# Virtual Bioequivalence Assessment of Two Tramadol Formulations using the Advanced Dissolution Absorption and Metabolism (ADAM) Model via Simcyp R Package

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## Objective

A qualified PBPK model of tramadol has previously been used to simulate virtual bioequivalence (BE) trials using a random error approach [1]. In this research work we aim to expand this approach using the Simcyp16 R package [2] to assess the impact of inter-occasion variability on the bioequivalence (BE) of two tramadol formulations.

## Background

Assessing *in vivo* equivalence of drug products virtually has always been a subject of great interest for the pharmaceutical scientists as well as regulatory agencies. Mechanistic absorption models such as the Advanced Dissolution Absorption and Metabolism (ADAM) model implemented within population based Physiology-Based Pharmacokinetic (PBPK) models are useful tools in integrating various physiological parameters and formulation specifications affecting drug products. An important feature of PBPK modelling is accounting for inter-subject and inter occasion variability (IOV), when reference and test formulations are compared from a BE perspective.

Although the current modelling techniques can estimate inter-individual variability reasonably well, there still exists gaps in the reliable prediction of in vivo-performance of drug products as a result of inter-occasion variability. In literature, there are two independent modelling approaches to incorporate IOV in virtual BE studies; 1) The random error terms using IOV estimated priori in replicate clinical study are added to the predicted PK parameters i.e. $C_{max}$ and AUC; 2) The IOV is incorporated in the system parameters and propagated in simulations.

Recently, we used a qualified PBPK model of tramadol to run virtual bioequivalence trials within the Simcyp Simulator using the random error approach [1]. The virtual BE trials based approach was used to inform setting dissolution specifications- Upper Limit (UL) and Lower Limit (LL).

The Simcyp-R library package now allows modellers to propagate IOV mechanistically by defining the variation attributes (%CV, and lower and upper bound values) for selected drug and/or system parameters. In this research work we tested virtual BE of these two established specifications (UL and LL) with the target formulation using the Simcyp16 R package.

## Methods

1. Simulate the Target/Reference formulation workspace in R for 16 individuals and output individual values of Gastric emptying time, Small intestine transit time and Colon transit time.

2. For each individual in the workspace, generate a new value of Gastric emptying time, Small intestine transit time and Colon transit time, from a normal distribution assuming the mean value for an individual to be the value generated in step 1 and a CV of 10%

3. In the Target formulation workspace set Gastric emptying time, Small intestine transit time and Colon transit time individual values to those values generated in Step 2. Run the simulation with the new parameter values in R and log the individual AUC and Cmax values

4. Import the LL/UL workspace into R. Generate new values of Gastric, Small intestine and Colon transit time from the same normal distribution described in step 2. Run a simulation using the new parameter values in R and log individual AUC and $C_{max}$ values

5. Repeat inter-occasion variability by repeating step 2-4 for 10 trials of the same 16 individuals

6. Assess the bioequivalence of Target and LL/UL formulations by comparing the AUC and $C_{max}$ using the Phoenix bioequivalence module.

**Figure 1. Sequential Modelling Workflow Followed in the Study**

## Results

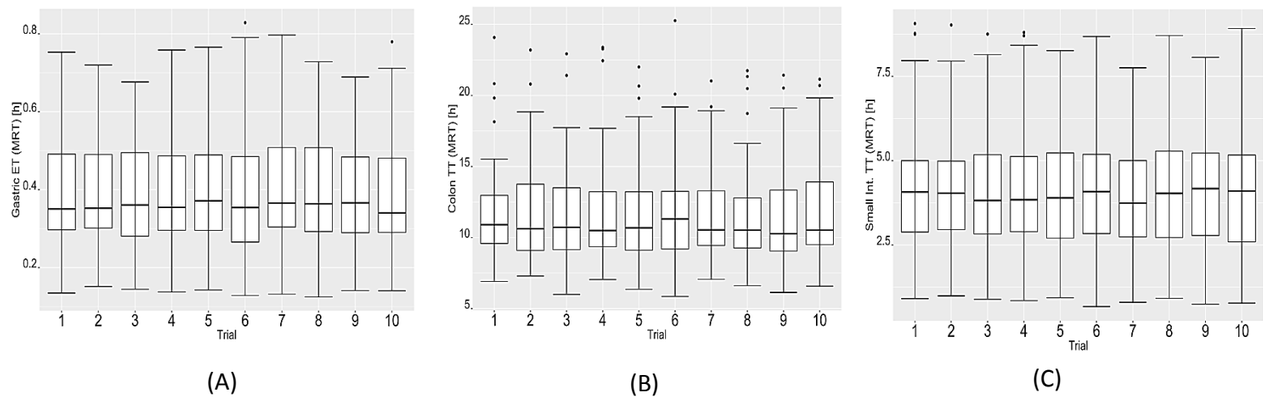


**Figure 2: Variability in Gastric emptying time (A), Colon transit time (B)and Small intestine transit time (C) simulated across the trials. Whiskers show the 1.5 x IQR and the top and bottom of a box shows the 75th and 25th quartile while the outliers are classified to lie more above/below 3 x IQR. (IQR=Inter quartile range]**

The Version 16 Simcyp-R Package and Phoenix® bioequivalence module were used to assess the BE of two new LL/UL with the Target formulation in the previously qualified PBPK model of tramadol. For each of ten trials of either the Target *vs.* LL or Target *vs* UL formulations, new values of Gastric emptying time, Small intestine transit time and Colon transit time were generated. These are presented in the box-plots in Figure 2 by trial for each parameter. Figure 3 presents the mean and 90% confidence intervals of the AUC and $C_{max}$ ratios of the Target and LL/UL formulation, by trial. The red lines represent the BE limits. It can be observed in Figure 3 that the two new formulations, LL and UL, are bioequivalent with the Target/Reference formulation over all trials.

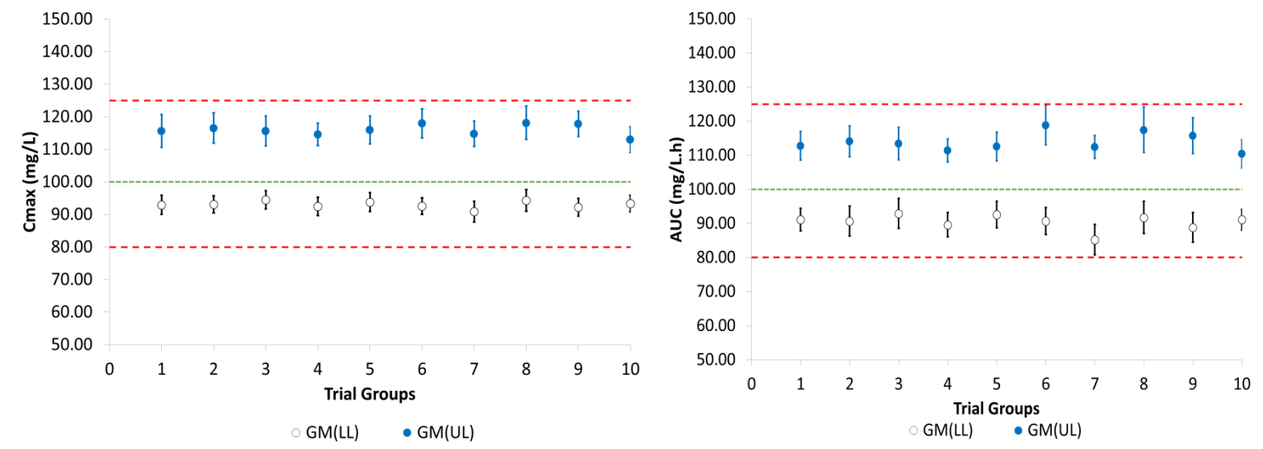


**Figure 3. T/R ratio of Geometric Mean Ratio of AUC and $C_{max}$ ± 90% CI's using 16 subjects per simulated trial. The red lines demark 80-125% BE Limits.**

## Conclusions

Mechanistic absorption models incorporated within the population-based PBPK model can be used to run virtual BE studies and evaluate reference and test formulations. Such approach allows incorporation of inter-occasion variability in parameters that affect the formulations performance. These simulations thus may inform the optimal design of BE studies.

This study also demonstrates the capabilities of the Simcyp platform to explore different approaches to run virtual BE trials with potential application to dissolution specification settings, defining formulation design space, informing QbD, alcohol dose dumping and beyond. Further validation of the proposed approach with a range of drugs, formulations and appropriate clinical studies to validate the results is needed to increase the confidence in this novel approach and raise awareness.

## References

[1] Pathak et al., Establishment of Virtual Bioequivalence Using Population-Based PBPK Modelling: Application to the Setting of Dissolution Limits, CRS Annual Meeting 2016, Edinburgh, Scotland, UK.

[2] Cain et al. Application of Simcyp's R Library Package in Simulation and Prediction of Metoprolol Compliance Using a Single Plasma Concentration Sample. 24th PAGE meeting, Crete, 2nd-5th June 2015 (poster presentation).