

**COMMENTS ON FDA PRIMARY MOTIVATIONS
IN THE PRESENCE OF
ESTIMATED VARIABILITIES**

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PRIMARY MOTIVATIONS OF FDA

1. SUBJECT-BY-FORMULATION INTERACTION
2. REFERENCE SCALING
3. REWARD FOR REDUCED VARIABILITY IN
THE TEST PRODUCT

3547s 1-1

MOTIVATION 1: SUBJECT-BY-FORMULATION INTERACTION

- **IS THERE A DEMONSTRATED CLINICAL PROBLEM?
NO EVIDENCE, NO INDICATION**
- **FDA: "ABSENCE OF EVIDENCE
IS NOT EVIDENCE OF ABSENCE"**
- ***A NEW REGULATORY APPROACH?***

MOTIVATION 2: REFERENCE SCALING (RS)

**Highly variable drugs
RS widens BE limits**

**Narrow therapeutic range (NTR) drugs
RS narrows BE limits
 $\epsilon = 0$**

REFERENCE SCALING: COMMENTS

Highly variable drugs

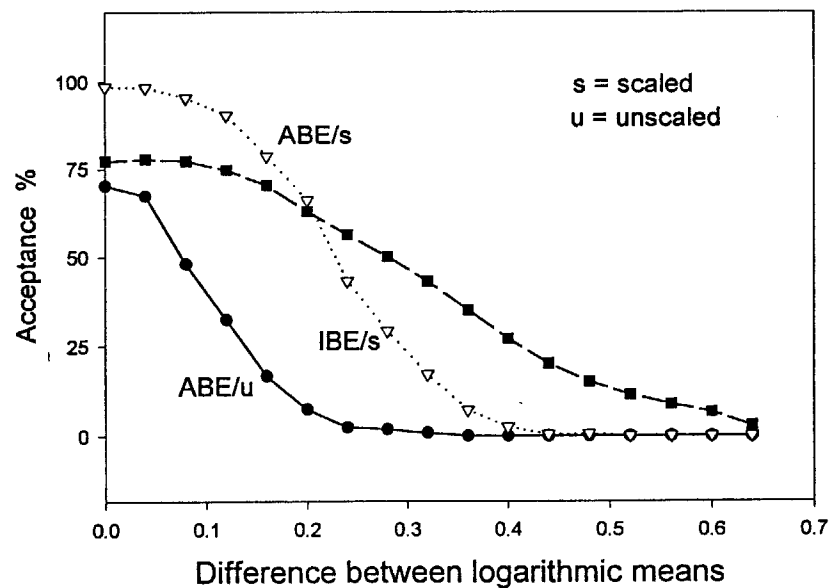
Scaled ABE probably more effective than scaled IBE
Expert Panel has asked for scaled ABE in October, 1998
FDA is very reluctant to consider it

NTR drugs

Scaled IBE with $\epsilon = 0$ can be punitive
E. Masson & A. Yacobi, Montreal Workshop on IBE:
2 warfarin formulations were:
ABE with 95% CI within 90-111%
IBE with constant scaling

4-PERIOD REPLICATE-DESIGN STUDIES POWER CURVES FOR ABE & IBE

(24 Subjects, CV = 40%)



MOTIVATION 3: REWARD FOR $\sigma_{WT}^2 < \sigma_{WR}^2$

A consequence of the *aggregate criterion*

Numerator of proposed criterion (setting constant σ_D^2):

$$(\mu_T - \mu_R)^2 + (\sigma_{WT}^2 - \sigma_{WR}^2) < \text{Constant}$$

If $\sigma_{WT}^2 < \sigma_{WR}^2$ $(\mu_T - \mu_R)^2$ can expand
and still be acceptable

Hauck et al. (1996) Int. J. Clin. Pharmacol. Ther. 34: 535-541

AGGREGATE CRITERION: COMMENTS

Components of proposed aggregate criterion:

Difference between means

Difference between intrasubject variances

Subject-by-formulation interaction

Aggregate criterion is:

Attractive in principle, difficult in practice

L. Endrenyi, G.L. Amidon, K.K. Midha, J.P.
Skelly (1998) Pharm. Res. 15: 1321-1325

Difficulties with aggregate criterion:

- Conceptual
 - Individual BE should include population BE
 - Population BE should include average BE
- Technical

Montreal workshop on individual BE

(August 30 - Sept. 1, 1999)

Disaggregation was proposed by all speakers,
outside FDA, considering the subject:

A.L. Gould

R. Schall

V.W. Steinijans

PhRMA

L. Endrenyi

REWARD FOR $\sigma^2_{WT} < \sigma^2_{WR}$: COMMENTS

In the presence of random variations:

1. Not only rewards can be gained but also penalties can be incurred
2. The *rewards* and penalties *dominate* the difference between the two means
3. *Both rewards and penalties can be large due to random chance !!*

Endrenyi and Hao. (1998). Int. J. Clin. Pharmacol. Ther. 36: 450-457

ESTIMATED PROBABILITY (%) FOR A CHANGE IN AUC-DIFFERENCE, BY CHANCE, BY AT LEAST A GIVEN %, STILL COMPATIBLE WITH BIOEQUIVALENCE

ΔAUC	CV^0_{WR}		
	20%	30%	40%
5%	85.0	93.4	96.3
10%	43.8	73.3	84.3
15%	8.5	44.1	64.5

REWARD FOR $\sigma_{WT}^2 < \sigma_{WR}^2$: COMMENTS

Analysis of FDA data, August, 1999
55 data sets

Estimated s_{WT}^2 and s_{WR}^2

	Reward $s_{WT}^2 < s_{WR}^2$	Penalty $s_{WT}^2 > s_{WR}^2$	Total
AUC	27	28	55
C_{max}	22	33	55
Total	49	61	110

- Rewards and penalties occur apparently at random

REWARD FOR $\sigma_{WT}^2 < \sigma_{WR}^2$: COMMENTS

Analysis of FDA data, August, 1999
55 data sets
Estimated s_{WT}^2 and s_{WR}^2

	Reward $s_{WT}^2/s_{WR}^2 < 0.70$	Penalty $s_{WT}^2/s_{WR}^2 > 1.41$	Total
AUC	6	3	9
C_{max}	3	9	12
Total	9	12	21

s_{WT}^2/s_{WR}^2 significantly different from 1.0 ($\alpha = 0.10$):

	Reward $s_{WT}^2 < s_{WR}^2$	Penalty $s_{WT}^2 > s_{WR}^2$	Total
AUC	5	7	12
C_{max}	6	5	11
Total	11	12	23

- Large (and statistically significant) rewards and penalties can occur fairly frequently

MEAN-VARIABILITY TRADEOFF

FDA DATA, 1998

Mean Diff vs. Variability Diff

$(\mu_T - \mu_R)^2$ vs. $|s_{WT}^2 - s_{WR}^2|$

	MeanDiff < VarDiff	Mean Diff > VarDiff
AUC	30	3
C _{max}	28	6
Total	58	9

Without weighting in the aggregate model:
Difference between variances dominates
difference between means