BioBridges 2023

BIOEQUIVALENCE FOR NARROW THERAPEUTIC INDEX DRUGS

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OUTLINE

- Definition of NTI drugs
- Bioequivalence for NTI drugs
- Alternative approach
- Conclusions

DEFINITION ON NTI DRUGS

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.

NTI DEFINITIONS (SOME EXAMPLES)

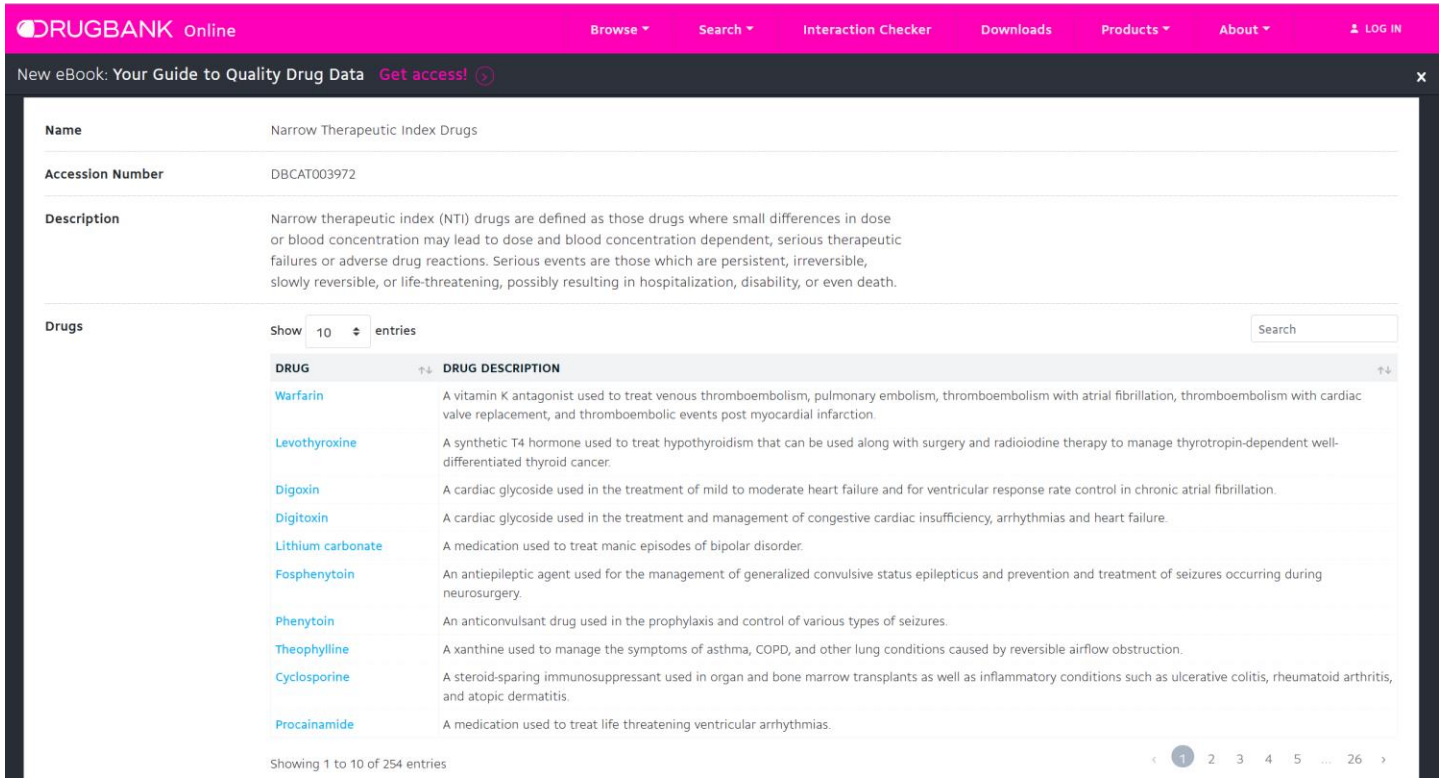
The narrow therapeutic range drugs are those having less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and those for which specific drug treatment control fees are approved as remuneration for treatment.

Critical dose drugs are defined as those drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death.

It is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTID based on clinical considerations.

NTI DEFINITIONS (FDA)

- Little separation between therapeutic and (serious) toxic doses
- Sub-therapeutic levels result in serious therapeutic failure
- Frequently optimized individually by TDM
- Drugs with low-to-moderate within-subject variability (< 30%)
- Doses are often adjusted in small increments (< 20%)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Name
Narrow Therapeutic Index Drugs
Accession Number
DBCAT003972
Description
Narrow therapeutic index (NTI) drugs are defined as those drugs where small differences in dose or blood concentration may lead to dose and blood concentration dependent, serious therapeutic failures or adverse drug reactions. Serious events are those which are persistent, irreversible, slowly reversible, or life-threatening, possibly resulting in hospitalization, disability, or even death.
Drugs
Show 10 entries
Search
DRUG
DRUG DESCRIPTION
Warfarin
A vitamin K antagonist used to treat venous thromboembolism, pulmonary embolism, thromboembolism with atrial fibrillation, thromboembolism with cardiac valve replacement, and thromboembolic events post myocardial infarction.
Levothyroxine
A synthetic T4 hormone used to treat hypothyroidism that can be used along with surgery and radioiodine therapy to manage thyrotropin-dependent well-differentiated thyroid cancer.
Digoxin
A cardiac glycoside used in the treatment of mild to moderate heart failure and for ventricular response rate control in chronic atrial fibrillation.
Digitoxin
A cardiac glycoside used in the treatment and management of congestive cardiac insufficiency, arrhythmias and heart failure.
Lithium carbonate
A medication used to treat manic episodes of bipolar disorder.
Fosphenytoin
An antiepileptic agent used for the management of generalized convulsive status epilepticus and prevention and treatment of seizures occurring during neurosurgery.
Phenytoin
An anticonvulsant drug used in the prophylaxis and control of various types of seizures.
Theophylline
A xanthine used to manage the symptoms of asthma, COPD, and other lung conditions caused by reversible airflow obstruction.
Cyclosporine
A steroid-sparing immunosuppressant used in organ and bone marrow transplants as well as inflammatory conditions such as ulcerative colitis, rheumatoid arthritis, and atopic dermatitis.
Procainamide
A medication used to treat life threatening ventricular arrhythmias.
Showing 1 to 10 of 254 entries
1 2 3 4 5 ... 26

NTI LISTS

REGULATORY NTI LISTS

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

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

Warfarin, tacrolimus, sirolimus, phenytoin, carbamazepine, levothyroxyine, etc.

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

BIOEQUIVALENCE FOR NTI

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
- …

APPROACH II

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
- …

APPROACH III

BE study based on a 2-way crossover study

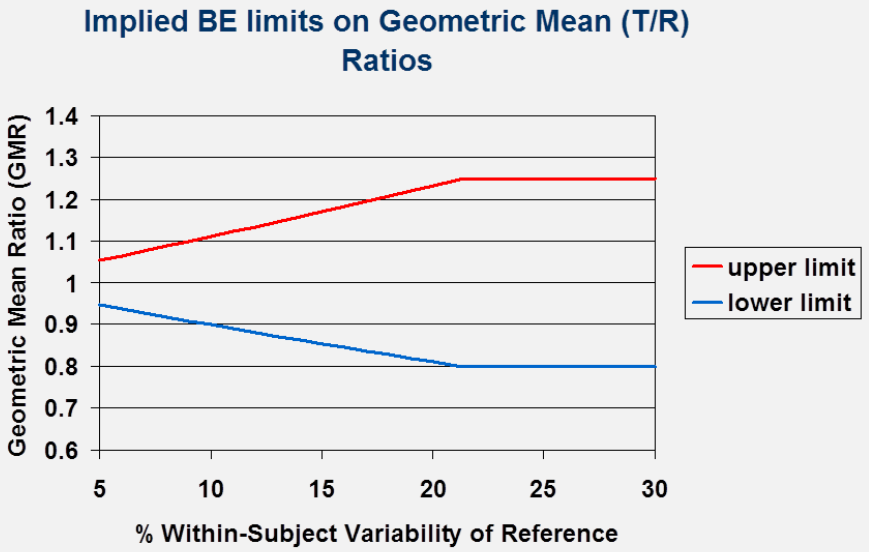
90% CI for the T/R ratio should fall within the acceptance range of 80.00 – 125.00% and PE within 90.00 – 111.11%

Examples

- Japan

APPROACH IV

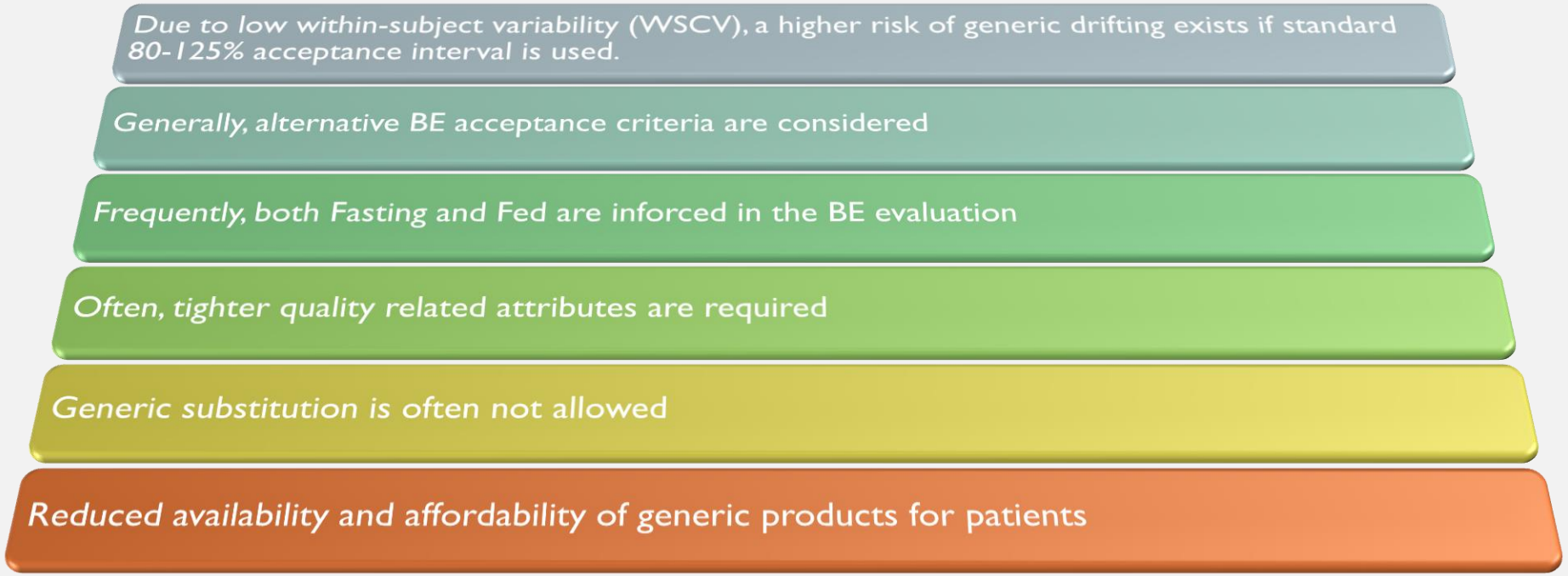
- Four-way crossover, fully replicated design
- This design allows to:
  - Scale a criterion to the within-subject variability of the reference standard
  - Compare test and reference within-subject variances to confirm that they do not differ significantly



Examples

- FDA

REGULATORY CONSEQUENCES FOR NTI



ALTERNATIVE PROPOSAL

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 $s_{WR} \leq 0.29356$), 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;

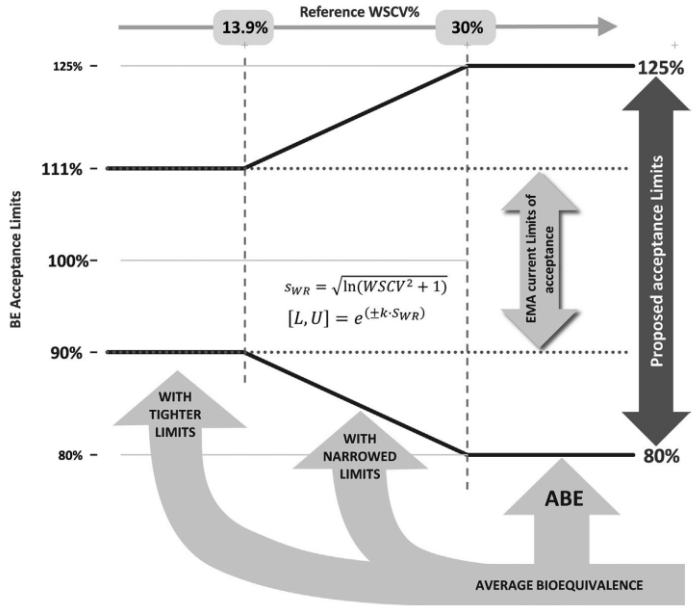


Figure 1 Acceptance limits for the 90% CI of the test-to-reference GMR of NTI drugs according to the WSCV of the reference product. BE, bioequivalence; EMA, European Medicines Agency; GMR, geometric means ratio; NTI, narrow therapeutic index; s_{WR}, within-subject standard deviation of the log-transformed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

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 and shown in Figure 1.
- The WSCV was varied from 6% to 40%. Same WSCV in T and R was assumed (homoscedasticity)
- s_{WR} was estimated only from the data of the reference product.

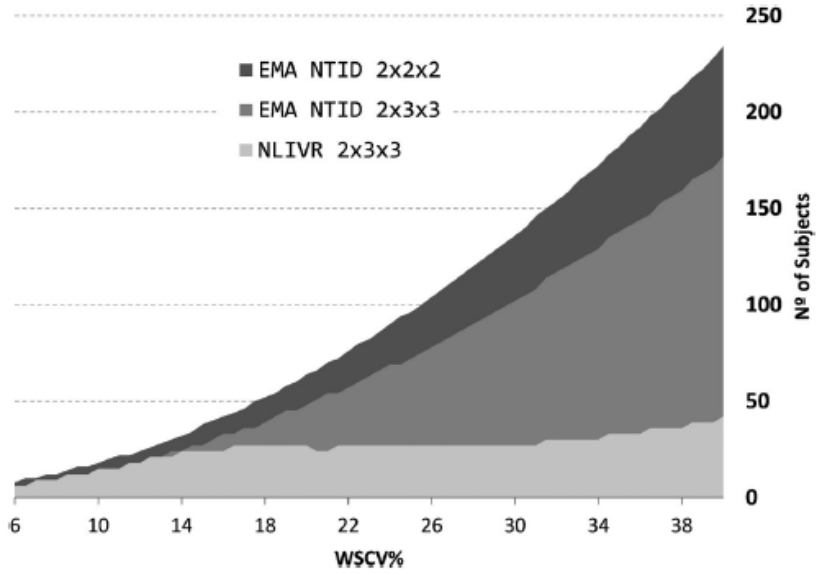


Figure 2 Sample sizes to demonstrate bioequivalence with 80% power between two products that are assumed to be equal (test/reference ratio = 1), according to the current EMA NTI drugs bioequivalence criterion and to the proposed method for 2 × 2 × 2 and 2 × 3 × 3 study designs. EMA, European Medicines 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.

Table 2 Comparison between the actual sample size of the BE studies of NTI drugs and the expected sample size

			EMA NTI 2 × 2 × 2		EMA NTI 2 × 3 × 3		Proposed approach	
Drug	Condition	*N*	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
Everolimus	Fasting	26–55	14[a] (12–14)[a]	28 (20–40)	12[a] (12–12)[a]	21 (15–30)	27 (27–27)	21 (15–24)
	Fed	36–184	20[a] (14–28)[a]	26 (16–38)	15[a](12–21)[a]	21 (12–27)	27 (27–27)	21 (12–24)
Tacrolimus	Fasting	36–141	20[a] (16–28)[a]	52 (42–132)	15[a] (12–21)[a]	39 (33–99)	27 (27–27)	27 (24–27)
	Fed	68	14[a]	22	12[a]	15	27	15
Colchicine	Fasting	28–64	30[a] (28–34)[a]	58 (54–70)	24[a] (21–24)[a]	45 (42–54)	27 (27–30)	27 (27–27)
Ciclosporin	Fasting	24–62	44 (32–60)	24 (12–42)	33 (24–45)	18 (12–33)	27 (24–27)	18 (9–24)
	Fed	>150	266	64	201	48	45	27
Levothyroxine	Fasting	34–204	12[a] (12–18)[a]	32 (22–94)	12[a] (12–15)[a]	24 (18–69)	21 (15–27)	24 (18–27)

Comparison between the actual sample size of the BE studies of NTI drugs and the expected sample size required for the demonstration of bioequivalence under the current EMA NTI criterion (90.00–111.11%) and with the proposed alternative criterion, with an a priori power of 80% and assuming that GMR is equal to 1 for 2 × 2 × 2 or 2 × 3 × 3 study designs, according to the observed within-subject variability. *N* is the range of the number of subjects in the BE clinical studies. AUC, area under the plasma concentration–time curve; C_{max}, maximum plasma drug concentration; EMA, European Medicines Agency; NTI, narrow therapeutic index; WSCV, within-subject coefficient of variation.

[a]Sample size estimation based on the usual acceptance interval of 80.00–125.00% since C_{max} acceptance range is not narrowed in those drugs. Results are presented for the median (range) based on the reported WSCV shown in **Table 1**.

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

RESULTS ON SAMPLE SIZE

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
- GMR of 0.9 and 0.85.
- The final power results represent the percentage of studies concluding for BE in each simulated scenario.

PERFORMANCE OF THE APPROACH

Type I error

- For the estimation of the type I error (consumer's risk – T1E) 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].

RESULTS

Figure 4 – Type I error (T1E) for the proposed NLIVR conditions with (B) and without (A) a GMR constraint for different WSCV and number of subjects.

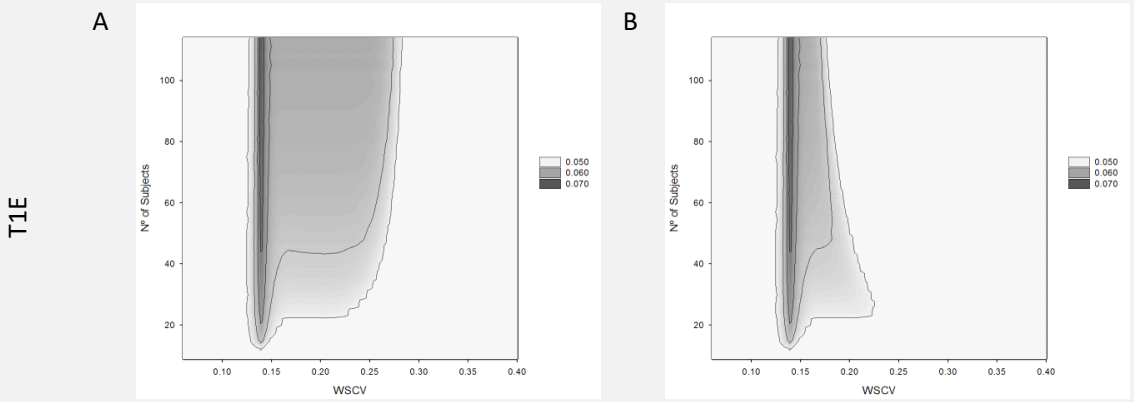
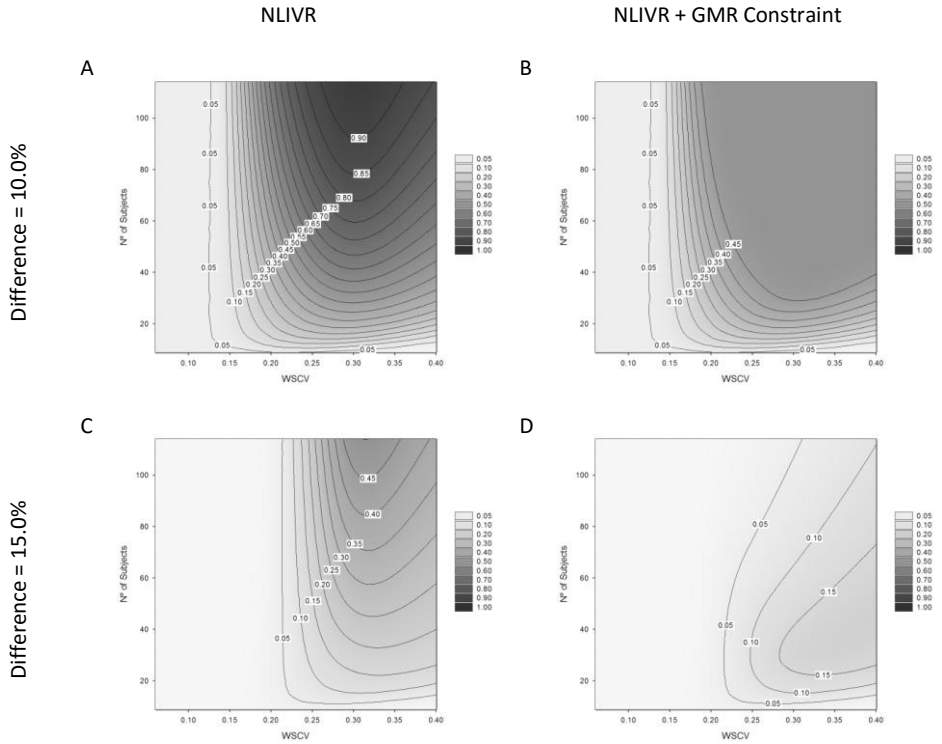


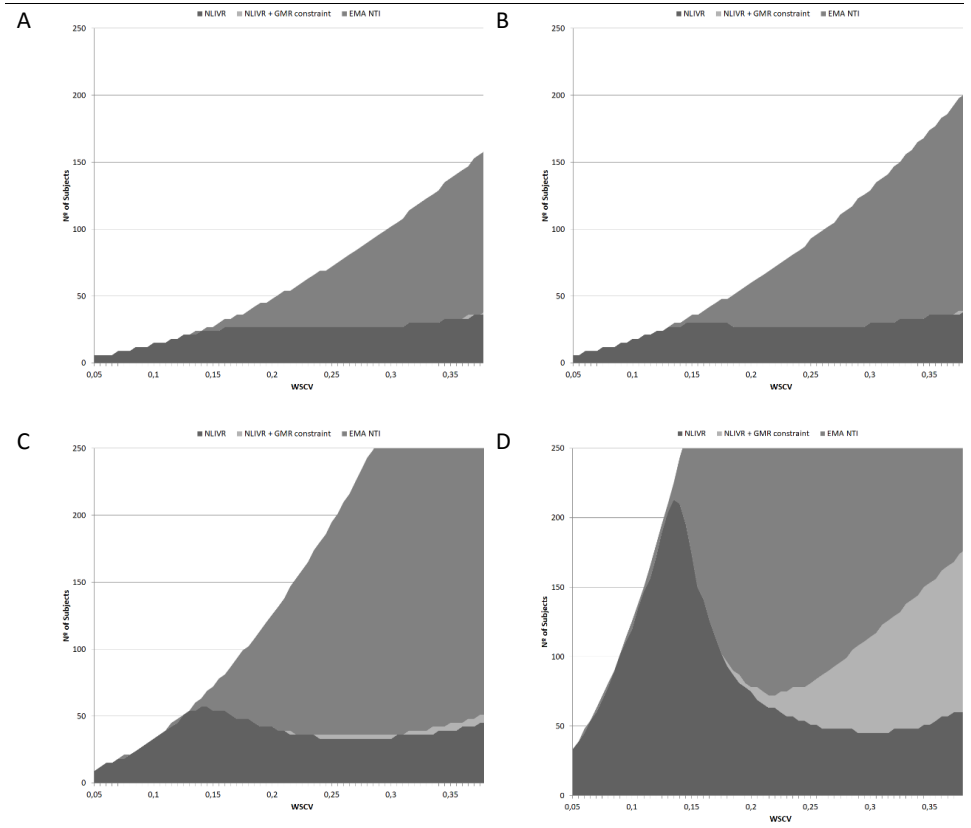
Figure 3 – Power analysis for the proposed NLIVR conditions with and without a GMR constraint assuming increasing nominal differences between the test and reference formulation, for different WSCV and number of subjects. Legend represents the probability of concluding bioequivalence.



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

SAMPLE SIZE

Figure 5 - Sample sizes for the EMA current NTI criteria (EMA NTI), the proposed NLIVR conditions with (NLIVR + GMR constraint) and without (NLIVR) the GMR constraint for a power of 80%, assuming a GMR of A) 1.000, B) 0.975, C) 0.950 and D) 0.925



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

CONCLUSION

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 approach could be a step to harmonization on both EMA and FDA approaches, if the comparison of the test and reference variabilities are not considered.
- This approach could also help in harmonizing the list of NTI drugs.
- ICH M13 Tier 3 (expected to start by July 2024) will deal with this topic for harmonization.

ACKNOWLEDGMENTS

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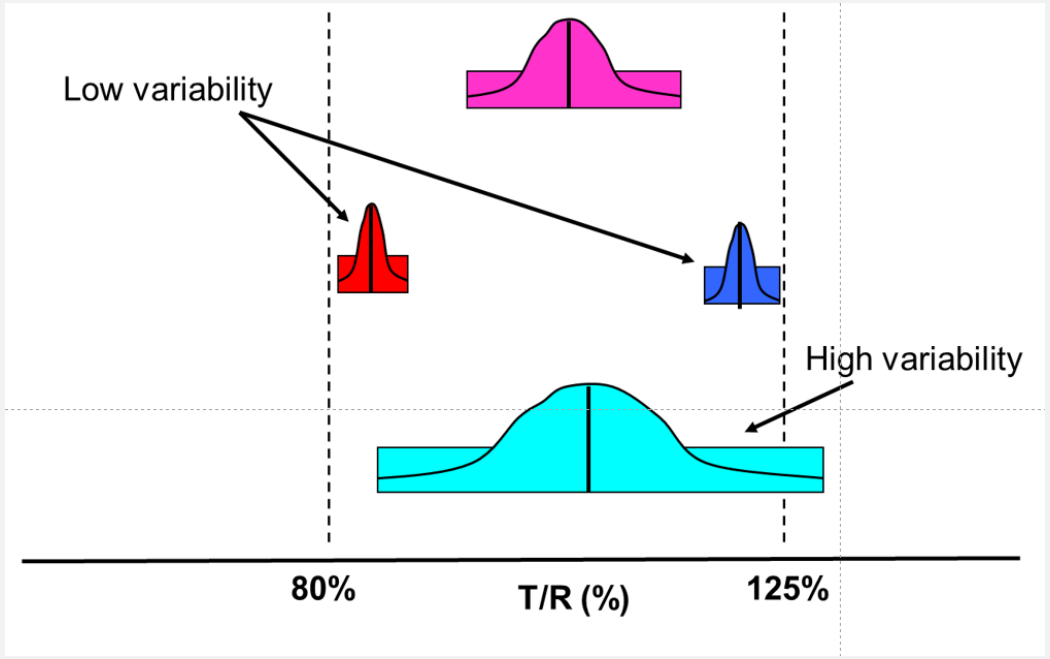
Thank You

BIOEQUIVALENCE CONSEQUENCES FOR NTI



CRITICS FOR APPR I

A normal regulatory criterion only ensures a difference lower than 20% between T and R products

May not provide sufficient confidence of use in the patient population.

May put more strength on the need for TDM.

May prevent the use of generic substitution.

CRITICS FOR APPR II

A tighter regulatory criterion ensures a difference lower than 10% between T and R products

In order to satisfy the tighter regulatory criterion 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.

SOME EXAMPLES 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.

CRITICS FOR APPR III

Relying only on the tighter PE requirement does not ensures a difference lower than 10% between T and R products

May not provide sufficient confidence of use in the patient population.

May put more strength on the need for TDM.

May prevent the use of generic substitution.

CRITICS FOR APPR IV

Requirement of a full replicate study imposes complex studies with frequently high number of drop-outs

Scaling criteria is too demanding for WSCV < 10% and too permissive for WSCV > 20%

The need for within-subject variance comparison not fully justifyed

May prevent the development of generic products.