Advisory Committee for Pharmaceutical Science

CRITERIA AND UPDATE OF GUIDANCE

Mei-Ling Chen, Ph.D.
Director
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics
Food and Drug Administration

September 23-24, 1999

FDA DRAFT GUIDANCE (1999)

Average, Population, and Individual Approaches to Establishing Bioequivalence

http://www.fda.gov/cder/guidance/index.htm

STATISTICAL GUIDANCE (1999)

- **Updates 1997 Preliminary Draft Guidance**

  In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches

- **Incorporates 1992 Guidance**

  Statistical Procedures for Bioequivalence Studies Using Standard Two-Treatment Crossover Design

- **Focuses on statistical methods**

- **"When to use" - in the general BA/BE guidance**

GUIDANCE OUTLINE

- Statistical Model
- Bioequivalence Criteria
- Study Design
- Statistical Analysis
- Miscellaneous Issues

BIOEQUIVALENCE CRITERIA

- **Average BE**
  - Population means (μ_T, μ_R)
- **Population BE**
  - Population means
  - Total variances (σ_{TT}^2, σ_{TR}^2)
- **Individual BE**
  - Population means
  - Within-subject variances (σ_{WT}^2, σ_{WR}^2)
  - Subject-by-formulation interaction (σ_D^2)

BIOEQUIVALENCE ASSESSMENT

GENERAL PRINCIPLE

- **DR = Difference between T and R / Difference between R and R′**

- **Administration**
  - Individual BE - T and R to the same individual
  - Population BE - T and R to different individuals

- **Difference Ratio**
  - Individual Difference Ratio (IDR)
  - Population Difference Ratio (PDR)

- **Goal:** IDR or PDR not substantially greater than 1.0

BIOEQUIVALENCE CRITERIA

- **Average Difference + Variance Terms / Reference Variance ≤ BE Limit**

Individual BE	$\dfrac{(\mu_T - \mu_R)^2 + \sigma_D^2 + (\sigma_{WT}^2 - \sigma_{WR}^2)}{\sigma_{WR}^2} \le \theta_I$
Population BE	$\dfrac{(\mu_T - \mu_R)^2 + (\sigma_{TT}^2 - \sigma_{TR}^2)}{\sigma_{TR}^2} \le \theta_P$

RATIONALE FOR REFERENCE-SCALING

- Pioneer/reference product has been demonstrated to be safe and efficacious clinically.
- The variability of the reference product defines the therapeutic window and thus, should set or otherwise adjust the public standard (e.g., BE limits).
- Away from the "one-size-fits-all" approach
- The goalpost may be widened for highly variable drugs and/or products, and narrowed for NTR drugs/products.

AGGREGATE VS. DISAGGREGATE CRITERIA

- **Aggregate**

  The means and variances are considered together in one criterion.
  - reward for reduced variability
  - tradeoff between means and variances

- **Disaggregate**

  The means and variances are considered separately, e.g., one criterion for means, and another criterion for variances.

DISAGGREGATE CRITERIA

- **Reasons for -**
  - Preserve the current average BE criterion
  - Avoid mean-variance trade-off
- **Reasons against -**
  - Multiplicity of tests - increase in regulatory burden
  - Ignore the fundamental "switching" concept
  - No reward/encouragement for lower variability
- **The FDA draft guidance recommends the aggregate criterion.**

MEAN VS. VARIANCE TRADE-OFF

$$\frac{(\mu_T - \mu_R)^2 + \sigma_D^2 + (\sigma_{WT}^2 - \sigma_{WR}^2)}{\sigma_{WR}^2} \leq \theta_I$$

Approaches considered for resolution of concerns -

- Weighting of the appropriate variance terms
  - disturbs the IDR concept which underlies the IBE criterion

- Constraint on the allowable mean difference
  (e.g., $\leq$ 10 % ~ 20%)

STATISTICAL ISSUES - RESOLUTION

- **Two major improvements in the 1999 Guidance**
- **Estimation of Variances**
  - Restricted maximum likelihood method (1997)
  - Method of moments (1999)
- **Computation of Confidence Intervals**
  - Bootstrap method (1997)
  - Non-bootstrap method (1999)