Impact of Variability on Therapeutic Success for Drugs with Narrow Therapeutic Index

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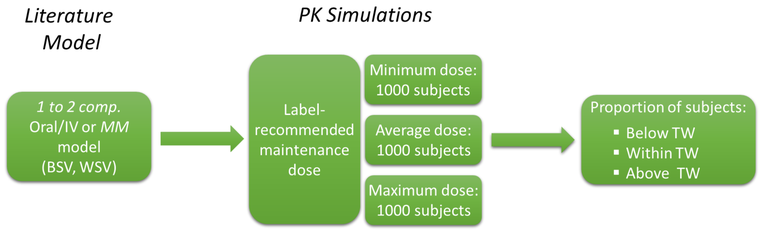
Rationale

Controversy surrounding the interchangeability between brand and generic drugs, some of them known as narrow therapeutic index (NTI) drugs, raised the need to modify FDA bioequivalence criteria. Proper identification of NTI drugs is a prerequisite to apply these new bioequivalence criteria.

The objective of this work is to quantify the impact of between-subject variability (BSV), within-subject variability (WSV) 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

- 1st simulation set-up: PK/PD simulations, from literature-selected models, were performed for 21 drugs (anticoagulants, antiarrhythmics, antiepileptics and immunosuppressants) for which therapeutic windows (TW) have been reported.

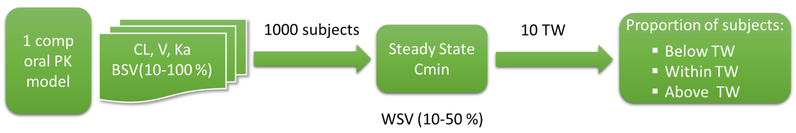


Model selection:
- *Accounted for major covariates.*
- *Good predictive performance.*
- *Data include steady state doses, multiple sampling.*

Simulation:
- *Steady state concentration.*
- *Subject ideal/mean physiological and demographic characteristics.*
- *Covarites: drug interaction in adjuvant therapies*

  - Anticoagulants: argatroban(ARGAT), dabigatran (DABIG), *warfarin (WARF)*.
  - Antiarrhythmics: *digoxin (DIGO), flecainide (FLECA), quinidine (QUINI)*.
  - Antiepileptics: *carbamazepine (CBZ)*, felbamate (FELB), lamotrigine (LAMO), oxcarbazepine (OXCBZ), *phenobarbital (PHB)*, *phenytoin (PHENY)*, tiagabine (TIAGA), topiramate (TOPI), *valproic acid (VPA)*, zonisamide (ZONI).
  - Immunosuppressants: *cyclosporine (CsA), everolimus (EVE), mycophenolate (MPA), sirolimus (SRL), tacrolimus (TAC)*.

- 2nd simulation set-up: Generic PK simulations from a hypothetical drug in order to build a predictive model:



- *10 BSV's * 10 WSV's *10 TW = 1000 unique simulated scenarios*
- *1000 subjects per scenario*
- *Total number of simulated* Cmin,ss *= 1,000,000*
- *10 generated TW =* ± 10 – 90 % of median Cmin,ss
- CL = 10 L/h, V = 500 L, Ka = 1 h^{-1}

- PK simulations were performed at one occasion, therefore the 10 increasing WSV levels used in simulations could be considered as total-WSV: lumped between-occasion variability and residual variability.

Results

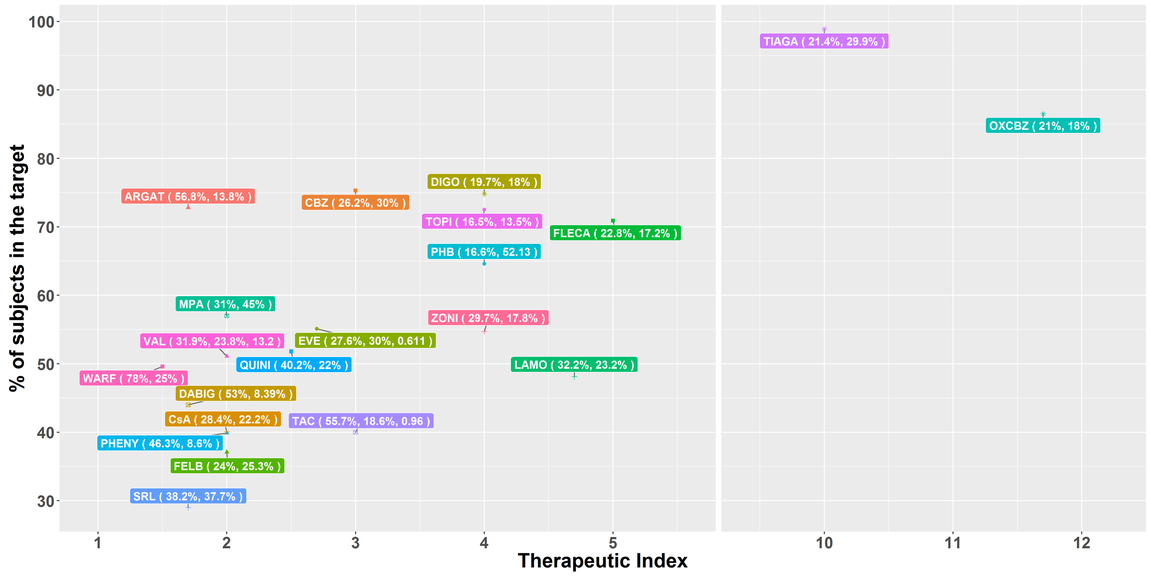


Figure 1. Proportion of subjects within target versus therapeutic index of simulated drugs from literature. Labels: drugs names followed by BSV (%CV) and WSV (%CV for the proportional error and/or additive residual error) . Therapeutic index (TI) is the ratio between the upper and lower limits of a therapeutic window.

- 13 out of 21 drugs have been categorized as NTI drugs *(see methods: italic drug names).*
- 10 out 13 known NTI drugs have a TI ≤ 3 and 3 have a TI between 3 - 5.
- WSV and BSV (%CV) ranged from to 10 to 30% and 20 to 70 %, respectively.
- For 85% of drugs with TI ≤ 3: proportion of subjects within the target < 60% (BSV: 30 to 70%).
- 66% of drugs with TI between 3 – 5: proportion of subjects within target increased to 60-80% (BSV: 20 to 30%).
- Drugs with the largest TI (≥10), have a proportion of subjects within target > 80% (BSV ~ 20%).

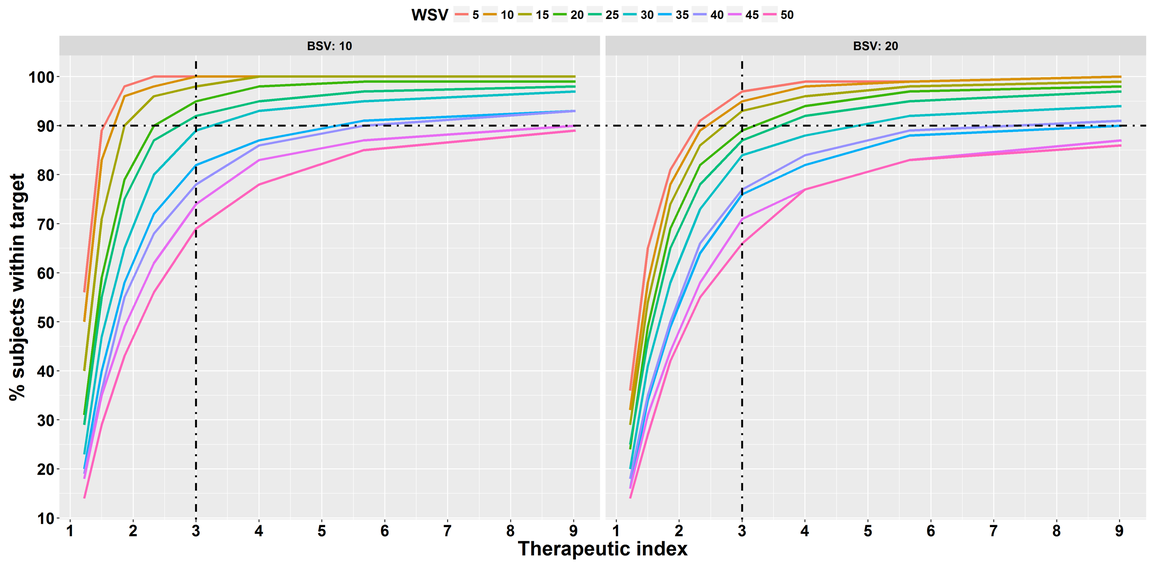


Figure 2. Proportion of subjects within target versus drugs therapeutic index of the generic PK simulations. Colored lines: 10 different WSV scenarios (%CV). Legend on each facet: BSV (%CV).

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

Conclusions

- A TI of 3 may be the ideal cut-off to define a drug as NTI.
- 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 (MTC) and minimum effective concentration (MEC).
  - possess low-to-moderate within-subject variability (i.e. ≤ 30%).

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