EVALUATION OF BIOEQUIVALENCE FOR HIGHLY-VARIABLE DRUGS AND DRUG PRODUCTS

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SYNOPSIS

Introduction

Several questions to be raised for the for the consideration of the Advisory Committee and CDER

- Is there a problem?
- Which study condition?
- Which study design?
- Which method of evaluation?
- What is the limiting variation for HVD/P?
- Is test/estimation for the ratio of variations needed?
- Is a secondary BE test needed/useful?

USUAL REGULATORY CRITERION

Record:	Parameters (AUC and C_{max}) 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 (HVD/P)

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

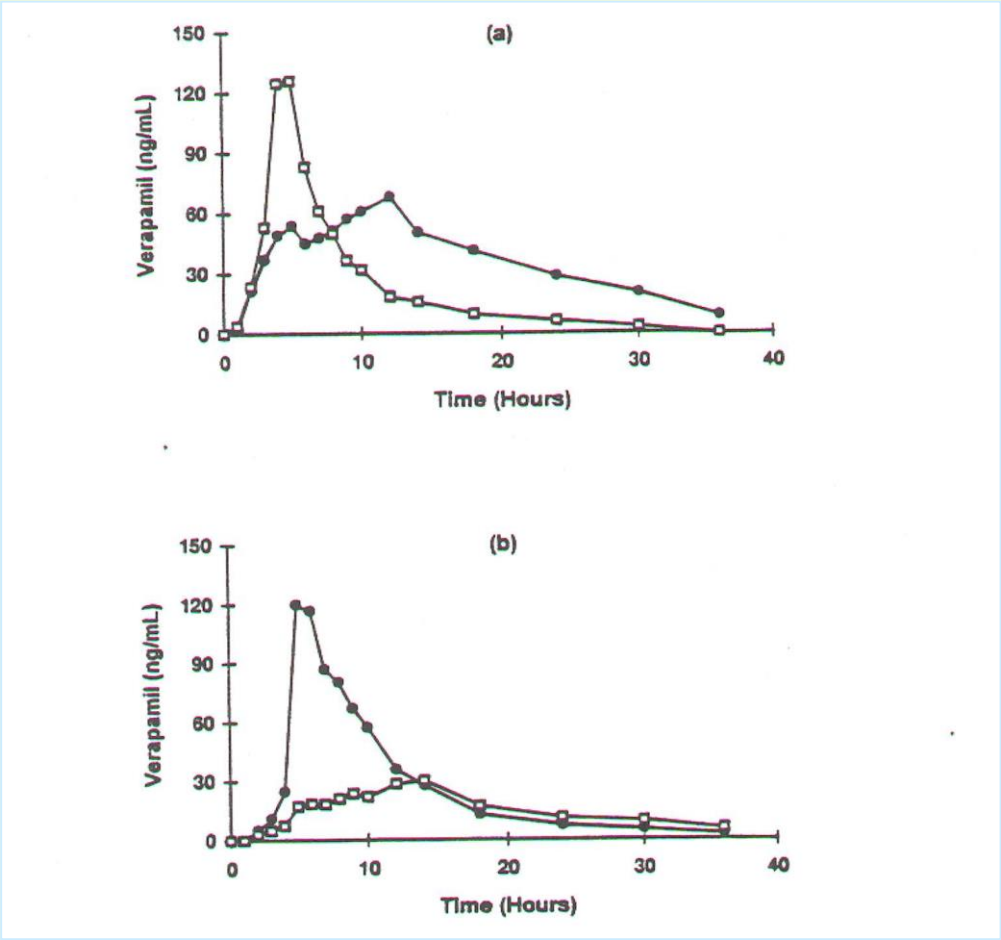
if coefficient of variation CV $\geq$ 30%

IS THERE A PROBLEM WITH BE FOR HVD/P?
- 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)

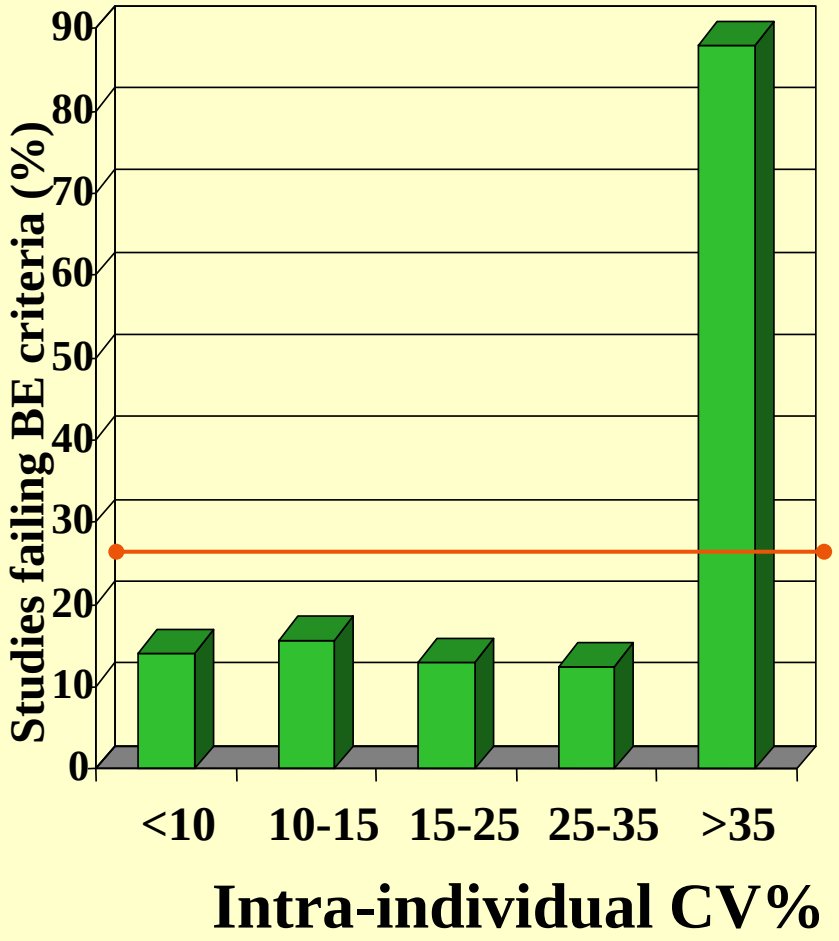


Lack of bioequivalence
Apparent Subject*Period interaction

IS THERE A PROBLEM WITH BE FOR HVD/P?

FAILURE RATE OF BE STUDIES INCREASES WITH C.V.

Failing BE criteria: statistics on 1300 studies



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 C_{max}
but still a substantial number

WHICH STUDY CONDITION?

- Single dosing

- Steady state

WHICH STUDY CONDITION?

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 (%) after single and multiple dosing
(Blume, Schug, et al.)

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
✂ipoic acid (R+)	23	73	15	61
✂ipoic acid (S+)-	23	76	15	53

WHICH STUDY CONDITION?
STEADY-STATE STUDIES

- **Single dosing**

- **Steady state**

  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)

  In Europe but not in U.S.

  In Canada, for modified release (if accumulation)

WHICH STUDY DESIGN?

- **2x2 crossover**

  2 periods

  2 sequences

- **Replicate design**

  3 or 4 periods

  2 sequences (recommended)

  Example:

  T R T R

  R T R T

WHICH STUDY DESIGN?

REPLICATE DESIGN

Advantage:

Get clear, directly estimated

- Within-subject variations

  (s_{WT}^2, s_{WR}^2)

- Subject-by-formulation interaction

  (s_{S*F}^2)

Note: Favored by K.K. Midha

Comment:

Longer duration

Subject dropouts, greater expense

Issue:

Various possible methods of evaluation

E.g.: ANOVA

Linear mixed-effect model

Maximum likelihood

Restricted max. likelihood

Variance component estim'n

Question:

- *IS A TEST COMPARING T AND R VARIATIONS NEEDED?*
- *OR AN ESTIMATE?*

WHICH STUDY DESIGN?
2x2 CROSSOVER

Advantages:

Simple execution
Simple evaluation

Available studies can be evaluated retrospectively

Comment::

Can estimate ratio of within-subject variabilities

Guilbaud, 1993, 1999; Gould, 2000

$Y_i = T_i + R_i$ (i-th subject)
$X_i = T_i - R_i$

Regression of Y *vs.* X
Slope = b

Ratio of within-subject variances:
$s_{WT}^2/s_{WR}^2 = (1+b)/(1-b)$

Issue:

Features of the method have not been studied

WHICH METHOD OF EVALUATION?

- **Unscaled average BE**

  The customary procedure,
  with BE limits of GMR = 0.80-1.25

- **Unscaled average BE with expanded BE limits**

  *** Preset BE limits**

  e.g. GMR = 0.75-1.33
  GMR = 0.70-1.43

  *** BE limits proportional to estimated variation**

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

- **Scaled average BE**

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

- **(Scaled individual BE)**

  For comparisons only

WHICH METHOD OF EVALUATION?

UNSCALED AVERAGE BE WITH EXPANDED LIMITS - PRESET LIMITS

Unscaled average BE

$1/BEL \leq GMR \leq BEL$

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

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

BEL: BE limit

lgBEL: logarithm of BEL

GMR: Ratio of geometric means

m_T, m_R: Estimated logarithmic means

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

WHICH METHOD OF EVALUATION?
UNSCALED AVERAGE BE WITH EXPANDED LIMITS
-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)

- $lgBEL_A*s$? $m_T - m_R$? $lgBEL_A*s$

Proportionality factor, $lgBEL_A = 1.0$ 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 ($lgBEL_A*s$)
- Therefore, application of the two one-sided tests procedure is not correct (However, approximately correct with large N)

WHICH METHOD OF EVALUATION?
SCALED AVERAGE BE

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)

$-\ lgBEL_A \leq (m_T - m_R)/s \leq lgBEL_A$

General procedure 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

Comment:

Confidence limits estimated by:

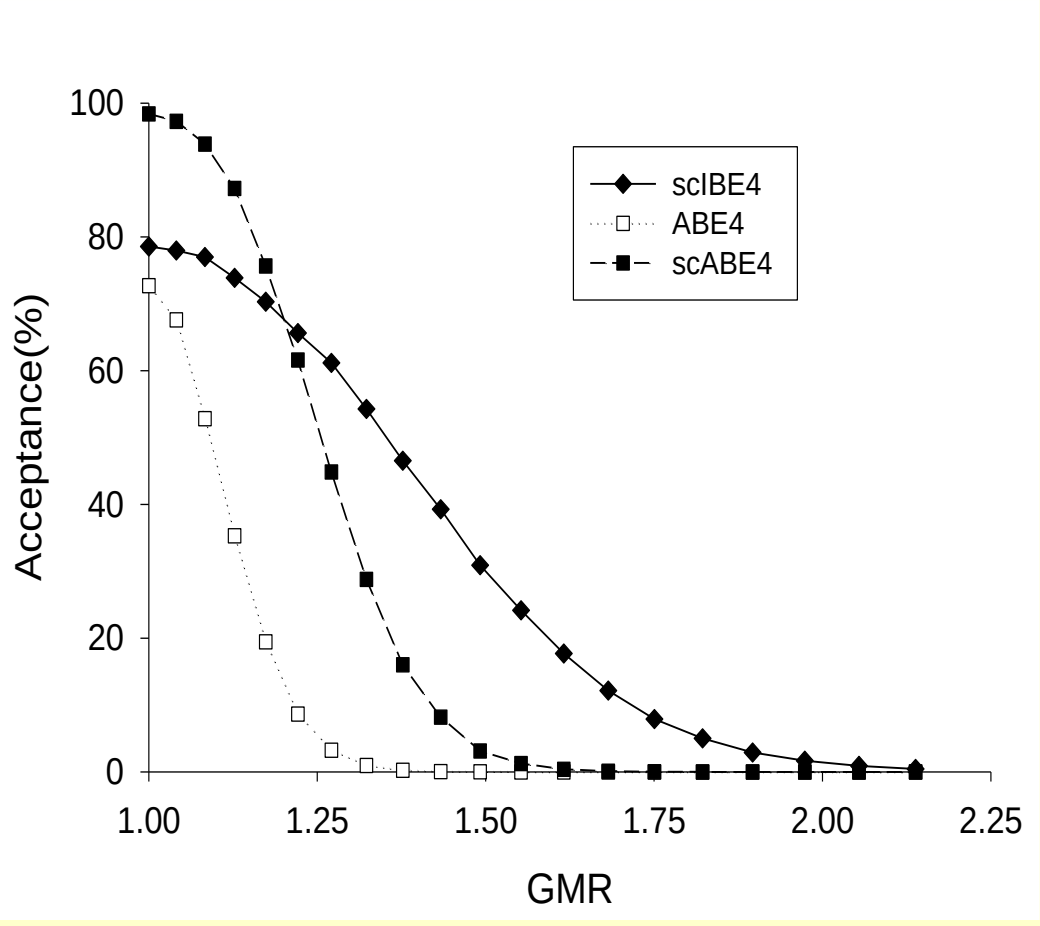
- Noncentral t-test (2x2 crossover)
- Hyslop's procedure (replicate or 2x2 crossover)

WHICH METHOD OF EVALUATION?
SCALED AVERAGE BE

Comparative performance of method

Simulations

4 periods
N = 24
$CV_{WT} = CV_{WR} = 40\%$



Scaled average BE is much less permissive than scaled individual BE (lower GMR's)

Scaled average BE, at large variations, has much higher statistical power than unscaled average BE

WHAT IS THE LIMITING VARIATION FOR HVD/P?

Subject to regulatory decision
(except with unscaled average BE with preset limits)

For unscaled average BE with expanding limits, scaled average BE:
Mixed regulatory model:
Unscaled average BE if $\sigma \leq \sigma_o$,
HVD/P procedure if $\sigma > \sigma_o$
(σ_o: limiting variation)

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

CV_o = 20% (as for individual BE)
CV_o = 25% (as in Boddy et al., 1995; preferred by K. Midha)
CV_o = 30% (usual definition of HVD/P)

Sponsor's intention for using HVD/P procedure to be stated in protocol

IS A SECONDARY CRITERION NEEDED?

Concern about possibly large deviations between estimated logarithmic means

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

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

Concern arose due to features of individual BE

Comments:

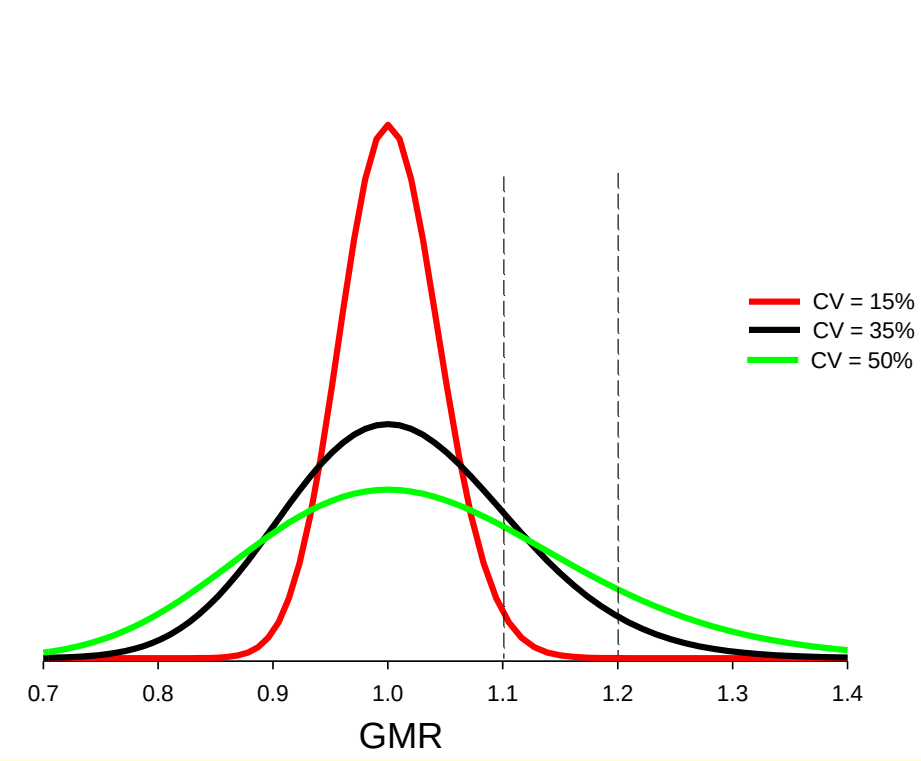
Individual BE (IBE) vs. HVD/P

- With HVD/P the potential deviation is much smaller than with IBE

- Differing sources of the deviation
  * IBE: expanded, more permissive regulatory criterion
  * HVD/P: Arises as a natural, direct consequence of variability

IS A SECONDARY CRITERION NEEDED?

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

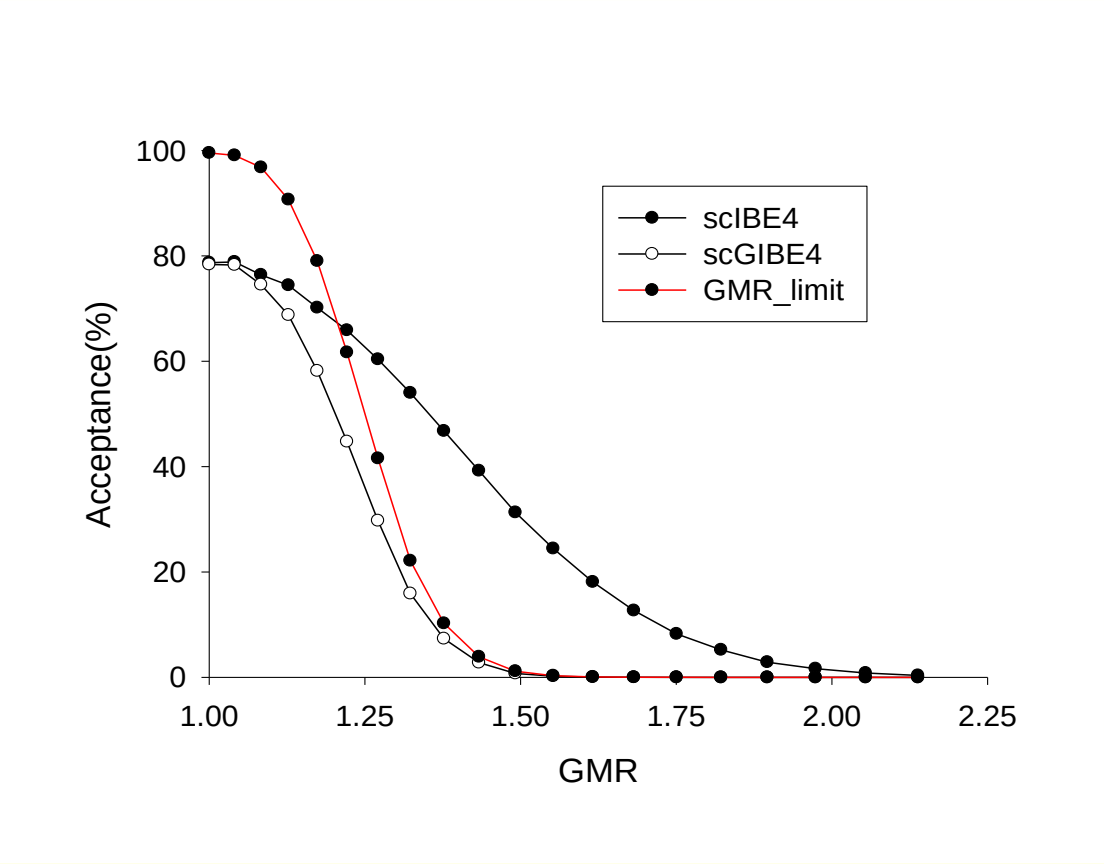


Larger deviations occur at higher variations

IS A SECONDARY CRITERION USEFUL?

Illustrative example:

Effect of secondary criterion on the determination of (scaled) individual BE



GMR limit: Constraint of GMR 1.25 alone
scIBE4: Scaled individual BE
scGIBE4: Combination of the two criteria

Acceptance by the combined criterion does not exceed acceptances by either separate criterion

Strong constraint on GMR could remove the combined criterion from the BE criterion

SUMMARY

Several questions for the consideration of the Advisory Committee and CDER

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Further investigation of designs and features of methods would be very useful