Model-based bioequivalence methods open new doors for generics

Presenter

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Background

Traditional bioequivalence (**BE**) via Non-Compartmental Analysis (**NCA**) has low power and requires prohibitive sample sizes for several classes of drugs, creating barriers to affordable generics. Model-Based Bioequivalence (**MBBE**) methods can increase the power significantly, while controlling Type I error.

- The objective was to demonstrate the improved power with an MBBE approach compared to standard NCA methodology.

Methods

A 2-way crossover study of a moderately variable oral drug (~50% IIV, ~15% IOV) was simulated 500 times with 24 subjects and 10 samples per subject and analyzed using MBBE and NCA + TOST. Sample size required for 80% statistical power was calculated.

MBBE

Single-model method with Sampling Importance Resampling (**SIR**) uncertainty

NCA

NCA and power via NCAPPC and powerTOST R packages

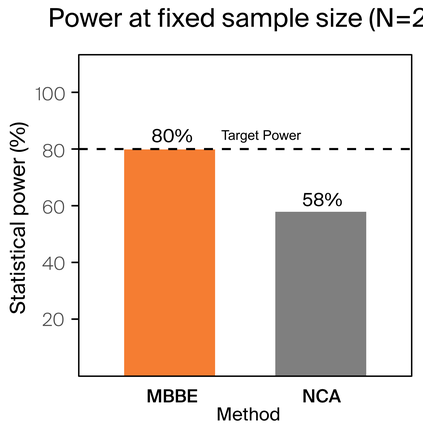
Results

MBBE significantly reduced the required sample size compared to NCA while maintaining target power.

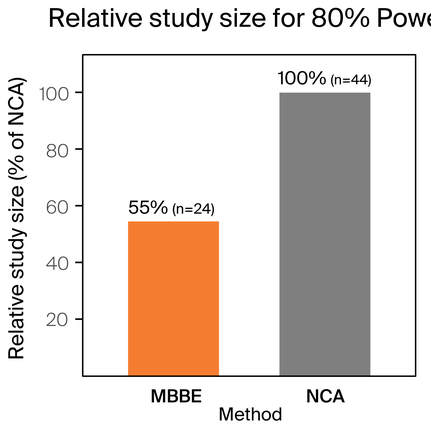
Metric	MBBE	NCA
N for 80% Power	24	44
Power at N=24	80%	58%

In this example, with a crossover design and moderate variability — where NCA is usually applied,

MBBE reduced the required sample size by 45%.

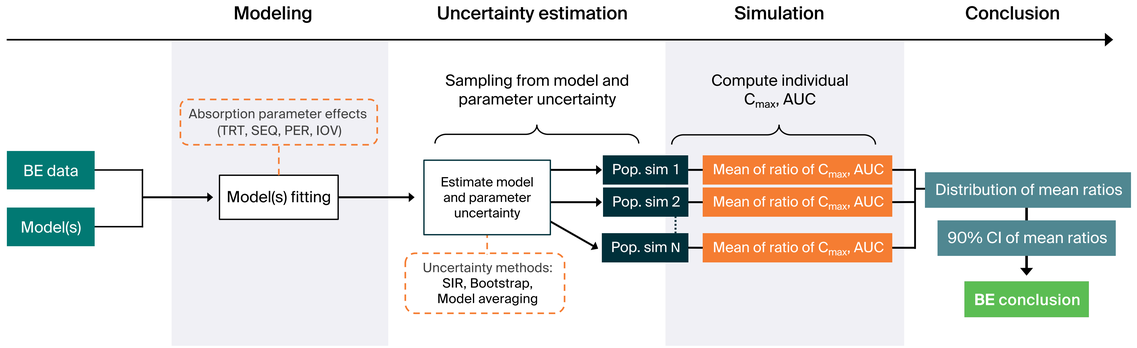


With a fixed sample size of 24 subjects, MBBE achieves the 80% target power, while NCA falls short.



Achieving 80% power with MBBE requires 45% fewer subjects than with NCA, making development programs more economically and ethically feasible.

↳ **Figure 1.** MBBE demonstrates superior statistical power compared to NCA



↳ **Figure 2.** Overview of the MBBE methods

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Extensions

This is a simple oral formulation example with rich sampling. **The impact of MBBE can be much greater in cases that are less well-suited to NCA**, such as,

- parallel designs for generic LAIs
- highly variable drugs
- ophthalmics

MBBE may also enable new concepts, e.g.

- new designs (e.g., switch study for LAI instead of steady-state)
- model-based calculation of BE limits
- alternative metrics to AUC and C_{max}

MBBE can lower barriers and improve efficiency for bioequivalence studies in general. It can make generics development programs for complex products economically viable, which improves pharmacoequity by making treatments more accessible to patients.

Authors

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References available upon request

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