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Bioequivalence Evaluation of Narrow Therapeutic Index Drugs
- Rationales for the Current Regulatory Approach by U.S. FDA

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Disclaimer: The views expressed in this presentation are those of the speaker and not necessarily those of the Food and Drug Administration (FDA).

Narrow Therapeutic Index Drugs

- Narrow therapeutic index (NTI) drugs are drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity.

Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs

LX Yu[1], W Jiang[1], X Zhang[1], R Lionberger[1], F Makhlouf[1], DJ Schuirmann[1], L Muldowney[1], M-L Chen[1], B Davit[1,2], D Conner[1] and J Woodcock[1]

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Novel bioequivalence approach for narrow therapeutic index drugs - PubMed (nih.gov)

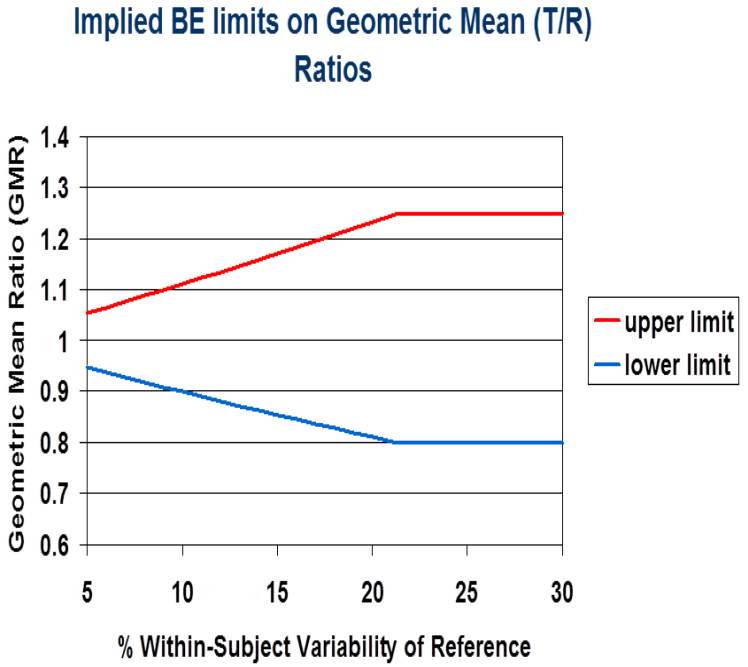
Bioequivalence Study Design and Criteria for NTI Drugs

Regulatory Agencies	Study Design	Bioequivalence (BE) Criteria	
		AUC	Cmax
Health Canada	2-way crossover	90.0% -112.0%	80.0-125.0%
European Medicine Agency (EMA)	2-way crossover	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	2-way crossover	80.0-125.0%	80.0-125.0%
Japan Pharmaceutical and Food Safety Bureau (MHLW/PMDA)	2-way crossover	80.0-125.0%	80.0-125.0%
U.S. FDA	**4-way, fully replicated crossover**	**Reference scaled BE limits**: Must pass both the reference scaled limits and the unscaled average bioequivalence limits of 80.00-125.00%. **Variability comparison**: the upper limit of the 90% confidence interval of the ratio of the within-subject standard deviation of the test to reference standard 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

U.S. FDA Recommended BE study Design and Limits for NTI drugs

- Four-way crossover, fully replicated design
- Test and reference standard given twice
- This design will provide the ability to
  - Scale a criterion to the within-subject variability of the reference standard; and
  - Compare test and reference within-subject variances to confirm that they do not differ significantly.



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

Rationales for the Current U.S. FDA BE Study Design and Criteria for NTI Drugs

Wenlei Jiang[1], Fairouz Makhlouf, Donald J Schuirmann, Xinyuan Zhang, Nan Zheng, Dale Conner, Lawrence X Yu, Robert Lionberger A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion - PMC (nih.gov) 2015 Jul;17(4):891-901. doi: 10.1208/s12248-015-9753-5

Within-subject Variability

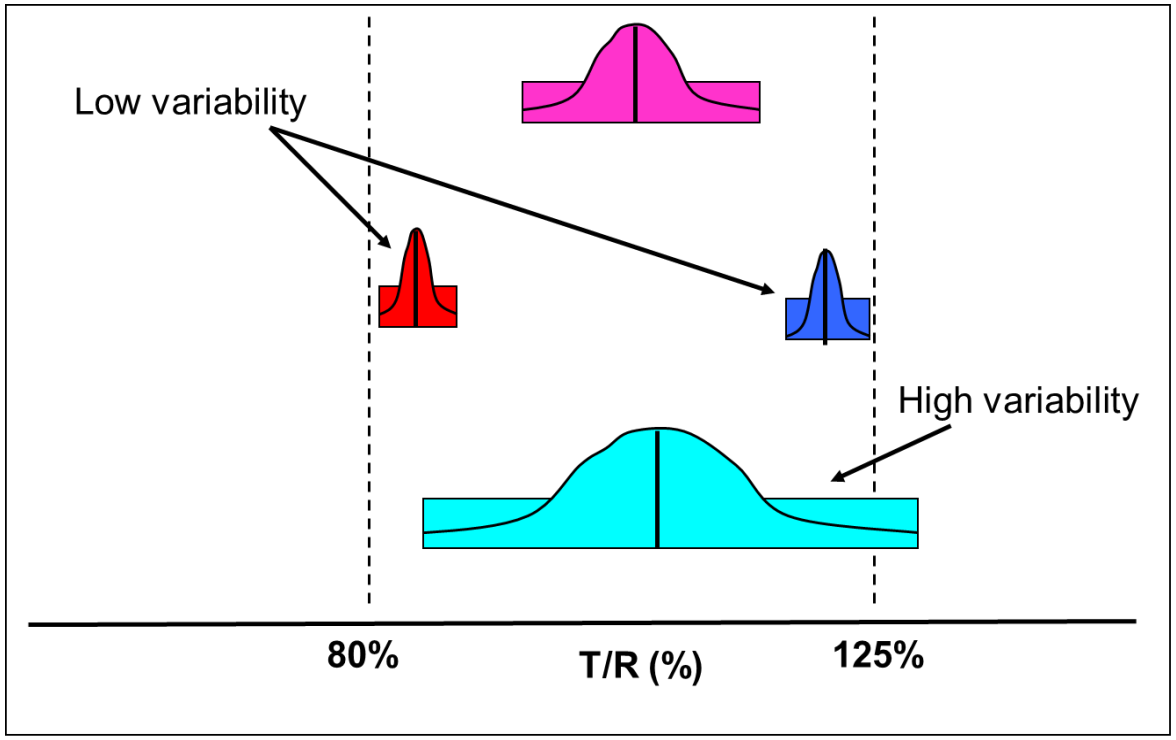
- Within-subject variability (WSV) refers to a measure of variability in a response within the same subject, when the subject is administered two doses of the same formulation on two different occasions.

- WSV is of particular importance for NTI drugs because variations in plasma concentrations may have severe consequences. If an NTI test product has higher WSV than the reference standard, the larger variation in blood concentration may result in higher likelihood of serious therapeutic failures and/or adverse reactions.

- NTI drugs usually have low to medium WSV.

- WSV can be obtained from a fully-replicated two-way crossover study or be estimated via root mean square error (RMSE) values of the bioequivalence parameters C_{max} and AUC_{0-t} from single-dose two-way crossover BE studies

One-Size Bioequivalence Criteria Does Not Fit All Drugs



Drugs	Within-subject variability (WSV)
NTI drugs	≤ 30%
Highly variable drugs (HVDs)	> 30%

4

2010 FDA Advisory Committee for Pharm. Sci. Meeting Concluded

- Average BE limits of 80.00-125.00% are not sufficient for critical dose or NTI drugs
- *The requirements for confidence intervals should perhaps be narrower (90-111%) and should include 100% (or 1.0)*" and "*Replicate studies are important*".

FDA's Simulation Efforts in Alternative BE Approaches for NTI Drugs

- Three- or four-way crossover study design, reference scaled average BE
  - Whether to add Point Estimate Constraints (PEC) in addition to the above (0.80-1.25; 0.90-1.11111, and 0.95-1.05263)
  - Whether to require the 90% confidence interval to contain 1.0
  - Within-subject variabilities (σ_{WR}) tested: 0.05, 0.10, 0.15, 0.20, and 0.25.
  - Geometric mean ratios: 0.80 – 1.25.
  - Regulatory constant, $\sigma_{W0} = 0.25$ or $\sigma_{W0} = 0.10$.
- Two-way crossover study design, regular unscaled average BE, but with tighter limits – 90-111.11% instead of 80-125%
- Sample size tested: 18, 24, 36, and 48.
- Variability comparison

Simulations were carried out in the *S-Plus*, *R*, or *APL* computer programming languages
Each estimated probability based on one million (1,000,000) simulated studies

Scaled Average BE

- Scaled average BE for both AUC and Cmax is evaluated by testing the following null hypothesis:

$$H_0 : \frac{\left(\mu_T - \mu_R\right)^2}{\sigma_{WR}^2} > \theta$$

- (For given $\theta > 0$) in favor of the alternative hypothesis:

$$H_1 : \frac{\left(\mu_T - \mu_R\right)^2}{\sigma_{WR}^2} \leq \theta$$

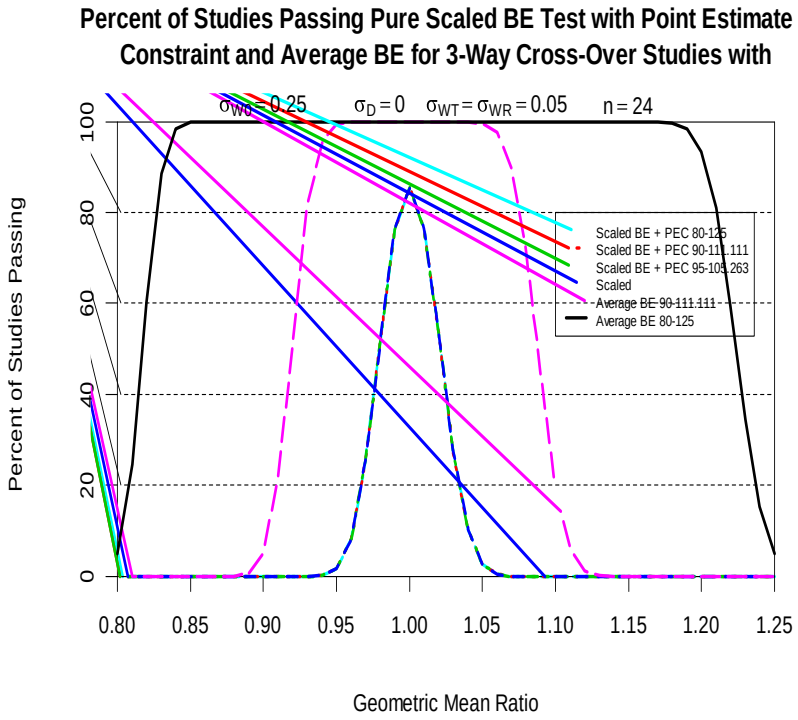
- Where μ_T and μ_R are the averages of the log-transformed measure (AUC and Cmax) for the test and reference standard, respectively; testing is done at α = 0.05, and θ is the scaled average BE limit. Furthermore

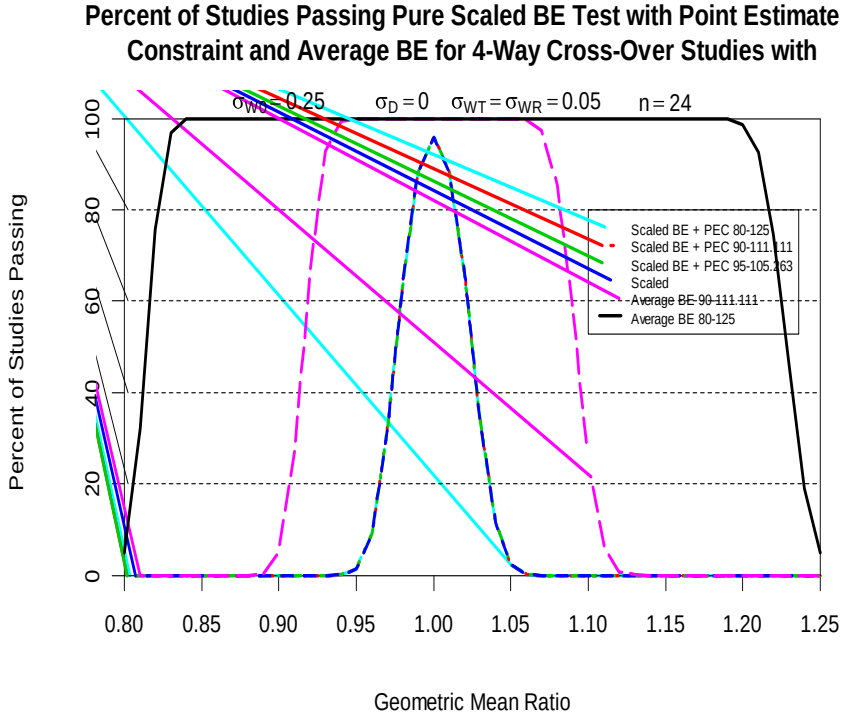
$$\theta = \frac{\left[\ln(\Delta)\right]^2}{\sigma_{W0}^2}$$

- Where Δ is the average BE limit for the untransformed test/reference ratio of the geometric means. The rejection of the null hypothesis supports the conclusion of equivalence.

With Reference Scaled Approach, Why Recommend 4-way Fully-replicated over 3-way Crossover Study?

Case I: $\Delta = 1.25$, $\sigma_{W0} = 0.25$,
$\sigma_{WT} = \sigma_{WR} = 0.05$

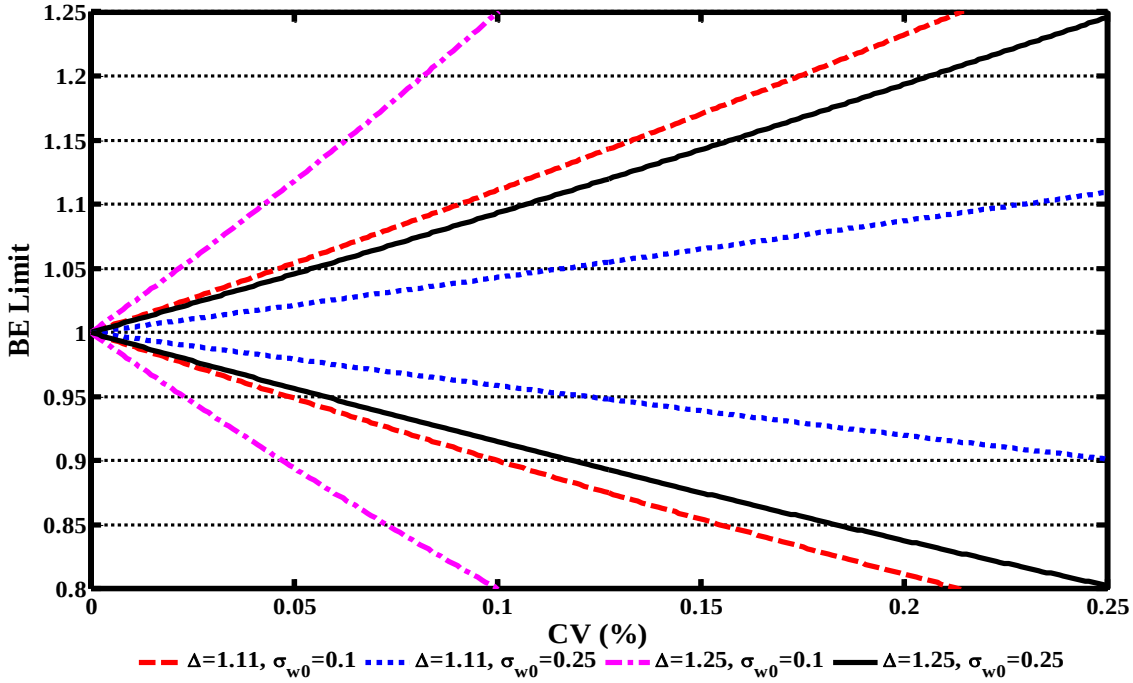




- Higher power obtained in 4-way than 3-way crossover study with scaled approach. In addition, test and reference variability comparison can be performed with 4-way crossover study, not with 3-way crossover study. Thus, 4-way crossover simulations were selected as most appropriate.

Why Select $\Delta = 1.11111$ $\sigma_{W0} = 0.10$ for Reference Scaled BE Approach?

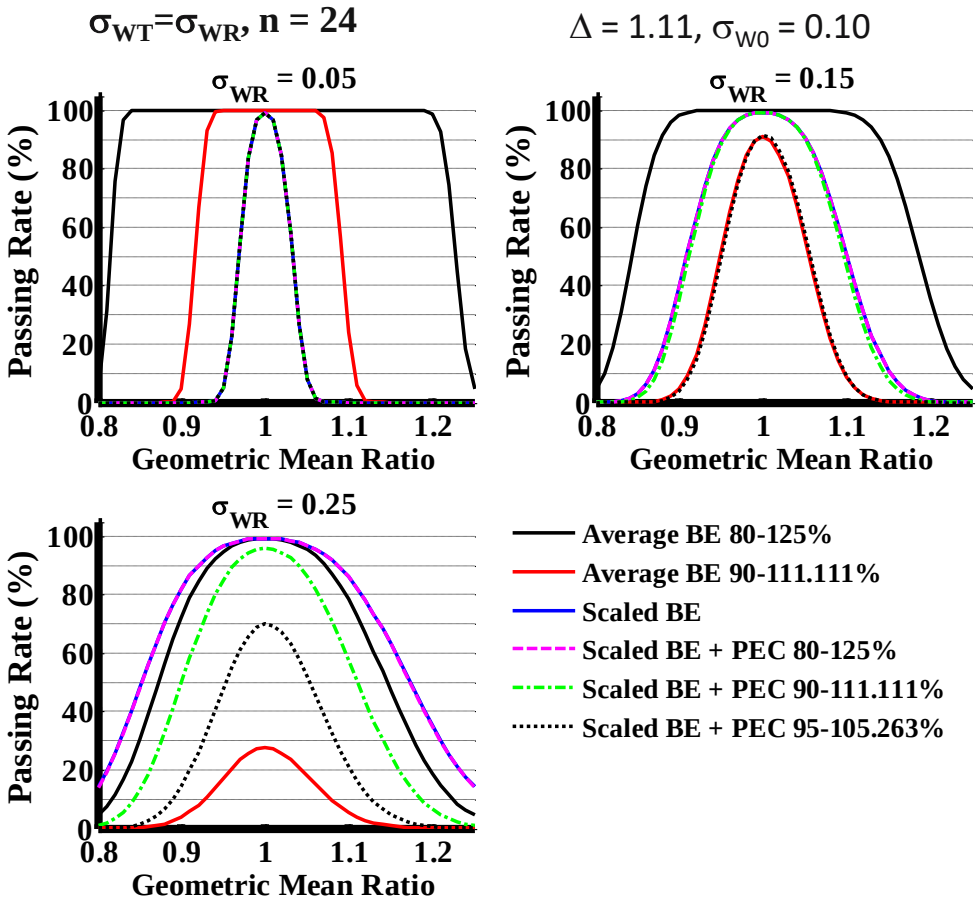
Effect of σ_{W0} and Δ on implied BE limits.



Red: $\Delta = 1.11$, $\sigma_{W0} = 0.10$; Blue: $\Delta = 1.11$, $\sigma_{W0} = 0.25$; Magenta; $\Delta = 1.25$, $\sigma_{W0} = 0.10$; and Black: $\Delta = 1.25$, $\sigma_{W0} = 0.25$. Note: 1.11 = 1/0.9.

- At a given Δ, the implied BE limits at σ_{W0}=0.25 are narrower than those at σ_{W0}=0.10.
- When Δ=1.11 and the CV is within 10%, the implied BE limits are within 90-111% at σ_{W0}=0.10 and are within 95-105% at σ_{W0}=0.25.
- Δ=1.11 and σ_{W0}=0.10 were selected for further analysis because at σ_{W0}=0.10 (i.e., a common value to define small WSV), the implied BE limits coincide with other major health regulatory standards for NTI drugs.

Why not Consider 2-way Crossover Study with Tighter Limits?



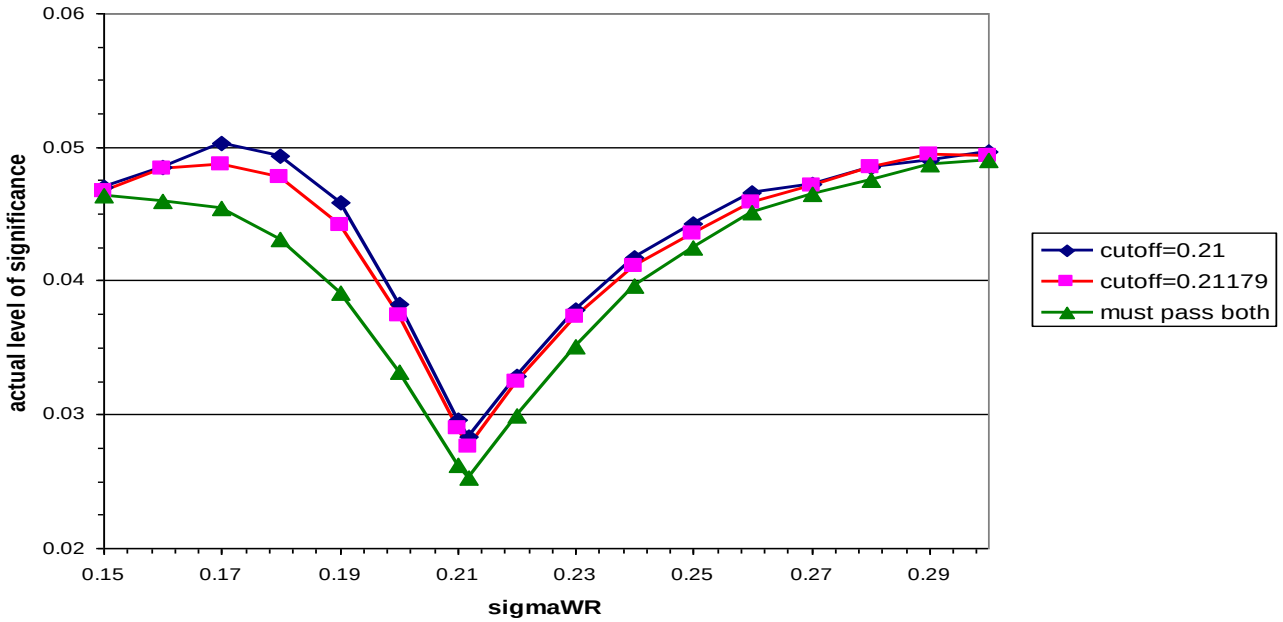
- Unable to perform variability comparison
- Low power of passing (unreasonably stringent) at medium WSV. (e.g., when the RLD is compared to itself or an identical generic product (i.e., GMR=1, σ_{WR}= σ_{WT}), the passing rate with BE limits of 90.00-111.11% is lower than 30% when σ_{WR}= 0.25.

With 4-way crossover study, impact of PEC limits evaluated:
PEC 80-125%
PEC 90-111%
PEC 95-105%

σ_{WT}=σ_{WR}	with refence scaled BE, impact of Point Estimate Constraints (PEC) on the study power
0.05	All evaluated PECs do not affect study power
0.15	PEC 95-105% slightly reduces the study power
0.25	PEC 90-111% and 95-105% reduce the study power; PEC 95-105% too stringent

- Not much value added by the PEC

How to Ensure Reference Scaled BE limits never wider than 80.00-125.00% for NTI Drugs

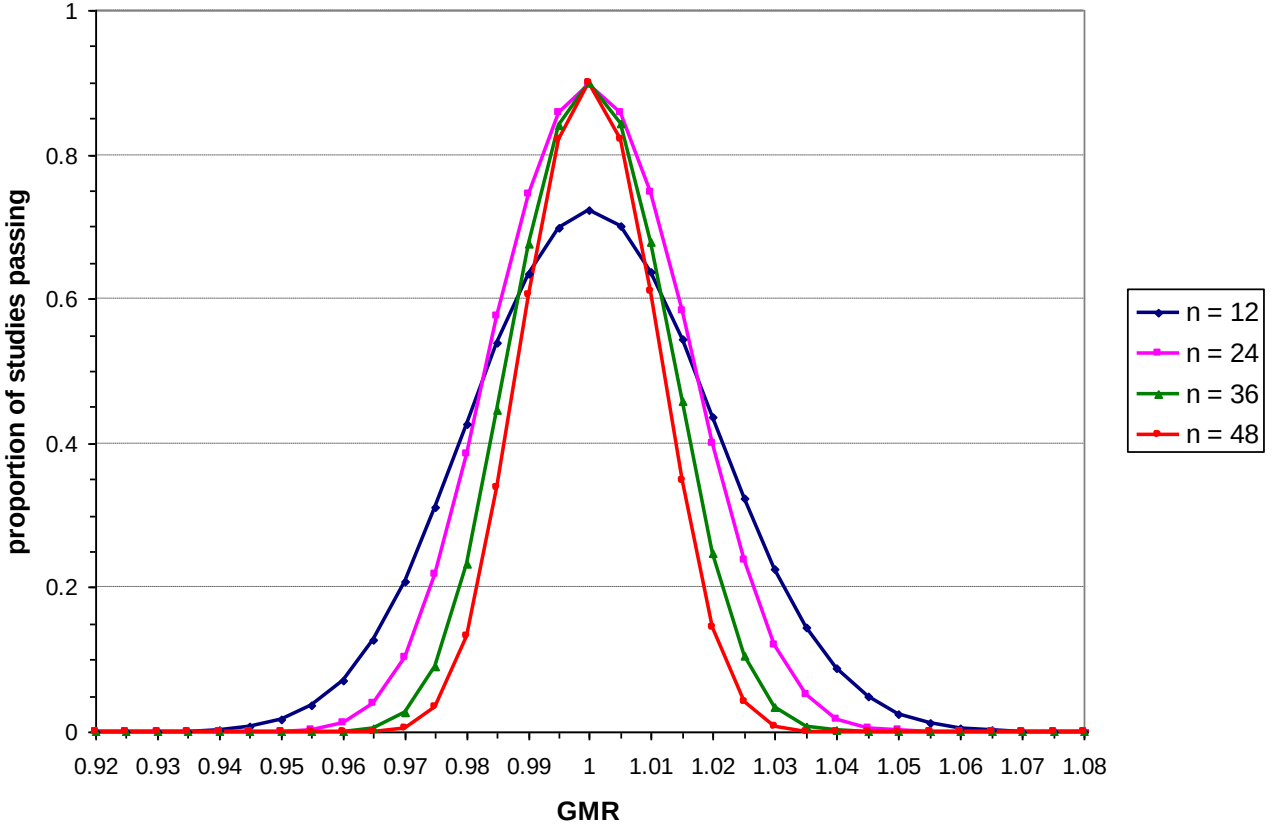


- Establish a cutoff value on s_{WR}, the *estimate* of σ_{WR}, and switch to average BE limits of 80-125% for studies where s_{WR} exceeds the cutoff. For Case 3, a reasonable cutoff would be s_{WR} =0.21179, or possibly 0.21.

- Use "Must Pass Both" – require every study to pass the criteria we propose (e.g., scaled average BE, possibly with or without a PEC) and *also* pass regular unscaled BE with limits of 80-125%.

- Both methods preserve the actual level of significance at no more than 5%.

Why Not Consider Additional Constraints of Containing 1 in the 90% Confidence Interval

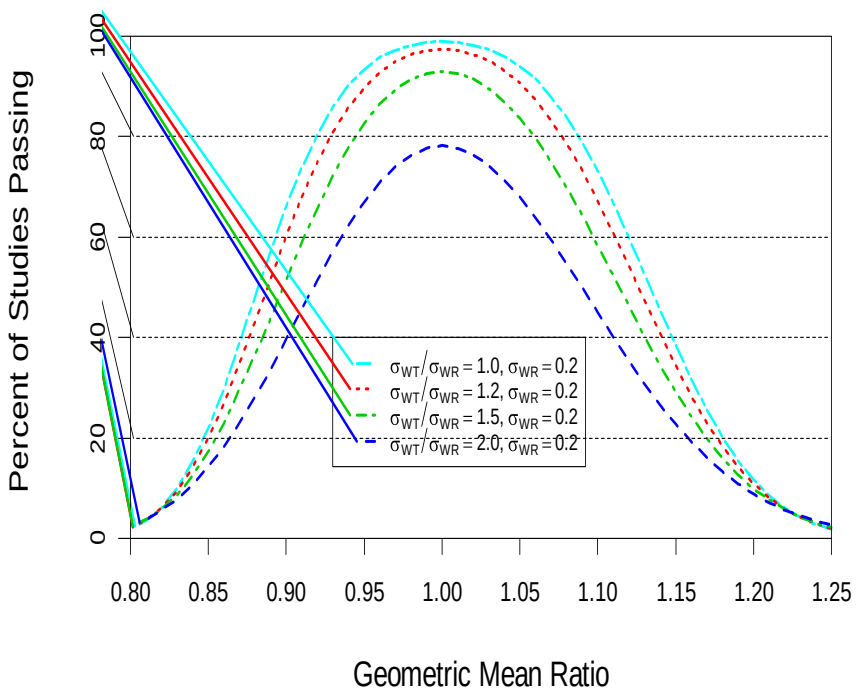


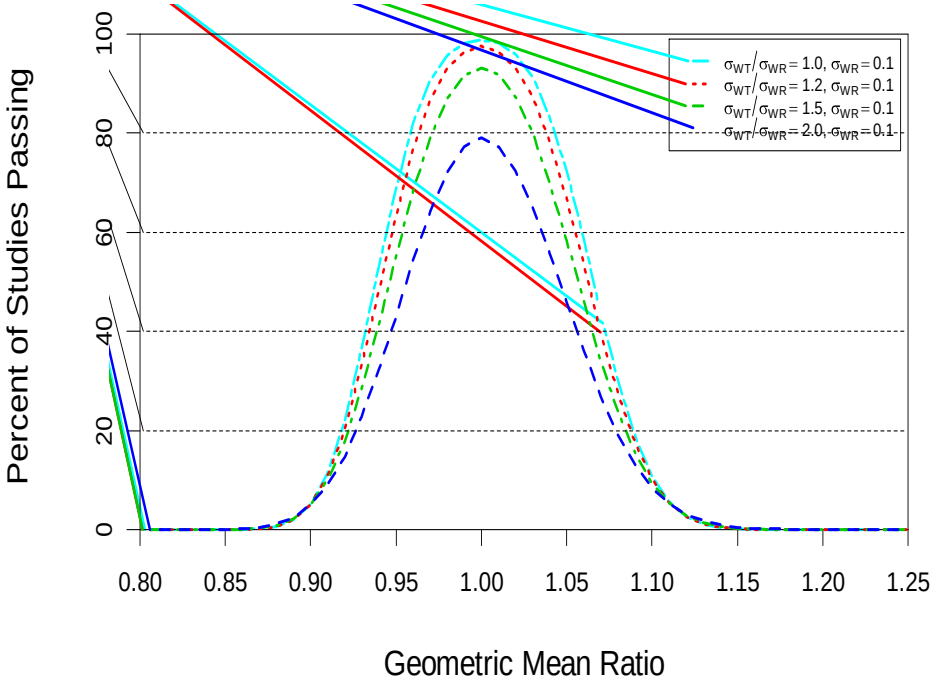
- Even for GMR very close to 1.0 (e.g., 0.98 – closer than required by potency testing), the higher the sample size, the ***lower*** the chance of passing the test.

- Even if the GMR = 1.0, no matter how great the sample size, the chance of passing never exceeds 0.90.

Why Recommend Variability Comparison?

Effect of refence scaled BE approach on the study power under different $\sigma_{WT} / \sigma_{WR}$

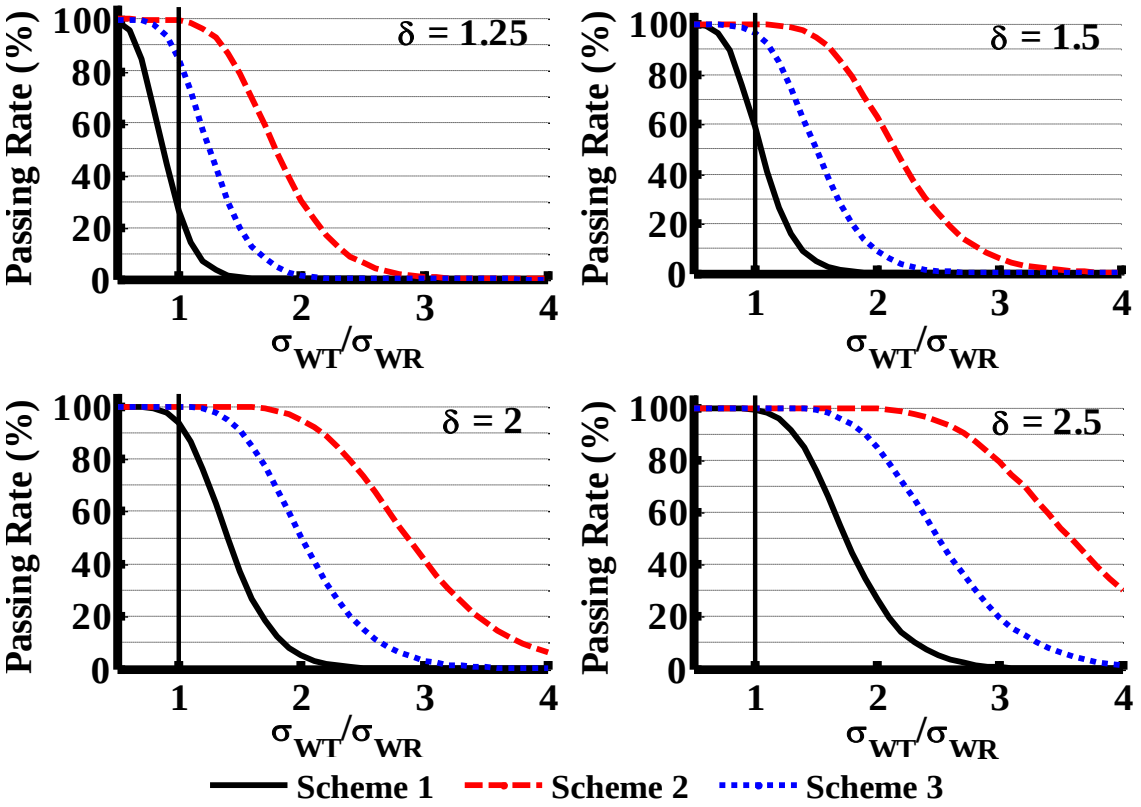




- Reference scaled BE limit alone is insufficient to fail BE studies with large differences (two-fold differences) in reference and test WSV when the GMR is close to 1. Therefore, variability comparison is necessary.
- An *F*-test is often used to test if the variances of two populations are equal.

Why Select Current Variability Comparison Standards?

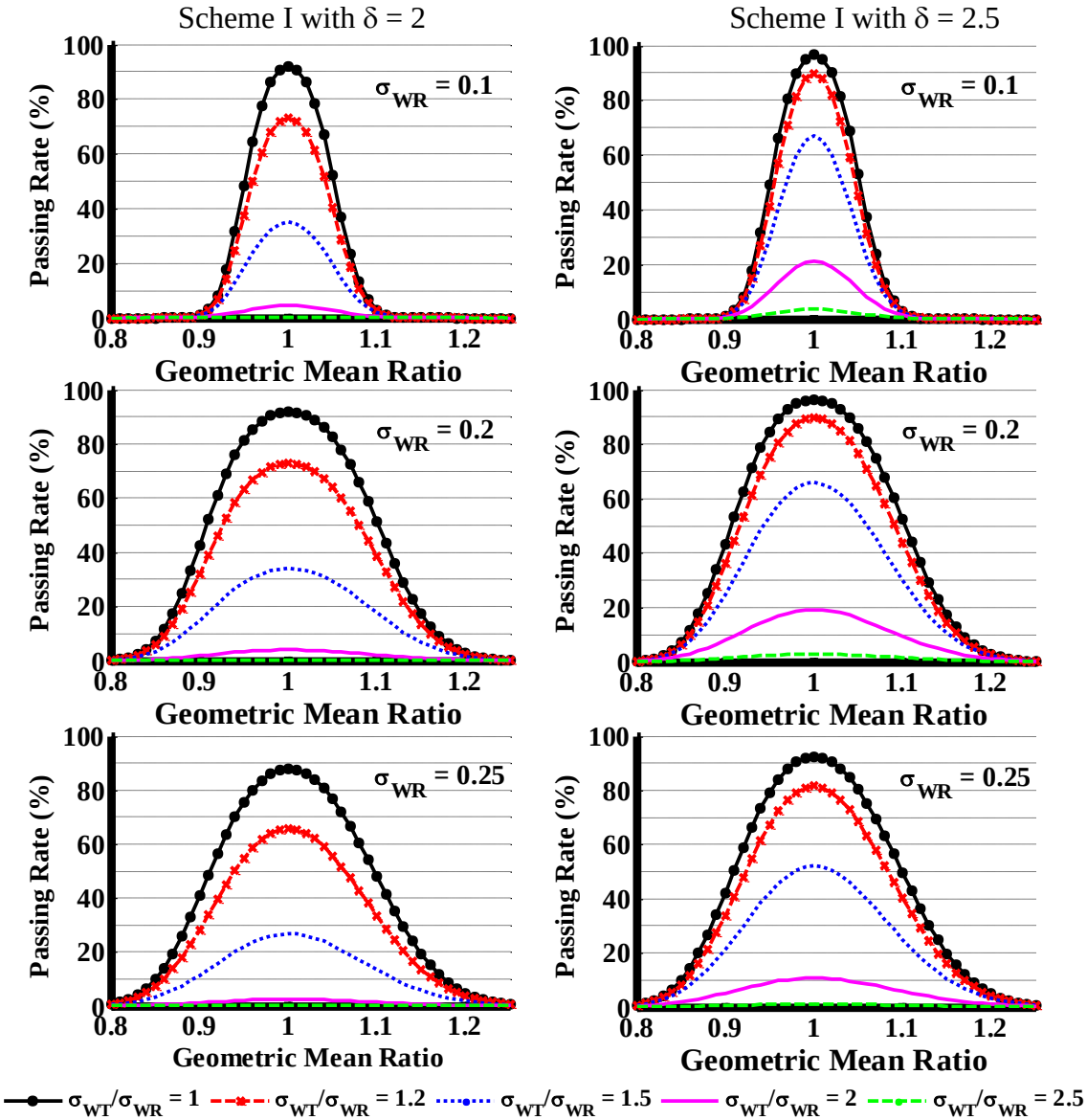
Effect of variability comparison evaluation schemes (1, 2, 3) and the regulatory standard (δ) on the study power (σ_{WR} = 0.1), n = 24.



Scheme Criteria	Evaluation
Scheme 1 (black) : pass if the UPPER limit of the 90% CI for $\sigma_{WT}/\sigma_{WR} \leq d$	Reasonable for further investigation
Scheme 2 (red): pass if the LOWER limit of the 90% CI for $\sigma_{WT}/\sigma_{WR} \leq d$	Give applicants the incentive to increase the chance of passing by under-powering a study
Scheme 3 (blue): pass if the ESTIMATE, s_{WT}/s_{WR}, is $\leq d$	Too relaxed

Why Select Current Variability Comparison Standards?

Effect of within-subject variability difference on the study power when evaluated by combination of Scaled+Capping BE and variability comparison criterion, n = 24.



Scheme I with δ=2.5 selected because

- More than 80% power for similar products (0.95<GMR<1.05 and σ_{WT}/σ_{WR}<1.2)
- Less than 20% power for products with larger than two-fold differences in within-subject standard deviation using 24 subjects

Current U.S. FDA Recommended Bioequivalence Study Design and Criteria

Types of Drugs	Study Design	Sequence	BE criteria	
			Mean comparison	Variability comparison
Non-NTI, Non HVD drugs	Single-dose 2-way crossover	T, R R, T	Yes, CI 80.00-125.00%	No
HVD drugs	Single-dose, partially replicated, 3-way crossover Single-dose, fully replicated 4-way crossover	T, R, R R, R, T T, R, T, R R, T, R, T	Yes, CI scaled, point estimate constraint	No
NTI drugs	Single-dose, fully replicated, 4-way crossover	T, R, T, R R, T, R, T	Yes Must pass both the reference scaled limits and the unscaled average bioequivalence limits of 80.00-125.00%.	Yes The upper limit of the 90% CI of the ratio of the within-subject standard deviation of the test to reference product is less than or equal to 2.5.

2011 FDA Advisory Committee for Pharmaceutical Science Meeting

- The FDA Advisory Committee for Pharm. Sci. supports
  - the FDA's draft definition of NTI drugs (YES: 11 NO: 0 ABSTAIN: 2)
  - the two-treatment, four-period, fully replicated crossover design (YES: 12 NO: 1 ABSTAIN: 0)
  - the reference-scaled average bioequivalence approach (YES: 12 NO: 0 ABSTAIN: 1)
  - tighten the assayed potency standard for NTI drugs to 95.0 – 105.0% (YES: 13 NO: 0 ABSTAIN: 0)

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Warfarin_Sodium_tab_09218_RC12-12.pdf

2012 Draft Guidance on Warfarin Sodium

Contains Nonbinding Recommendations

Draft Guidance on Warfarin Sodium

Active ingredient: Warfarin Sodium
Form/Route: Tablet/Oral
Recommended studies: 2 studies

1. Type of study: Fasting
Design: 4-way, fully replicated crossover design *in-vivo*
Strength: 10 mg

2. Type of study: Fasting
Design: 4-way, fully replicated crossover design *in-vivo*
Strength: 10 mg

Explanation: FDA has concluded that Warfarin sodium is a narrow therapeutic index (NTI) drug based on the following evidence:

- For warfarin there is a narrow range between therapeutic and toxic doses or the associated blood or plasma concentrations (i.e., exposures);
- Warfarin toxicities are serious and not symptomatic or reversible;
- Subtherapeutic warfarin concentrations may lead to serious and life-threatening complications;
- Warfarin is subject to therapeutic monitoring based on pharmacodynamic markers; and
- Warfarin has low within subject variability.

The study should be a fully replicated crossover design in order to

- Scale bioequivalence limits to the variability of the reference product; and
- Compare test and reference product within-subject variability.

Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for narrow therapeutic index drugs (SAS code provided in the guidance)

Summary

- FDA recommends four-way crossover, fully replicated design for BE study of NTI drugs. This design will provide the ability to
  - Scale the BE limit based on the WSV of the reference standard.
  - Compare test and reference WSV to confirm that they do not differ significantly.

- Current reference scaled BE limits

  - At low reference variability (e.g., <0.10), the reference scaled BE limit is more stringent than Health Canada's 90.0-112.0% average BE limits.

  - When the reference variability is equal or greater than 0.21, the BE limit is capped at 80.00-125.00 %.

  However, reference scaled BE limits alone are insufficient to fail test and reference standard with large differences in WSV. WSV is of particular importance for NTI drugs because higher variations of the test than the reference in plasma concentrations may have severe consequences. Therefore, variability comparison between reference and test is necessary.

- Current variability comparison standards

  - Fail products with differences in variability while also not significantly reducing power of studies where the test and reference variability are similar.

Acknowledgement

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U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Questions?

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General Characteristics

Little separation between therapeutic and toxic doses (or associated blood/plasma concentrations)

Sub-therapeutic concentration may lead to serious therapeutic failure

Drugs are subject to therapeutic drug monitoring (TDM) based on pharmacokinetic (PK) or pharmacodynamic (PD) measures

Drugs possess low-to-moderate (i.e., no more than 30%) within-subject variability

In clinical practice, doses are often adjusted in very small increments (less than 20%)

LX Yu, W Jiang, X Zhang, R Lionberger, F Makhlouf, DJ Schuirmann, L Muldowney, M-L Chen, B Davit, D Conner and J Woodcock. Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs. Clinical Pharmacology & Therapeutics 2015