Impact of Between-subject, Within-subject and Between-occasion Variability on Therapeutic Success for Narrow Therapeutic Index: a Bioequivalence Perspective

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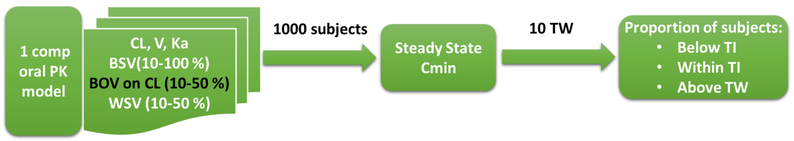
Rationale

Quantitatively classifying narrow therapeutic index (NTI) drugs and warranting interchangeability between brand and generic has been a challenging issue. Proper identification of NTI drugs is a prerequisite to apply new FDA bioequivalence criteria for NTIs.

The objective of this work is to quantify the impact of between-subject variability (BSV), within-subject variability (WSV), between-occasion variability (BOV) and drug's therapeutic index (TI) on the percentage of subjects achieving a target window when treated with NTI drugs, and identify cut-offs that will help classify NTI versus non-NTI drugs.

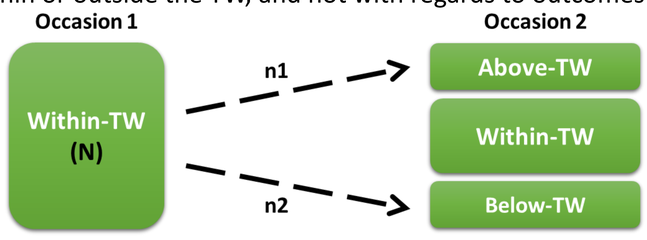
Methods

- Simulation set-up: Generic PK simulations from a hypothetical drug were performed:



- *10 BSV's * 10 WSV's *10BOV's *10 TI = 10,000 unique scenarios*
- *1000 subjects per scenario*
- *Total number of simulations = 10,000,000*
- *10 generated therapeutic windows (TW) = ± 10 – 90 % of population mean Cmin,ss*
- *CL/F = 10 L/h, V/F = 500 L, ka = 1 h^{-1}*
- *Therapeutic index (TI) = ratio between the upper and lower limits of a TW.*

- First, PK simulations were performed at 1 occasion (WSV levels could be considered as *total residual variability*: BOV+WSV. Second, simulation were performed at 2 different occasions (by including BOV on CL/F, therefore parsing the *total residual variability into BOV and WSV).*
- Therapeutic success defined as the proportion of subjects with Cmin,ss within a TW was calculated for each variability and TW scenario.
- Therapeutic failure (TF) defined as the proportion of individuals moving outside a TW between occasion 1 and 2 for each simulation scenario was also investigated.
- Assumption: Therapeutic success and failure relate to Cmin,ss within or outside the TW, and not with regards to outcomes



Results

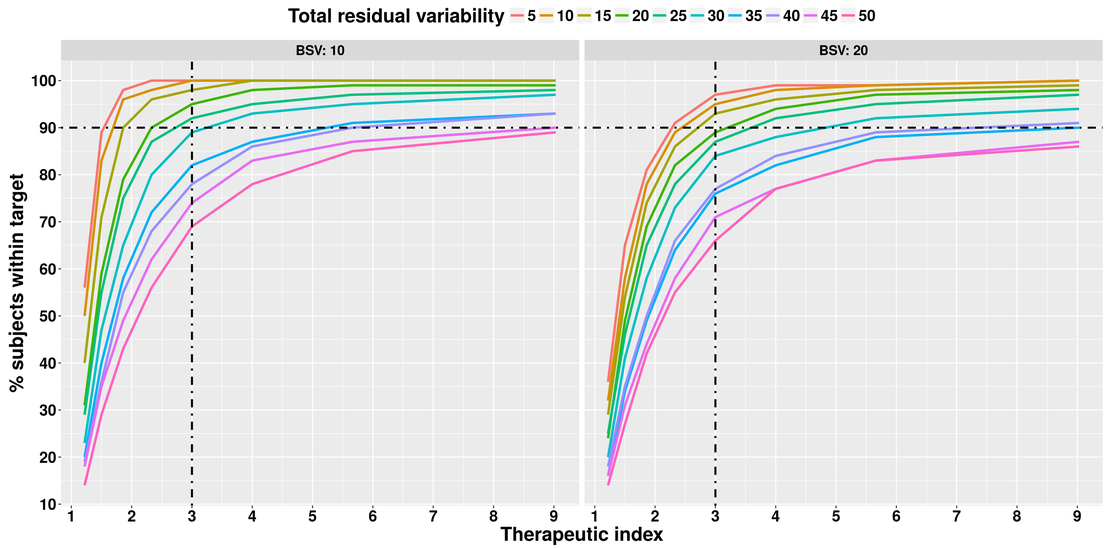


Figure 1. Proportion of subjects within target versus drug's TI in the generic PK simulations. Colored lines: 10 different WSV scenarios (%CV). Legend on each panel: BSV (%CV).

Subjects within-target (PR)	Therapeutic Index (TI)	Maximum BSV	BOV	WSV	Total residual variability (WSV+BOV)
PR ≥ 90 %	1.86	10	10	5	11
	2.33	10	15	10	18
	3.00	10	25 20	5 15	25
		20	15	5	16
PR ≥ 80 %	1.5	10	5	5	7
	1.86	10	15	10	18
	2.33	10	25	10	27
		20	5	20	21
	3.00	10	35 30	10 20	36
		20	10	30	32

Table 2. Detailed outlook of the maximum BSV, BOV and WSV cutoffs to achieve at least 90 % or 80% of subject within a therapeutic windows for different therapeutic indices.

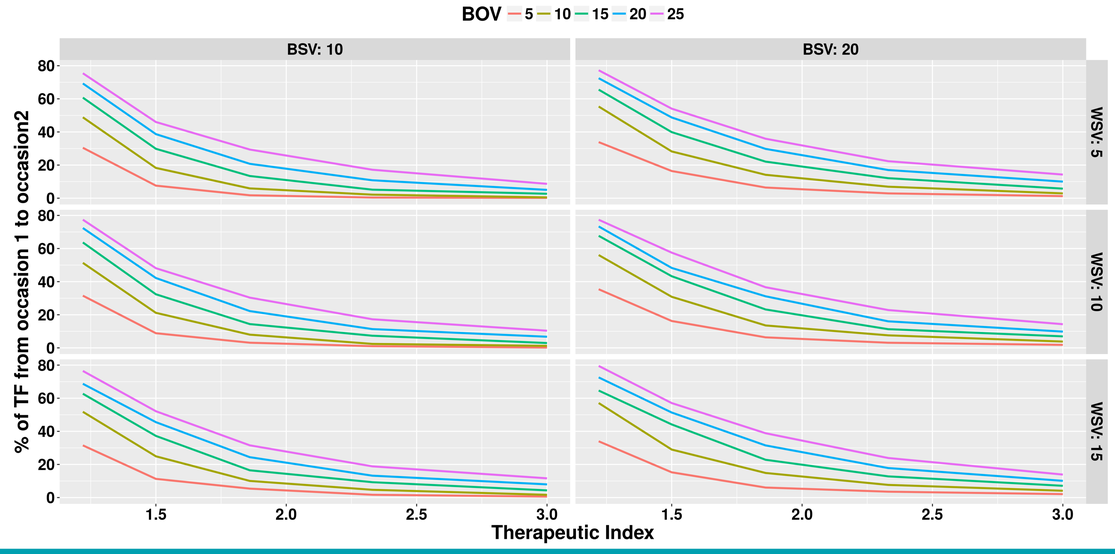


Figure 2. Relationship between BOV, WSV and TI on therapeutic failure (TF) defined as the proportion of subjects moving outside a TW between occasion 1 and 2 for given drug.

Under a controlled BSV either by dose titration or therapeutic drug monitoring (TDM):

- To achieve at least 90% of subjects within a target therapeutic window :
  - at 10% BSV: TI ≤ 3 and total residual variability ≤ 25% are required
- For at least 80% of subjects within a target therapeutic window:
  - at 10% BSV: TI ≤ 3 and total residual variability ≤ 35% are required
  - at 20% BSV: TI ≤ 3 and total residual variability ≤ 30% are required

- %TF increases with increasing BOV particularly for low TI <2.
- For a given drug with TI = 1.5, a 5% increase in BOV (from 5 to 10%) is associated with almost 10% increase in %TF (across the depicted WSV and BSV).

Conclusions

- At a controlled BSV and for drugs with TI ≤ 3, a cut-off of WSV ≤ 25% to 30% is necessary to achieve at least 90% to 80% of subject within a target window, respectively.
- These observations meet the following CFR criteria which partially define NTI drugs as:
  - *drugs that have less than 2-fold difference between minimum toxic concentration and minimum effective concentration.*
  - *possess low-to-moderate within-subject variability (i.e. ≤ 30%).*
- Comparison between the within-subject variability (BOV) of the reference and test drug seems to be warranted according to our early observation.

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