# Pirana–Simcyp Virtual Bioequivalence (VBE) Workflow: Software Demonstration and Case Study on Paliperidone Palmitate Long-Acting Injectables

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## Integrated **Pirana–Simcyp** *Virtual Bioequivalence* converts PBPK simulations into **rapid, reproducible, and extensible bioequivalence decisions**

## Background and Objective

Demonstrating bioequivalence for drug formulations *in vivo* can be a time and resource intensive process, however VBE studies can help streamline these assessments. The Pirana-Simcyp VBE module was developed to provide a user-friendly framework for the organization and optimization of PBPK model-based VBE workflows.

Pirana interfaces with the Simcyp-R package to run PBPK simulations and provides bespoke scripts for data analysis and visualization. We utilized the Pirana VBE module to implement a case study on 3-month long-acting injectable (LAI) suspension formulations of paliperidone palmitate (PP3M), in which the particle size distribution (PSD) initial mean radius is taken as the critical quality attribute (CQA).

This work showcases a systematic approach for conducting VBE analyses using the Pirana–Simcyp integration, and illustrates the influence of drug mean particle size on PP3M VBE outcomes.

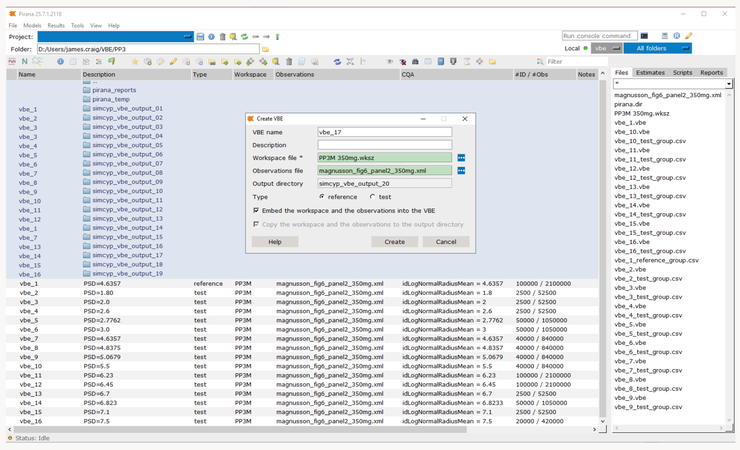
## Methods

A PBPK model of a PP3M reference formulation was developed in Simcyp, with an initial mean particle radius of 4.6357 µm. All VBE assessments were conducted with a parallel trial design.

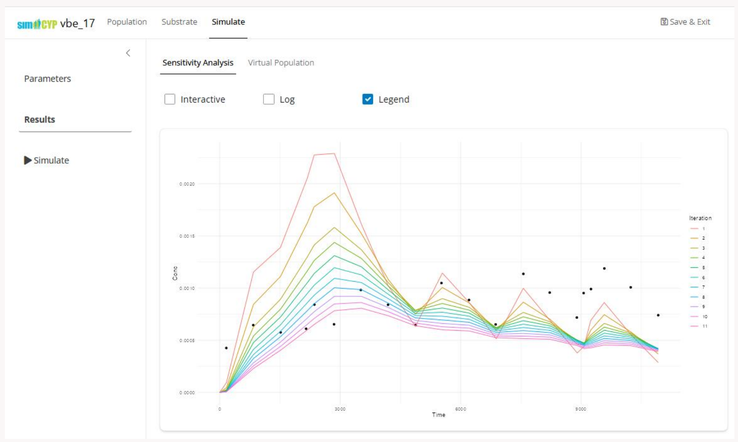
Using Pirana's Simcyp-VBE Shiny application and integrated R scripts, we performed the following workflow steps:

1. Sensitivity Analysis: Simulations were used to explore the impact of varying PSD means on plasma concentration profiles.
2. Virtual Trial Simulations: Virtual population simulations were conducted for the reference and a range of test formulations with different PSD mean radii. Up to 100,000 subjects were simulated for each formulation.
3. Data Processing/QC: Automated Pirana scripts aggregated and quality-checked the outputs.
4. Power Analysis: Combined test/reference datasets were analyzed with a Monte Carlo bootstrap resampling algorithm to assess the statistical power of two one-sided t (TOST) tests as a function of VBE trial size.
5. Type I Error: Linear regressions predicted the PSD mean radii likely to result in population geometric mean ratios (GMRs) of 0.80 and 1.25. Type I error was determined as the passing rate of VBE trials at those CQA values.
6. Safe Space: The range of initial mean particle sizes likely to result in VBE trials with ≥80% power was mapped for a given trial size.

## Pirana Workspace – PP3M Example




## Pirana VBE User Interface – Sensitivity Analysis



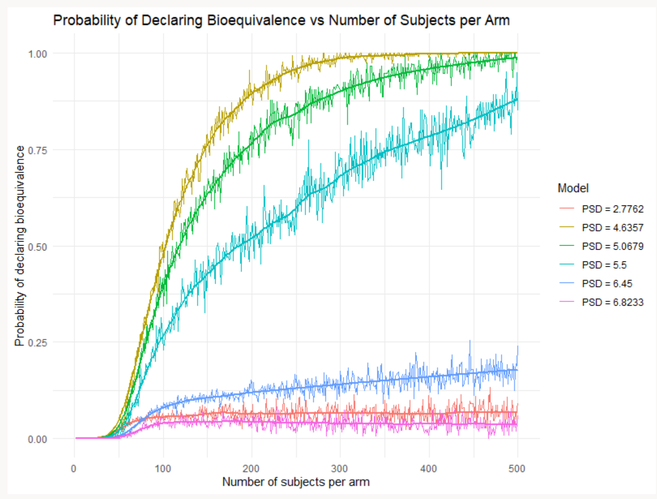

## Discussion

Integrating the Simcyp Simulator with Pirana allows the rapid simulation of bioequivalence trials for LAIs. Pirana handles file organization, offers standard R scripts for statistical tests, and supplies visual outputs that can be modified to suit specific study questions. The resulting in-silico analyses estimate the sample sizes and CQA ranges likely to achieve bioequivalence, reducing reliance on additional clinical studies. The Pirana–Simcyp VBE workflow provides a transparent, extensible, GUI and script-driven framework for conducting reproducible VBE assessments.

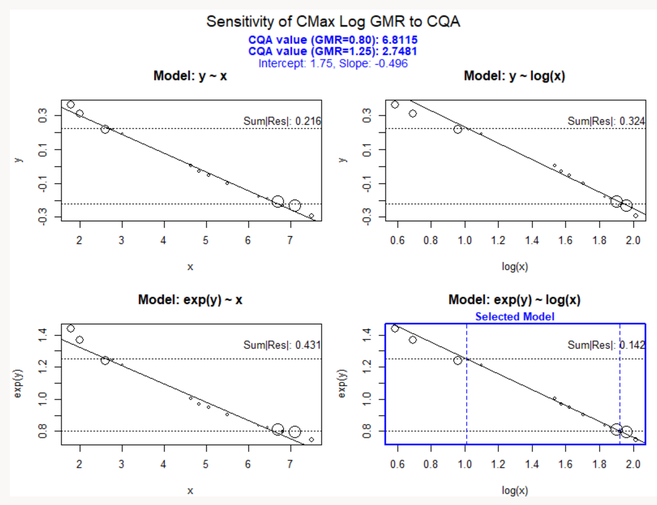
## Results

- Power analyses suggested that when provided a perfectly bioequivalent test formulation, 160 subjects per arm were required to reach 80% power. A deviation in test particle size of 20% from the reference doubled the sample size required for 80% power.
- Regression-based sensitivity analyses demonstrated a linear relationship between PSD mean and the GMR of $C_{max}$.
- Formulations predicted to yield GMRs of 0.80 and 1.25 had approximately a 5% chance of erroneously being declared bioequivalent, indicating that type I error was well-controlled.
- Safe space analysis determined that given a parallel VBE trial design with 200 patients per arm, test formulations with particle radiis between 4.27 - 5.08 µm were likely to remain bioequivalent with a power of over 80%.

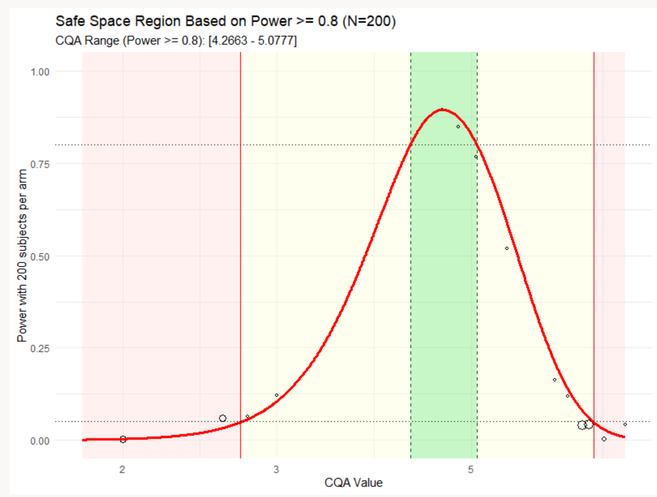
## Example VBE outputs




Power (probability of declaring bioequivalence) as a function of the number of subjects per arm for parallel VBE trials of test PP3M formulations with different initial mean particle radii. Both raw and smoothed curves for Monte Carlo estimated power are presented.




Model selection for assessing the sensitivity of $C_{max}$ Log(GMR) to the CQA, here represented as PSD mean radius. Four candidate models are evaluated using weighted residuals. Circle sizes are scaled by GMR variance. The best-fitting model is outlined in blue. Vertical dashed lines indicate the estimated CQA values corresponding to population-level GMR thresholds of 0.80 and 1.25; CQA values provided in plot subtitle.




Safe space for initial mean drug particle size of PP3M bioequivalent to the reference. The overlaid curve shows the statistical power of TOST tests applied to VBE trials at a fixed trial size (here, 200 subjects per arm) across varying CQA values. Simulated points are scaled by variance, with larger points corresponding to larger variance. The central green area represents the safe space, within which VBE trials declare BE with >80% power. The CQA boundaries of the safe space are returned to the user. The yellow region represents formulations with population-level GMRs within the 0.8 – 1.25 BE region but with power <80% at this specific trial size. Red regions mark CQAs with population-level GMRs outside of the BE limits. Horizontal dotted lines indicate 5% and 80% power.

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