2nd Annual Conference of the Society of Pharmacometrics and Health Analytics (ICOP- India, 2026)

A Workflow for Conducting Model-Based Bioequivalence (MBBE) in Pumas

Nikita Ramwani *[1,2], Pavan Rathina Muthu Kumar[2], Vijay Ivaturi[1,2], Srinivas Mutalik[2]

[1]Pumas-AI, USA, [2]Manipal Academy of Higher Education, India

ICC026

Background

Bioequivalence (BE) is usually assessed using clinical BE studies. Model-Based Bioequivalence (MBBE) uses population PK models and repeated simulations to answer the same question without always needing a full clinical trial.

This approach helps us:

- Understand how variability affects BE
- Explore different study designs
- Estimate power before running a study

Objective

To present a clear and reproducible workflow in Pumas for performing MBBE — starting from model building and ending with BE and power results.

Methods

1. Population PK Model

- We built a one-compartment PK model with oral absorption.
- Formulation, period, and sequence were included so that relative bioavailability (Test vs Reference) could be estimated.

2. Study Design

We simulated a parallel BE study:

- Test and Reference groups
- 5 mg once daily for 7 days
- Sample sizes per arm: 40, 80, 120, 160, 200
- So for n = 40 per arm → total subjects = 80.

Table 1: Study Design

Population	Study	Design	Total Subjects	Arms	Subjects	Sequence	Period	Formulation
1	Parallel	R | T	24	2	12	R	1	R
1	Parallel	R | T	24	2	12	T	1	T
2	Parallel	R | T	48	2	24	R	1	R
2	Parallel	R | T	48	2	24	T	1	T
3	Parallel	R | T	72	2	36	R	1	R
3	Parallel	R | T	72	2	36	T	1	T
4	Parallel	R | T	96	2	48	R	1	R
4	Parallel	R | T	96	2	48	T	1	T
5	Parallel	R | T	120	2	60	R	1	R
5	Parallel	R | T	120	2	60	T	1	T
6	Parallel	R | T	144	2	72	R	1	R
6	Parallel	R | T	144	2	72	T	1	T
7	Parallel	R | T	168	2	84	R	1	R
7	Parallel	R | T	168	2	84	T	1	T
8	Parallel	R | T	192	2	96	R	1	R
8	Parallel	R | T	192	2	96	T	1	T
9	Parallel	R | T	216	2	108	R	1	R
9	Parallel	R | T	216	2	108	T	1	T
10	Parallel	R | T	240	2	120	R	1	R
10	Parallel	R | T	240	2	120	T	1	T

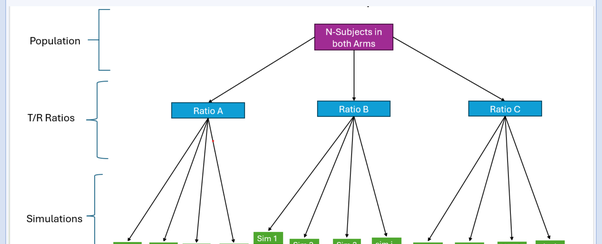
Abbreviations – BE= Bioequivalence, MBBE = Model Based Bioequivalence, T/R = Test/Reference, PK = Pharmacokinetic(s), GMR = Geometric Mean Ratio,

3. Simulations

For each sample size and each Test/Reference (T/R) ratio:

- 1000 virtual trials were simulated
- PK profiles were generated
- Cmax and AUC were calculated
- Power was later defined as the % of trials where BE passed.

Figure 1: MBBE Simulations



Footnote:
The flow chart represents a single population consisting of "*n*" subjects with three Test/Reference (T/R) ratios, simulated over "*j*" simulations. **sim j** denotes the "j" number of simulations conducted in the analysis.

4. Bioequivalence Analysis

For every trial, we calculated:

- Geometric Mean Ratio (GMR) for Cmax and AUC
- 90% confidence intervals

BE was considered to pass if the CI was within 80–125%.

5. Power Estimation

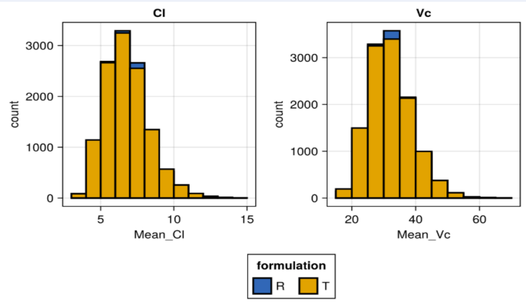
Power = the proportion of simulations that passed BE (for each T/R ratio and each sample size).

Results

Model Check

- Distributions of clearance and volume were similar between Test and Reference across simulations.
- This supports the assumption that the only difference is bioavailability, which is expected in BE work.

Figure 2: PK Parameter Distribution for Test and Reference



GMR vs T/R Ratio

GMR values increased in line with the T/R ratios, showing that:

- The model behaved consistently
- Exposure changes were captured correctly

Figure 3: True T/R Ratio vs Geometric Mean Ratio

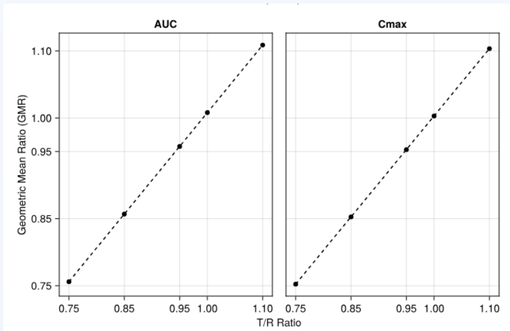


Table 2: GMR Mean and Quantiles From 1000 Simulations

Test/Reference Ratio	AUC GMR Mean	AUC GMR SD	AUC GMR Q10	AUC GMR Q90	Cmax GMR Mean	Cmax GMR SD	Cmax GMR Q10	Cmax GMR Q90
0.75	0.756	0.0792	0.661	0.86	0.752	0.0737	0.66	0.851
0.85	0.857	0.0897	0.749	0.975	0.853	0.0835	0.748	0.964
0.95	0.958	0.1	0.837	1.09	0.953	0.0933	0.836	1.08
1	1.01	0.106	0.881	1.15	1	0.0982	0.88	1.13
1.1	1.11	0.116	0.969	1.26	1.1	0.108	0.968	1.25

Power

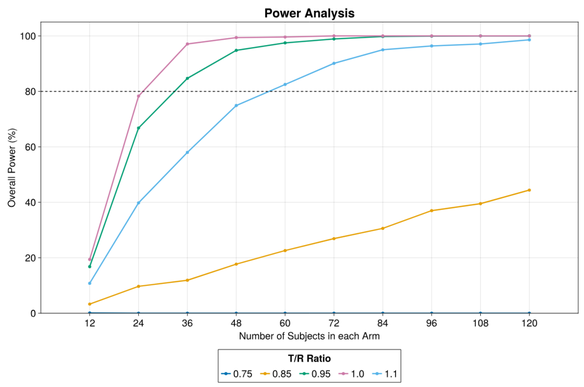
Key observations:

- Power increased as sample size increased
- When the T/R ratio moved further away from 1.0, larger sample sizes were needed to maintain ≥80% power
- These results help identify the minimum sample size required for different T/R ratios.

Table 3: Power for Different Sample Sizes From 1000 Simulations

T/R Ratio	Subjects per arm	AUC power	Cmax power	Overall power
1.1	12	25.5	31.7	10.8
1.1	24	55	61.1	39.8
1.1	36	69.9	77.3	58
1.1	48	83.6	86.7	74.9
1.1	60	87.6	91.8	82.5
1.1	72	93.2	95.8	90.1
1.1	84	96.7	97.5	95
1.1	96	97.5	98.7	96.4
1.1	108	97.8	99.2	97.1
1.1	120	98.7	99.8	98.6

Figure 4: Study Power at Different Sample Size for Different T/R Ratios



Conclusion

- This work shows how MBBE can be implemented in Pumas in a clear, step-by-step way, from building a PK model to estimating BE and power.
- MBBE can:
  - ✓ Reduce the number of physical BE trials required
  - ✓ Improve study planning
  - ✓ Support formulation development and regulatory decisions
- It also allows us to understand uncertainty and variability better than with a single clinical trial.

References

- Bonate, P.L. (2011). "Pharmacokinetic-Pharmacodynamic Modeling and Simulation." Springer.
- Darwich, A.S., et al. (2017). "Why has model-informed precision dosing not yet become common clinical reality?" Clinical Pharmacology & Therapeutics, 101(5), 646-656.
- FDA (2020). "Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA." U.S. Food and Drug Administration.
- Holford, N., & Buclin, T. (2012). "Safe and effective variability-a PK/PD perspective." European Journal of Pharmaceutical Sciences, 45(1-2), 1-6.
- Zhang, F., Jia, R., Gao, H. et al. In Silico Modeling and Simulation to Guide Bioequivalence Testing for Oral Drugs in a Virtual Population. Clin Pharmacokinet 60, 1373–1385 (2021). https://doi.org/10.1007/s40262-021-01045-7
- Predicting the Pharmacokinetics of Orally Administered Drugs across BCS Classes 1–4 by Virtual Bioequivalence Model; Fan Zhang, Xiaofei Wu, Keheng Wu, Mengyang Yu, Bo Liu, and Hongyun Wang; Molecular Pharmaceutics 2023 20 (1), 395-408
- Alotaiq N, Dermawan D. Advancements in Virtual Bioequivalence: A Systematic Review of Computational Methods and Regulatory Perspectives in the Pharmaceutical Industry. Pharmaceutics. 2024 Nov 3;16(11):1414. doi: 10.3390/pharmaceutics16111414. PMID: 39598538; PMCID: PMC11597508.
- Jayachandran P. Advances in quantitative methods and modeling for complex generic drugs and opportunities to hybridize learnings between innovator and generic drug developers. CPT Pharmacometrics Syst Pharmacol. 2023 May;12(5):549-551. doi: 10.1002/psp4.12968. Epub 2023 Apr 27. PMID: 37113050; PMCID: PMC10196422.

Disclosure

Nikita, Vijay, and Pavan are employees of Pumas-AI

Contact

nikita@pumas.ai
vijay@pumas.ai