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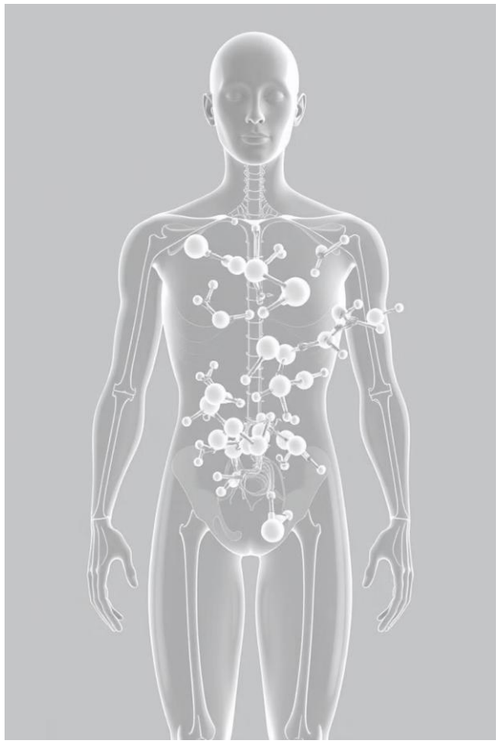


Model Based Bioequivalence (MBBE): Advancing Drug Development

PumasAI

Understanding Bioequivalence (BE)

- Bioequivalence signifies that two drug products, typically a generic (Test) and a brand-name (Reference) drug, exhibit similar rates and extents of drug absorption.

- This critical regulatory benchmark ensures that generic drugs are interchangeable with their reference counterparts without compromising efficacy or safety.

Understanding Bioequivalence (BE)

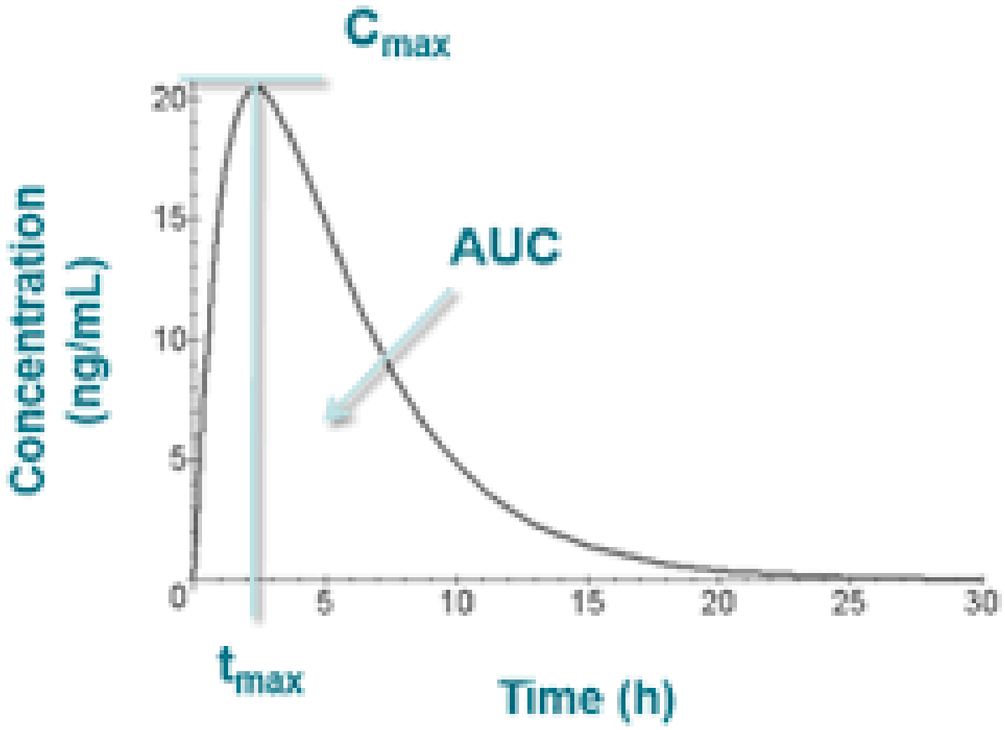
PumasAI

Key Metrics: AUC & Cmax

BE is primarily assessed by comparing the Area Under the Curve (AUC) and maximum plasma concentration (Cmax) of both products. The 90% Confidence Interval (CI) for the ratio of these parameters (Test/Reference) must fall within 80-125%.

Non-Compartmental Analysis (NCA)

Traditional BE evaluations rely on Non-Compartmental Analysis (NCA) of plasma concentration-time data to derive AUC and Cmax. This approach is straightforward but can be limited by data density.



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Challenges in Traditional Bioequivalence Studies

Long-Acting Drugs

- Long term BE Trials
- Parallel study leading to low power

Sparse Sampling & High Variability

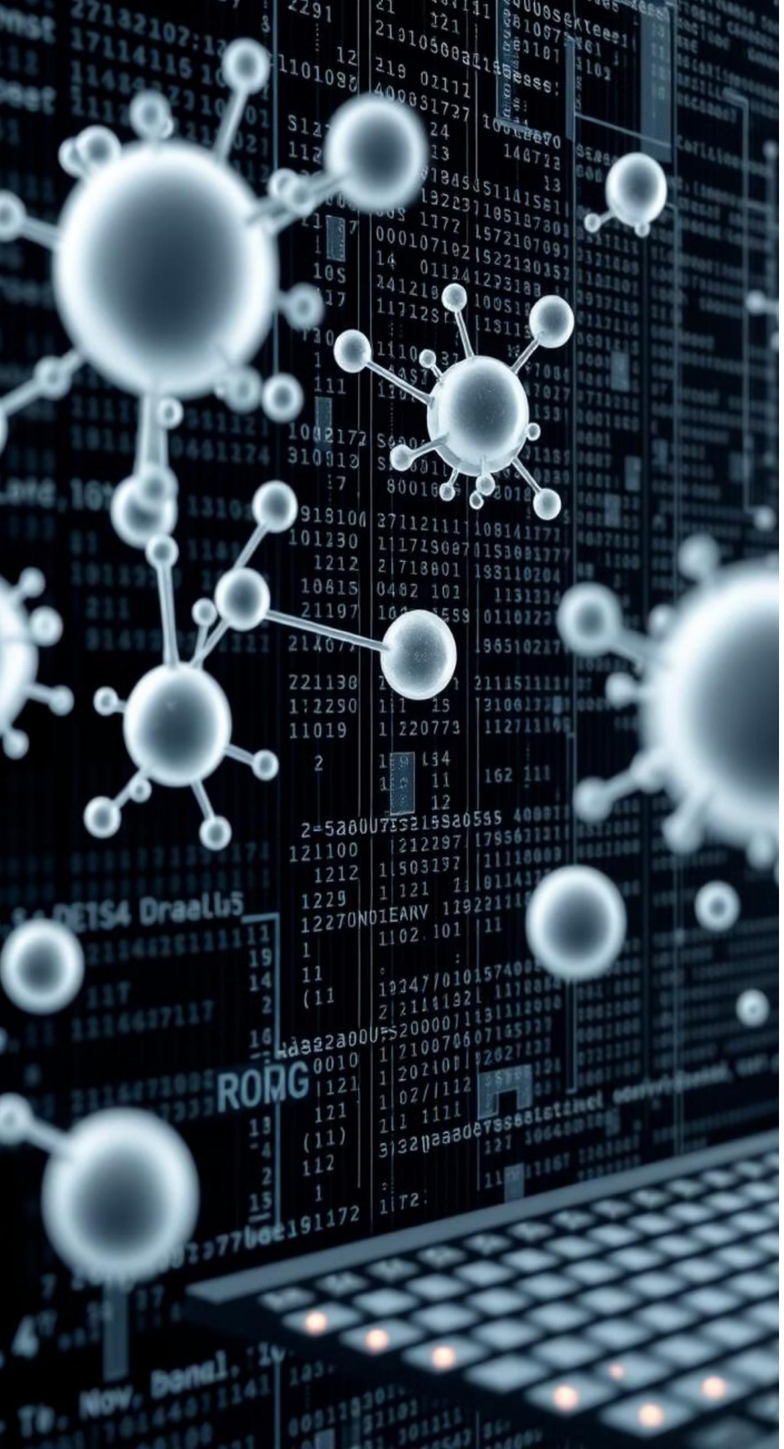
- BE design needs 3- or 4-way crossover study
- Estimation of between occasion variability can be biased/imprecise.

Steady-state BE studies

- Methods for establishing steady state can be inaccurate

Others

- Inefficient designs
- Special formulations, e.g. local drug product needs clinical endpoint BE study.



Introducing Model Based Bioequivalence (MBBE)

Model Based Bioequivalence (MBBE) leverages modeling and simulation to predict drug behavior in virtual patient populations. This methodology offers a powerful alternative to traditional clinical trials by:

- Enabling early prediction of study outcomes and optimization of trial designs.
- Facilitating exploration of scenarios impractical for real-world studies.
- Reducing the dependency on extensive in-vivo studies, saving time and resources.

Population (NLME) Model Based Bioequivalence

- Built to handle sparse data and works well with parallel-group studies

- NCA Problems solved:
  - Assumption about equal weight of all observations
  - Sensitivity to missing data
  - Sensitivity to data below the limit of quantification
  - Interpolation problems from the last observation to ∞
  - Sparse data problems

- Can separate variation of different levels
  - Between subject variation (BSV) on PK parameters
  - Within subject variation (WSV, occasion variation) on PK parameters
  - Residual error on concentration

- Higher power

- Can optimize design (for even higher power)

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Advantages of Model Based Bioequivalence

Pre-Clinical Optimization

Simulate numerous study designs and dosing regimens virtually to optimize trial parameters before committing to expensive in vivo studies.

Complex Drug Behavior

Effectively model and predict BE for drugs with challenging pharmacokinetic profiles, such as those with long half-lives or high inter-individual variability.

Cost & Time Efficiency

Significantly reduce the financial burden and duration associated with traditional BE trials by performing initial assessments in a simulated environment.

Risk Mitigation

Identify potential false positives or false negatives early in the development pipeline, minimizing late-stage failures and regulatory setbacks.

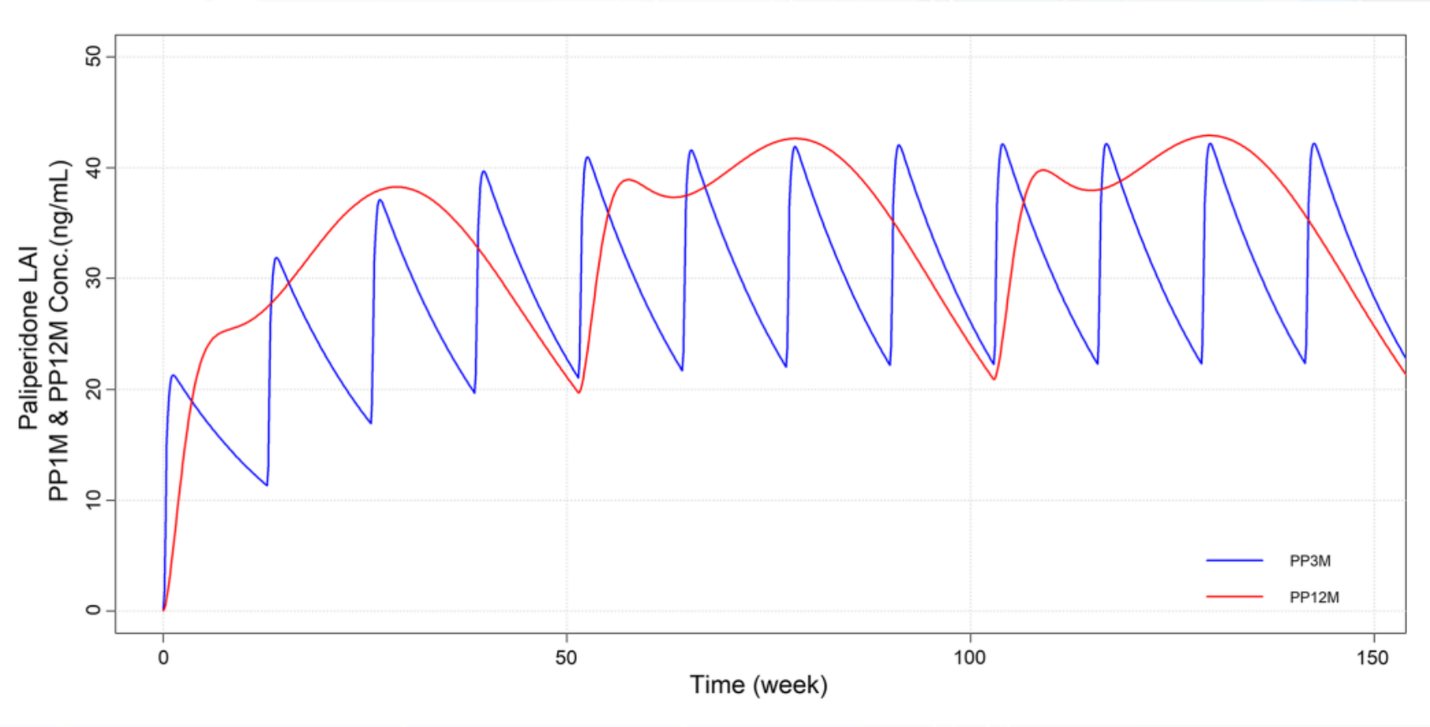
Scenario Analysis

Conduct "what-if" scenarios, such as assessing the impact of interim data on early BE conclusions, to inform adaptive trial designs.

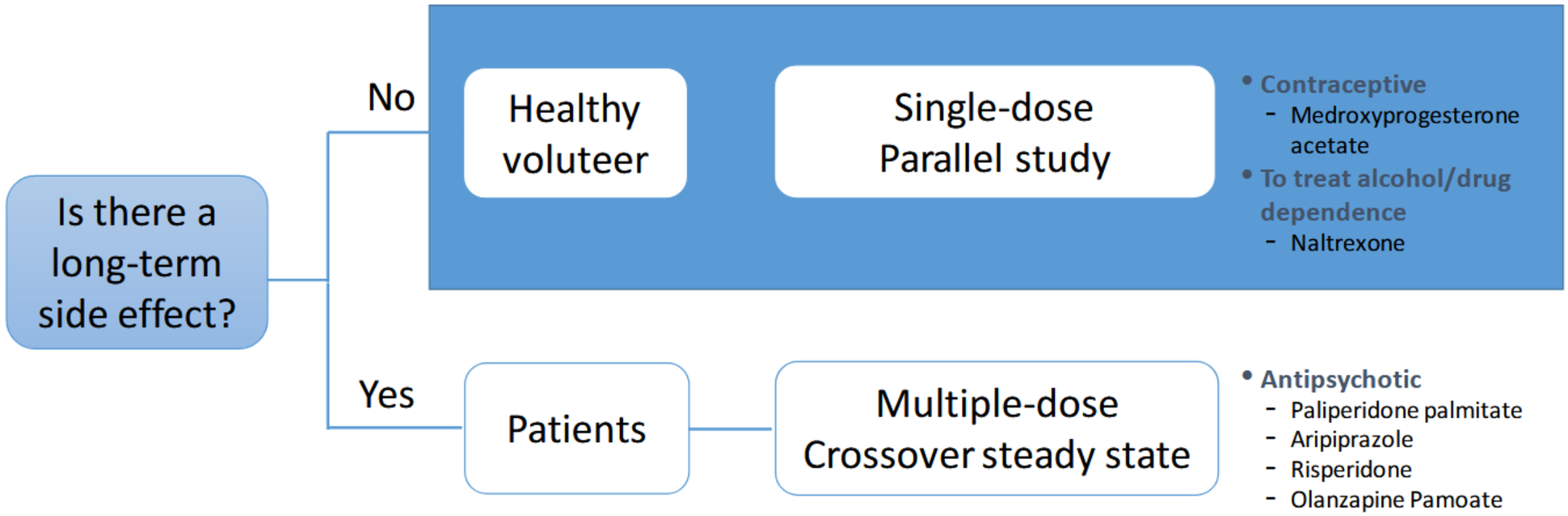
Case Study: Long Half-Life Drugs

Traditional BE studies for drugs with prolonged half-lives typically necessitate parallel designs, which are time-consuming and demand substantial subject enrollment over several months.

MBBE has the potential to accelerate BE conclusions for such drugs. By simulating clinical trials with early, partial pharmacokinetic profiles, we aim to determine if VBE can accurately predict bioequivalence without requiring full study completion. This could significantly reduce development timelines and resource allocation.

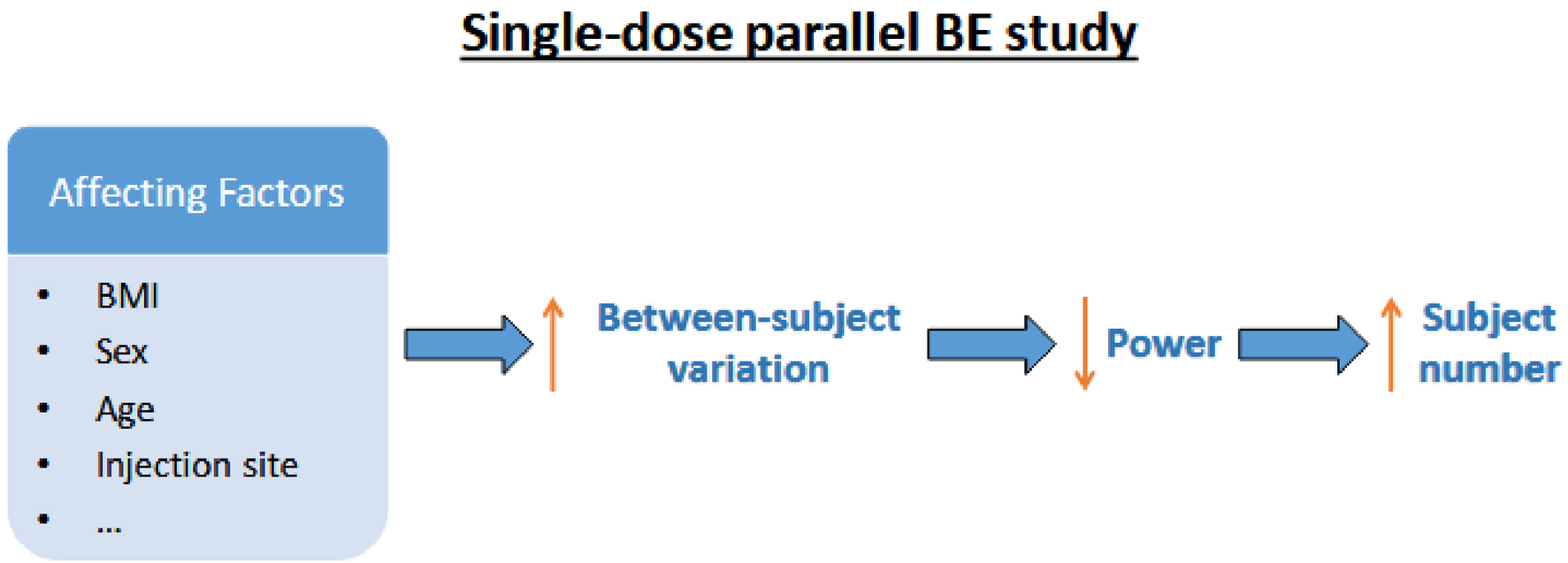


Two types of BE study designs for long-acting injectables (LAI)



https://www.complexgenerics.org/wp-content/uploads/2023/06/S2-1-Andrew_Hooker.pdf

Multiple covariates affects LAI absorption, increasing variation



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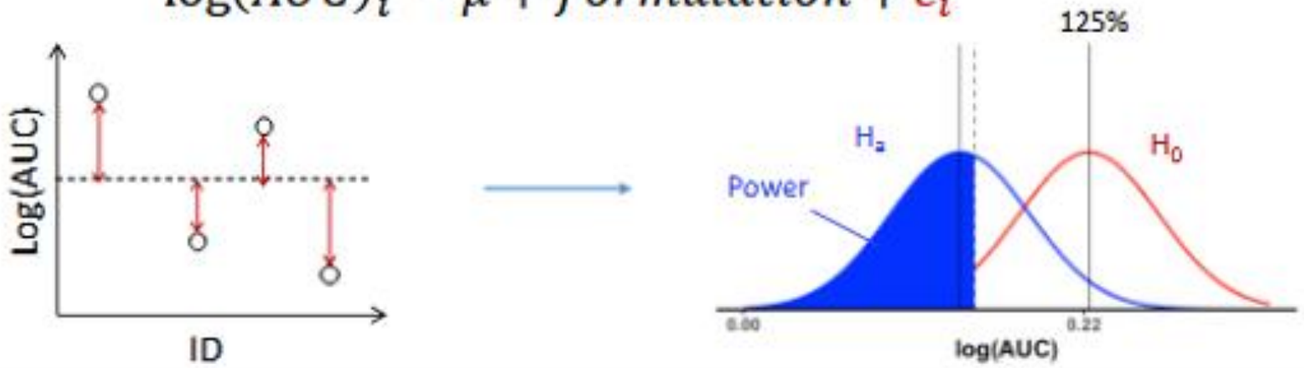
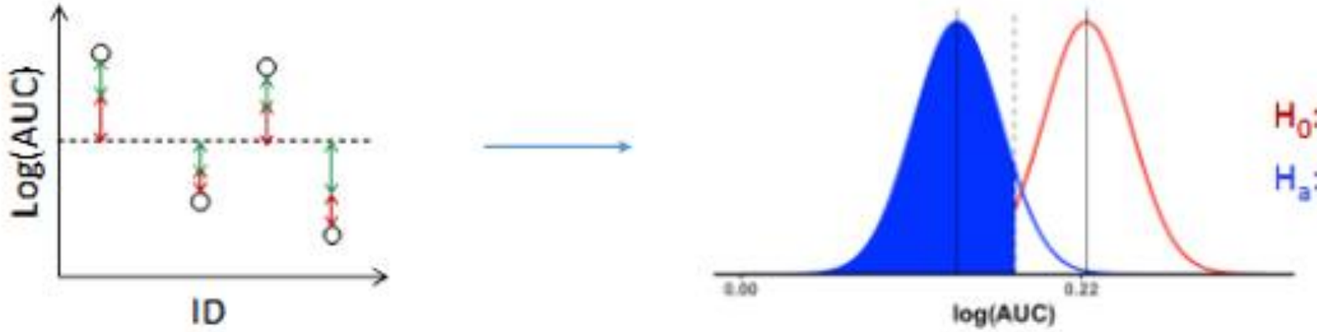
Potential solution to increase power: Adding fixed covariate effects in the analysis

$$\log(AUC)_i = \mu + formulation + \varepsilon_i$$



$$\log(AUC)_i = \mu + formulation + other\ covariates + \varepsilon_i$$

M&S

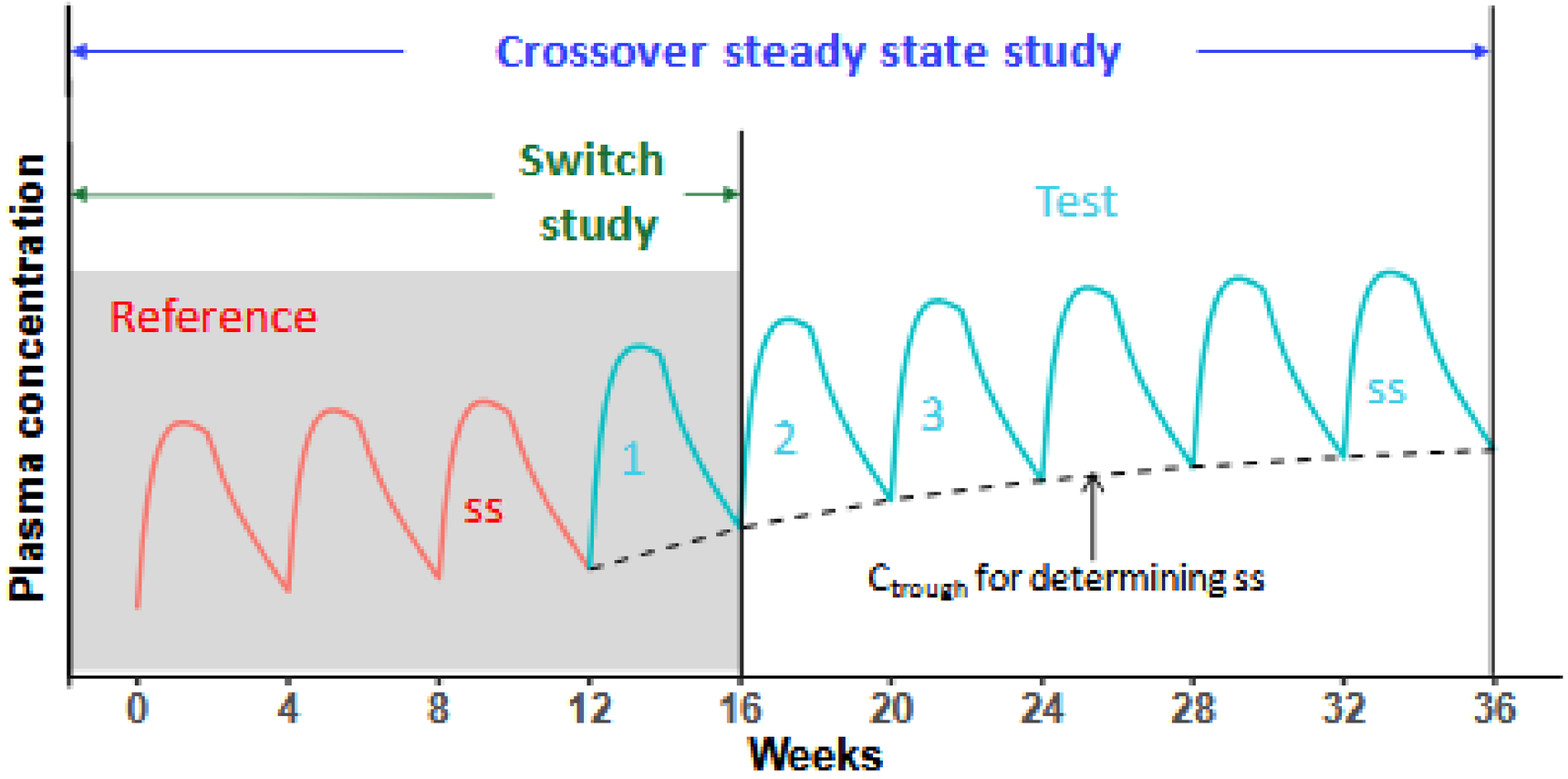


$H_0: \mu_{test} - \mu_0 \geq 0.22$

$H_a: \mu_{test} - \mu_0 < 0.22$

https://www.complexgenerics.org/wp-content/uploads/2023/06/S2-1-Andrew_Hooker.pdf

Possible solution to reduce BE study duration : use switch study instead of requiring steady state



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How Model-Based Bioequivalence (MBBE) Helped: Levothyroxine Case

Key Challenge

- ✓ Endogenous T4 production and long half-life make conventional PK BE noisy
- ✓ Small PK differences raised concerns about clinically meaningful TSH impact

MBBE Contribution

- ✓ Population PK modeling enabled baseline correction of endogenous T4
- ✓ Separated exogenous drug exposure from physiological background hormone levels
- ✓ Reduced variability and improved sensitivity of BE assessment

Clinical Relevance

- ✓ Model-based PK equivalence supported similar systemic T4 exposure

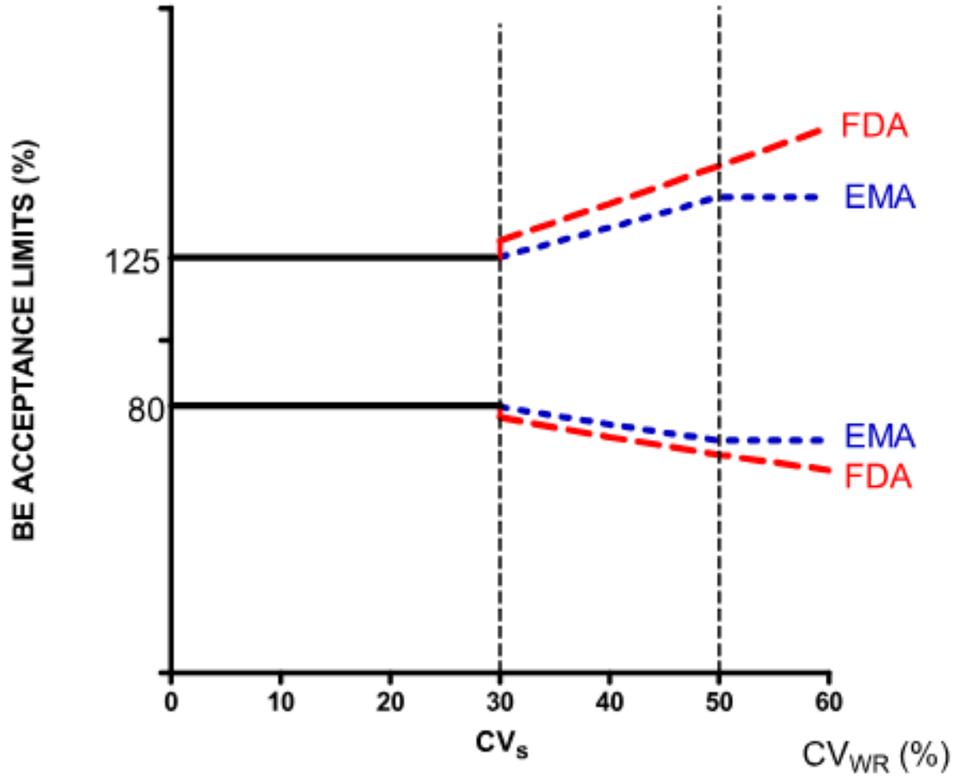
Outcome

- ✓ MBBE strengthened confidence in generic levothyroxine approval
- ✓ Later real-world data (JAMA 2020) showed no meaningful TSH differences, validating the model-based approach

https://pmc.ncbi.nlm.nih.gov/articles/PMC7527873/

BE for highly variable drugs (HVD) using reference- scaled average bioequivalence (RSABE)

RSABE: when within-subject variability (WSV) of the reference product is > 30% CV



Standard RSABE studies

- Study design
  - 4-way study with sequences of (TRTR, RTRT)
  - 3-way study with sequences of (TRR, RTR, RRT)
- Sample size: at least 24 subjects
- Using NCA:
  - Requires rich sampling
  - Extrapolation for AUCt-inf

Model based RSABE

- Shorter studies
- Smaller studies
- Better evaluation of WSV

- AAPS J. 2012 Dec; 14(4): 915–924, BM Davit, et.al Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration
- FDA draft guidance on Progesterone, 2011
- Verbeeck, Musuamba, 2012

BE Criteria for NTI Drugs

Regulatory Agencies	Bioequivalence Criteria	
	AUC	Cmax
Health Canada	90.0% -112.0%	80.0-125.0%
EMA	90.00-111.11%	80.00-125.00% Where Cmax is of particular importance for safety, efficacy or drug level monitoring, the 90.00-111.11% acceptance interval should also be applied to Cmax
South Africa Medicine Control Council	80.0-125.0%	80.0-125.0%
MHLW/PMDA	80.0-125.0%	80.0-125.0%
U.S. FDA	Must pass both the reference scaled limits and the unscaled average bioequivalence limits of 80.00-125.00%. In addition, the upper limit of the 90% confidence interval of the ratio of the within-subject standard deviation of the test to reference product is less than or equal to 2.5.	

W. Jiang. Bioequivalence Approach for Narrow Therapeutic Index (NTI) Drugs. Antiepileptic drug and device trials XIII, May 13-15, 2015

Tighter Assay Limits for NTI Drugs

Drugs	Assumption	Assay Limits
Non-NTI	20% variation in pharmacokinetics (PK) won't lead to clinically relevant difference	90.0-110.0%
NTI	10% or lower variation in PK won't lead to clinically relevant difference	95.0-105.0%

Wenlei Jiang. Pharmaceutical Quality of NTI Drug Products. 2011 Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology, Jul 26, 2011
https://wayback.archiveit.org/7993/20170405230007/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM266777.pdf

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Reference Scaled Average Bioequivalence

The RSABE for both AUC and C_{max} is evaluated as shown below:

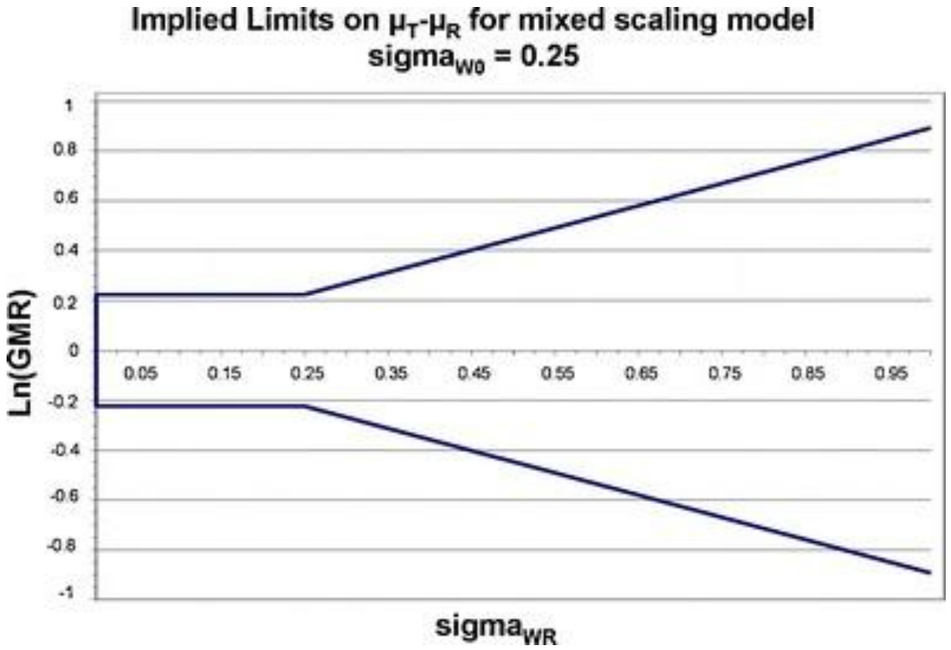
$$\frac{(\mu_T - \mu_R)^2}{\sigma^2_{WR}} \leqslant \theta_S$$

where σ^2_{WR} is the population within-subject variance of the reference formulation, $\theta_S = \frac{(\ln(1.25))^2}{\sigma^2_{W0}}$ is the BE limit, and σ^2_{W0} is a predetermined constant set by the regulatory agency.

Under this model, the implied limits (which represent FDA's desired consumer risk model) on $\mu_T - \mu_R$ are:

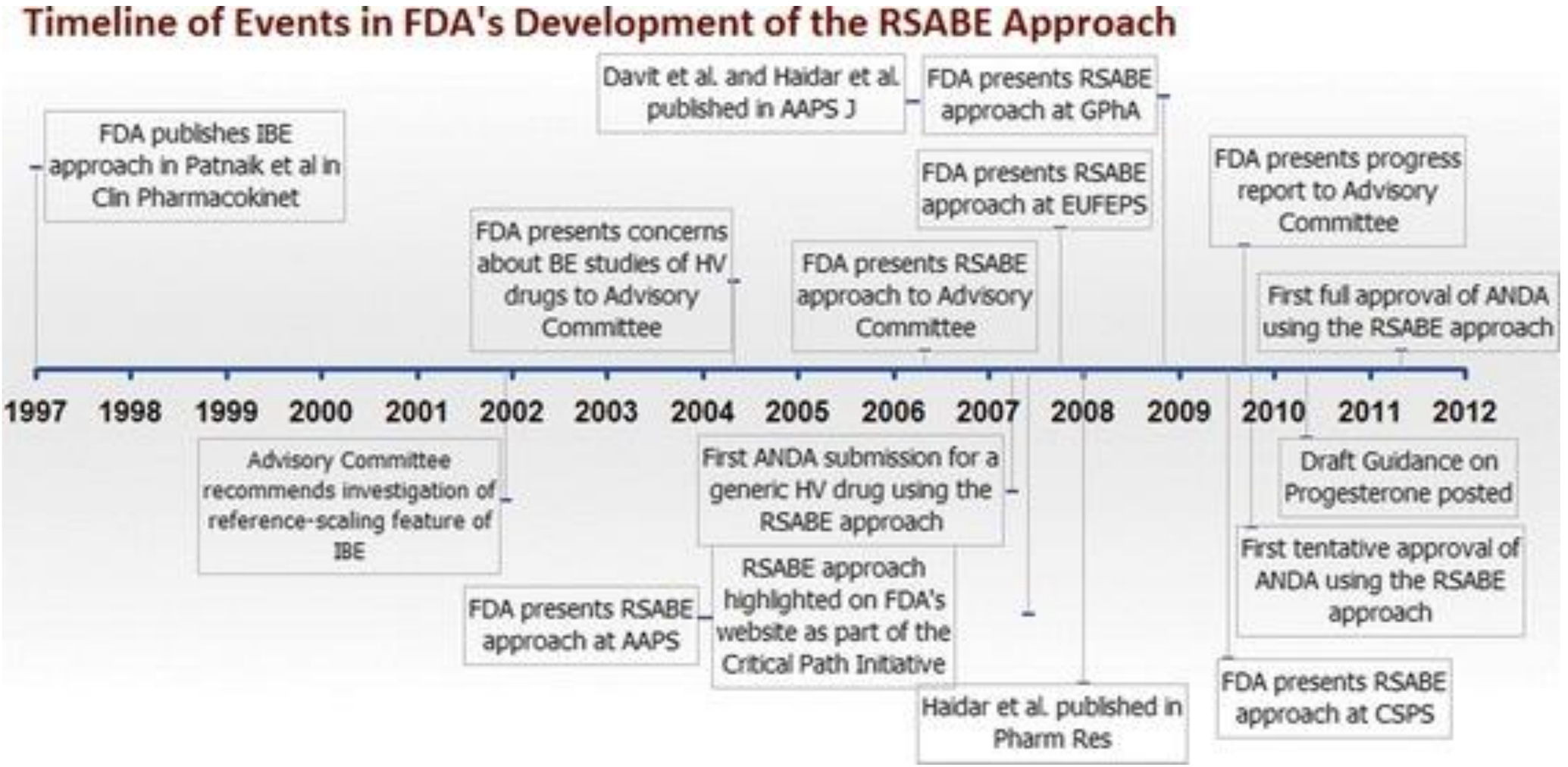
$$-\left[\ln(1.25)\frac{\sigma_{WR}}{\sigma_{W0}}\right] \leqslant \mu_T - \mu_R \leqslant \ln(1.25)\frac{\sigma_{WR}}{\sigma_{W0}}$$

If $\sigma_{WR} = \sigma_{W0}$, the implied limits are equal to the standard unscaled BE limits of ±ln(1.25) (0.80 to 1.25). If $\sigma_{WR} > \sigma_{W0}$, the implied limits are wider than the standard limits. If $\sigma_{WR} < \sigma_{W0}$, the implied limits are narrower than the standard limits.



EMA recommends that BE limits scale with variability only for C_{max} and only up to a maximum within-subject variability value of 50% (where %CV is defined as $100\sqrt{e^{s^2_{WR}} - 1}$), after which they remain constant at the static limits of 69.84% to 143.19%.

https://doi.org/10.1208/s12248-012-9406-x


Timeline of Events in FDA's Development of the RSABE Approach
FDA publishes IBE approach in Patnaik et al in Clin Pharmacokinet
Davit et al. and Haidar et al. published in AAPS J
FDA presents RSABE approach at GPhA
FDA presents RSABE approach at EUFEPS
FDA presents progress report to Advisory Committee
FDA presents concerns about BE studies of HV drugs to Advisory Committee
FDA presents RSABE approach to Advisory Committee
First full approval of ANDA using the RSABE approach
1997
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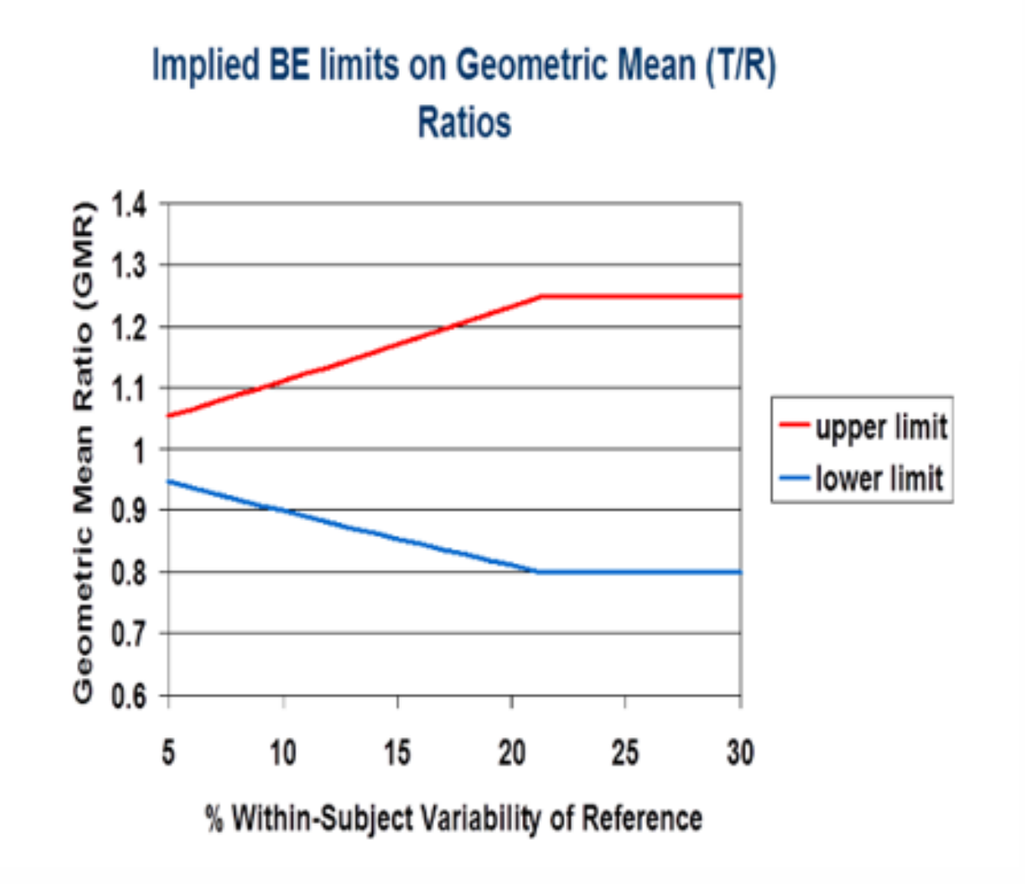
Advisory Committee recommends investigation of reference-scaling feature of IBE
First ANDA submission for a generic HV drug using the RSABE approach
Draft Guidance on Progesterone posted
First tentative approval of ANDA using the RSABE approach
FDA presents RSABE approach at AAPS
RSABE approach highlighted on FDA's website as part of the Critical Path Initiative
Haidar et al. published in Pharm Res
FDA presents RSABE approach at CSPS

BE for NTIs



CV_{WR}	Reference Scaled BE limits
5	94.87 - 105.41
10	90.02 - 111.08
15	85.35 - 117.02
20	81.17 - 123.20
>21.42	80.00 - 125.00

Warfarin Sodium Product Specific Guidance.
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201283.pdf

Paulo's Proposed NTI Guideline

1. sWR is calculated in the same replicate crossover study where the acceptance range is to be narrowed;

2. If the estimated WSCV does not exceed 13.93% (corresponding to sWR ≤ 0.1386), the 90.00–111.11% acceptance range is applied;

3. If the estimated WSCV exceeds 30% (corresponding to sWR ≤ 0.29356), the 80.00–125.00% acceptance range is applied);

4. If the estimated WSCV ranges between 13.93% and 30%, the acceptance range is defined by (U, L) = exp (±k . sWR)

5. The regulatory "proportionality" constant k is set to 0.760, like for HVD products;

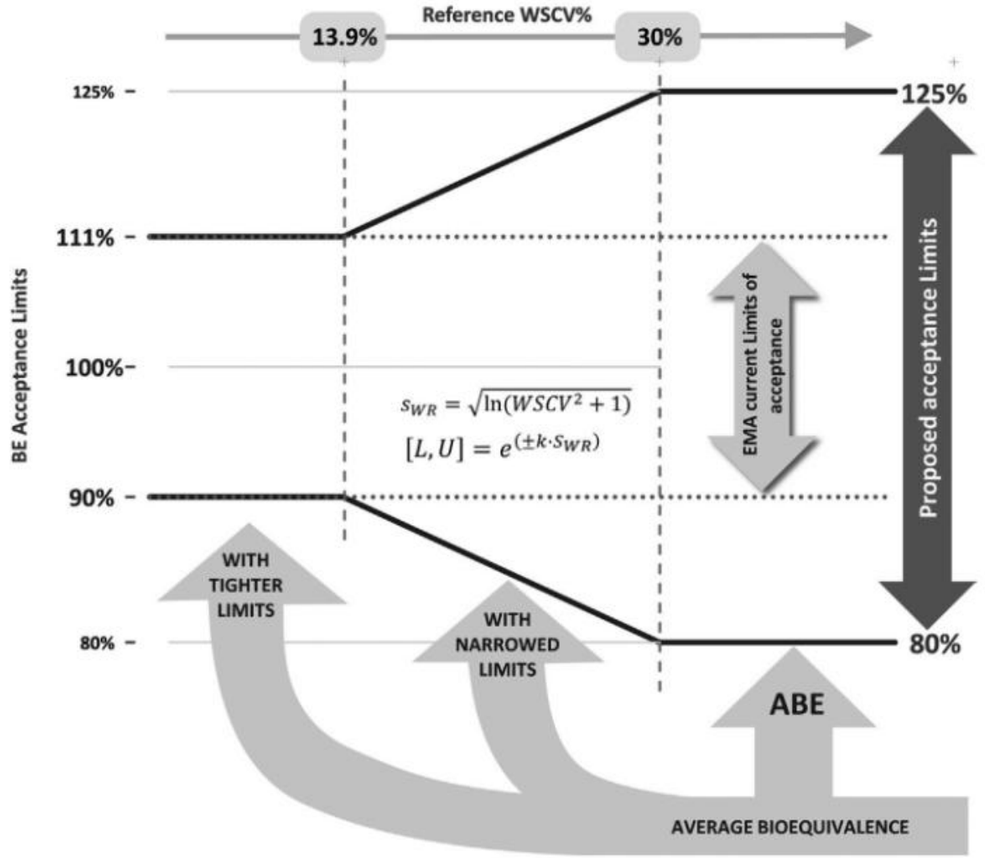


Figure 1 Acceptance limits for the 90% CI of the test-to-reference GMR of NTI drugs according to the WSCV of the reference product. BE, bioequivalence; EMA, European Medicines Agency; GMR, geometric means ratio; NTI, narrow therapeutic index; s_{WR}, within-subject standard deviation of the log-transformed pharmacokinetic parameter of the reference product; WSCV, within-subject coefficient of variation.

The relationship between GMR and $(\mu_T - \mu_R)$ can be expressed by

$$\ln\text{GMR} = \mu_T - \mu_R$$

The alternative hypothesis can be re-written as

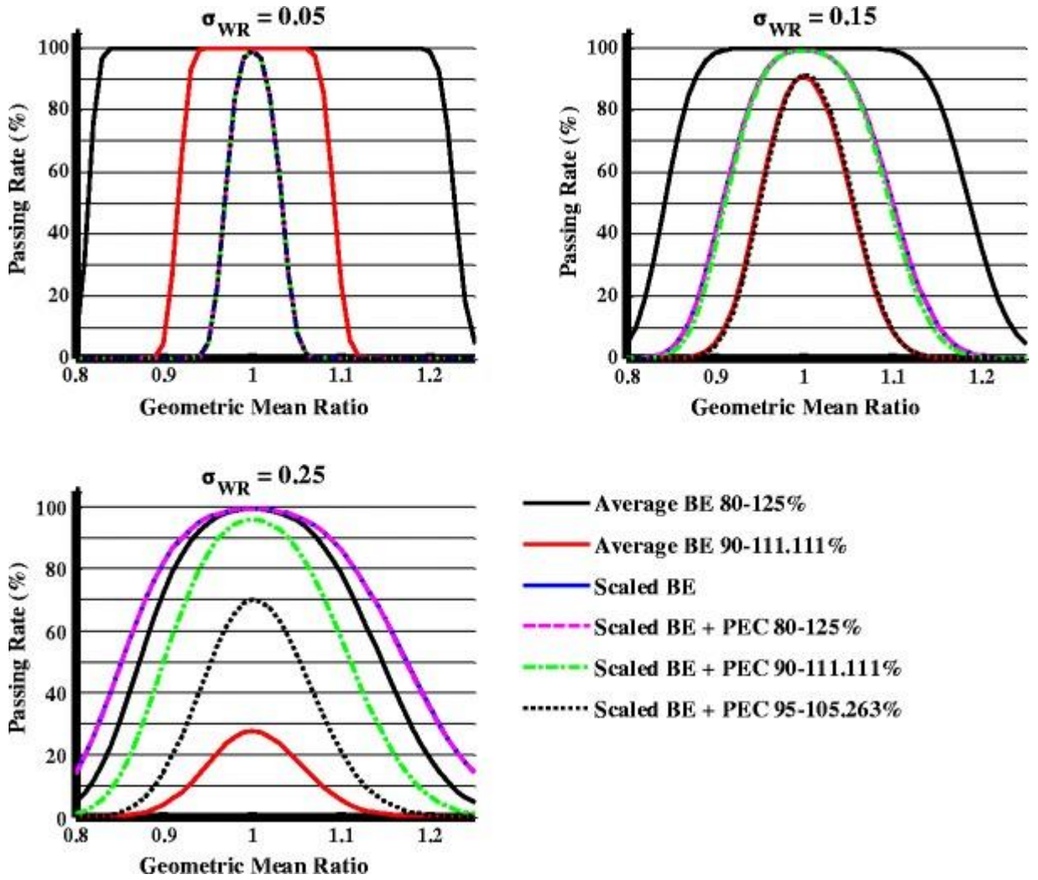
$$H_1 : (\mu_T - \mu_R)^2 - \theta \times \sigma^2_{\text{WR}} \leq 0$$

Furthermore,

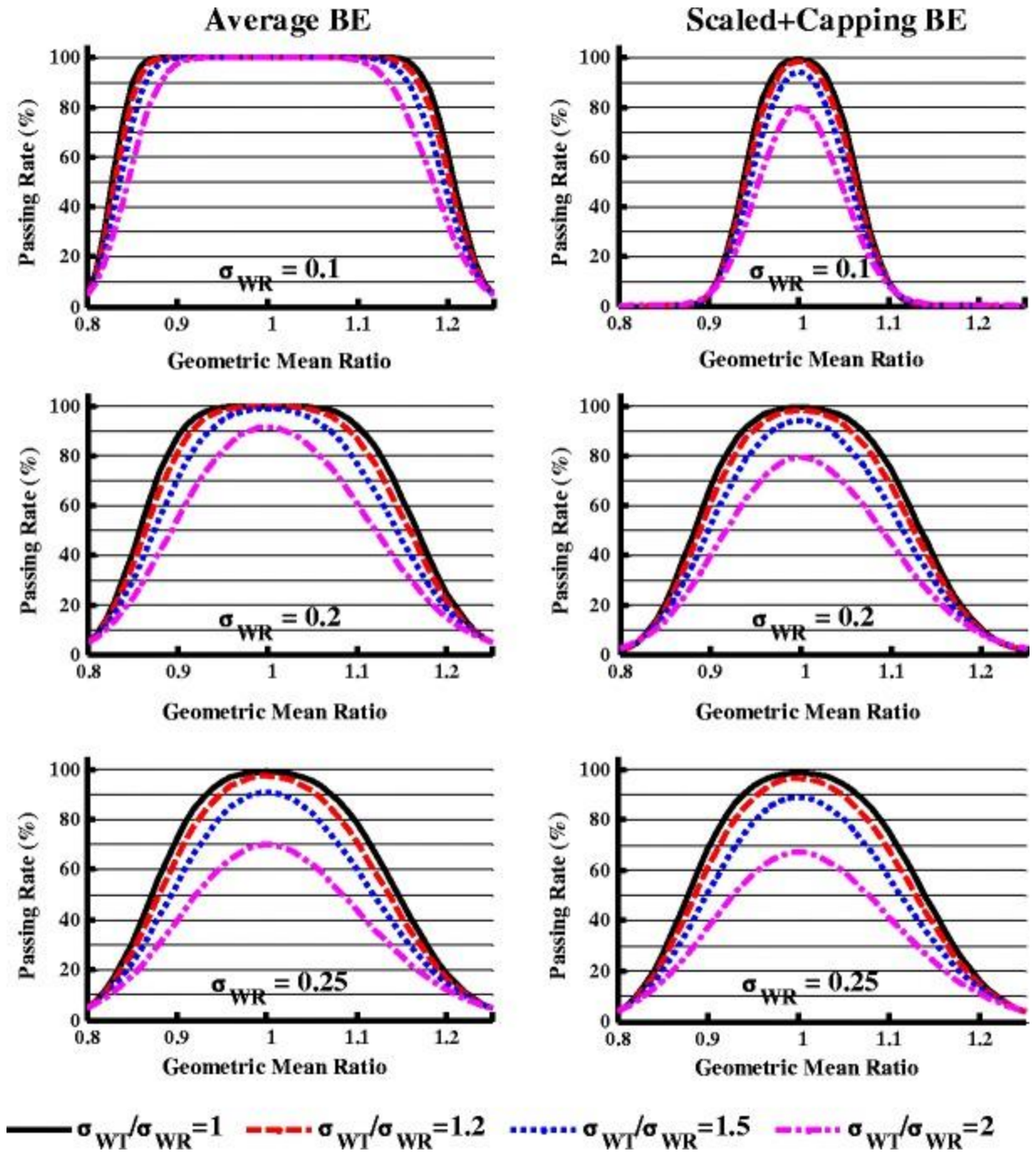
$$\theta = \frac{[\ln(\Delta)]^2}{\sigma^2_{\text{W0}}}$$

where Δ is the upper BE limit for test/reference ratio of geometric means, and σ_{W0} is a regulatory constant.

where μ_T and μ_R are the averages of the natural log-transformed PK measure (such as AUC and Cmax) for the test and reference products, respectively; σ_{WR} is the within-subject standard deviation for the reference product; and θ is the scaled average BE limit ($\theta > 0$).



https://doi.org/10.1208/s12248-015-9753-5



https://doi.org/10.1208/s12248-015-9753-5

Extensive Simulations

To execute this extensive simulation-based validation for pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation.

Virtual Patient Populations

Creation of diverse virtual patient cohorts, reflecting human variability.

Flexible Study Designs

Simulation of varied dosing regimens and blood sampling schedules.

Realistic Data Noise

Incorporation of random noise and outlier data for heightened realism.

Performance Analysis

Analysis of VBE performance across numerous challenging scenarios.