A PROPOSED SCALING APPROACH FOR BE OF NTI DRUGS IN THE EU WITHOUT ALPHA INFLATION

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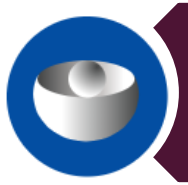
DISCLAIMER

The views expressed in this presentation are those of the speaker and are not necessarily those of INFARMED or EMA

NARROW THERAPEUTIC DRUGS

- Drugs with a narrow therapeutic index (NTI) are those where a small difference in the administered dose may result in either serious therapeutic failures or the appearance of adverse drug reactions.
- There has been an extensive debate, especially at the regulatory level, on defining NTI (and Critical Dose Drugs) criteria.
- It has been proposed that low-to-moderate within-subject variability (not more than 30%) being one of those criteria.
- However, in the EU, decision is made case-by-case based on clinical considerations.

REGULATORY NTI LISTS



acenocoumarol, ciclosporin, colchicine, everolimus, levothyroxine, sirolimus and tacrolimus.

cyclosporine, digoxin, flecainide, lithium, phenytoin, sirolimus, tacrolimus, theophylline and warfarin

carbamazepine, cyclosporin, Digoxin, Divalproex, levothyroxyine, Liothyronine, Lithium, phenytoin, sirolimus, tacrolimus, theophylline, Warfarin and Valproic acid

Aprindine, Carbamazepine, Clindamycin, Clonazepam, Clonidine, Cyclosporine, Digitoxin, Digoxin, Disopyramide, EthinylEstradiol, Ethosuximide, Guanethidine, Isoprenaline, Lithium, Methotrexate, Phenobarbital, Phenytoin, Prazosin, Primidone, Procainamide, Quinidine, Sulfonylurea antidiabetic drugs compounds, Tacrolimus, Theophylline compounds, ValproicAcid, Warfarin, Zonisamide, Glybuzole

APPROACH 1

BE study based on a 2-way crossover study

90% CI for the T/R ratio should fall within the acceptance range of 80.00 – 125.00%

Examples

- Argentina
- Brasil (until 2022)
- Republic of Korea
- Taiwan
- …

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doi: 10.3389/jpps.2024.12398

APPROACH II

BE study based on a 2-way crossover study

90% CI for the T/R ratio should fall within the acceptance range of 80.00 – 125.00% and PE within 90.00 – 111.11%

Examples

- Japan

European Journal of Pharmaceutical Sciences 190 (2023) 106566

APPROACH III

BE study based on a 2-way crossover study

90% CI for the T/R ratio of AUC (sometimes Cmax) should fall within the acceptance range of 90.00 – 111.11% (112.00% HC)

Examples

- Europe
- Brasil (after 2022)
- Canada
- Australia
- Singapore
- …

J. Pharm. Pharm. Sci 27:12398.
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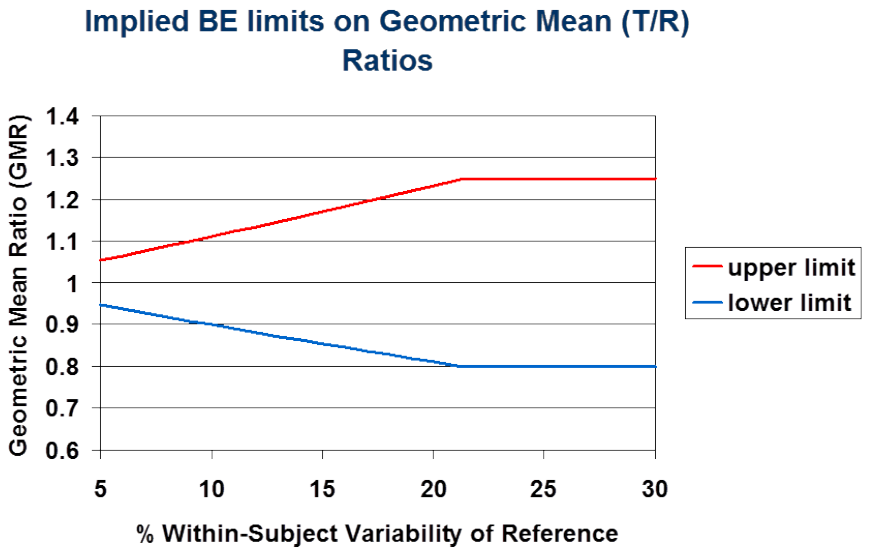
APPROACH IV

- Four-way crossover, fully replicated design
- This design allows to:
  - Scale a criterion to the within-subject variability of the reference standard
  - Compare test and reference within-subject variances to confirm that they do not differ significantly



Examples

- FDA

Clin Pharmacol Ther. 2015 Mar;97(3):286-91. doi: 10.1002/cpt.28. Epub 2014 Dec 15.

SOME NTI DRUGS FROM EUROPE

Table 1 Main results of the bioequivalence studies available from HMA Public Assessment Reports

				WSCV (%)	
Drug	**Condition**	**Dose (mg)**	***N***	**C_{max}**	**AUC**
Everolimus	Fasting	10	26–55	17.6 (16.3–19.1)	12.9 (10.4–15.2)
	Fed	10	36–184	22.4 (18.7–27.7)	12.6 (9.1–14.9)
Tacrolimus	Fasting	0.5–5	36–141	23.2 (19.3–27.4)	18.1 (15.9–29.3)
	Fed	5	68	19	11
Colchicine	Fasting	0.5	28–64	28.7 (27.3–30.5)	18.9 (18.4–20.8)
Ciclosporin	Fasting	100	24–62	16.7 (14.0–19.4)	12.0 (8.0–16.0)
	Fed	100	>150	43	20
Levothyroxine	Fasting	0.6	34–204	13.5 (10.4–21.5)	13.9 (11.6–24.6)

N—range of number of subjects in the BE studies; WSCV was derived from ANOVA residual variance. Results are shown as median (range).
AUC, area under the plasma concentration–time curve; C_{max}, maximum plasma drug concentration; HMA, Heads of Medicines Agencies; WSCV, within-subject coefficient of variation.

Clin Pharmacol Ther. 2022 Feb;111(2):470-476. doi: 10.1002/cpt.2451. Epub 2021 Nov 3.

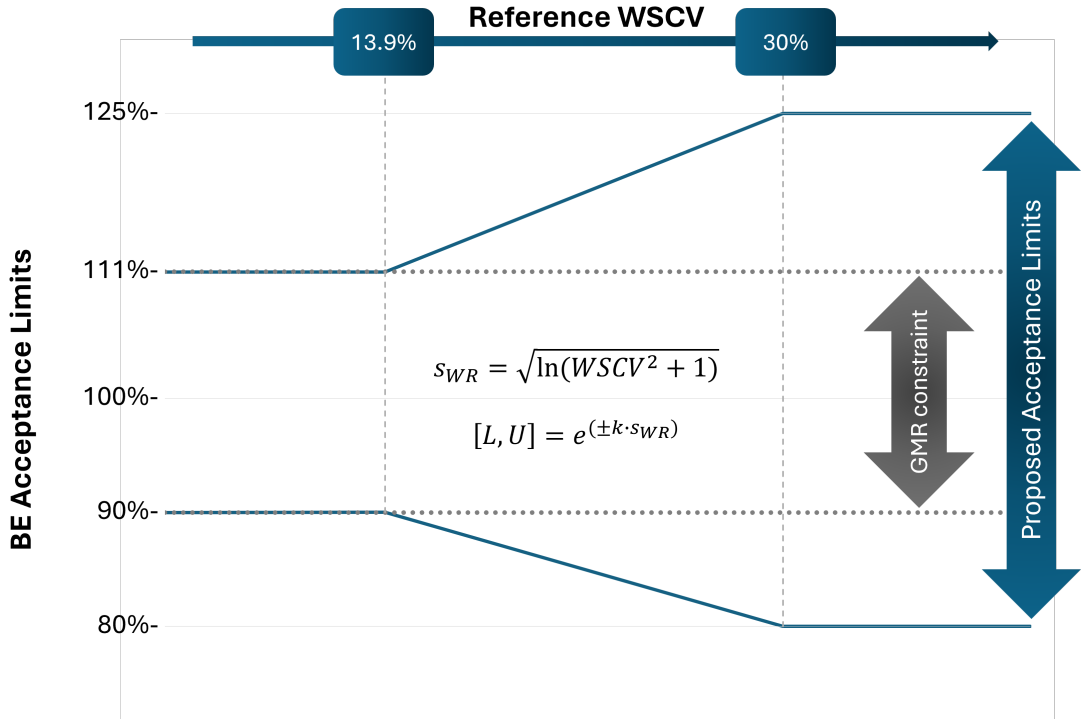
PROBLEMATICS WITH NTI

- Due to low within-subject variability (WSCV), a higher risk of generic drifting exists if standard 80-125% acceptance interval is used.
- A tighter regulatory criterion, 90% CI for the GMR between 0.90 – 1.11, is required by EMA
- To satisfy the tighter acceptance limits very large numbers of subjects are required if WSCV is moderate to high.
- This results in both ethical and economic concerns.
- This is not only a “generic” concern.
- There is a need to harmonization.

A PROPOSAL

NARROWED LIMITS BASED ON THE WITHIN-SUBJECT VARIABILITY OF THE REFERENCE PRODUCT

1. s_{WR} 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 $s_{WR} \leq 0.1386$), the 90.00–111.11% acceptance range is applied;
3. If the estimated WSCV exceeds 30% (corresponding to $s_{WR} > 0.29356$) 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 $(U, L) = \exp(\pm k \cdot s_{WR})$
5. The regulatory "proportionality" constant k is set to 0.760, like for HVD products;
6. The GMR must be within the 90.00–111.11% acceptance range



Clin Pharmacol Ther. 2022 Feb;111(2):470-476. doi: 10.1002/cpt.2451. Epub 2021 Nov 3.

SIMULATIONS ON SAMPLE SIZE

- PowerTOST for R (sampleN.scABEL + reg_const) was used.
- In order to calculate the sample size for a BE trial, it was defined
  - the significance level one-sided α, with a value of **0.05**
  - the type-II error β that defines the power of the trial $(1-\beta)$, fixed as **80%**,
  - the expected GMR of the BE metrics, fixed at **1.00**
  - the BE margins,
  - the WSCV, related to the within-subject variance.
- For the current EMA criterion, the BE margins are the present regulatory tight limits, defined as 90.00 to 111.11%.
- For the proposed approach, the BE margins are defined as explained previously.
- The WSCV was varied from 6% to 40% under homoscedasticity.
- s_{WR} was estimated from the reference product's data.

PERFORMANCE OF THE APPROACH

Power analysis

- PowerTOST for R (power.scABEL + reg_const) was used.
- A two-treatment, three-sequence (TRR-RTR-RRT), three-period (2x3x3) partial replicate design was considered.
- Number of subjects in the simulations were varied from 9 to 114 (in steps of 3 subjects)
- WSCV of the Reference product was varied from 5% to 40% (in steps of 0.125%).
- One million BE studies were simulated in each conditions
- The final power results represent the percentage of studies concluding for BE in each simulated scenario.

PERFORMANCE OF THE APPROACH

Type I error

- A similar protocol to the power analysis was performed.
- GMR values varied depending on the WSCV of the Reference formulation according to:
  - GMR = 0.90 if WSCV≤ 13.92%
  - GMR = $e^{-0.76 s_{WR}}$ if 13.92% < WSCV < 30.00%
  - GMR = 0.80 if WSCV ≥ 30.00%
- WSCV of Test = WSCV of Reference.
- T1E rate above 0.05036 was shown to be considered statistically significantly inflated [Pharm Res, 2016. 33(11): p. 2805-14].

SIMULATION RESULTS

Sample Size Estimation

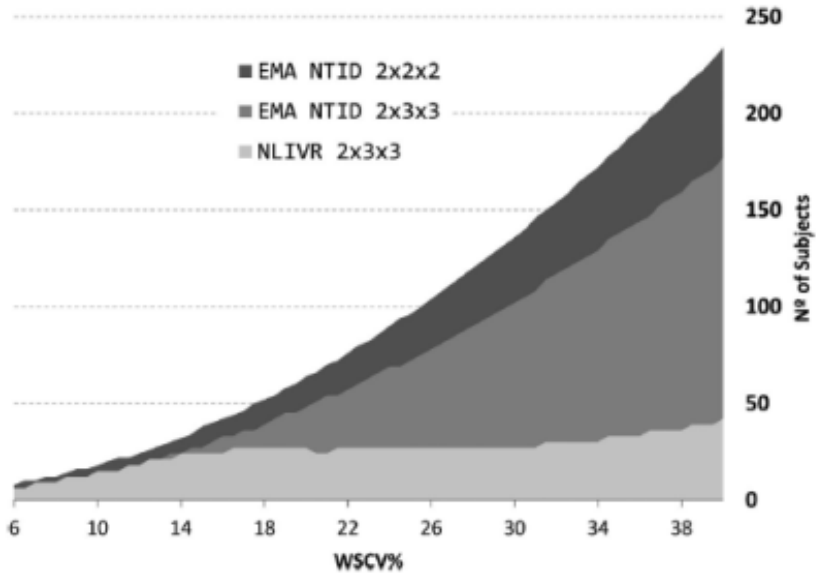


Figure 2 Sample sizes to demonstrate bioequivalence with 80% power between two products that are assumed to be equal (test/reference ratio = 1), according to the current EMA NTI drugs bioequivalence criterion and to the proposed method for 2 × 2 × 2 and 2 × 3 × 3 study designs. EMA, European Medicines Agency; NLIVR, narrowed limits based on the within-subject variability of the reference product; NTI, narrow therapeutic index; NTID, narrow therapeutic index drugs study design; WSCV, within-subject coefficient of variation.

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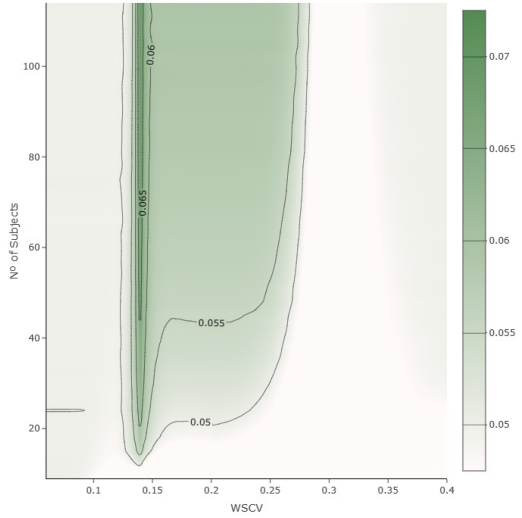
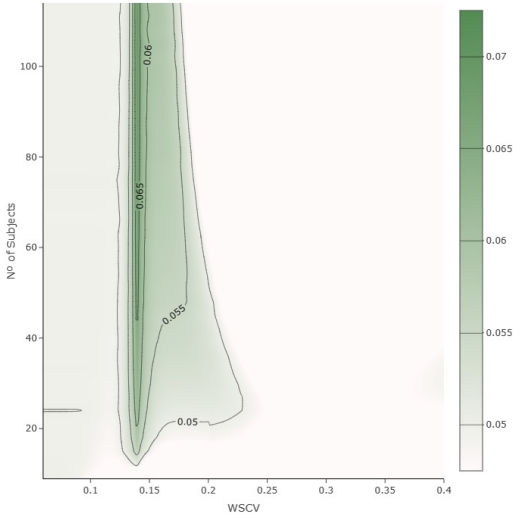
Type I Error Estimation

No GMR constraint



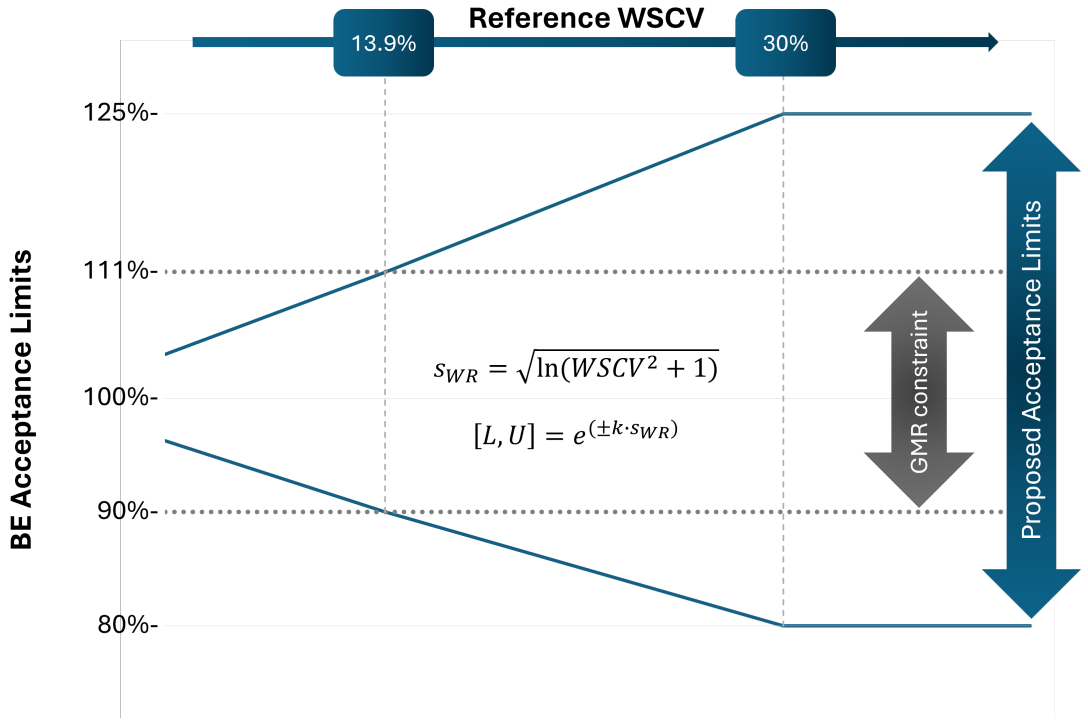
With GMR constraint



Pharmaceutics. 2022 Oct 31;14(11):2349. doi: 10.3390/pharmaceutics14112349.

AN ALTERNATIVE PROPOSAL:
CONTINUOUS NARROWED LIMITS BASED ON THE WITHIN-SUBJECT VARIABILITY OF THE REFERENCE PRODUCT

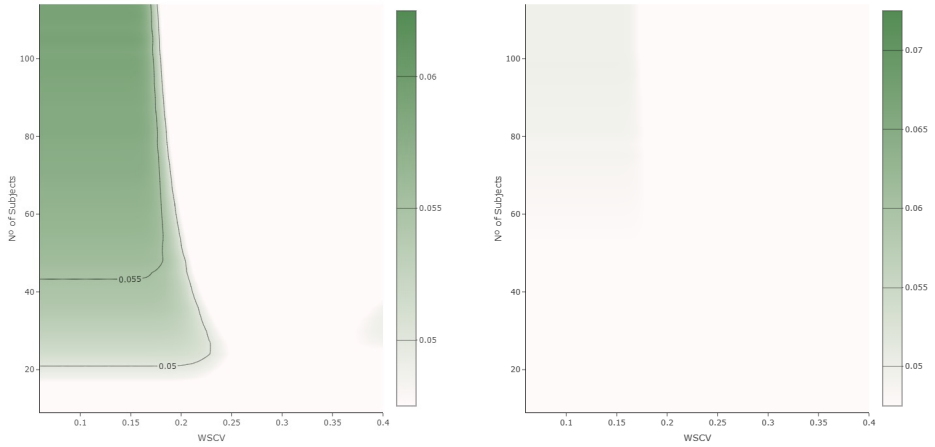
1. s_{WR} is calculated in the same replicate crossover study where the acceptance range is to be narrowed;
2. If the estimated WSCV does not exceed 30% (corresponding to $s_{WR} \leq 0.29356$), the acceptance range is defined by $(U, L) = \exp(\pm k \cdot s_{WR})$;
3. If the estimated WSCV exceeds 30% (corresponding to $s_{WR} > 0.29356$), the 80.00–125.00% acceptance range is applied;
4. The regulatory "proportionality" constant k is set to 0.760, like for HVD products;
5. The GMR must be within the 90.00–111.11% acceptance range



Pharmaceutics. 2024 Apr 28;16(5):598. doi: 10.3390/pharmaceutics16050598.

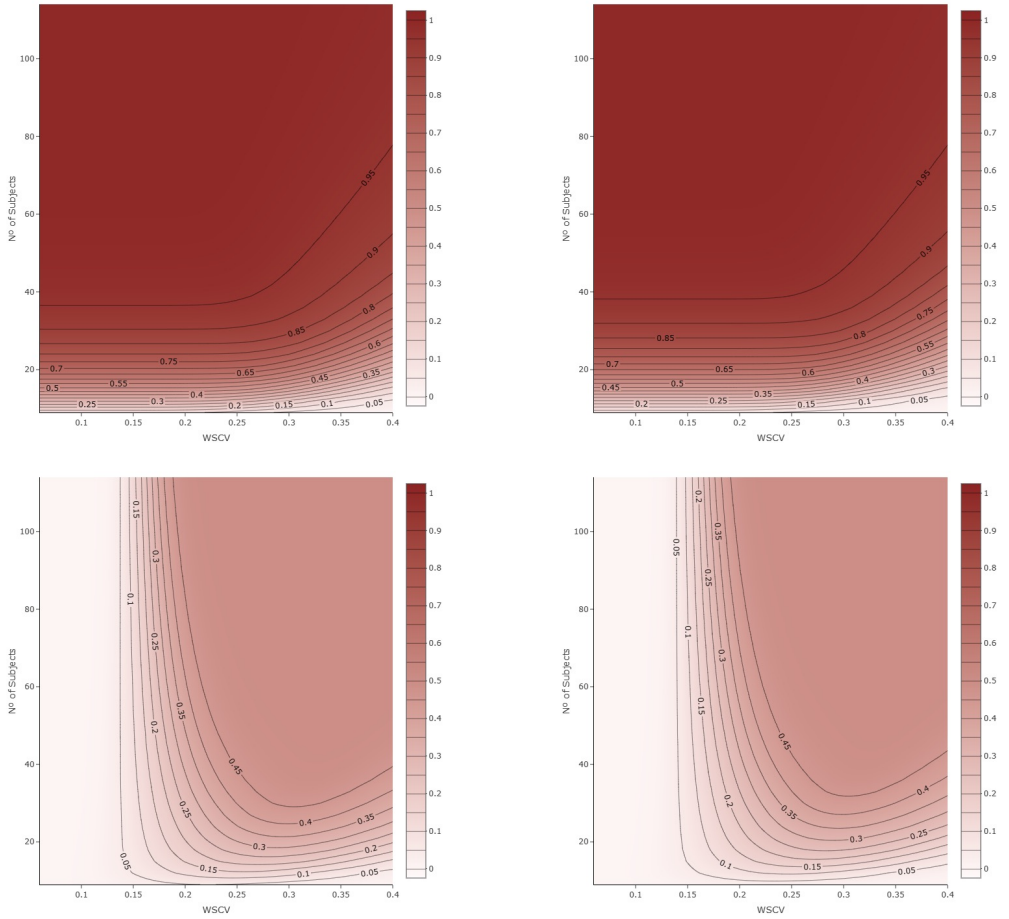
PERFORMANCE
2 X 3 X 3 TRIAL

α = 0.05 α = 0.042



Type I Error Estimation

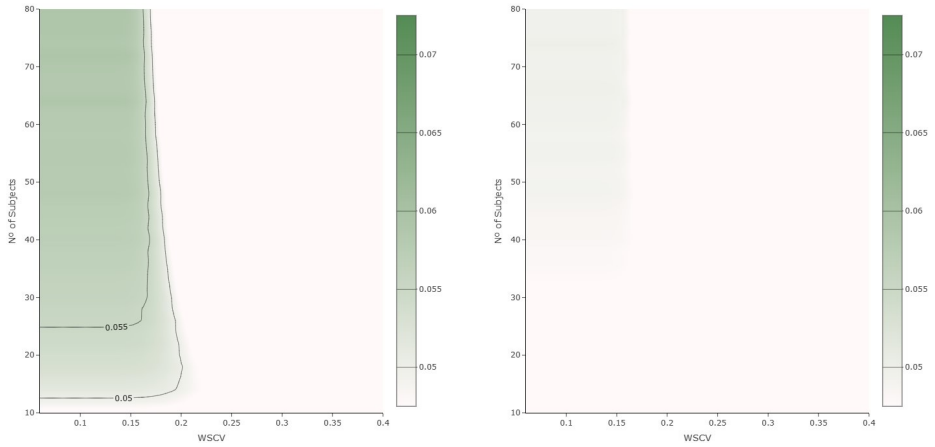
α = 0.05 α = 0.042



Power Analysis

PERFORMANCE
2 X 2 X 4 TRIAL

α = 0.05 α = 0.0347



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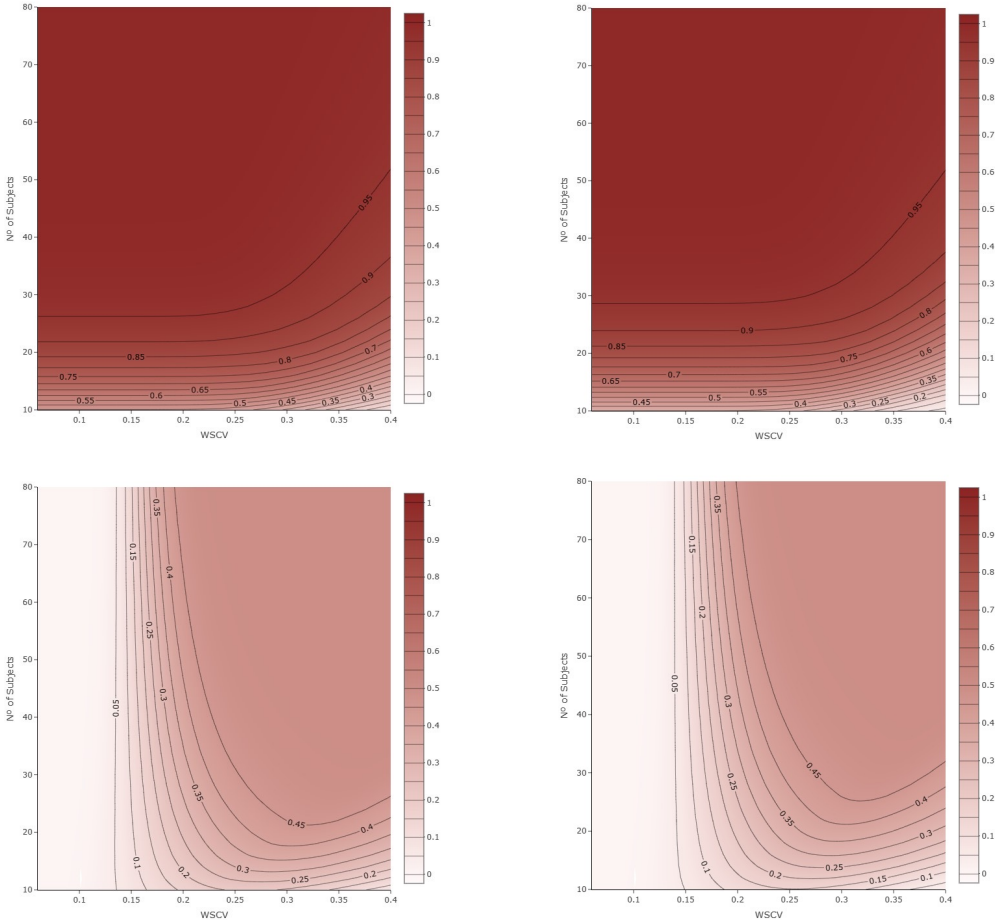
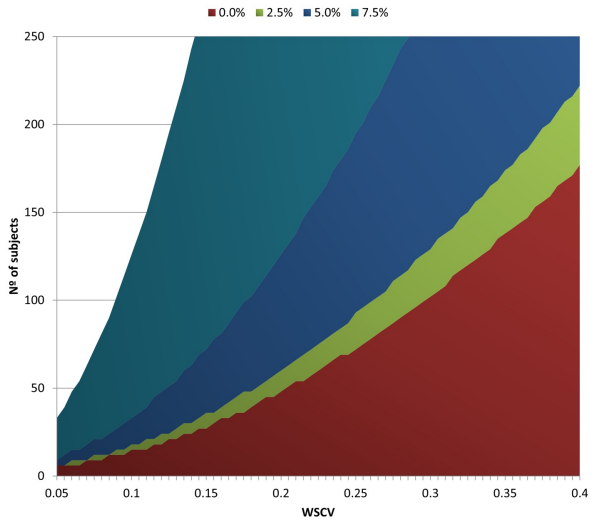
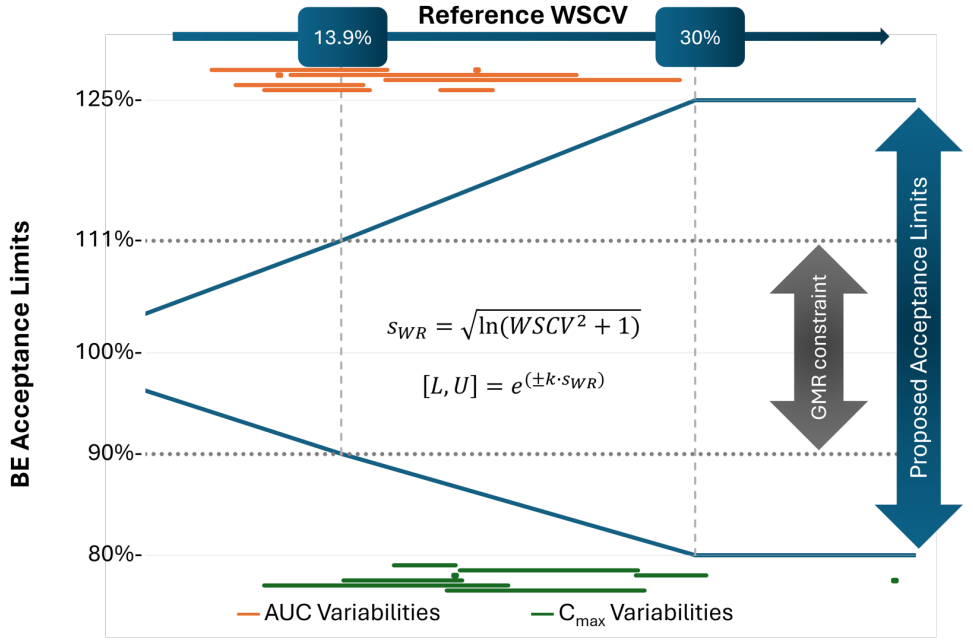
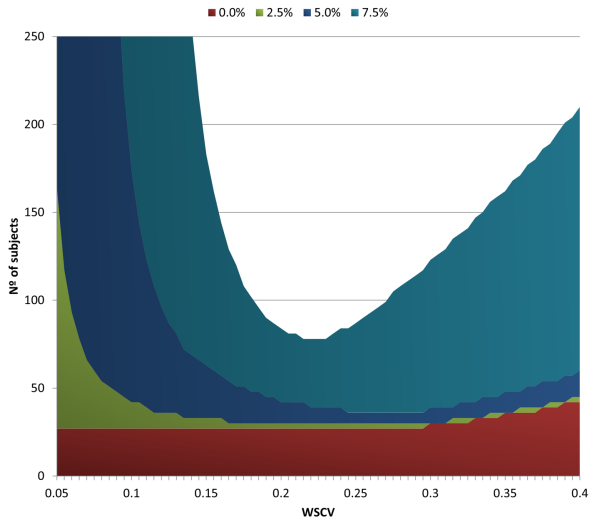


Power Analysis

VARIABILITIES VS SAMPLE SIZES







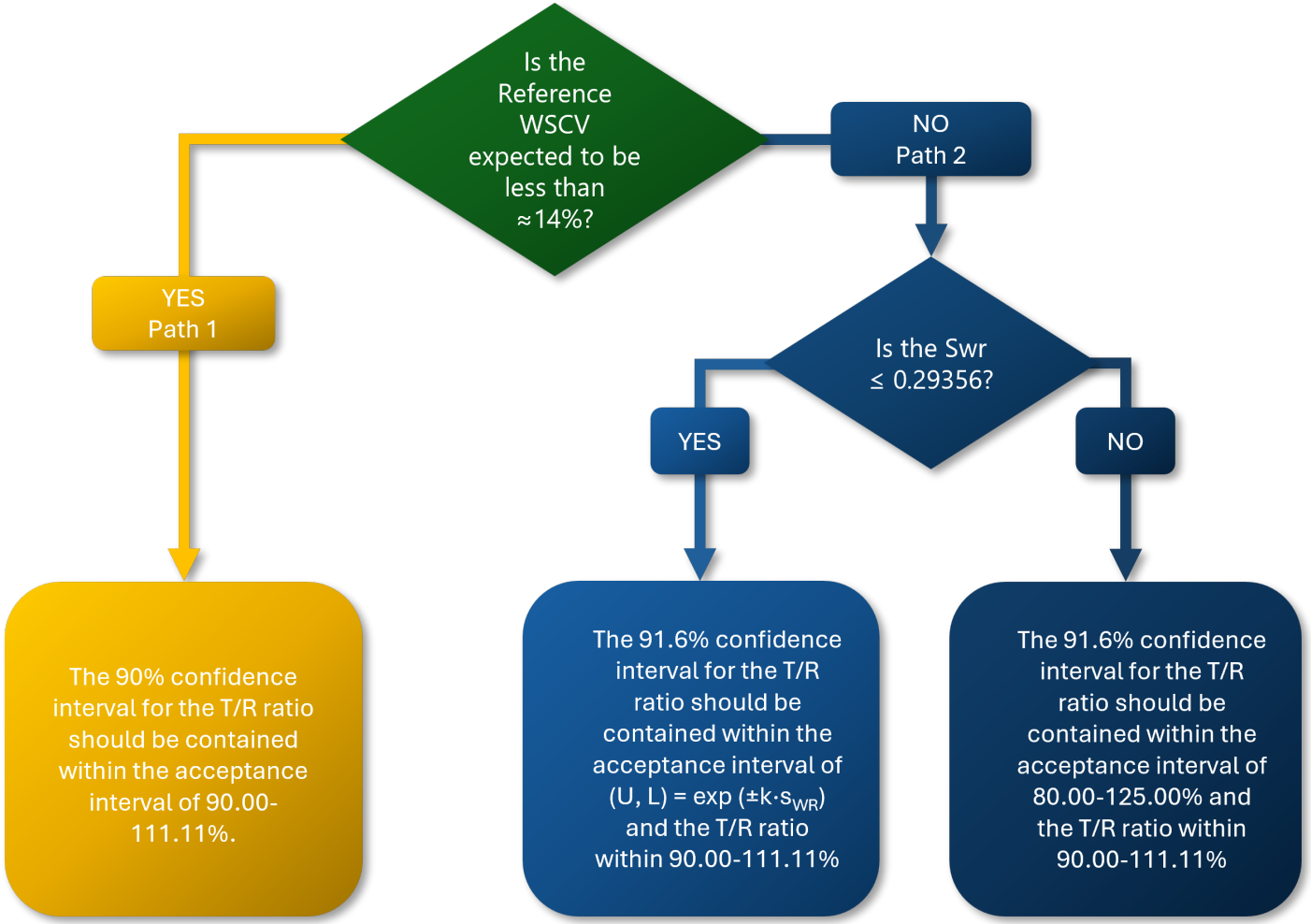
AN ADDITIONAL PROPOSAL

Applicant should decide, prior to analysis, if BE should be evaluated by Route I or by Route II. This should be dependent of the expected (prior study) WSCV and could be different for each PK parameter.

- Route I
  - BE if the 90%CI of the GMR is inside [90 – 111%]
- Route II
  - BE if the 91.6% CI (2x3x3) of the GMR is inside (U, L) = exp ($\pm 0.76 \cdot s_{WR}$) limited to a maximum of [80 – 125%].
  - The GMR itself should be inside [90 – 111%].

The two routes of analysis are independent and exclusive.

DECISION TREE FOR A 2X3X3 TRIAL



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FINAL THOUGHTS

- The use of tighter acceptance limits reduce the risk of generic drifting.
- Requiring even stricter acceptance limits would result in the rejection of the difference in potency that can be found between batches of the innovator product (±5%).
- Use of narrowing limits by scaling based on WSCV will also control the risk of generic drifting because differences are assessed under standardisation.
- Clinical risk is also limited due to therapeutic monitoring and most regulatory agencies still do not allow generic substitution of products containing NTI drugs.
- This proposal could be a step to harmonization on both EMA and FDA approaches.
- This proposal could also help in harmonizing the list of NTI drugs.
- A similar solution could also be proposed for solving known HVDP TIE issues

ACKNOWLEDGMENTS

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THANK YOU

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Prague, Czech Republic