Electronic Supplementary Material 2: Narrow Therapeutic Index Drug Definitions

1. Food and Drug Administration (FDA) Narrow Therapeutic Index (NTI)/Narrow Therapeutic Range (NTR) Drug Definitions

1.1 FDA Guidance for Industry: Drug Interaction Studies (page 45) [1]:

“NTR (narrow therapeutic range) drugs are defined as those drugs for which there is little separation between therapeutic and toxic doses or the associated blood or plasma concentrations (i.e., exposures). In general, the toxicity in question is serious toxicity, not symptomatic reversible toxicity.”

Some areas of discussion about this definition:

- “Little separation” is not quantitative nor does it provide a clear, reproducible guideline.
- Some experts have used a 2-fold increase or 50% decrease in object drug exposure associated with adverse response (in some/most) patients as a general guide. However, this may be too conservative for some drugs (e.g., beta blockers in hypertension) and too liberal for others (e.g., warfarin).

1.2 FDA Guidance for Industry: Drug Interaction Studies (page 44, footnote under Table 5) [1]:

“All CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., torsades de pointes).”

Some areas of discussion about this definition:

- Specific only to increase in exposure AND CYP substrates. What about other enzymes or transporters? What about loss of efficacy?
- What change in drug exposure constitutes a ‘small increase’?
- Other than torsades de pointes, what constitutes a ‘serious safety concern’?

1.3 According to 21 CFR 320.33(c), narrow therapeutic ratio is defined as follows [2]:

- Less than a 2-fold difference in median lethal dose (LD50) and median effective dose (ED50) values; or
- Less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood; and
- Safe and effective use of the drug products requires careful titration and patient monitoring.

2. G-Standard (a Dutch National DDI Database) NTI Definition

In specific cases of products with a NTI, the acceptance interval for AUC may need to be tightened to 90.00-111.11%. Where Cmax of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter. It is not possible to define a set of criteria to categorize drugs as NTI drugs and it must be decided case by case if an active substance is an NTI drug based on clinical considerations [3].

The G-Standard consulted the following data and definitions from Canadian, Belgian, Spanish and American authorities to develop their NTI definition (M. le Comte, personal communication, 4/18/2013):

- Belgische substitution guidelinen (translated from Dutch to “Prescribing on generic name”)
- Besluit Spaanse ministerie voor Gezondheid en Consumentenzaken (translated from Dutch to “Decision Spanish Ministry for Health and Consumer Issues”)
- FDA, Center for Drug Evaluation and Research (CDER), Code of Federal Regulations 21 CFR 320.33 (c), December 2005
3. **European Medicines Agency – No Definition**

The European Medicines Agency (EMA) states in their guideline on the investigation of bioequivalence, “It is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTID) and it must be decided case by case if an active substance is an NTID based on clinical considerations” [4].

**References**