BIOEQUIVALENCE OF HIGHLY VARIABLE DRUG PRODUCTS – AN UPDATE

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BIOEQUIVALENCE FOR HIGHLY VARIABLE DRUG PRODUCTS

OUTLINE

- Average and scaled average bioequivalence (ABE, SABE and RSABE)
- The problem of bioequivalence for highly variable drugs
- Properties of RSABE
- Regulatory requirements in various jurisdictions, and their problems

USUAL REGULATORY CRITERION

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

BEL: BE limit - Usually 1.25

GMR: Ratio of geometric means

Expectation: The 90% confidence limits for GMR should be between 0.80 and 1.25

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

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

lgBEL: Logarithm of BEL

m_T, m_R: Estimated logarithmic means

REFERENCE SCALED AVERAGE BE (RSABE)

Difference between estimated logarithmic means is normalized by estimated variation:

$$-\,lgBEL_S \le (m_T - m_R)/s_{WR} \le lgBEL_S$$

s_{WR} is the within-subject variation of the reference product

BEL (and lgBEL): BE limit set by regulatory authorities

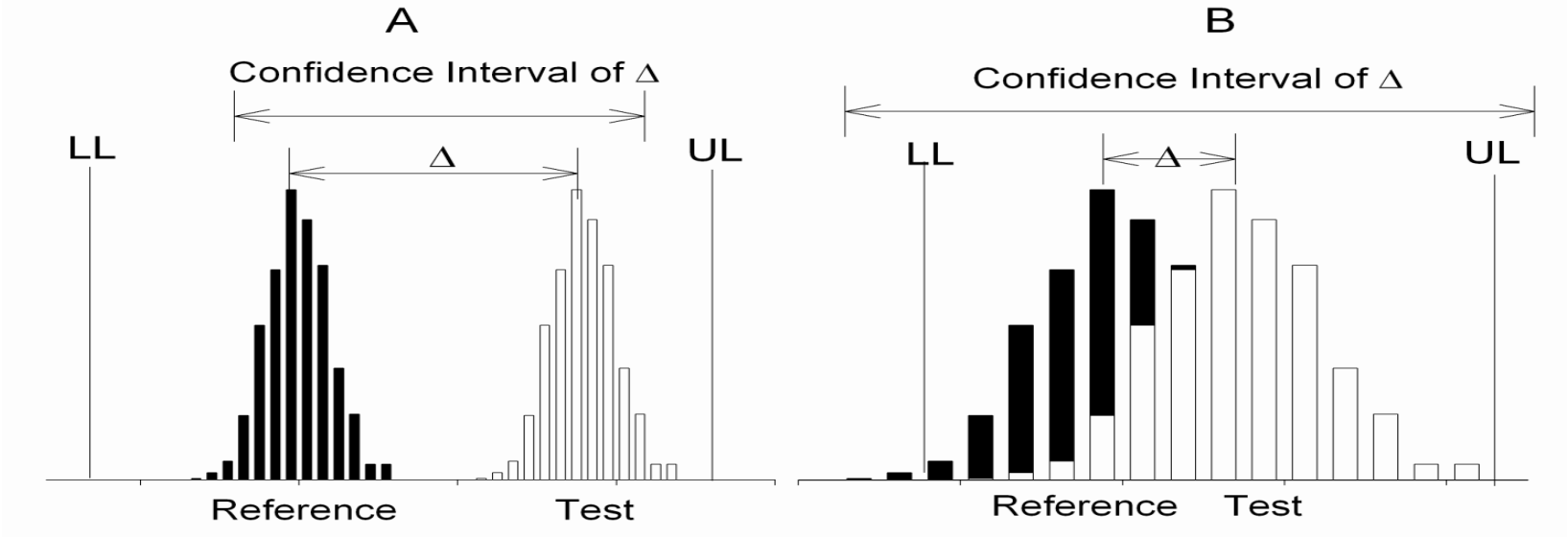
R. Schall, BioInternational 2, 91-106 (1995)

L.Tothfalusi et al., Pharm.Res. 18: 728-733 (2001)

L. Tothfalusi and L. Endrenyi, Pharm.Res. 20: 382-389 (2003)

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)

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:

Coefficient of variation CV $\geq$ 30%

DEALING WITH HIGH VARIATION:

REFERENCE-SCALED AVERAGE BE (RSABE)

Difference between logarithmic means is normalized by estimated variation

$$-\,lgBEL_S \le (m_T - m_R)/s_{WR} \le lgBEL_S$$

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**

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 **[GMR = Ratio of geometric means]**

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

Plot power curve:

Acceptance% *vs*. GMR

Properties:

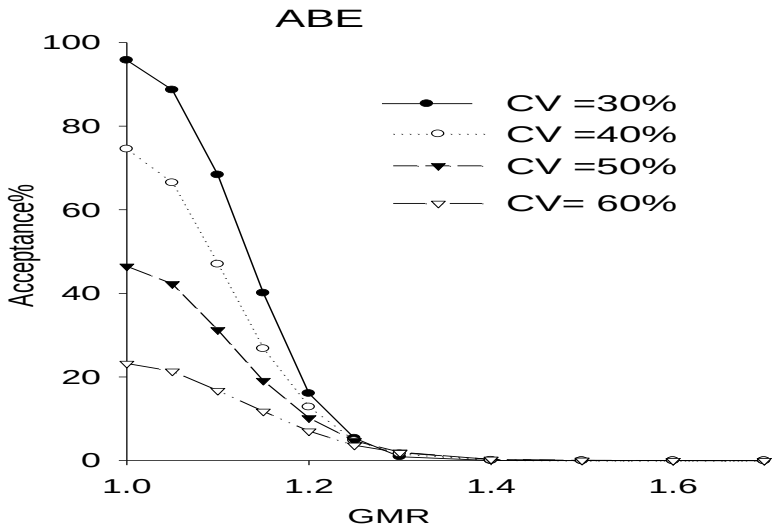
***Consumer risk*: Probability of accepting BE even when the two products are not equivalent**

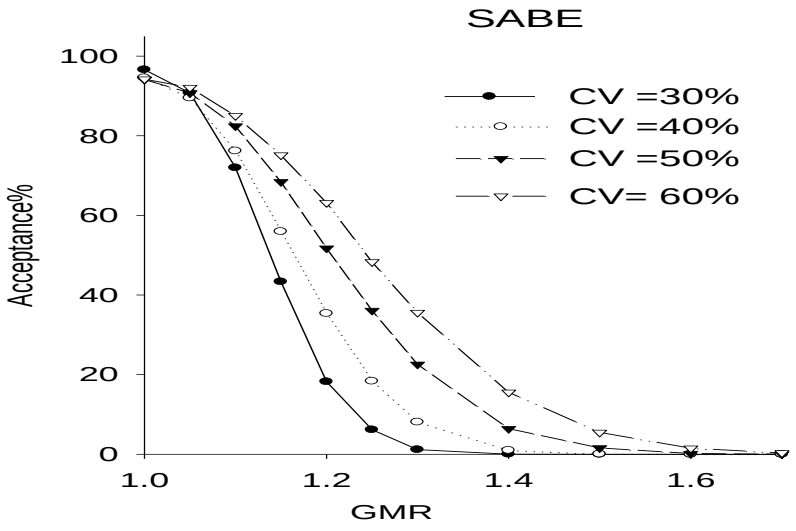
- Low level controlled by regulatory agencies

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

CHARACTERISTICS OF SCALED (& UNSCALED) AVERAGE BE

N = 48, 2 PERIODS





Unscaled average BE yields low acceptance of BE at high variations

Scaled average BE does not yield low acceptance at high variations

Scaled average BE Large, robust producer risk

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

REFERENCE SCALED AVERAGE BE WITH EXPANDING LIMITS (ABEL)

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

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

$$-\lg BEL_S * s_{WR} \le m_T - m_R \le \lg BEL_S * s_{WR}$$

(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)

EUROPEAN PROCEDURE (EMA)

Guideline on Bioequivalence (2010):

- Average BE with Expanding limits (ABEL)

  $lgBEL = \ln(1.25)/\sigma_{W0} = 0.76$

  $\sigma_{W0} = 0.294$ (regulatory constant)

  $CV_{W0} = 30\%$

- Mixed procedure:

  ABE if $s_{WR} \leq 0.294$

  SABE if $s_{WR} > 0.294$

- Constraint: Only up to CV = 50%

  Beyond 50%: BE limits 70% to 143%

- Constraint on point estimate of GMR:

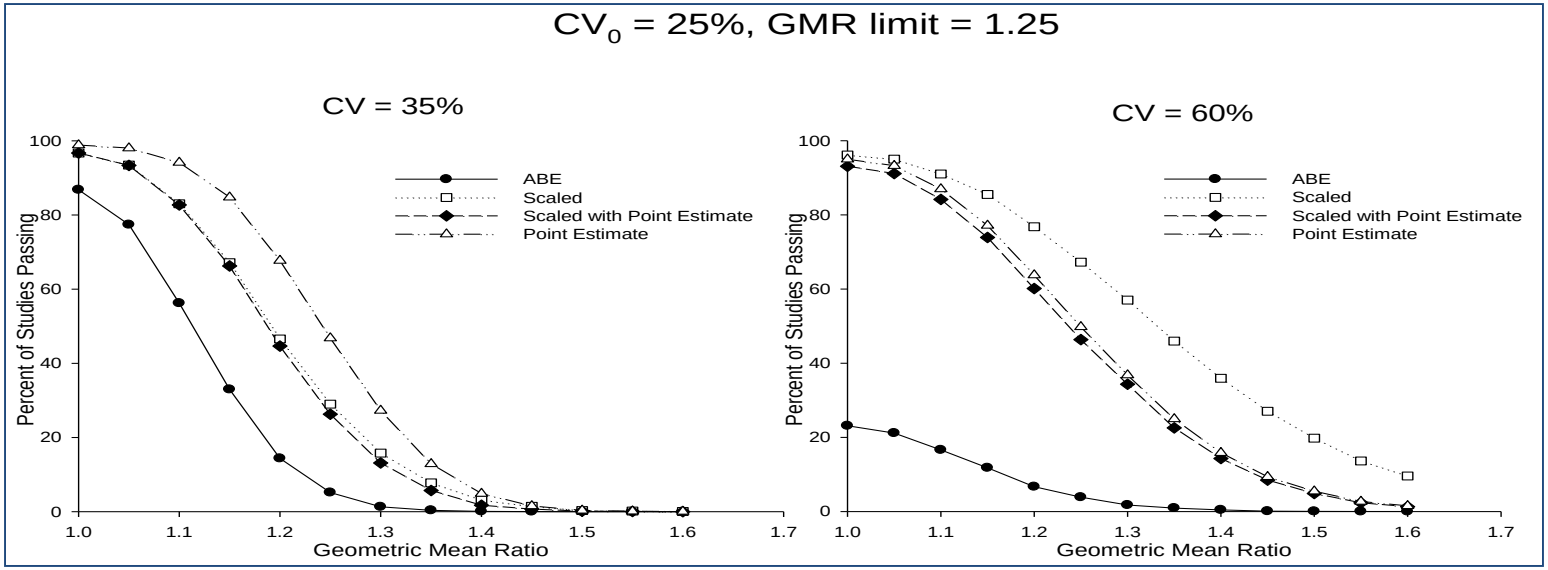
  Between 80% and 125%

- Only C_{max}

- Replicate design, 3 or 4 periods

CONSTRAINT ON GMR

Point estimate of GMR (and not confidence interval criterion) dominates at high variation



Joint criterion:

Always lower than either of the component criteria

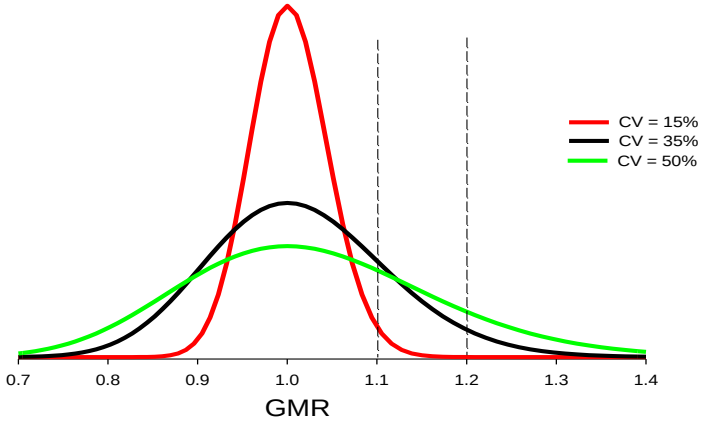
At low variation: similar to Scaled ABE
Confidence interval criterion

At high variation: similar to Point estimate
Joint criterion similar to Point estimate criterion

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

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)

CONSTRAINT ON GMR

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

Concern about possibly large deviations between estimated logarithmic means [i.e., about log(GMR)]

Concern about interpretation to physicians & patients

L.Z. Benet, FDA Committee on Pharmaceutical Sciences, 2006:

"1. There is no scientific basis or rationale for the point estimate recommendations.
2. There is no belief that addition of the point estimate criteria will improve the safety of approved generic drugs.
3. The point estimate recommendations are only "political" to give greater assurance to clinicians and patients who are not familiar (don't understand) the statistics of highly variable drugs."

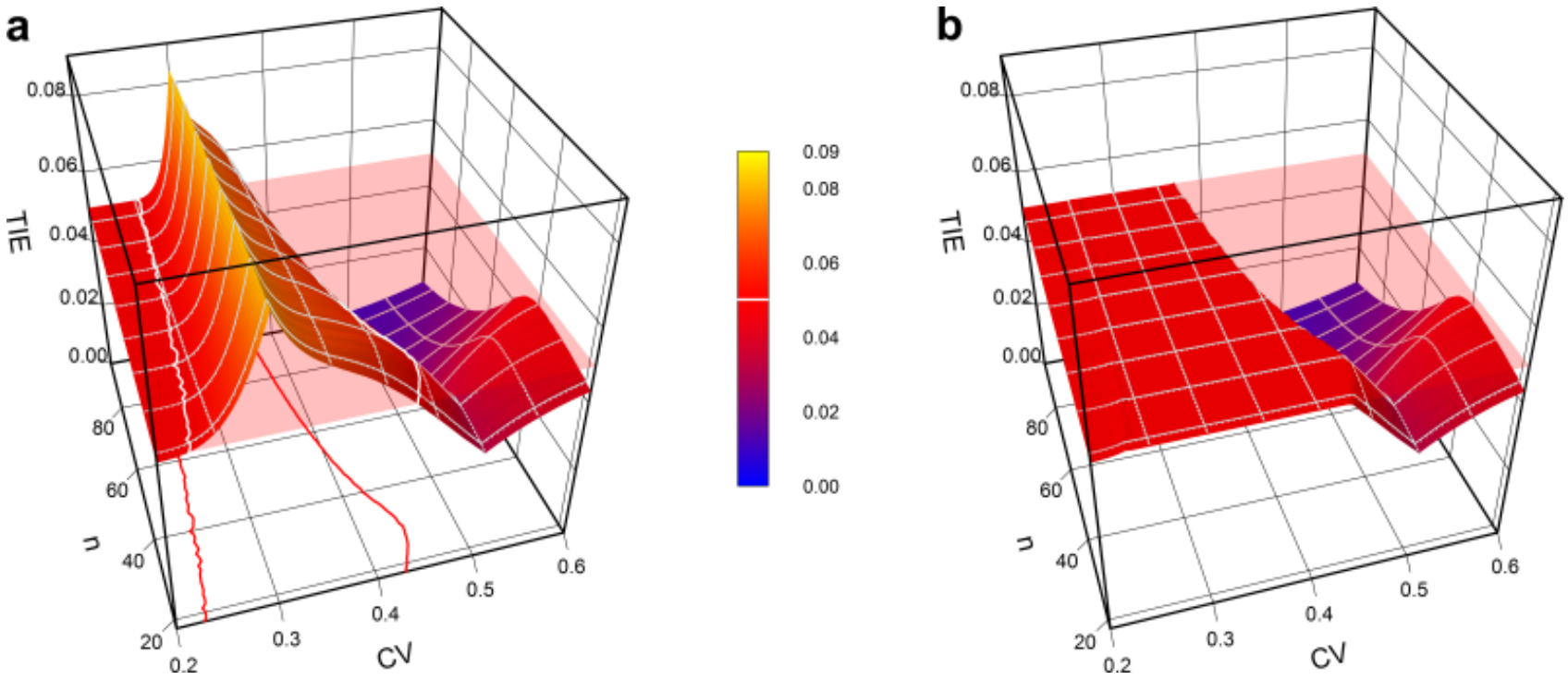
UPPER CONSTRAINT ON USING SABE/ABEL

	EMA, WHO	FDA	Health Canada
CV_{WR}	50%	None	57.4%

No scientific rationale for the constraint!

Recommend: None

TYPE I ERROR – CONSUMER RISK



Type I error reaches 8 % (rather than 5%) at CV = 30% (a)
Can be controlled by iteratively adjusting α (b)

D. Labes, H. Schütz, Pharm. Res. 33(11) 2805-2814 (2016)

TYPE I ERROR – CONSUMER RISK

Type I error of 7-8% around CV = 30% has been of much concern recently.

Remedies have been suggested.

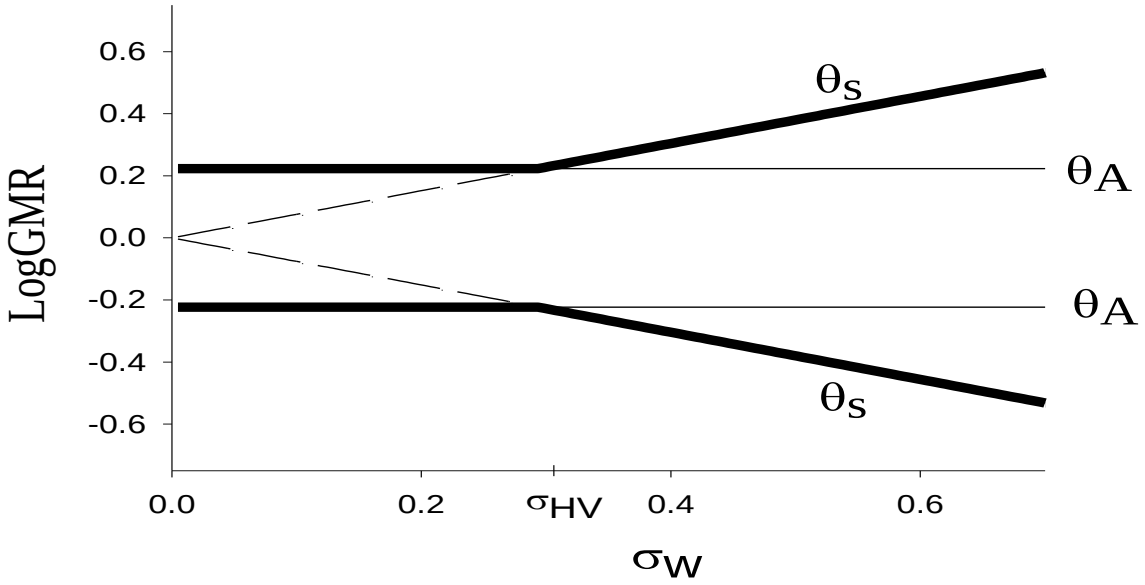
D. Labes, H. Schütz, Pharm. Res. (2016) Iterative adjustment of α
M. Wonnemann, et al. Pharm. Res. 21: 135-143 (2015) Two-stage design
L. Tothfalusi, L. Endrenyi, AAPS J. 18: 376-489 (2016) Corrective algorithms
L. Tothfalusi, L. Endrenyi, Stat. Med. 36: 4378-4390 (2017) Corrective algorithms

Also:

D. Labes, Bioeq. Bioavail. Forum (2013)
L. Endrenyi, L. Tothfalusi, J. Pharm. Pharmaceut. Sci. 12: 138-149 (2009)
J. Munoz, et al. Stat. Med. 35: 1933-1943 (2016)

TYPE I ERROR – CONSUMER RISK

BACKGROUND: MIXED MODEL OF BE



Unscaled average BE if $s_{WR} \leq s_{HV}$,

Scaled average BE if $s_{WR} > s_{HV}$

(s_{HV}: Limiting variation =0.294; CV_{HV} = 30%)

The probability of making an incorrect choice is highest around 30%

FDA PROCEDURE

S.H. Haidar et al. (FDA) Pharm. Res. 25: 237-241 (2008)
B.M. Davit et al. (FDA) AAPS J. 14: 915-924 (2012)

Reference-scaled average BE (RSABE)

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

$lgBEL = \ln(1.25)/\sigma_{W0} = 0.89$
$\sigma_{W0} = 0.246$ (regulatory constant)
$CV_{W0} = 25\%$

- Mixed procedure:
  ABE if $s_{WR} \leq 0.294$
  RSABE if $s_{WR} > 0.294$

- Constraint on point estimate of GMR:
  Between 80% and 125%

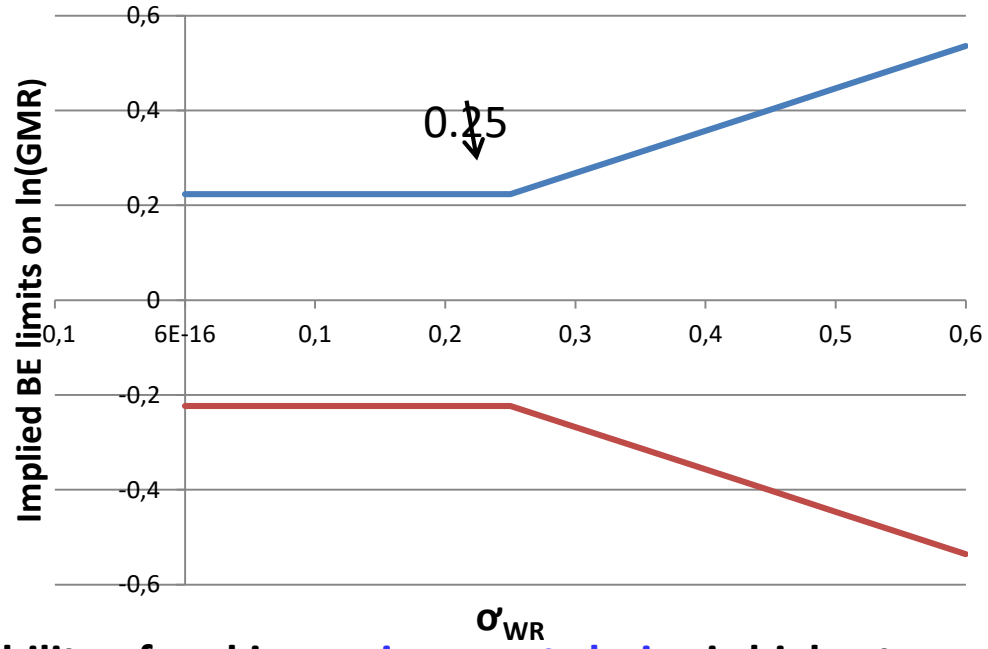
- Both AUC and C_{max}

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

- 4-period, fully replicated design
  RTRT, TRTR

FDA PROCEDURE - BACKGROUND

Implied BE limits on μT- μR [= ln(GMR)] using the mixed scaling procedure



The probability of making an incorrect choice is highest around 25%

The true, population variation σ'_{WR} is considered.

B.M. Davit, D.P. Conner, In "BE Requirements in Various Global Jurisdictions" (I. Kanfer, ed.) 269-305, 2017.

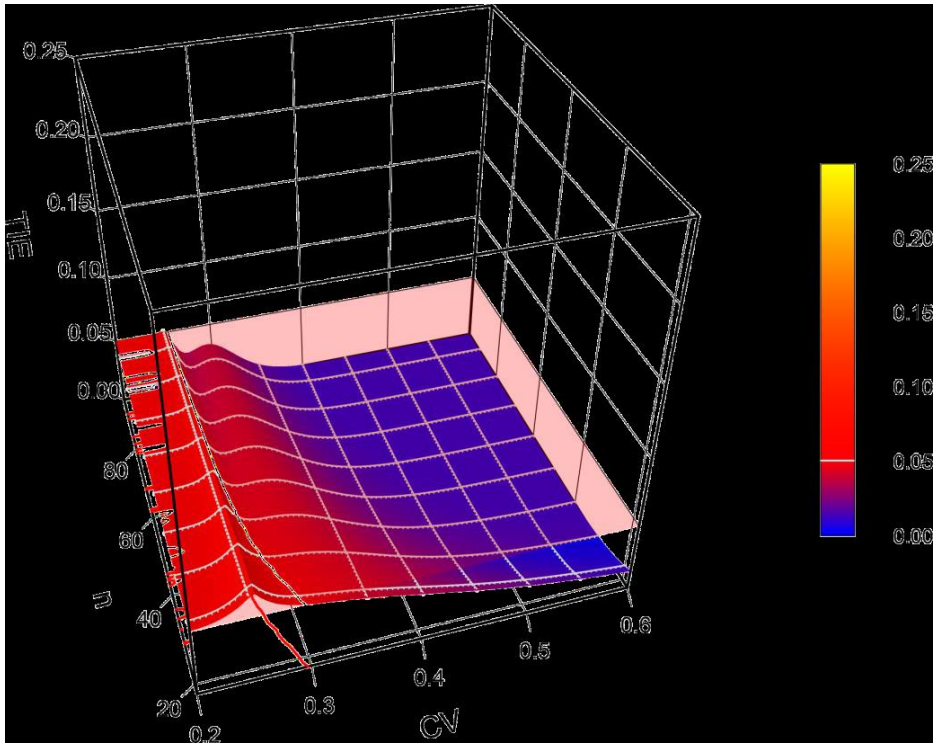
IMPLIED TYPE I ERROR FOR THE FDA PROCEDURE

TIE: Type I Error

Largest TIE: 0.068
at CV = 0.25

Of concern to FDA/OGD

Similar to that of ABEL
at CV = 0.30



CV

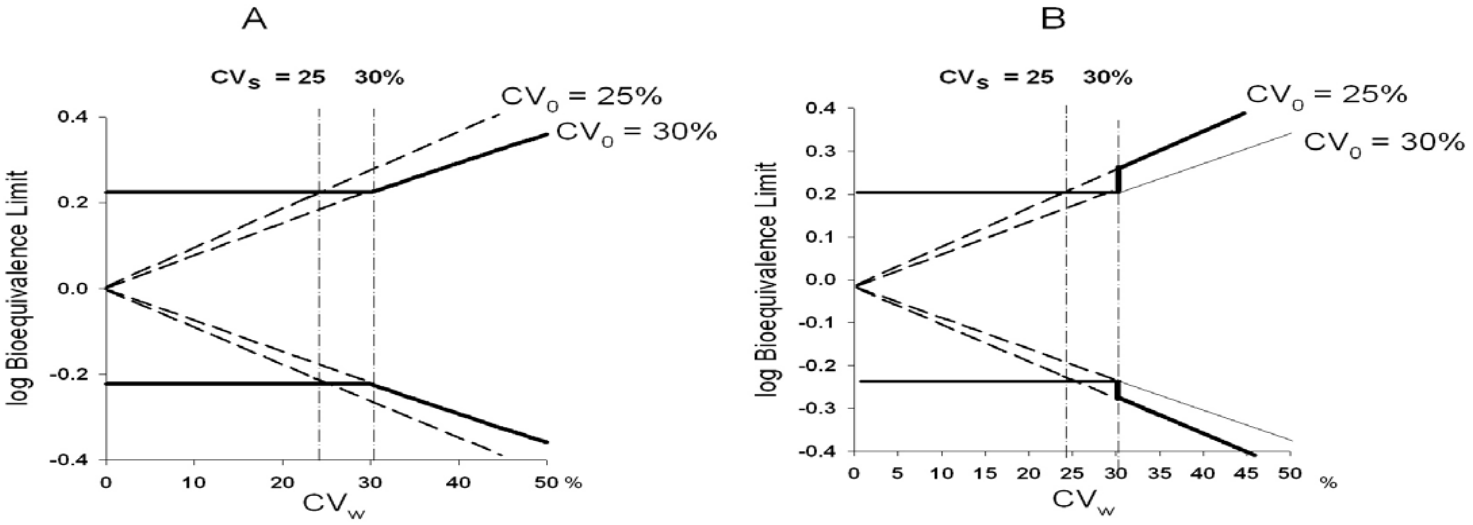
H. Schütz, Bioeq. Bioavail. Forum
Also: D. Schuirmann, T. Hyslop, FDA

EMA AND FDA REGULATORY CONSTANTS

Mixed model of BE

A: Regulatory constant $CV_0 = 30\%$ - EMA

B: Regulatory constant $CV_0 = 25\%$ - FDA



Regulatory limits:

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

The estimated s_W (or CV_W) is considered.

FDA REGULATORY CONSTANT

LARGE TYPE I ERROR – CONSUMER RISK

lgBEL = ln(1.25)/σ_{W0}

σ_{W0} = 0.25 (FDA regulatory constant)

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

Consequence: discontinuity

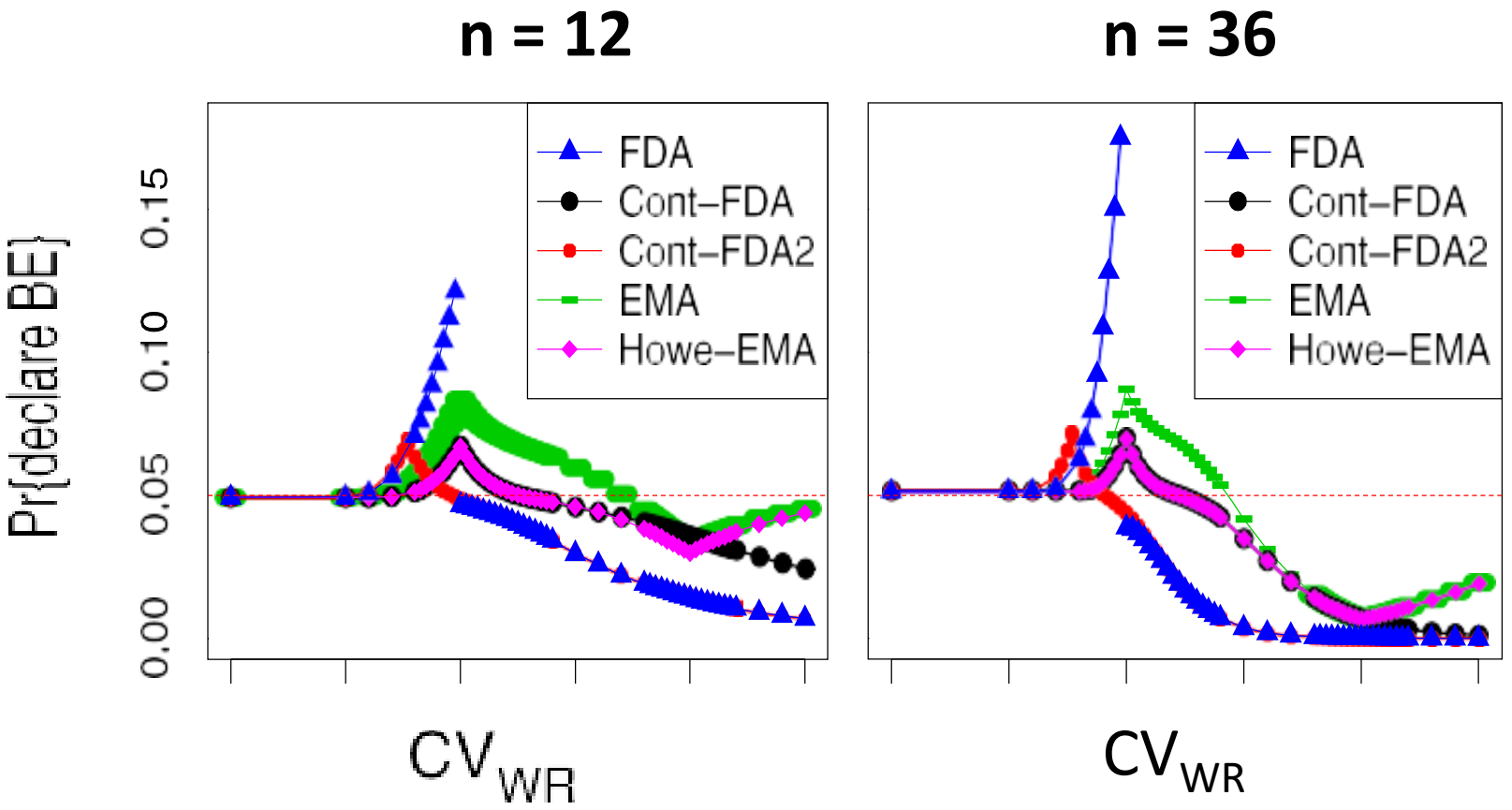
Mixed strategy	Regulatory standardized var'n (%)	Consumer risk (%) Unscaled ABE	Scaled ABE
No	30	4.95	5.56
No	25	4.98	16.50
Yes	30	5.01	6.98
Yes	25	4.94	14.78

Very large consumer risk is possible

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

FDA REGULATORY CONSTANT

LARGE TYPE I ERROR – CONSUMER RISK



Type I error – Consumer risk:

EMA: 7 - 8%

FDA: 13 – 18%

J. Munoz, et al. Stat. Med. 35: 1933-1943 (2016)

Also:

D. Labes, Bioeq. Bioavail. Forum (2013)

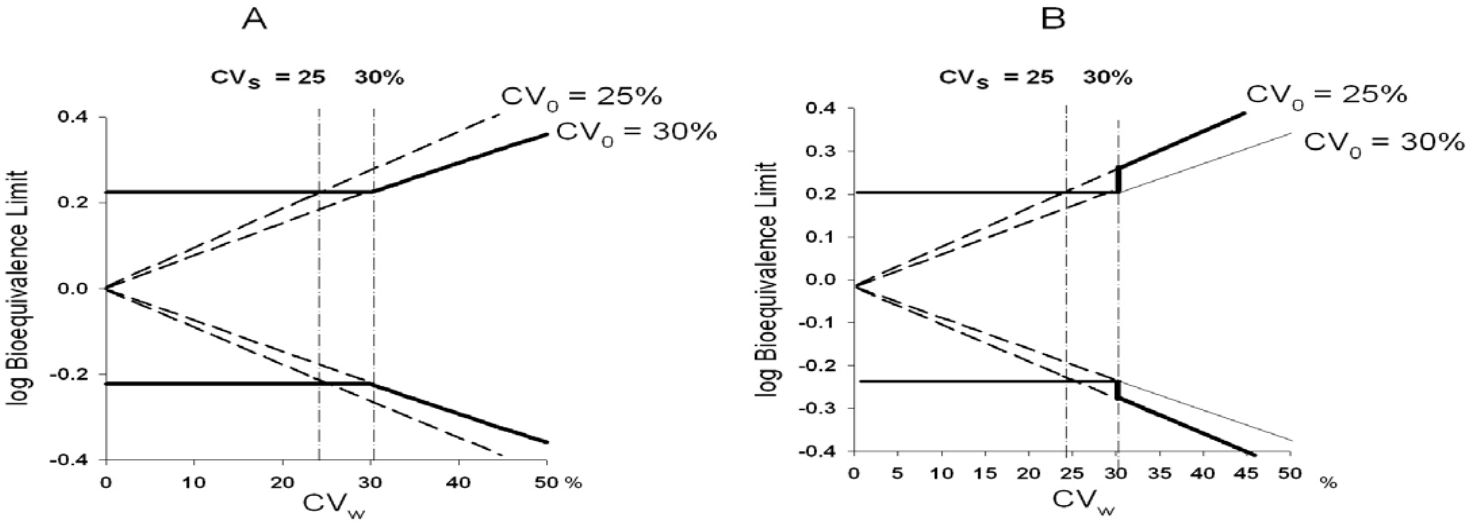
L. Endrenyi, L. Tothfalusi. J. Pharm. Pharmaceut. Sci. 12: 138-149 (2009)

EMA AND FDA REGULATORY CONSTANTS BACKGROUNF OF TYPE I ERROR

Mixed model of BE

A: Regulatory constant CV_{W0} = 30% - EMA

B: Regulatory constant CV_{W0} = 25% - FDA



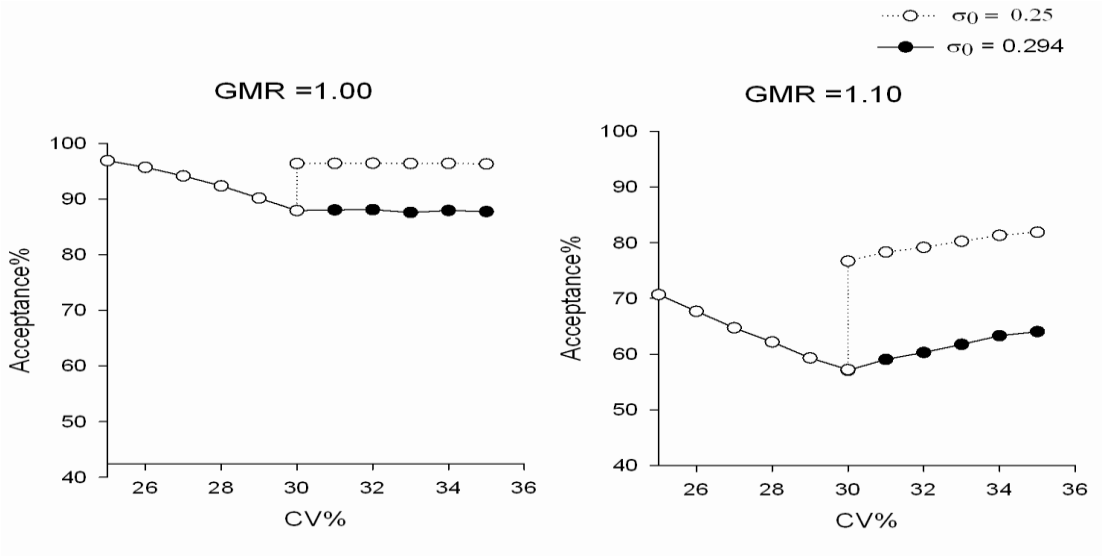
The estimated s_W (or CV_W) is considered.

The probability of making an incorrect choice is highest around 30%

The probability is larger with the FDA than the EMA procedure

EMA & FDA REGULATORY CONSTANTS :

REGULATORY UNCERTAINTY



$\sigma_0 = 0.25$

- Discontinuity in acceptance

Regulatory uncertainty

- Higher CV_W results in higher acceptance

Anomalous

$\sigma_0 = 0.294$

- Continuity in acceptance

No regulatory uncertainty

BIASES OF RSABE AND ITS IMPLEMENTATION - 1

The estimated RSABE has a positive bias

It can be corrected by exact algorithms using Hedges' procedure

L. Tothfalusi, L. Endrenyi, AAPS J. 18: 476-479 (2016)
L. V. Hedges, J. Educ. Stat. 6: 107-128 (1981)

BIASES OF RSABE AND ITS IMPLEMENTATION - 2

The FDA approach for estimating RSABE has bias

- **BE is rejected if estimates in the squared, linearized model are positive (larger than 0.00) - See below**

Actual limits for rejecting BE:

	Sequences	
n	2	3
24	0.0600	0.0619
36	0.0442	0.0451
48	0.0353	0.0358
60	0.0295	0.0299

T. Hyslop, et al. Stat. Med. 19: 2885-2897 (2000)
FDA draft guidance for BE of progesterone oral capsules (2011)
L. Tothfalusi, L. Endrenyi, AAPS J. 18: 476-479 (2016)

IMPLEMENTATION OF THE FDA APPROACH

Calculate upper 95% confidence limit:

Square, linearize RSABE model:

$$(m_T - m_R)^2 - lgBEL_S^2 * s_{WR}^2 \leq 0$$

Use distributions of m_T, m_R, s_{WR}^2 to obtain confidence limit

Bioequivalence if the limit is not positive

Computer program (SAS) presented

FDA. Draft guidance for BE of progesterone oral capsules (2011)

Difficulties:

- **The method has a bias (see earlier)**
- **Requires balanced data**
- **Computation is unstable with partial replicate design**

FDA vs. EMA - COMMENTS

Implementation

FDA (SABE)

Linearize model, calculate upper confidence limit (see later)

Use computer program

Progesterone draft guidance (FDA, 2011)

For studies with full design

EMA (ABEL)

Usual computational procedure for crossover studies

Simple!

Regulatory constant

FDA: $\sigma_{W0} = 0.25$

Discontinuity

EMA: $\sigma_{W0} = 0.294$

No discontinuity

EMA AND FDA REGULATORY CONSTANTS

Regulatory constant	EMA	FDA
σ_{w0}	0.294	0.246
CV_{w0}	30%	25%
Switching var'n	Same	Different
BE Limits	Continuous	Discontinuous
Regul. uncertainty	High	Low
Type I error (max)	7-8%	13-18%

Recommend:

$\sigma_{w0} = 0.294$

$CV_{w0} = 30\%$

BE FOR HIGHLY VARIABLE DRUGS: 3 REGULATORY AUTHORITIES

EMA	FDA	HEALTH CANADA
ABEL	RSABE	ABEL
C_{max} only	C_{max} & AUC	AUC only
$\sigma_{W0} = 0.294$	0.25	0.294

PARALLEL BUT SEPARATE CONSIDERATIONS

DIFFERING REGULATORY RULES!

HARMONIZATION WOULD BE DESIRABLE

STUDY DESIGNS

More information is obtained
from more sophisticated designs

Hierarchy of designs:

- **Full replicate (TRTR / RTRT or TRT / RTR)**

- **Partial replicate (TRR / RTR / RRT)**

- **Standard 2×2 crossover (RT / TR)**

- **Parallel (R / T)**

STUDY DESIGNS

More information is obtained
from more sophisticated designs

Variances which can be estimated:

- **Parallel:**
  Total variance (between + within)

- **2×2 crossover:**
  Between, "within" subjects

- **Partial replicate:**
  Within subjects (Reference)

- **Full replicate:**
  Within subjects (Reference & Test)

SCALED AVERAGE BE FOR PARALLEL DESIGN (?)

$-\lg BEL_{SP} \leq (\mu_T - \mu_R)/\sigma'_{Total} \leq \lg BEL_{SP}$

Total variation = Between-subject + Within-subject variations

$\sigma'^2_{Total} = \sigma'^2_B + \sigma'^2_W$ [Variance components]

Regulatory question: What should be the regulatory limit (BEL_{SP})??

It is related to the ratio σ'^2_B/σ'^2_W

Would a ratio = 1.0 be the best assumption?

SUMMARY

1. RSABE and ABEL have largely remedied the difficulties with highly variable drugs.
2. Regulatory agencies have followed differing paths towards resolving the problem.
3. Constraints are not based on science, have adverse consequences.
4. Discontinuity of regulatory requirements can have serious adverse consequences.
5. Magnitude of Type I error and its correction are important.
6. Attention should be paid to biases of estimates.
7. Harmonization of requirements and procedures would be desirable and important.

CITED REFERENCES

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

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L.Tothfalusi et al., Pharm.Res. 18: 728-733 (2001)

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L. Tothfalusi, L. Endrenyi, Stat. Med. 36: 4378-4390 (2017)

M. Wonnemann, et al. Pharm. Res. 21: 135-143 (2015)

THANK YOU!

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