A PRACTICAL ALTERNATIVE METHOD FOR ASSESSING INDIVIDUAL AND POPULATION BIOEQUIVALENCE

A. Lawrence Gould
Merck Research Laboratories

FDA PHARMACEUTICAL SCIENCE ADVISORY COMMITTEE

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INTRODUCTION (1)

- Subjects' bioavailabilities of two formulations not independent:

Different kinds of bioequivalence
Average ($\mu_T = \mu_R$)

Population (marginal distns coincide)  
$\Rightarrow$ formulations equally prescribable

Individual (large differences between subject's response to formulations unlikely)  $\Rightarrow$ formulations are switchable
INTRODUCTION (2)

- Some scenarios (eg, log AUC)

**Ideal:**
Distns nearly coincide

**Not even average BEQ**

**Problem:**
Either Test as Rx-able as Ref, but not vice versa nor with each other – not avg BEQ

- Avoid asymmetric decision scenarios
MIXED MODEL

- Standard model:
  \[ Y_{tj} = \text{Value for subject } j \text{ on formulation } t \]
  \[ = \text{Population Formulation Effect} \]
  \[ + \text{Subject Effect (Var = } \sigma^2_{BT} \text{ or } \sigma^2_{BR} \text{)} \]
  \[ + \text{Within-Subject Error} \]
  \[ (\text{Var = } \sigma^2_{WT} \text{ or } \sigma^2_{WR} \text{)} \]

  Test \((t = T)\) or Reference \((t = R)\)

- Subject x Formulation Interaction = \(\sigma^2_D\)
  \[ = \text{Var(Subject T effect – Subject R effect)} \]
  \[ = (\sigma^2_{BT} - \sigma^2_{BR})^2 + 2(1-\rho)\sigma^2_{BT}\sigma^2_{BR} \]
FDA CRITERIA

- FDA population & individual BEQ criteria based on expectations of squares of Test - Reference bioavailability differences

⇒ Combine mean bioavailability difference and variance components:

Population: \((\mu_T - \mu_R)^2 + \sigma_T^2 - \sigma_R^2 < \lambda \theta\)

Individual: \((\mu_T - \mu_R)^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2 < \lambda \theta\)

Average: \((\mu_T - \mu_R)^2 < \Delta\)

⇒ \(\lambda = \) constant or scaling factor (\(\sigma_R^2\) for popn BEQ, \(\sigma_{WR}^2\) for indiv BEQ)

⇒ Requires 3- or 4-period designs
ISSUES

- Justifiable regulatory burden?
- Practical importance for most drugs?
- Prescribability & switchability intuitively sensible in principle, but

  No published evidence of clinical problems from substituting formulations that are average but not popn/indiv BEQ

- FDA criteria are an approach to evaluating individual BEQ, but not the only one
ALTERNATIVE APPROACH (1)

- Requiring

  Individual BEQ $\Rightarrow$ Population BEQ
  Population BEQ $\Rightarrow$ Average BEQ

prevents scenarios like

![Diagram showing the relationship between Individual BEQ, Population BEQ, and Average BEQ]

- ABE
- ABE
ALTERNATIVE APPROACH (2)

- Recall distributional picture:

- Individual & population BEQ can be evaluated using standard regression/correlation calculations on data from 2 x 2 crossover designs

  ⇒ Statistical properties of estimators well known in normal case, nonparametric & robust analogues exist
ALTERNATIVE APPROACH (3)

- Take sum of each subject's obsns on T, sum of each subject's obsns on R
- Correlation between obsns on T & R $\rightarrow$ intuitive measure of individual BEQ
- Correlation coeff consistently estimates

$$\rho \frac{\sigma_{BT} \sigma_{BR}}{\sqrt{\left(\sigma_{BT}^2 + \sigma_{WT}^2\right)\left(\sigma_{BR}^2 + \sigma_{WR}^2\right)}}$$

$$= \rho \sqrt{\frac{\sigma_{WT}^2}{\sigma_{BT}^2} + \frac{\sigma_{WR}^2}{\sigma_{BR}^2}}$$

- Includes within-subject variability as well as sfi -- large within-subject variation diminishes correlation
- Since subject x formulation is

$$\sigma_D^2 = (\sigma_{BT} - \sigma_{BR})^2 + 2(1-\rho)\sigma_{BT}\sigma_{BR}$$

large s x f interaction diminishes correlation
ALTERNATIVE APPROACH (3)

• Slope of regression of \((T + R)\) on \((T - R)\) consistently estimates

\[
\gamma = \frac{\sigma_T^2 - \sigma_R^2}{\sigma_T^2 + \sigma_R^2 - 2\rho \sigma_{BT} \sigma_{BR}}
\]

• Scaled difference between total variances on \(T\) & \(R\) ⇒ reasonable measure of population BEQ

• High correlation (good indiv BEQ) exaggerates \(\gamma\), more difficult to conclude popn BEQ

⇒ I.E., if not popn BEQ, then indiv BEQ probably not meaningful

• Conclusions appear to be close in most cases to FDA method, perhaps less sensitive to pathologies & biases
KEY POINTS

• Population and Individual BEQ are intuitively appealing concepts

• There does not appear to be any evidence that these concepts are needed for the evaluation of most (> 90%) drugs

• Population and Individual bioequivalence can be evaluated in various ways

• Guidance proposal has some statistical appeal, but

  ⇒ Expensive

  ⇒ raises issues of clinical relevance

  ⇒ justification of regulatory burden?

• Can assess PBE and IBE using data from conventional 2 x 2 crossovers – results consistent w/Guidance