SCALED AVERAGE BIOEQUIVALENCE: AN APPROACH TO RESOLVE A DIFFICULT PROGRAM

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BIOEQUIVALENCE: USUAL REGULATORY CRITERION

Record: Parameters (AUC and Cmax) of N subjects for the Test (T) and Reference (R) products

Calculate: Averages of the logarithmic parameters for both formulations

By taking antilogs, get geometric means for the two formulations

Take the ratio (T/R) of the two geometric means (GMR)

Calculate the 90% confidence limits of GMR

Criterion: The confidence limits for GMR should be between 0.80 and 1.25.

THE PROBLEM OF HIGHLY-VARIABLE DRUGS AND DRUG PRODUCTS

Criterion: The confidence limits for GMR should be between 0.80 and 1.25

Problem: With large variation (wide confidence limits):

it is very difficult to satisfy the regulatory criterion,

unless the number of subjects (N) is very large

Problem especially with C_{max}
which often has higher variation than AUC

Definition: Highly-variable drug
if coefficient of variation CV $\geq$ 30%

USUAL REGULATORY CRITERION:
FORMALIZATION

$$1/BEL \leq GMR \leq BEL$$

BEL: BE limit - Usually 1.25

GMR: Ratio of geometric means

$$-\lg BEL \leq \log(GMR) \leq \lg BEL$$

$$-\lg BEL \leq m_T - m_R \leq \lg BEL$$

lgBEL: Logarithm of BEL

m_T, m_R: Estimated logarithmic means

IS THERE A PROBLEM WITH BE FOR HVD/P?

MANY DRUGS PRESENTED TO FDA

B.M. Davit et al. (FDA) AAPS J. 10: 148-156 (2008).

Between 2003-2005:

1,010 acceptable studies

180 different drugs

57 drugs (31%) were highly variable

Note: Only acceptable studies at FDA!

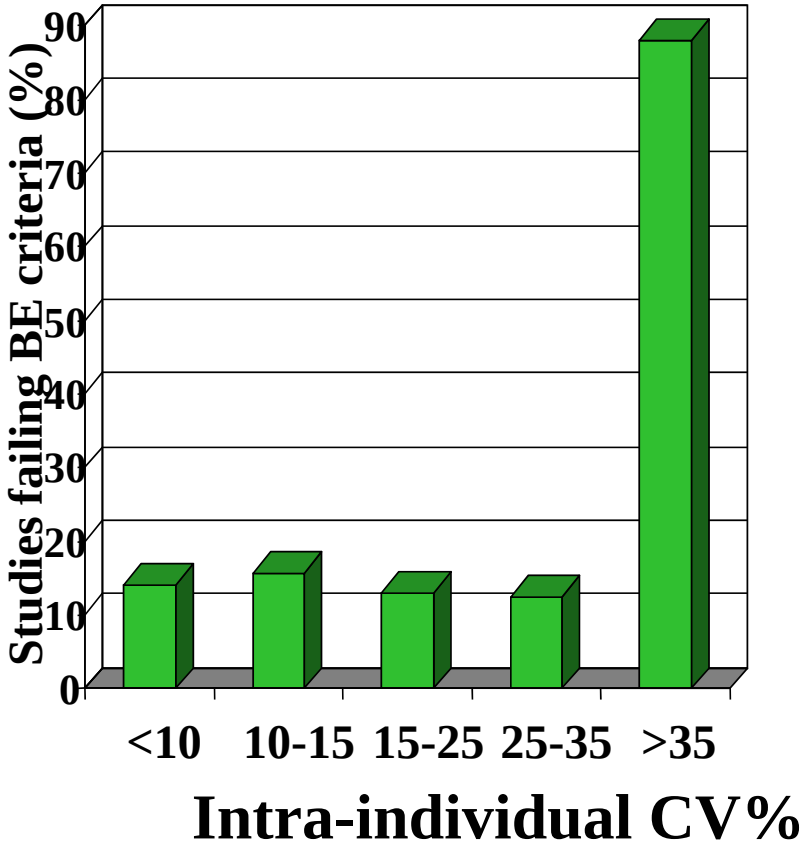
With all studies,

percentage is probably higher

IS THERE A PROBLEM WITH BE FOR HVD?

FAILURE RATE OF BE STUDIES INCREASES WITH C.V.

Failing BE criteria: statistics on 1300 studies



Diane Potvin, MDS Pharma Services

IS THERE A PROBLEM WITH BE FOR HVD/P?

FAILURE RATE OF BE STUDIES INCREASES WITH C.V.

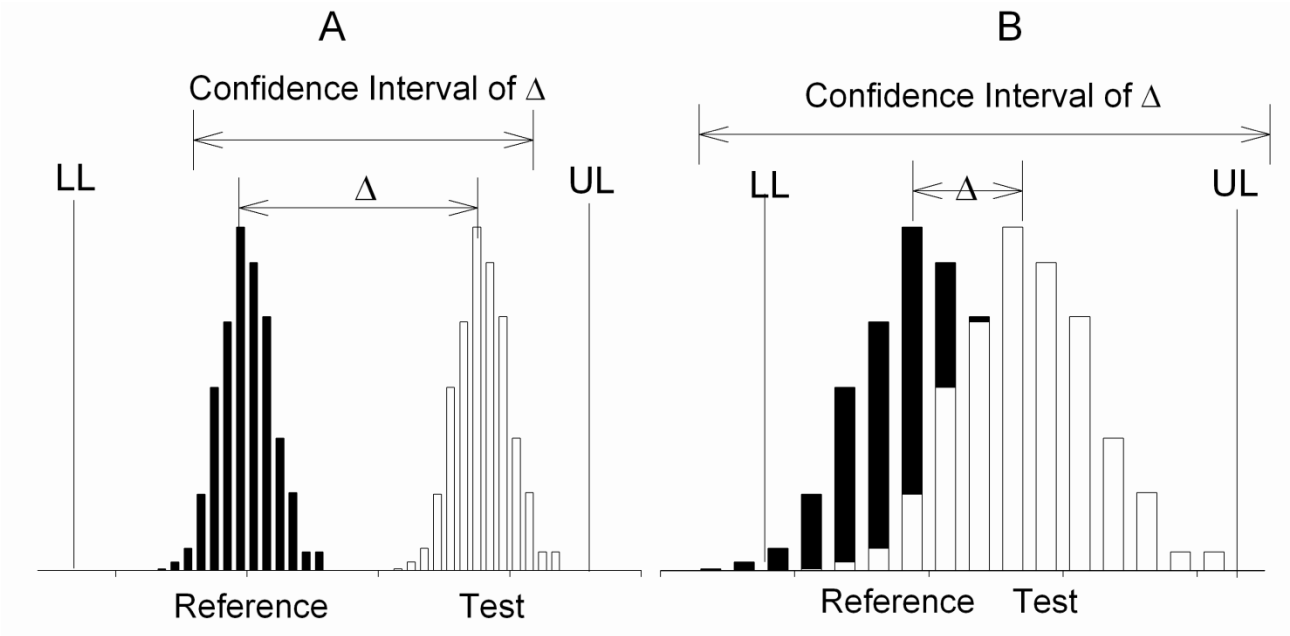
Failed BE studies (% of analytes) #

	C_{max}		AUC	
C.V.	Fail	No.	Fail	No.
35-40%	68%	31	73%	22
40-45%	52%	21	87%	15
45-50%	87%	15	90%	10
50-55%	93%	14	100%	2
55-60%	80%	5	80%	5
60-65%	100%	3	100%	2
≥ 65%	100%	7	100%	5
Total		96		61

Diane Potvin, MDS Pharma, Montréal

Failure rate is high and increases with C.V.
Fewer failures for AUC than for Cmax
but still a substantial number

IS THERE A PROBLEM WITH BE FOR HVD/P?
SIMILAR PRODUCTS "NOT BIOEQUIVALENT"



A: **2 products distinct**
But small variation
"Bioequivalent"

B: **2 products very similar**
But large variation
"Not bioequivalent"

L. Tothfalusi, L. Endrenyi, H.G. Arieta, Clin. Pharmacokin. 21: 725-743 (2009)

IS THERE A PROBLEM WITH BE FOR HVD?

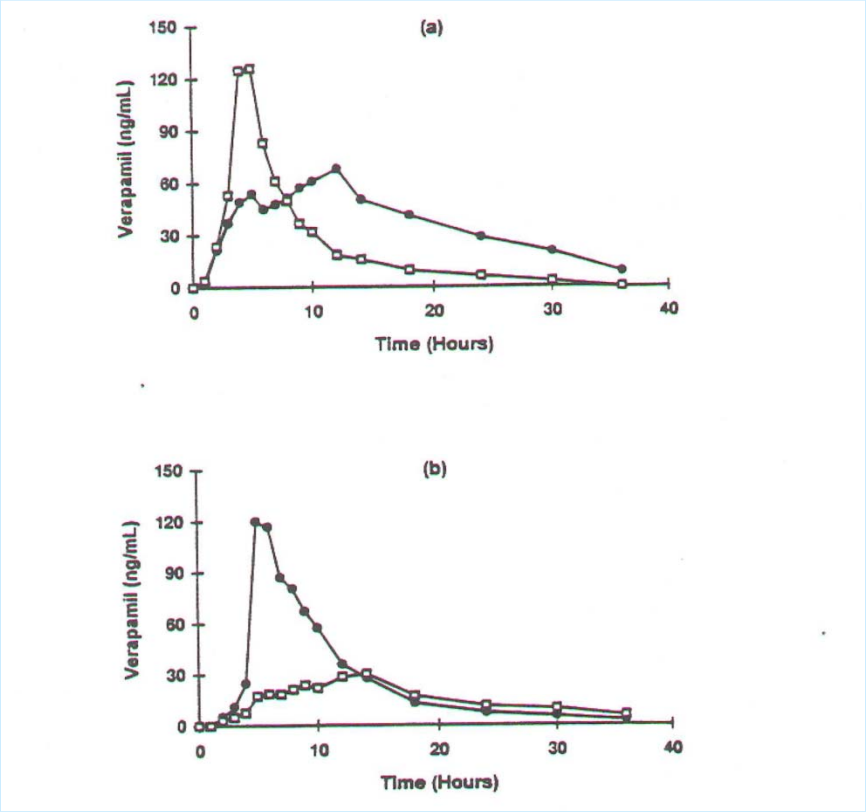
- BIOEQUIVALENT WITH ITSELF?

Administer the same HVD formulation twice:

- generally can not demonstrate BE

Example: oral administration, on two occasions, of IsoptinSR 240 mg tablets

Y.-C. Tsang et al., Pharm. Res. 3: 846 - 850(1996)



Lack of bioequivalence – with itself

Also: chlorpromazine formulations

K.K. Midha et al., Int. J. Clin. Pharmacol. Ther. 43: 465-498 (2005)

POSSIBLE REDUCTION OF VARIATION
USING METABOLITE DATA

Concentrations of metabolites are often less variable than of the parent drug

Simulations:

Preference depends on the contrast of intrinsic clearance and liver blood flow

M.-L. Chen and A.J. Jackson, Pharm. Res. 8: 25-32 (1991)
Pharm. Res. 12: 700-708 (1995)

G. Tucker et al., BioInternational

A.J. Jackson, Pharm. Res. 17: 142-14236 (2000)

But: simulations considered simple assumptions (single metabolite, no subsequent metabolism)

More general conditions:

Safer to rely on data of parent drug

K.K. Midha et al., Pharm. Res. 21: 1331-1344 (2004)

POSSIBLE REDUCTION OF VARIATION

STEADY-STATE STUDIES

Comparative parameters, especially of Cmax, have often (but not always) smaller variation in steady-state studies than following single oral administration

Theoretical:

A.A. El-Tahtawy et al., Pharm. Res. 11:1330-1336 (1994)
12:1634-1641 (1995)
15: 98-104 (1998)

J. Zha and L. Endrenyi, Biopharm. Stat. 7:191-204 (1997)

Observations:

H.H. Blume et al., "BioInternational 2", pp. 117-122 (1995)
B. Schug et al., "BioInternational 96", pp. 101-106 (1996)

Coefficients of variation (%)

Drug	Single dose		Steady state	
	AUC	C_{max}	AUC	C_{max}
Loratadine	44	51	15	29
Verapamil	31	32	19	23
Propafenone	34	39	15	16
✂lipoic acid (R+)	23	73	15	61
✂lipoic acid (S+)-	23	76	15	53

POSSIBLE REDUCTION OF VARIATION

STEADY-STATE STUDIES

Often (but not always) lower variability

But: reduction of variability is

- **Poorly defined (large, small, negative)**
- **Arbitrary (changes with accumulation)**

Estimated C_{max} has positive bias

L.Tothfalusi and L. Endrenyi, J.Pharmacokin. Pharmacodyn. 30: 363-385 (2003)

Lower variability means reduced PK sensitivity for comparing the two drug products, diminished quality control

In Europe but not in U.S.

In Canada, for modified release (if accumulation)

DEALING WITH HIGH VARIATION:

RELAX A REGULATORY REQUIREMENT

Health Canada:

Does not require that the 90% confidence interval of the C_{max} ratio be between 0.80 and 1.25

Expects only that the C_{max} ratio itself should be within these limits

DEALING WITH HIGH VARIATION:

UNSCALED AVERAGE BE WITH EXPANDED LIMITS - PRESET

Unscaled average BE:

$$1/BEL \leq GMR \leq BEL$$

$$-\lg BEL \leq \log(GMR) \leq \lg BEL$$
$$-\lg BEL \leq m_T - m_R \leq \lg BEL$$

For example:

$$0.75 \leq GMR \leq 1.33$$
$$-0.288 \leq m_T - m_R \leq 0.288$$

instead of:

$$0.80 \leq GMR \leq 1.25$$
$$-0.223 \leq m_T - m_R \leq 0.223$$

Advantage:

Simple

Disadvantage:

Arbitrary

Only partial reduction of sample size

Not for higher variabilities

DEALING WITH HIGH VARIATION:

UNSCALED AVERAGE BE WITH EXPANDED LIMITS (ABEL) - PROPORTIONAL TO ESTIMATED VARIATION

Confidence interval of log(GMR) is proportional to estimated variation:

A.W. Boddy et al. Pharm. Res. 12: 1865-1868 (1995)

$$-\lg BEL_S * s_W \le m_T - m_R \le \lg BEL_S * s_W$$

Proportionality factor: $\lg BEL_S = 1.0$ suggested

Advantages:

- Can apply the usual two one-sided t-tests procedure
  (However, see below)
- Statistical power is independent of sample size
- Statistical power is, with same sample size, much higher than of unscaled average BE

Comments:

- The estimated limits are random variables ($\lg BEL_S * s_W$)
- Therefore, application of the two one-sided tests procedure is not correct
  (However, approximately correct with reasonably large N)

DEALING WITH HIGH VARIATION:
SCALED AVERAGE BE (SABE)

Difference between logarithmic means is normalized by estimated variation

R. Schall, BioInternational 2, 91-106 (1995)
L.Tothfalusi et al., Pharm.Res. 18: 728-733 (2001)
L. Tothfalusi and L. Endrenyi, Pharm.Res. 20: 382-389 (2003)

$$-\ lgBEL_S \le (m_T - m_R)/s_W \le lgBEL_S$$

General procedure was suggested for setting BE limits

Advantages:

- Statistical power is independent of variation
- Statistical power is, with same sample size, much higher than of unscaled average BE
- Interpretation: Compare expected change due to switching with expected difference between replicate administrations
- Interpretation: Standardized effect size, as in clinical comparisons

TESTING WITH CONFIDENCE INTERVALS

Scaled Average Bioequivalence (SABE)

$$-\lg BEL_S \le (m_T - m_R)/s_W \le \lg BEL_S$$

$$(m_T - m_R)^2/s_W^2 \le \lg BEL_S^2$$

Linearizing:

$$(m_T - m_R)^2 - \lg BEL_S^2 * s_W^2 \le 0$$

Reject SABE if upper 95% confidence limit is positive

T. Hyslop, F. Hsuan, D.J. Holder, StatMed 19:2885 (2000)

Average Bioequivalence with Expanding Limits (ABEL)

$$-\lg BEL_S * s_W \le m_T - m_R \le \lg BEL_S * s_W$$

Apply two one-sided tests procedure with the wider limits

L. Tothfalusi et al, ClinPharmacokin 48: 725-743 (2009)

INDIVIDUAL BIOEQUIVALENCE

Was much discussed between 1993 and 2003,
and was almost adopted.

The bioequivalence model:

$$\frac{\left(\mu_T-\mu_R\right)^2+\sigma_D^2+\left(\sigma_{WT}^2-\sigma_{WR}^2\right)}{\sigma_W^2}$$

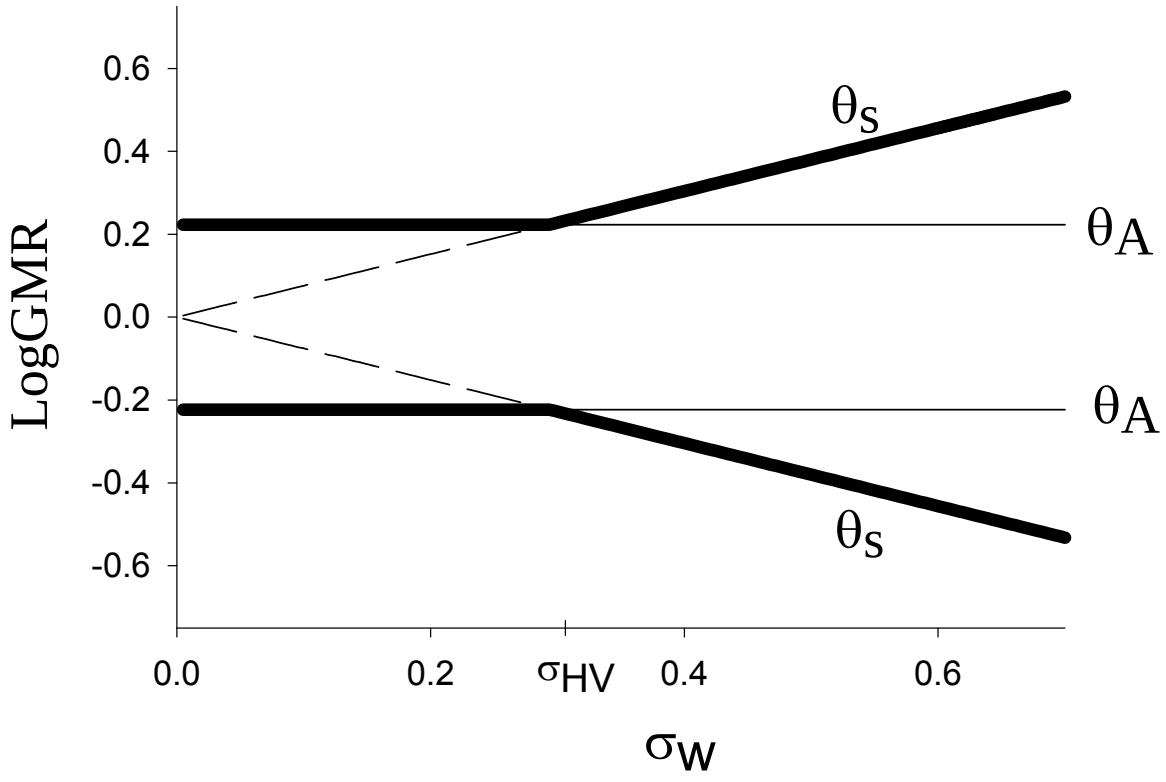
μ_T: population mean of log response to T
μ_R: population mean of log response to R
σ_D: variance component for Subject-by-Formulation interaction
σ_{WT}: within-subject standard deviation of log response to T
σ_{WR}: within-subject standard deviation of log response to R

σ_W in the denominator:

If $\sigma_{WR} \leq 0.294$ ($CV_{WR} \leq 30\%$) then $\sigma_W = \sigma_0$, a constant

If $\sigma_{WR} > 0.294$ ($CV_{WR} > 30\%$) then $\sigma_W = \sigma_{WR}$

SCALED AVERAGE BE –
MIXED MODEL OF BE



Unscaled average BE if $\sigma \leq \sigma_{HV}$,

Scaled average BE if $\sigma > \sigma_{HV}$
(σ_{HV}: Limiting variation)

METHODS FOR DETERMINING BE

DEMONSTRATION OF QUANTITATIVE PROPERTIES (SIMULATIONS)

Simulate 10,000 BE studies under each condition

Determine, at each condition, the proportion (in %) of studies in which BE is accepted: Acceptance%

Assume:

First, true bioequivalence: GMR = 1.0

Then, gradually deviate from true BE, increase GMR in steps

Plot power curve:

Acceptance% vs. GMR

Properties:

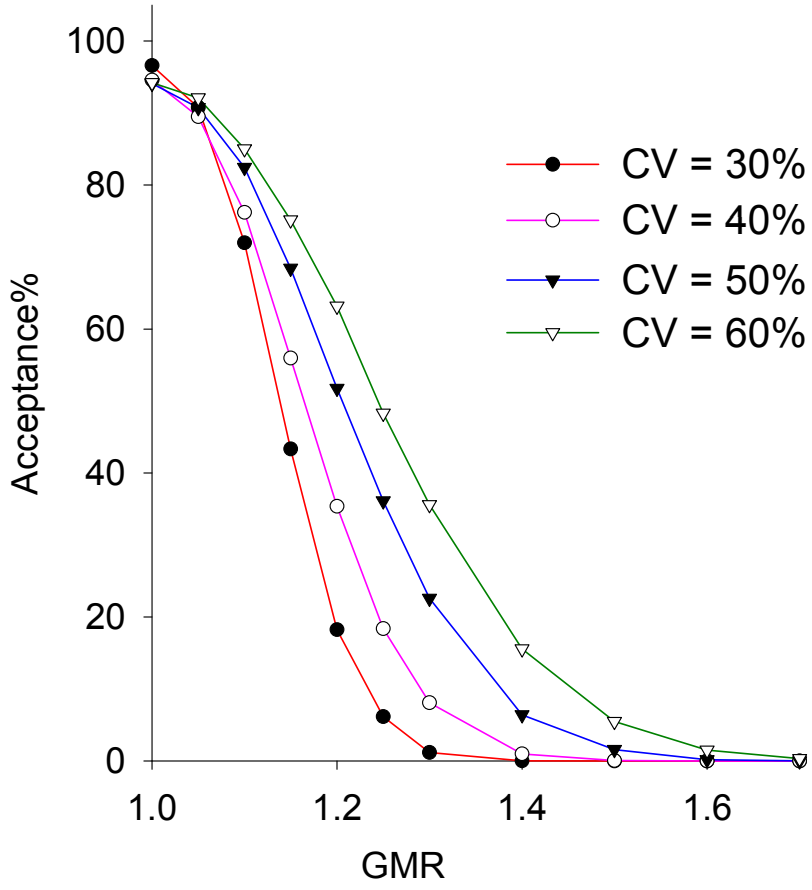
Consumer risk: Probability of accepting BE even when the two products are not equivalent

- Low level controlled by regulatory agencies

Producer risk: Probability of rejecting BE when the two products are equivalent (i.e. when GMR = 1.0)

CHARACTERISTICS OF SCALED AVERAGE BE

N = 48, 2 PERIODS



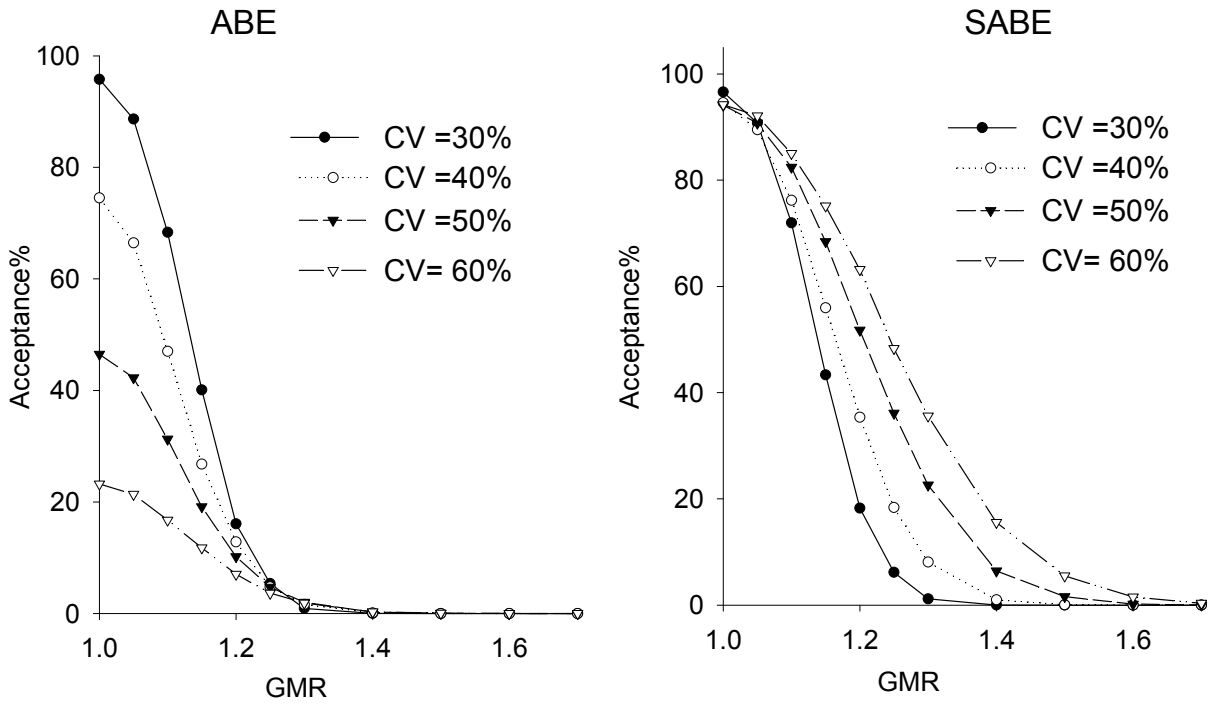
Producer risk is independent of variability

Satisfactory producer risk with 48 subjects

Larger GMRs are permitted when variability is higher

CHARACTERISTICS OF SCALED (& UNSCALED) AVERAGE BE

N = 48, 2 PERIODS



Unscaled average BE yields low acceptance of BE with high variations

Scaled average BE does not yield low acceptance with high variations

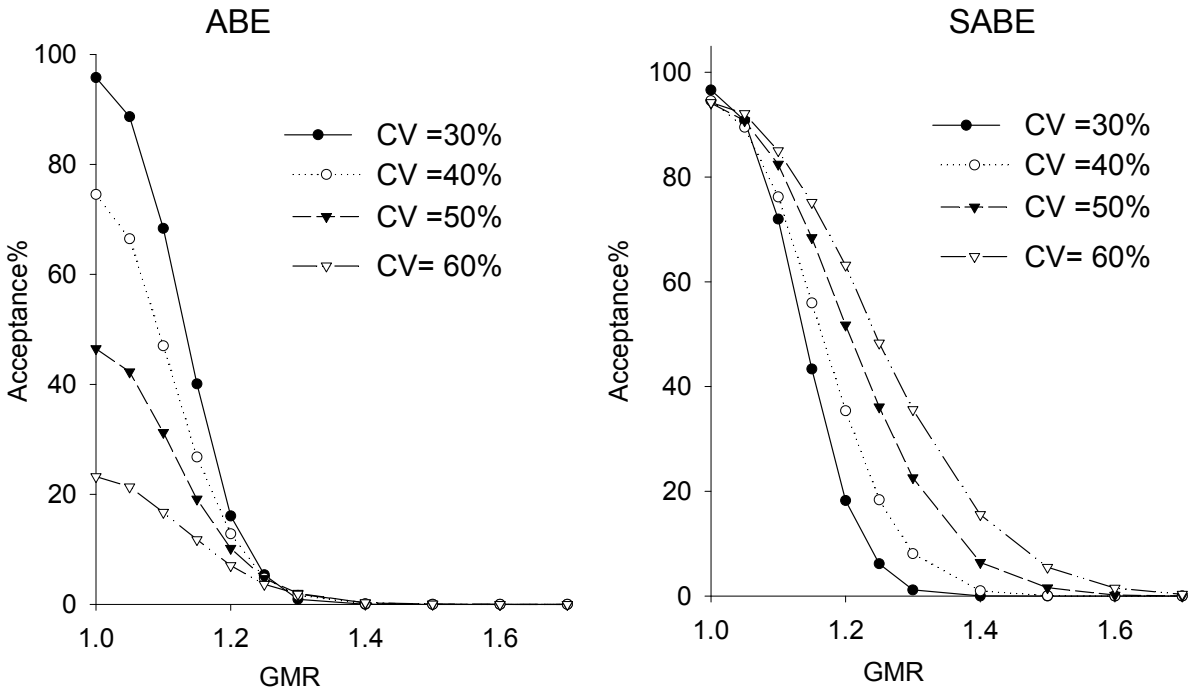
L. Endrenyi, L. Tothfalusi. Clin. Res. Regul. Affairs, 25: 93-117 (2008).
S.H. Haidar et al. AAPS J. 10: 450-454 (2008)

CHARACTERISTICS OF METHODS EVALUATING BE

UNSCALED AND SCALED AVERAGE BE

PARALLEL DESIGN

N = 48



Unscaled average BE yields low acceptance of BE with high variations

Scaled average BE does not yield low acceptance with high variations

INTERPRETATIONS OF SCALED AVERAGE BIOEQUIVALENCE

Equivalence test for effect sizes

Standard/standardized effect size

$(m_A - m_B)/s$

used in medicine, psychology, quality control, etc.

Therapeutic switchability

Individual BE characterized switchability within subjects.

IBE reduces to SABE under some conditions.

FDA PROCEDURE

S.H. Haidar et al. (FDA) Pharm. Res. 25: 237-241 (2008)

3-period, reference-replicated design (at least)
TRR, RTR, RRT

HV drugs: Reference within-subject variation:
CV > 30%

Both AUC and C_{max}

Analysis by scaled average BE (SABE)

Acceptance criterion 1:
lgBEL = ln(1.25)/σ_{W0}
σ_{W0} = 0.25 (regulatory constant)

Acceptance criterion 2:
Point estimate of GMR should be
between 0.80 and 1.25

SOME OUTSTANDING ISSUES:

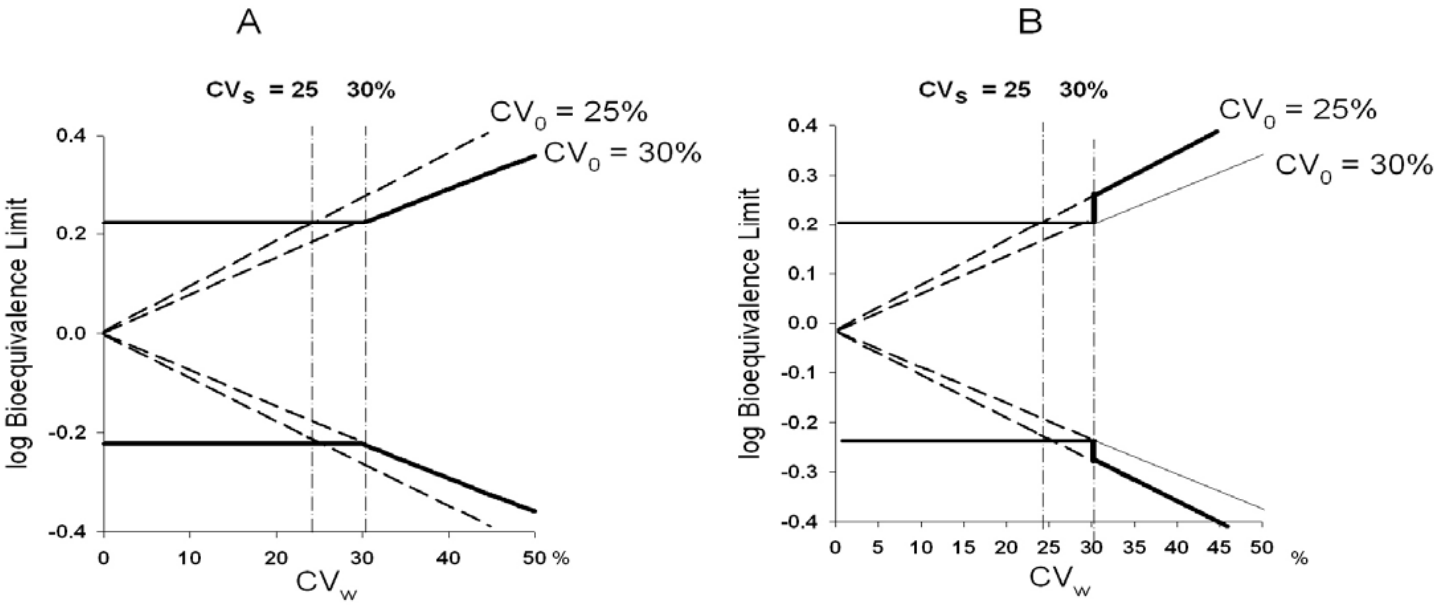
REGULATORY CONSTANT

Acceptance criterion 1

Mixed model of BE

A: Regulatory constant $CV_0 = 30\%$

B: Regulatory constant $CV_0 = 25\%$



Regulatory limits:

- **Continuous with $CV_0 = 30\%$**
- **Discontinuous with $CV_0 = 25\%$**

SOME OUTSTANDING ISSUES:
REGULATORY CONSTANT

Acceptance criterion 1:

lgBEL = ln(1.25)/σ_{W0}

σ_{W0} = 0.25 (regulatory constant)

Regulatory constant is different from CV = 30% (defining HV drugs)

Consequence: discontinuity

Mixed strategy	Regulatory standardized var'n (%)	Consumer risk (%) Unscaled ABE	Scaled ABE
No	30	4.95	5.56
No	25	4.98	16.50
Yes	30	5.01	6.98
Yes	25	4.94	14.78

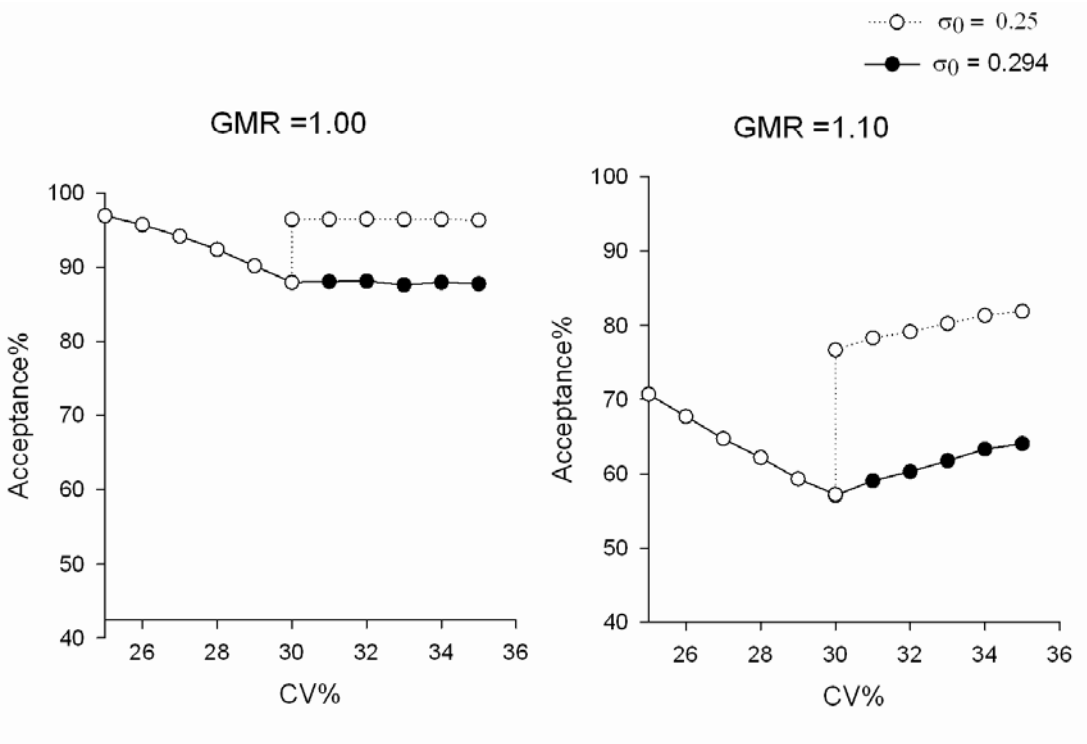
High consumer risk is possible

Also: Regulatory uncertainty (decision on acceptance or rejection) is enhanced

L. Endrenyi, L. Tothfalusi, J. Pharm. Pharmaceut. Sci. 12: 138-149 (2009)

SOME OUTSTANDING ISSUES:

REGULATORY CONSTANT



$\sigma_0 = 0.25$

- Discontinuity in acceptance
  Regulatory uncertainty
- Higher CV_W results in higher acceptance
  Anomalous

$\sigma_0 = 0.294$

- Continuity in acceptance
  No regulatory uncertainty

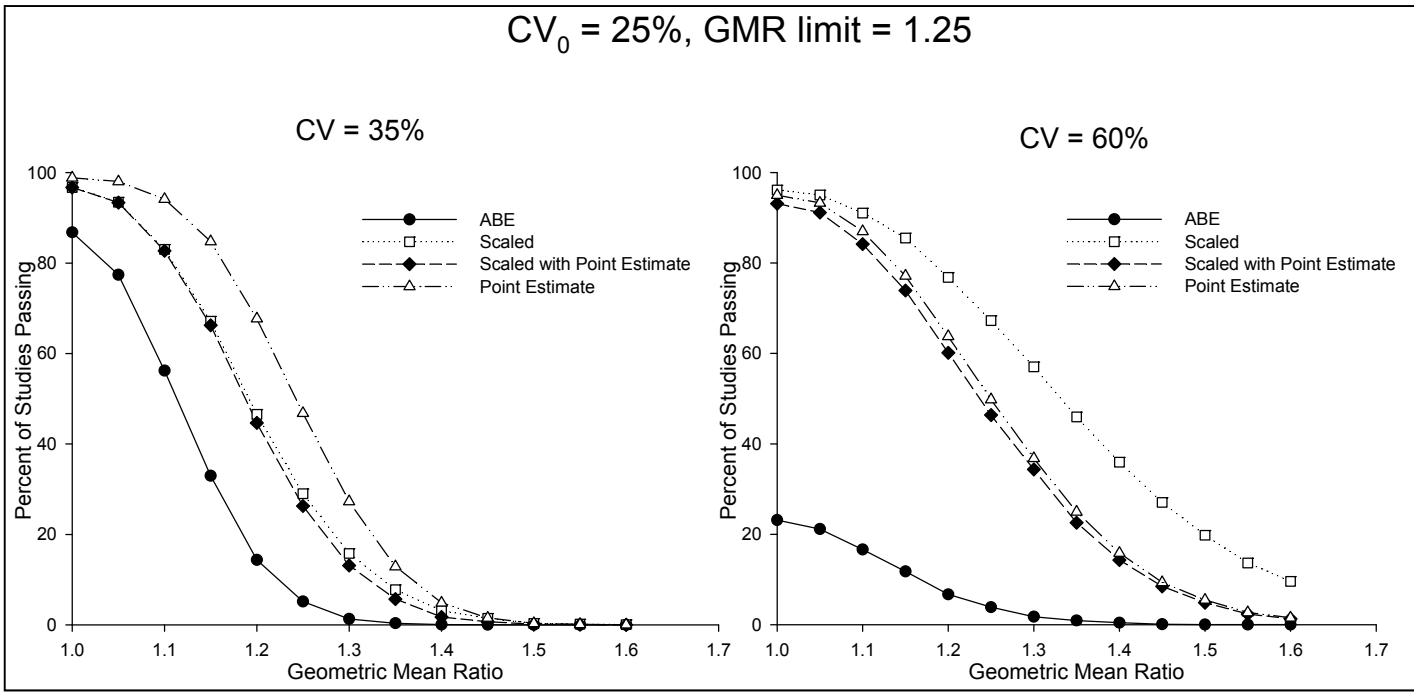
SOME OUTSTANDING ISSUES:
REGULATORY CONSTANT

Acceptance criterion 1:

lgBEL = ln(1.25)/σ_{W0}

σ_{W0} = 0.25 (regulatory constant)

Consequence: Point estimate of GMR can dominate



Joint criterion:

Always lower than either of the component criteria

At low variation: similar to Scaled ABE

Confidence interval criterion

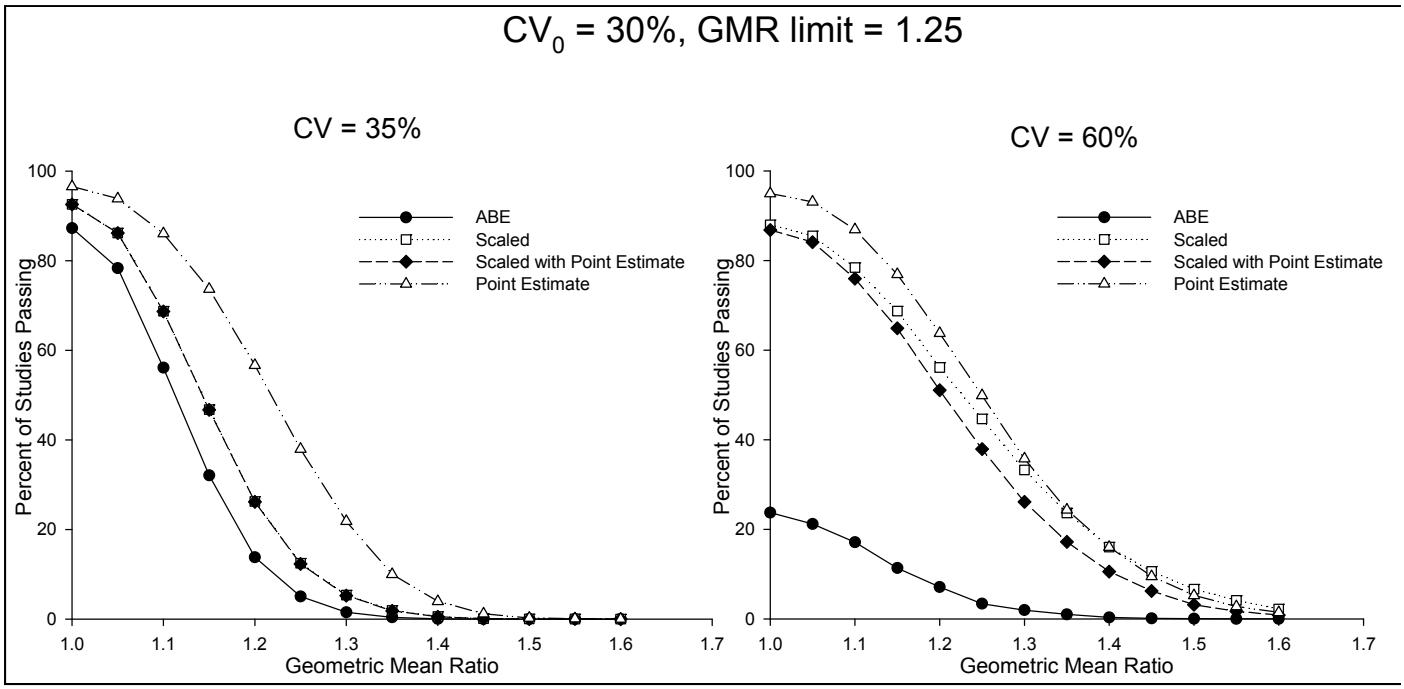
At high variation: similar to Point estimate

Joint criterion ~ Point estimate criterion

SOME OUTSTANDING ISSUES:
REGULATORY CONSTANT

lgBEL = ln(1.25)/σ_{W0}

σ_{W0} = 0.294 (regulatory constant)



Joint criterion:

Low variation: almost identical to Scaled ABE

Confidence interval criterion

High variation: still fairly similar to Scaled ABE, especially at not high GMR

Joint criterion ~ Still confidence interval criterion

L. Endrenyi, L. Tothfalusi, J. Pharm. Pharmaceut. Sci. 12: 138-149 (2009)

SOME OUTSTANDING ISSUES:

CONSTRAINT ON GMR

(Acceptance criterion 2)

Concern about possibly large deviations between estimated logarithmic means

[i.e., about log(GMR)]

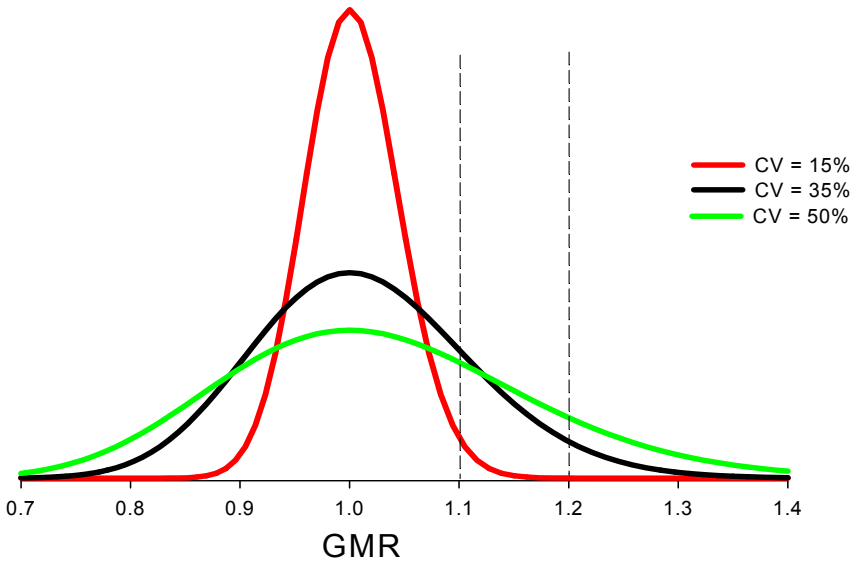
L. Benet, AAPS Workshop on Individual BE, 1999.

Concern about interpretation to physicians & patients

SOME OUTSTANDING ISSUES:

CONSTRAINT ON GMR

Larger deviation between the (logarithmic) means arises as a natural, direct consequence of the higher variability



Larger deviations occur at higher variations

They would be truncated by GMR constraint

Confidence interval of log(GMR), assuming normal distribution, would not be correct

Proposals of GMR constraints with levelling-off properties

V. Karalis et al., Pharm. Res. 21: 1933-1942 (2004)
V. Karalis et al., Eur. J. Pharm. Sci. 26: 34-61 (2005)
J. Kytariolos et al., Pharm. Res. 23: 2657-2664 (2006)
V. Karalis et al., Eur. J. Pharm. Sci. 38: 55-63 (2009)

SOME OUTSTANDING ISSUES: DETERMINATION OF s_{WR}

From observed data

FDA (Haidar et al., 2008)

For a given reference product,

differing estimates for each test product

Awkward, especially with regulatory uncertainty

Pooled information from all available data

Preferable

SOME OUTSTANDING ISSUES:
- STUDY DESIGN

An additional goal:

To compare within-subject variations of the two drug products:

$$s_{WT}/s_{WR}$$

Could identify highly variable drug products

Replications of both RR and TT are required

For example:

RRT

TTR

SOME OUTSTANDING ISSUES:
- STUDY DESIGN

Refine the additional goal:

To compare variations of the two drug products:

$$s_{WT}/s_{WR}$$

within the same subject

More effective identification of highly-variable drug products

Also: can identify (some) outlying observations

Example of study design:

RTRT

TRTR

SOME OUTSTANDING ISSUES:

- BASIS OF s_W

- Specific to the study

  Justified in the protocol

- From all available information

  Same for all products of a drug

  (Not modified release,

  not special preparations)

EUROPEAN PROCEDURE (EMA)

Guideline on Bioequivalence (2010):

- Average BE with expanding limits (ABEL)

- Only up to CV = 50%

  Beyond 50%:

  BE limits 70% to 143%

- Only C_{max}

- Constraint on GMR:

  Between 80% and 125%

- Replicate design

  3 or 4 periods

HEALTH CANADA

THERAPEUTIC PRODUCTS DIRECTORATE (TPD)

Advisory Committee (2004),
Draft Guidance (2010):

"BE for highly-variable drugs is not an issue"

[Perhaps because for C_{max} only the ratio of geometric means needs to be between 0.80-1.25]

TPD is reconsidering the issue

(E. Ormsby, 2008, 2009)

- **Expanding BE limits (ABEL)**
- **AUC only**
- **s_W based on all available information**

SOUTH AFRICAN MEDICINES CONTROL COUNCIL

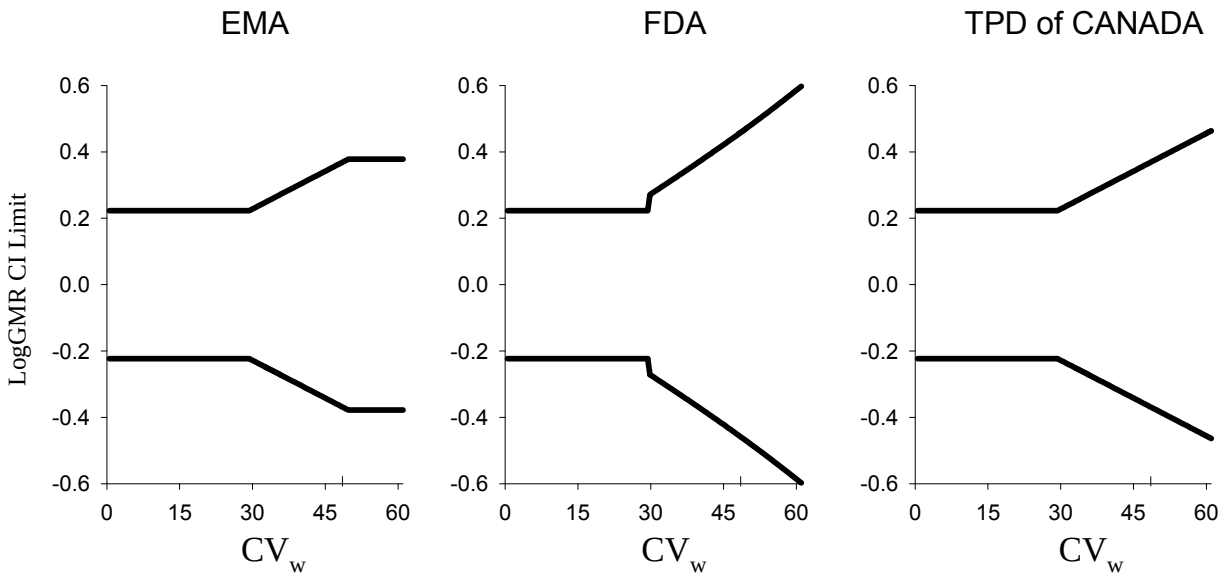
Either scaled average BE (SABE)

or average BE with expanding limits (ABEL)

C_{max} only

R.B. Walker, I. Kanfer, M.F. Skinner. Clin. Res. Regul. Affairs, 23: 11-20 (2006)

BE FOR HIGHLY VARIABLE DRUGS: 3 REGULATORY AUTHORITIES



ABEL	SABE	ABEL
GMR	GMR	No GMR
C_{max} only	C_{max} & AUC	AUC only

PARALLEL BUT SEPARATE CONSIDERATIONS

DIFFERING REGULATORY RULES!

CONCLUSIONS

1. Evaluation of bioequivalence for HV drugs has been a difficult issue for many years.

2. Major regulatory agencies are moving towards the resolution of the problem. However, the considerations are very different; no thought appears to be given to harmonization.