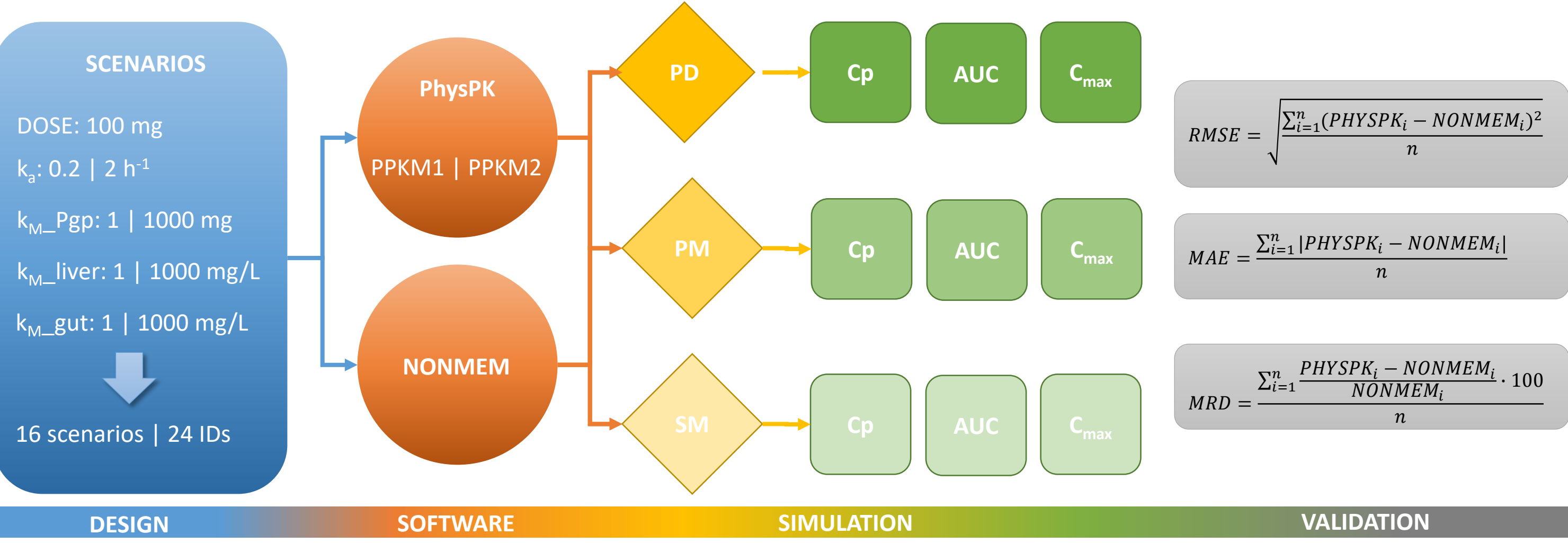


Figure 1. Modelling workflow implemented.

A previously semi-mechanistic model (**Figure 2a**) served as a basis for the analysis. Details concerning the mathematical description were justified previously [3]. The semi-mechanistic model of **Fig. 2a** is implemented in PhysPK using two approaches. A first one (PPKM1) is a replicate of the mathematical formulation used in NONMEM (eq. 1 – 17 from [3]), whereas the second one (PPKM2) is based on the standard graphics and virtual prototyping modeling of PhysPK. The structure of PPKM2 is shown in **Fig. 2b**.

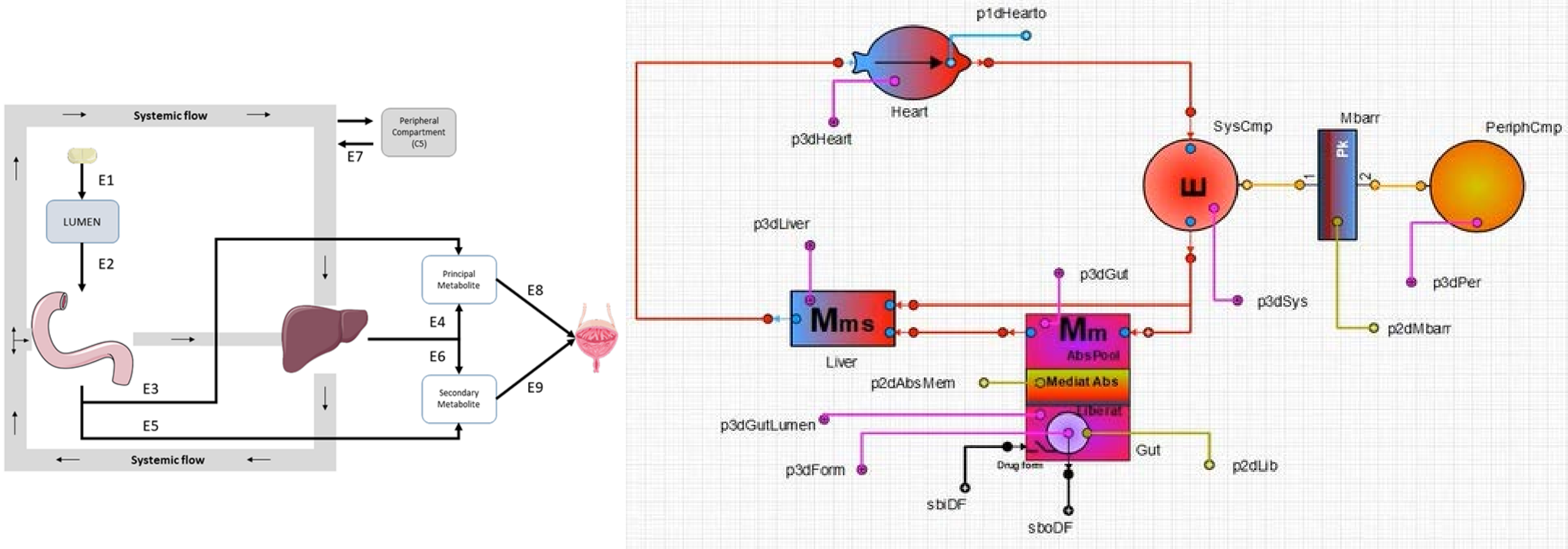


Figure 2. (a) Left - Base model for the analysis. Adapted from [3]. (b) Right - Model diagram of PPKM2 implemented in PhysPK. Diagram symbols refer to compartments (plasma and peripheral), tissues (liver and gut), and barriers, with internal text associated with mechanisms processes (E: elimination, Mms: saturable metabolism).

RESULTS

Individual plasma concentration (C_p)-time profiles of PD, PM and SM obtained with equivalent models in PhysPK (PPKM1) and NONMEM were represented (**Figure 3**). Relative differences in exposure metrics (AUC and $C_{\max}$) and error standard metrics were computed, considering NONMEM estimates as the reference value (**Figure 4**). Results showed that PD AUC differences for PPKM1-NONMEM comparison were in the range -1.37 - 8.89 %. Average of the mean relative differences were 3.78, 6.65, 5.83 % for PD, PM and SM AUC, respectively, and -0.19, 2.81 and 1.33 % for PD, PM and SM $C_{\max}$, respectively.

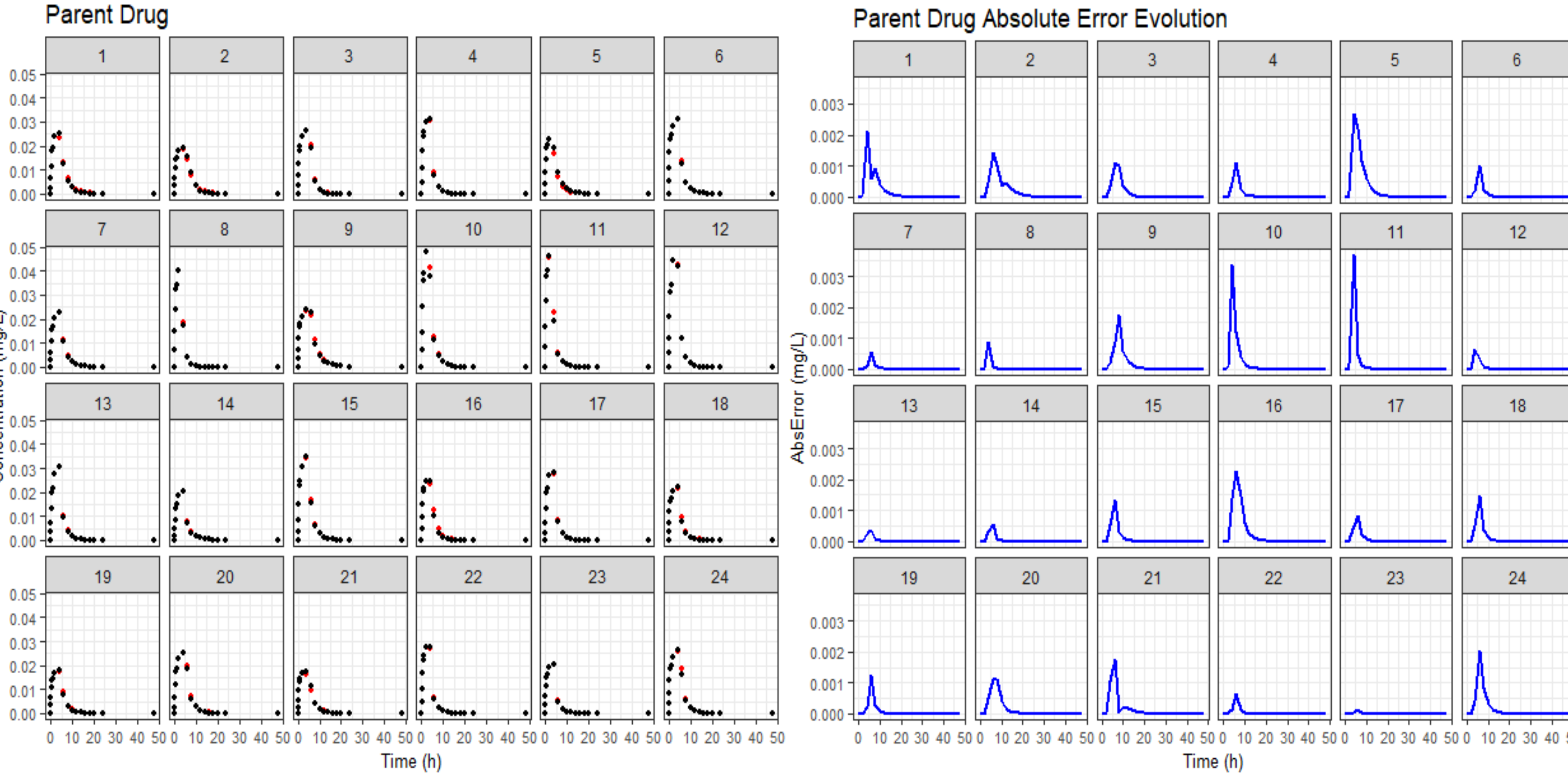


Figure 3. Graphical analysis of PD Cps for equivalent models (scenario 4). (Red: NM; black PhysPK)

These differences between formal equivalent models could be attributed to numerical integration error propagation related to a local numerical integration accuracy of 10^{-6} for both simulation software. This was confirmed by estimation of propagation errors and by plotting the absolute difference of C_p value for each model at each time (**Fig. 3**). Left blue plots let us observe how absolute error was lower than 10^{-6} during first hour, and grew to a maximum value within range 10^{-3} - 10^{-2} around $C_{\max}$.

This behavior occurred for all compared analytes and all scenarios, as is expected for an error independent of any model mechanisms' influence (i.e. absorption, intestinal efflux, metabolism, distribution and excretion), and with unique dependency on numerical integration errors.

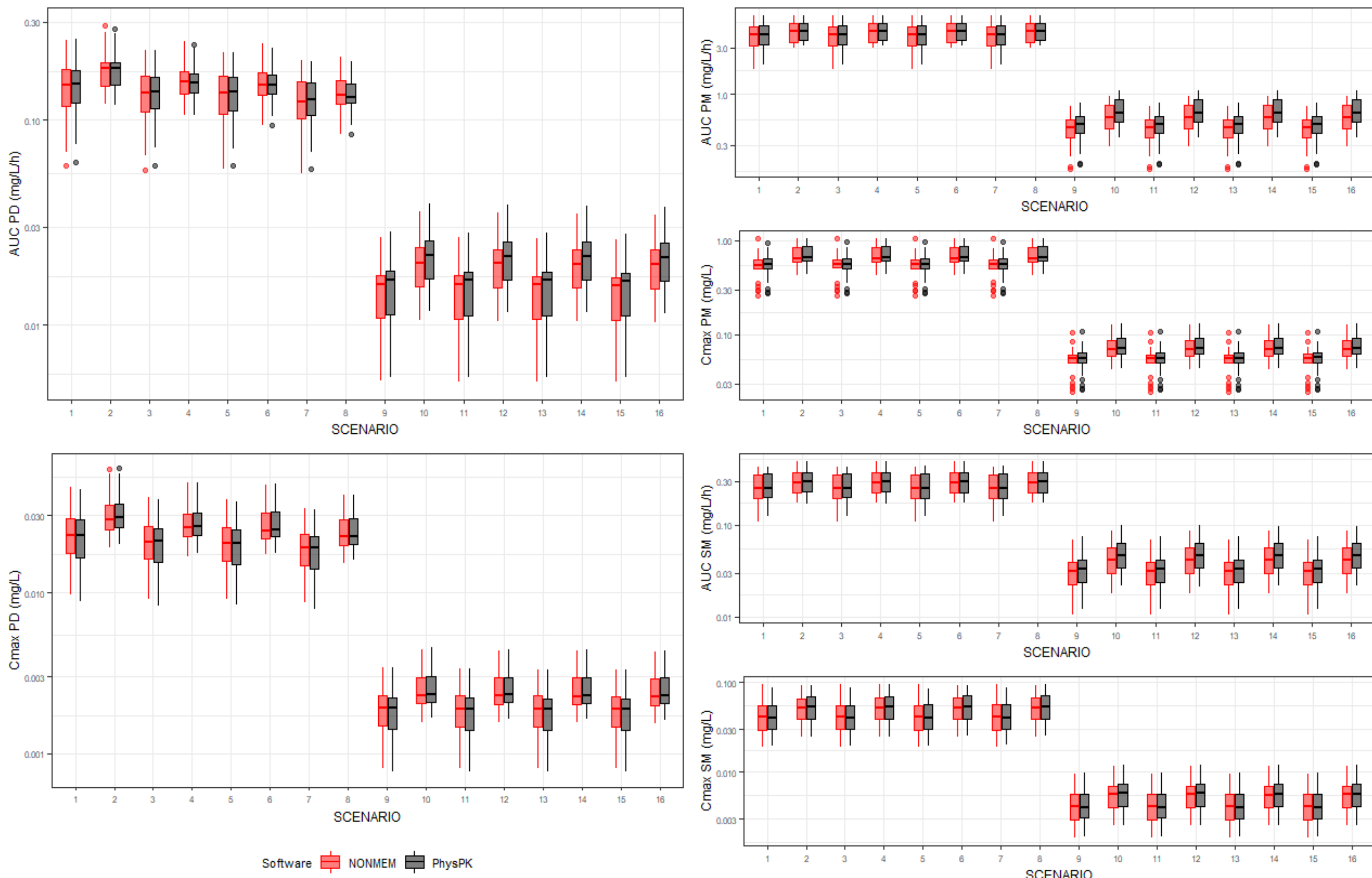


Figure 4. Numerical analysis of simulations for equivalent models.

After confirming that PPKM1 has the expected behavior with respect to the NONMEM model (**Fig. 4**), we can conclude that PhysPK deals correctly with the model of **Fig. 1a**. In this context, comparison of PPKM2 model (**Fig. 1b**) against the NONMEM model (**Fig. 1a**) can be executed and interpreted.

PPKM2 was simulated in the same 16 scenarios than PPKM1. The same graphical (**Figure 5**) and numerical (**Figure 6, Table 1**) analysis was performed in order to establish the agreement between the modeling approaches of PhysPK and NONMEM.

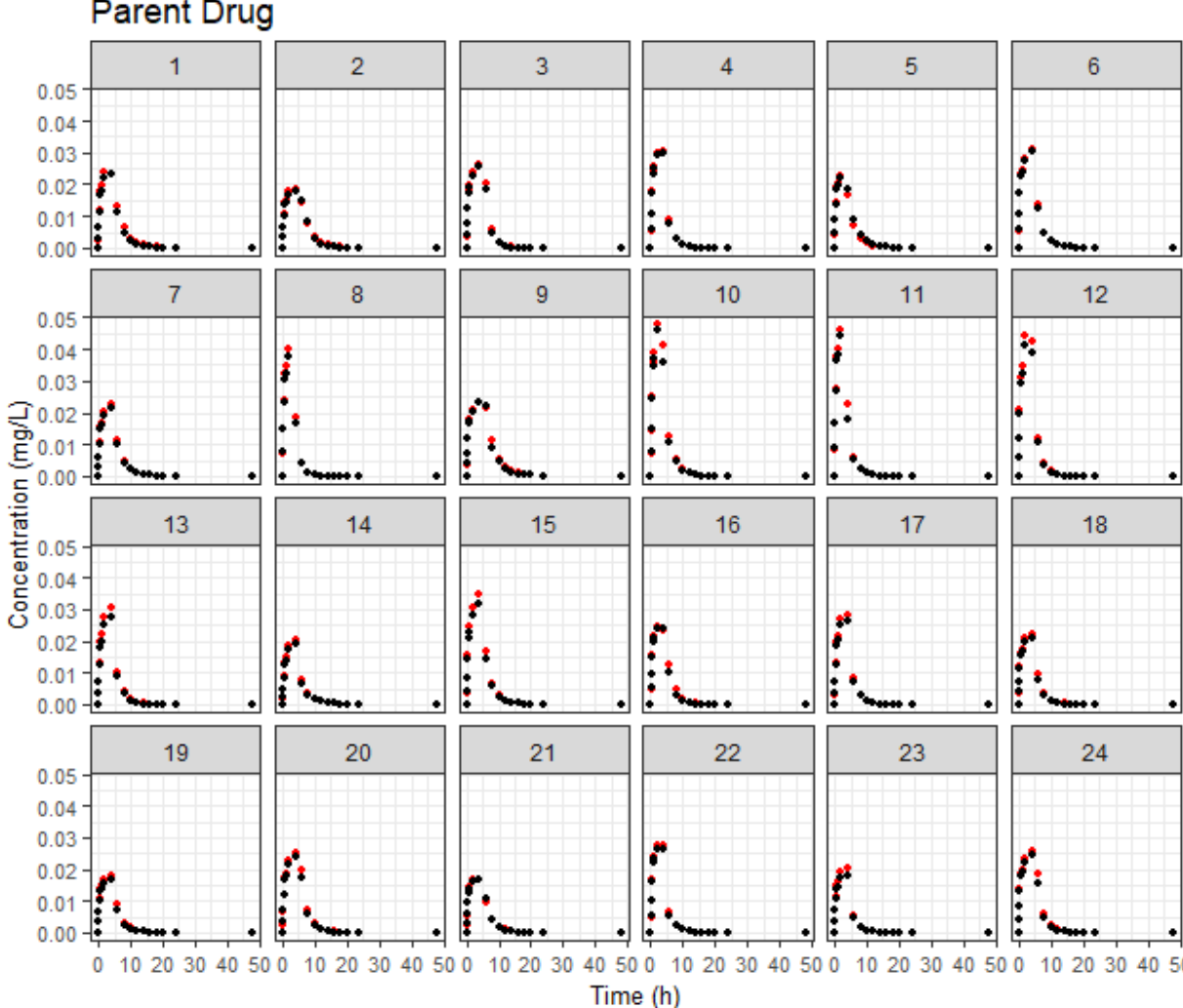


Figure 5. Graphical analysis for PD Cps of PPKM2 and NONMEM simulations (scenario 4). (Red: NM; black PhysPK)

Parent Drug		
PK Param	AUC	$C_{\max}$
Error		
MAE	$7.39 \cdot 10^{-3}$	$9.04 \cdot 10^{-4}$
RMSE	$1.14 \cdot 10^{-2}$	$1.81 \cdot 10^{-3}$

Table 1. Numerical analysis of PPKM2 and NONMEM simulations. (PK param: pharmacokinetic parameter)

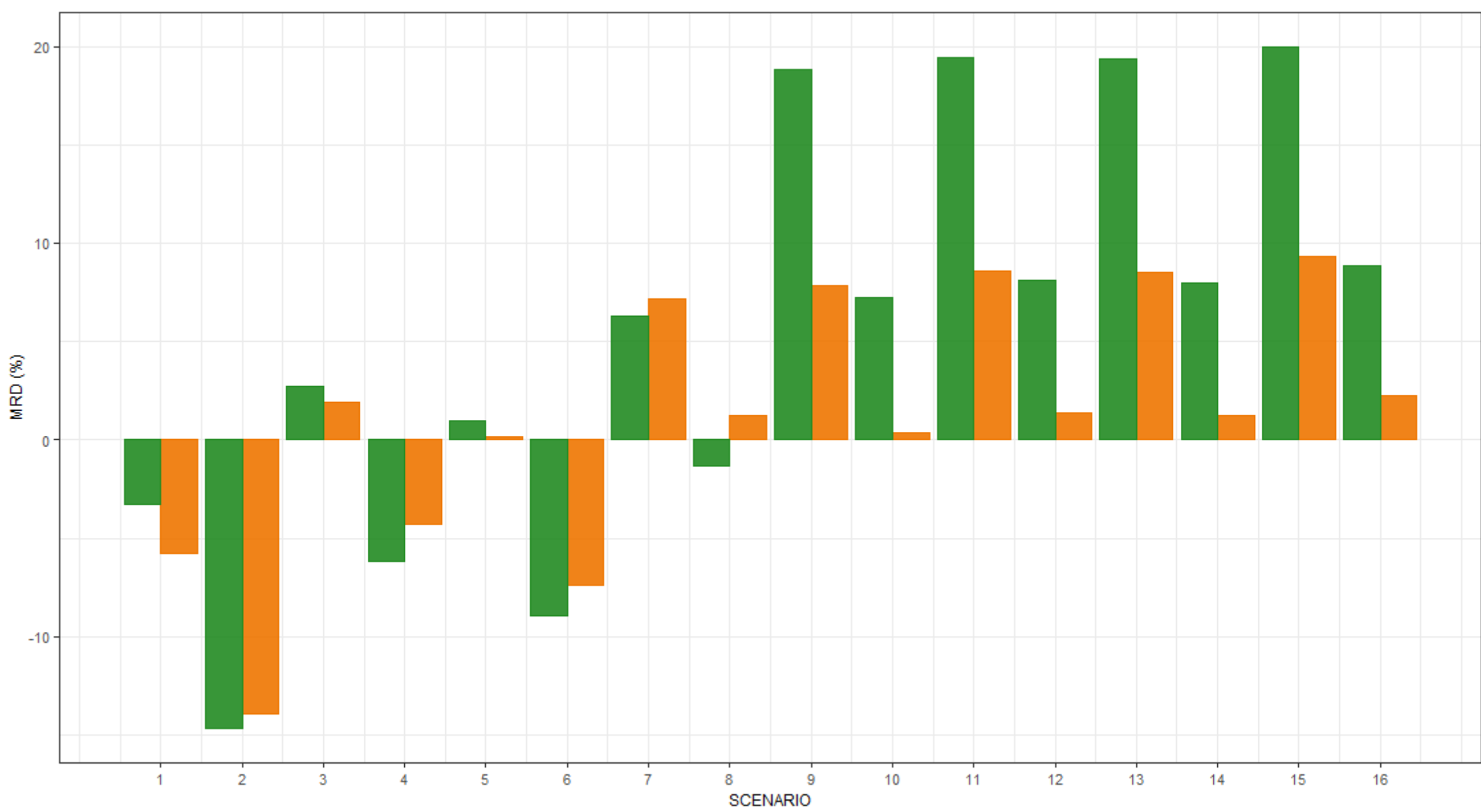


Figure 6. MRD average for PD AUC and $C_{\max}$ estimated by numerical analysis of PPKM2 and NONMEM simulations.

Average of the mean relative differences for PD AUC and $C_{\max}$ for PPKM2-NONMEM comparison were 5.33 and 1.16 %, respectively, in contrast with the differences of 3.78 and -0.19 % corresponding to the PPKM1-NONMEM one. As a consequence of the basis of the PPKM2, PhysPK model predictions differed from NONMEM ones more than expected for numerical accuracy. Therefore, differences in PPKM2-NONMEM comparison depend on the model's mechanisms.

DISCUSSION AND CONCLUSION

PhysPK is a physiological biosimulation software oriented to the development of multilevel models using virtual prototyping with compartments, tissues and physiological systems. Although PPKM2 and NONMEM model were described according to the same pharmacokinetics and physiological initial assumptions, their different modeling approaches were associated to significant mechanisms-related differences detected in the final dynamic predictions.

Subsequent research is required to detect which are the mechanisms that induce the differences observed and to reach conclusions with respect to their importance in bioequivalence studies and other research scenarios.

References

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