A PRACTICAL ALTERNATIVE METHOD FOR ASSESSING INDIVIDUAL AND POPULATION BIOEQUIVALENCE

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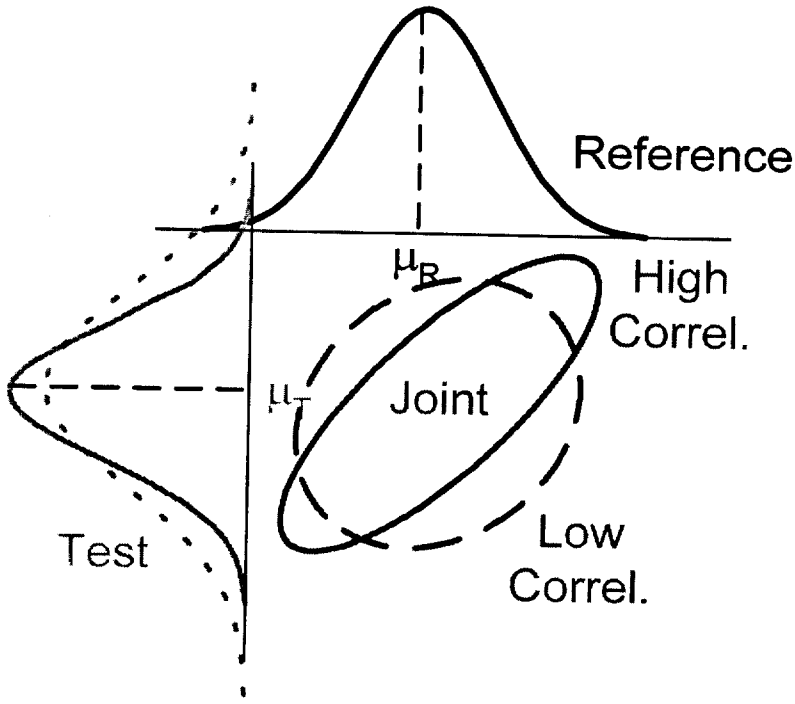
INTRODUCTION (1)

- Subjects' bioavailabilities of two formulations not independent:



Different kinds of bioequivalence

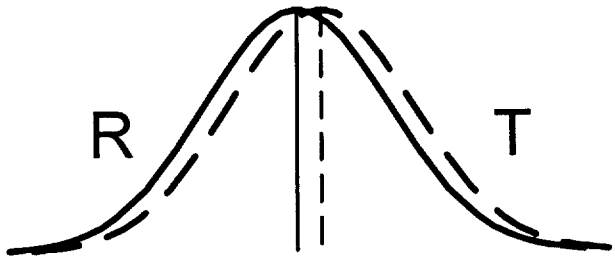
Average ($\mu_T = \mu_R$)

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

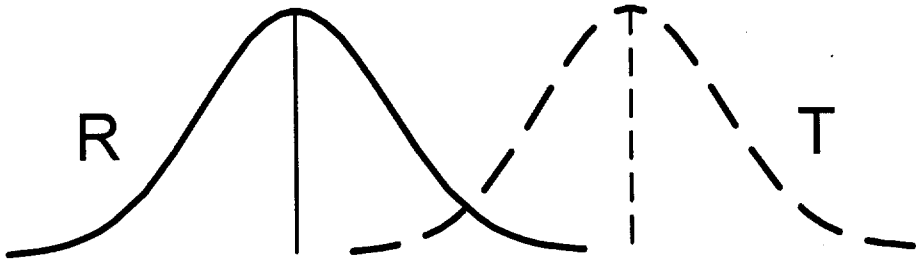
Individual (large differences between subject's response to formulations unlikely) $\Rightarrow$ formulations are switchable

INTRODUCTION (2)

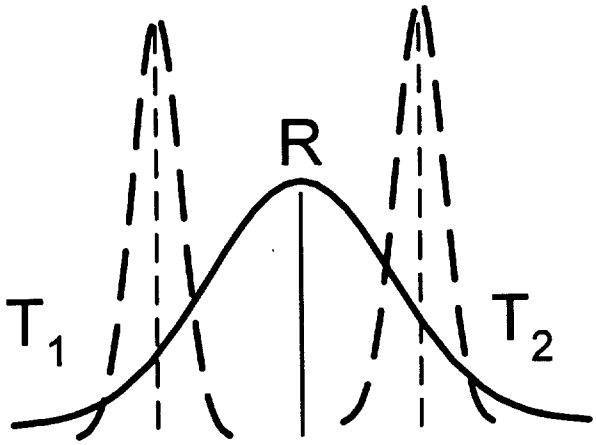
- Some scenarios (eg, log AUC)



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} = Value for subject j on formulation t
= Population Formulation Effect
+ Subject Effect (Var = σ^2_{BT} or σ^2_{BR})
+ Within-Subject Error
(Var = σ^2_{WT} or σ^2_{WR})

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

- Subject x Formulation Interaction = σ^2_D

= Var(Subject T effect – Subject R effect)

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

FDA CRITERIA

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

$\Rightarrow$ 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: $(\mu_T-\mu_R)^2 < \Delta$

$\Rightarrow$ λ = constant or scaling factor (σ_R^2 for popn BEQ, σ_{WR}^2 for indiv BEQ)

$\Rightarrow$ 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 <u>an</u> approach to evaluating individual BEQ, but <u>not the only one</u>

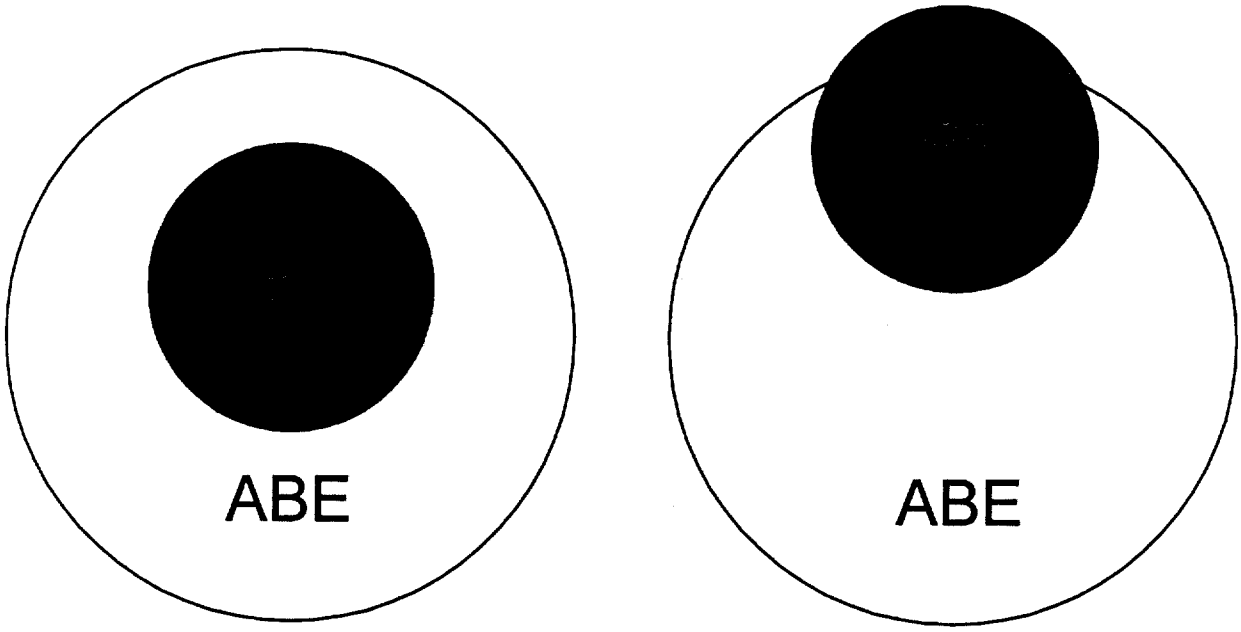
ALTERNATIVE APPROACH (1)

- Requiring

  Individual BEQ $\Rightarrow$ Population BEQ

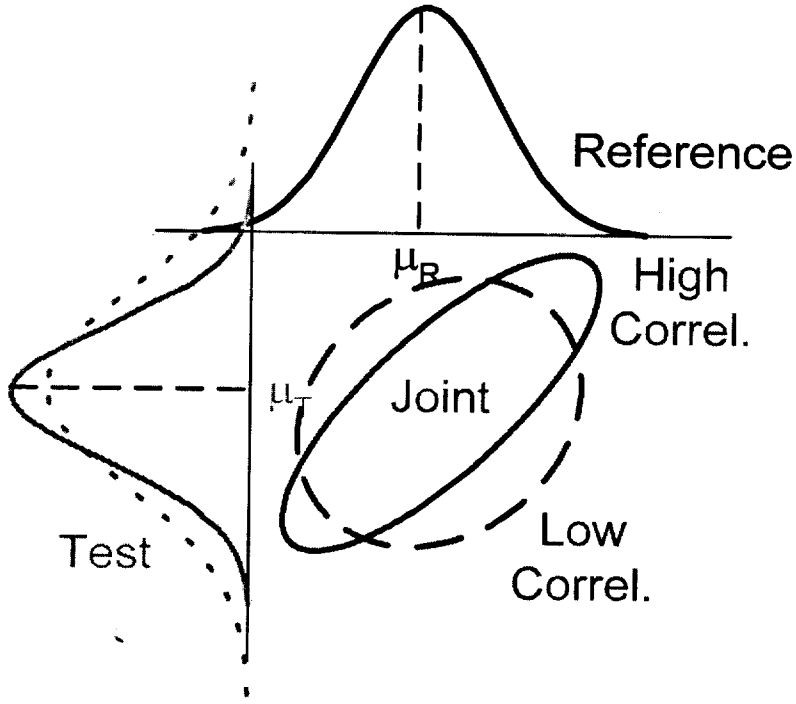
  Population BEQ $\Rightarrow$ Average BEQ

  prevents scenarios like



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

  $\Rightarrow$ 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 → intuitive measure of individual BEQ
- Correlation coeff consistently estimates

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

$$= \rho \Big/ \sqrt{\left(1+\sigma_{WT}^2/\sigma_{BT}^2\right)\left(1+\sigma_{WR}^2/\sigma_{BR}^2\right)}$$

- 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 diminshes correlation

ALTERNATIVE APPROACH (3)

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

$$\gamma = (\sigma_T^2 - \sigma_R^2)/(\sigma_T^2 + \sigma_R^2 - 2\rho\sigma_{BT}\sigma_{BR})$$

- Scaled difference between total variances on T & R $\Rightarrow$ reasonable measure of population BEQ
- High correlation (good indiv BEQ) exaggerates γ, more difficult to conclude popn BEQ

  $\Rightarrow$ 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