FDA Proposal for Bioequivalence of Generic Narrow Therapeutic Index Drugs

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Outline

• Objectives of proposal
• Establishment of regulatory definition of narrow therapeutic index (NTI)
• Other regulatory agencies and NTI drugs
• Potency
• Study design
• Bioequivalence (BE) limits
• Summary and conclusions
Objectives of proposing a new BE approach for generic narrow therapeutic index (NTI) drugs
Objectives of proposing a new BE approach for generic NTI drugs

• For NTI drugs, comparatively small differences in plasma concentrations may lead to serious therapeutic failures or adverse reactions

• Do we need to have a new BE approach that adds additional assurance of similarity of delivered doses and plasma concentrations following brand-generic or generic-generic switches?
Establishing a regulatory definition of NTI drugs
Elements of proposed regulatory definition of NTI drugs

• Small differences in dose or plasma concentration may lead to serious therapeutic failures and/or adverse reactions;
• Serious events are persistent, irreversible, slowly reversible, and/or life-threatening;
• Steep dose-response curves;
• Subject to therapeutic drug monitoring;
• Small within-subject variability.
NTI drugs have steep plasma concentration-response curves

- **Serious adverse reactions**: > 20 units/mL
- **Moderate adverse reactions**: 12-16 units/mL
- **Mild side effects**: 8-10 units/mL

**Therapeutic range**: 4-10 units/mL

Response vs. Log [plasma concentration]
NTI drugs generally have small within-subject variability

Estimated within-subject variability from BE studies of approved generic NTI drugs reviewed from 1996-2008
Possible theoretical worst-case scenarios for BE study outcomes

- GMR = 1.00 [0.95, 1.05]
- GMR = 0.85 [0.80, 0.90]
- GMR = 1.20 [1.15, 1.25]
What do other regulatory agencies require in generic NTI drug submissions?
BE study acceptance criteria for generic NTI drugs

- European Union (EMA)
  - AUC: 90-111.11%
  - Cmax: 90-111.11% or 80-125%; case-by-case

- South Africa (MCC)
  - AUC and Cmax: 80-125%**
  - Should not substitute generic NTI drugs unless patient adequately monitored during transition

** For non-NTI drugs, BE limits for Cmax are 70-133%
BE study acceptance criteria for generic NTI drugs (cont’d)

• Canada (Health Canada)
  – For “critical dose” drugs
  – AUC: 90-112%; Cmax: 80-125%

• Japan (NIHS) – AUC, Cmax: 80-125%
  – Compare in vitro dissolution profiles of lower strengths of test and reference products
  – If statistical tests show that test and reference dissolution profiles are not similar, then in vivo testing is necessary (no biowaiver)
Potency
Proposed potency specifications for NTI products

• Generic versions of NTI drug products will be expected to meet assayed potency specifications of 95.0% to 105.0%

• This will assure that switching between brand-to-generic or generic-to-generic will provide comparable doses

• This will also help ensure consistency of the dose delivered throughout shelf life
Recommended BE study design for NTI drugs
Recommended BE study design for NTI drugs

- Four-way crossover, fully replicated design
- Test product given twice
- Reference product given twice
- This design will provide the ability to
  - Scale a criterion to the within-subject variability of the reference product; and
  - Compare test and reference within-subject variances to confirm that they do not differ significantly.
Recommended BE limits for generic NTI drugs
Recommended BE limits for generic NTI drugs

• BE limits will change as a function of the within-subject variability of the reference product (reference-scaled average bioequivalence ("reference-scaled ABE"))

• If reference variability is \( \leq 10\% \), then BE limits are reference-scaled and are narrower than 90-111.11% 

• If reference variability is \( > 10\% \), then BE limits are reference-scaled and wider than 90-111.11%, but are capped at 80-125% limits 

• This proposal encourages development of low-variability formulations
Reference-scaled ABE approach

• T and R are considered BE if

\[
\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \theta
\]

• Where
  – \(\mu_T\) and \(\mu_R\) are the means of the ln-transformed pharmacokinetic (PK) endpoint;
  – \(\sigma_{WR}\) is the within-subject standard deviation (SD) of the ln-transformed PK endpoint of the reference
Reference-scaled ABE (cont’d)

• The regulatory limit $\theta$ is defined as

$$\theta \equiv \left( \frac{\ln(\Delta)}{\sigma_{W0}} \right)^2$$

• Where $\sigma_{W0}$ is a regulatory constant
• $\Delta$ is the upper BE limit that applies when $\sigma_{WR} = \sigma_{W0}$
• For NTI drugs, FDA proposes to set $\sigma_{W0}$ as 0.10 and $\Delta$ as 1.1111 ($= 1.0/0.9$)
Implied BE limits on Geometric Mean (T/R) Ratios

% Within-Subject Variability of Reference

Geometric Mean Ratio (GMR)

upper limit
lower limit
Summary and conclusions
Summary

• Applying a regulatory definition will permit classification of drugs which have a NTI

• Tightening potency specifications will reduce variation in delivered doses of NTI drugs upon brand-to-generic or generic-to-generic switches
Summary (cont’d)

• Conducting 4-way fully replicated BE studies will permit comparison of test and reference AUC and Cmax variances to assure that these do not differ significantly.

• Applying a reference-scaled ABE approach to analyze BE data from generic NTI drugs is more conservative and more appropriate to the PK characteristics of each NTI drug.
Overall, we conclude that using the proposed approaches will:

- Bring the US into harmony with other regulatory agencies who make special considerations for acceptance limits for BE studies of NTI drugs; and
- Improve public confidence in quality and switchability of generic formulations of NTI drugs.
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