Pharmacometric Approach To Define Narrow Therapeutic Index (NTI) Drugs & Evaluate Bioequivalence (BE) Criteria for NTI Drugs

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With input from US FDA
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Recommendations

1. Therapeutic index ≤ 3 is a reasonable cutoff to define NTI drugs.

2. Therapeutic index and small increments of dose adjustment are adequate for NTI classification.

3. To achieve a passing rate of 80% in a BE trial, the maximum observed $\frac{W_{SV_{\text{test}}}}{W_{SV_{\text{reference}}}}$ is 1.4.
Recommendation 1:

Therapeutic index ≤ 3
10 out 13 NTI drugs have a TI ≤ 3 and 3 have a TI between 3-5
Simulation setup
**Hypothetical drug simulation setup**

1 comp oral abs. PK model

- CL
  - BSV(10-100 %)
  - BOV (10-50 %)

- V
  - BSV(10-100 %)

- Ka
  - BSV(10-100 %)

1000 subjects → Steady State Cmin → 10 TW

Proportion > TW

Proportion in TW

Proportion < TW

- ± 10 – 90 % of Mean C_{ss, min}

- 10 BSV * 10 BOV * 10 TW = 1000 unique scenario

- 1000 subjects per scenario

- Total number of simulations – 1,000,000

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\( Ka \) – Absorption rate constant

\( Cl \) – Clearance

\( V \) – Volume of distribution

BSV – Between Subject Variability

BOV – Between Occasion Variability

WSV – Within Subject Variability

TW – Therapeutic Window
Proportion of subjects within target is a function of Therapeutic index and WSV

<table>
<thead>
<tr>
<th>WSV (%)</th>
<th>1.22</th>
<th>1.5</th>
<th>1.86</th>
<th>2.33</th>
<th>3</th>
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- For a **BSV of 10%**
- E.g. At
  - **TI ≤ 3**
  - **WSV ≤ 35%**
  - **80 % responders within target**
Proportion of subjects within target is a function of Therapeutic index and WSV

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- For a **BSV of 20%**
- E.g. At
  - **TI ≤ 3**
  - **WSV ≤ 30%**
  - **80 % responders within target**
Recommendation 2:

Therapeutic index and small increments of dose adjustment are adequate for NTI classification.
Current NTI classification criteria

• The 5 following criteria were evaluated for drugs from 4 therapeutic areas:

1. maximum of 2 fold difference between minimum effective and minimum toxic dose or maximum recommended therapeutic dose.

2. maximum of 2 fold difference between the lowest and the highest drug concentration from the recommended or observed therapeutic index.

3. Routine therapeutic monitoring.

4. Low-to-moderate within subject variability (≤ 30%).

5. doses often adjusted in small increments (<20%).
<table>
<thead>
<tr>
<th>ANTICOAGULANTS</th>
<th>ANTIARRHYTHMICS</th>
<th>ANTIEPILEPTICS</th>
<th>IMMUNOSUPPRESSANTS</th>
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<tbody>
<tr>
<td>• Argatroban</td>
<td>• Amiodarone</td>
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<td>• Vigabatrin</td>
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<td>• Zonisamide</td>
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Green: drugs known as non NTIs
Red: known NTI drugs,
Blue: drugs thought to be NTI but not listed by most agencies as NTIs
NTI Criteria 2, 5 are adequate differentiators univariately
54% of NTI’s meet both criteria 2 and 5
Recommendation 3:

Limits for $WSV_{Test} / WSV_{Reference}$ for NTI BE evaluation
Simulation of a bioequivalence trial for a hypothetical test and reference drug

• Hypothetical drug pharmacokinetic parameters:
  • $CL = 10 \text{ L/h}$, $V = 500 \text{ L}$, $ka = 1 \text{ h}^{-1}$, $F = 100 \%$.
  • Half-life = 34 h, $Tmax = 4 \text{ h}$.

• Difference in F between Reference and test drug:
  • $F_{tr \, ratio} = F_{test} / F_{drug} = GMR \text{ = ranges from 80 \% to 125 \%.}$

• WSVr (reference drug) and WSVt (test drug) ranges each form:
  • 5 to 40 (\% CV).

• Rich PK simulation (0 to 120h) for:
  • 24 subjects per unique scenario* of WSVr, WSVt and GMR permutation.

* 57,000 scenarios evaluated
Simulate a *bioequivalence trial* for a hypothetical test and reference drug

- 4 periods, 2 sequence bioequivalence trial: *TRTR* and *RTRT*.

- 100 trials per WSVr, WSVt and GMR permutation scenario.

- $\text{AUC}_{0-\text{inf}}, \text{AUC}_{0-\text{tlast}}$ and $\text{C}_{\text{max}}$ were calculated.

- Bioequivalence test: Test and reference drugs are equivalent if the following three conditions passed:
  - *RSABE*
  - *Upper limit of the 90% CI of WSVt / WSVr ratio* $\leq 2.5$
  - *ABE*

- Validate the BE trials simulations: BE passing rate (%) versus GMR.
Simulation validation – our setup replicates the FDA results
Scenarios where $\text{WSV}_{\text{Test}} > \text{WSV}_{\text{Reference}}$:

Maximum difference for 80% BE passing rate (\textit{RSABE + ABE + WSV comparison}):

\[
\text{RSABE + ABE + WSV comparison}
\]

\[
\text{Ratio WSV (\%) = (WSV}_{\text{Test}}/\text{WSV}_{\text{Reference}})\]

\[
\begin{array}{ccc}
\text{GMR: 0.95} & \text{GMR: 0.96} & \text{GMR: 0.98} \\
\text{GMR: 1} & \text{GMR: 1.02} & \text{GMR: 1.04} \\
\text{GMR: 1.06} & \text{GMR: 1.08} & \\
\end{array}
\]
Scenarios where $\text{WSV}_{\text{Test}} > \text{WSV}_{\text{Reference}}$:

Maximum difference for 80% BE passing rate (\textit{RSABE + ABE + WSV comparison}):
Impact of BOV on *Individual Response* after switch from OCC1 to OCC2 for a Reference drug

Proportion of Therapeutic Failure (% TF) = \[
\frac{\text{Sum of subjects moved from within-TW} \Rightarrow \text{out of TW between occasions}}{\text{initial nb of subjects within-TW (at first occasion)}}
\]
Individual Response – Reference vs. Reference – at TI ≤ 2: BOV ↑ → %TF ↑
Up to 10 % TF at a dWSV of 10 %
Evaluation of Bioequivalence approach and impact of therapeutic success

• For bioequivalent Test and Reference drug according to the recommended RABE + WSV comparison approach:
  - A maximum to 10% difference between $\text{WSV}_{\text{Test}}$ and $\text{WSV}_{\text{Reference}}$ can be observed between bioequivalent (80% passing rate) Test and Reference drugs.
  - For such difference in WSV, where $\text{WSV}_{\text{Test}} > \text{WSV}_{\text{Reference}}$, the proportion of therapeutic failure (%TF= number of subject moving from within to outside a TW ) cannot be higher than 10% for a drug with a TI of 1.5.
Recommendations

1. Therapeutic index ≤ 3 is a reasonable cutoff to define NTI drugs.

2. Therapeutic index and small increments of dose adjustment are adequate for NTI classification.

3. To achieve a passing rate of 80% in a BE trial, the maximum observed $\frac{W_{SV_{test}}}{W_{SV_{reference}}}$ is 1.4