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Introduction to Biostatistics

Part III: Advanced Designs for Bioequivalence Studies

Helmut Schütz
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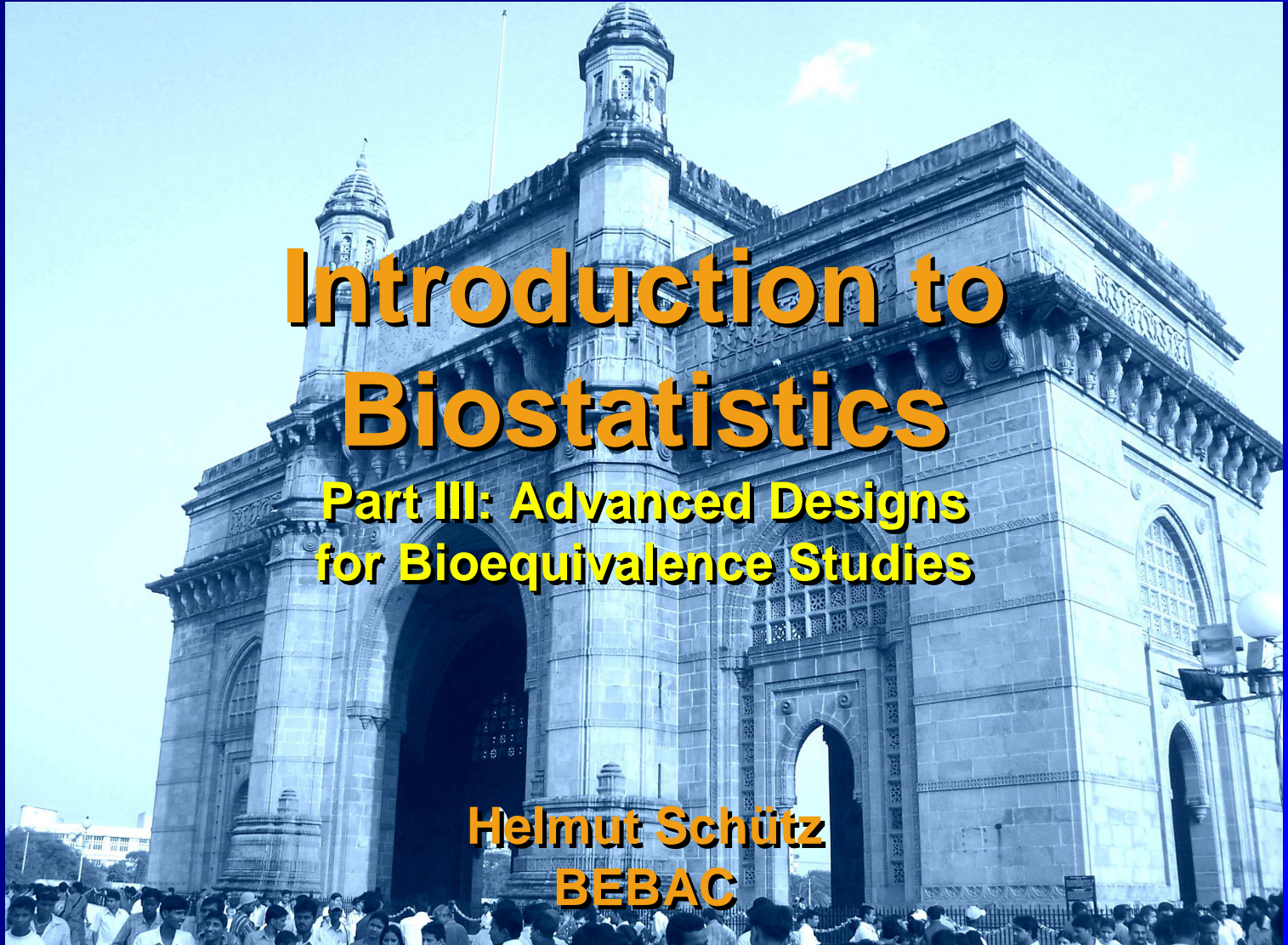
Hierarchy of Designs

● The more 'sophisticated' a design is, the more information can be extracted.

■ Hierarchy of designs:
Full replicate (TRTR | RTRT) ⇨
  Partial replicate (TRR | RTR | RRT) ⇨
    Standard 2×2 cross-over (RT | RT) ⇨
      Parallel (R | T)

■ Variances which can be estimated:
  Parallel: total variance (between + within)
  2×2 Xover: + between, within subjects ⇨
Partial replicate: + within subjects (reference) ⇨
Full replicate: + within subjects (reference, test) ⇨

Variances

- For Highly Variable Drugs / Drug Products (HVDs/HVDPs) it may be almost impossible to show BE with a reasonable sample size.

- The common 2×2 cross-over assumes Independent Identically Distributions (IDD), which may not hold. If *e.g.*, the variability of the reference is higher than the one of the test, one obtains a high common (pooled) variance and the test will be penalized for the 'bad' reference.
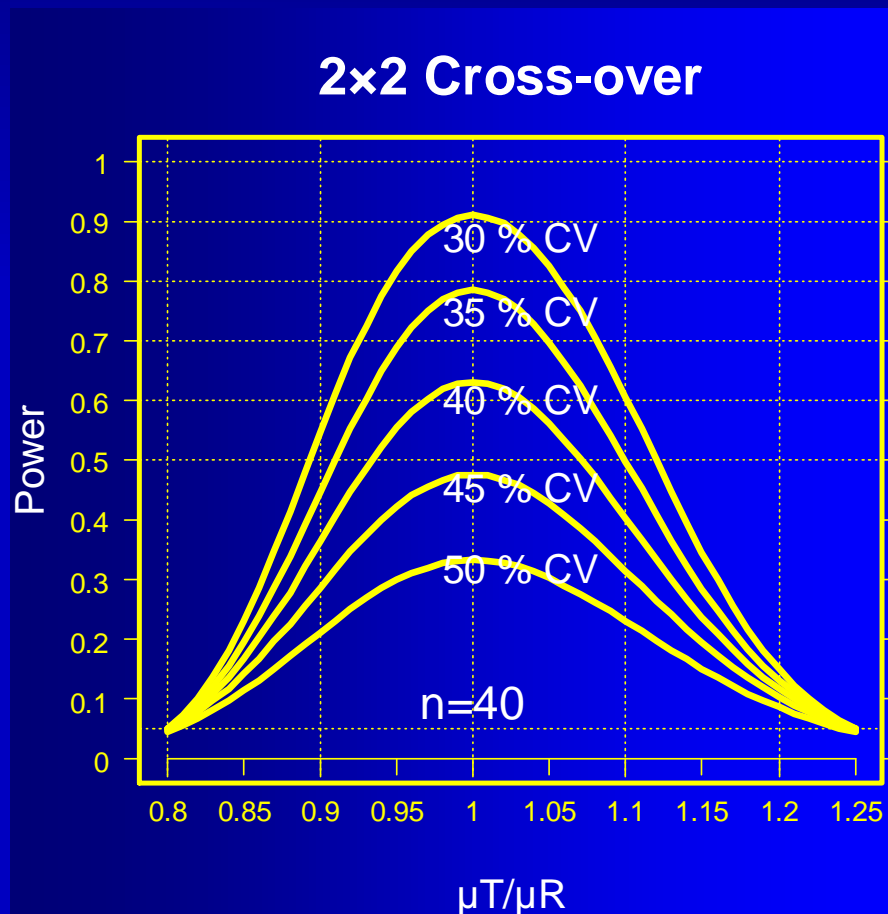
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Variances

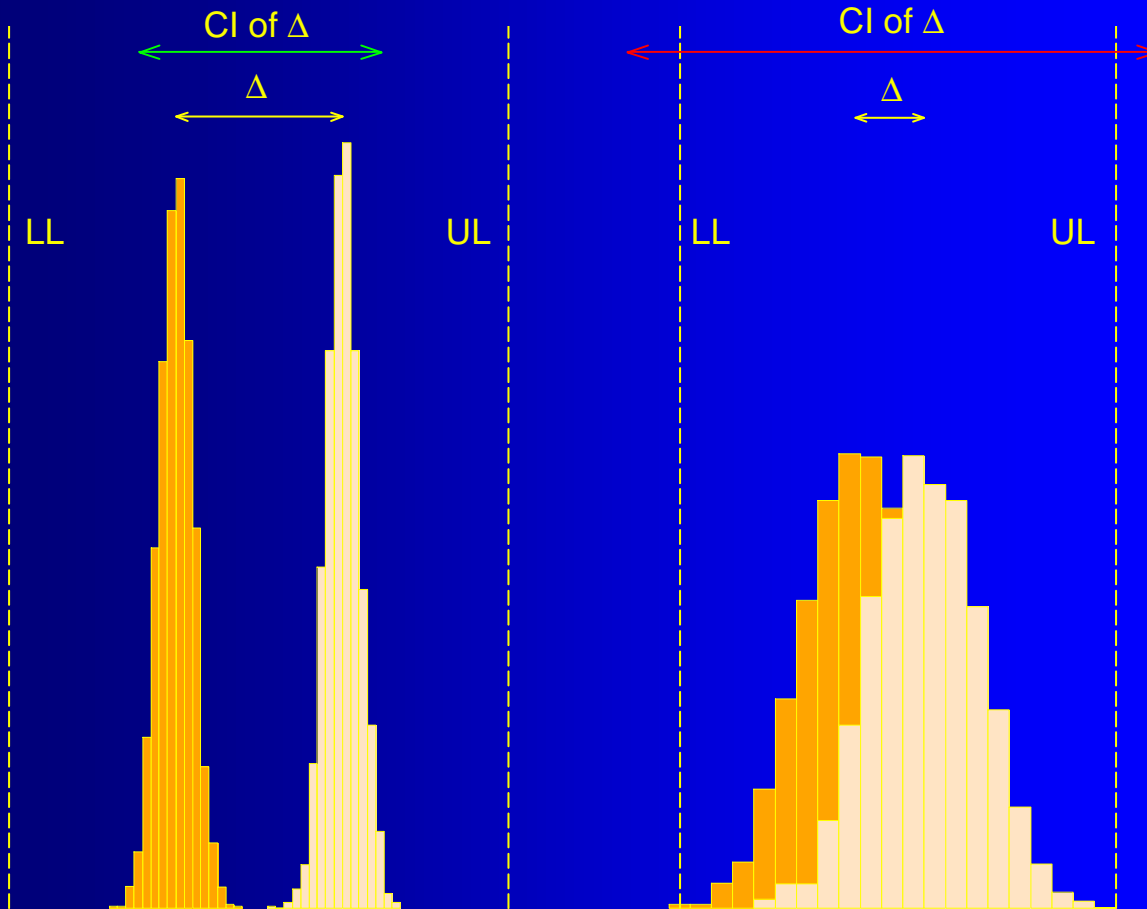Power to show BE with 40 subjects for CV_{intra} = 30–50%

μ_T/μ_R 0.95, CV_{intra} 30%
→ power 0.816

μ_T/μ_R 1.00, CV_{intra} 45%
→ power 0.476 <
Roulette 0.486 (!)

μ_T/μ_R 0.95, CV_{intra} 50%
→ n=98 (power 0.803)

2×2 Cross-over

Power

30 % CV

35 % CV

40 % CV

45 % CV

50 % CV

n=40

0.8 0.85 0.9 0.95 1 1.05 1.1 1.15 1.2 1.25

µT/µR

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Variances

CI of Δ

Δ

LL

UL

CI of Δ

Δ

LL

UL

Modified from Fig. 1
L Tóthfalusi, L Endrenyi and A García Arieta
Evaluation of Bioequivalence for Highly Variable Drugs with Scaled Average Bioequivalence
Clin Pharmacokinet 48, 725–743 (2009)

Counterintuitive concept of BE:
Two formulations with a large difference in means are declared bioequivalent if vari-ances are low, but not bioequivalent – even if the difference is quite small – due to high variability.

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Replicate designs

- Each subject is randomly assigned to sequences, where *at least one* of the treatments is administered *at least twice*.

  - Not only the *global within-subject variability*, but also the *within-subject variability per treatment* may be estimated.

  - Smaller subject numbers compared to a standard 2×2×2 design – but outweighed by an increased number of periods. Note: Same overall number of individual treatments!

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Replicate designs

- Required if reference-scaled average bioequiva-lence (RSABE) is targeted or widening of the AR for C_{max} (for countries following the 'old' EU guideline).
- Advantages
  - Some experience from FDA's initiative on Population Bioequivalence (PBE) and Individual Bioequivalence (IBE).
  - Mentioned in RSA's GL; FDA's API GLs and EMA.
  - RSABE of different metrics acceptable in some countries (FDA, RSA AUC/C_{max}, EMA C_{max}, TGD AUC).
  - Handling of outliers (Subject-by-Formulation Interaction may be ruled out).
  - SAS-code published by the FDA for their method in April 2010: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf

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Replicate designs

- **Disadvantages**
  - Statistical analysis quite complicated (especially in the case of drop-outs and if RSABE is the target) – not available in standard software.
  - Many publications, but still no agreement on methodology (!)
  - Handling of outliers. For the EMA it has to be shown that $CV_{WR} > 30\%$ is not caused by outliers. Method?
  - SAS-code and example datasets expected to be pubished by the EMA end of January 2011.

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Replicate designs

■ Examples

- ■ Two-sequence three-period
  T R T
  R T R
  Sample size to obtain the same power as a 2×2×2 study: 75%
- ■ Two-sequence four-period
  T R T R
  R T R T
  Sample size to obtain the same power as a 2×2×2 study: 50%
- ■ and many others… (FDA: TRR|RTR|RRT aka 'partial replicate')
- ■ The statistical model is quite complicated – and dependent on the actual design!

$$X_{ijkl} = \mu \cdot \pi_k \cdot \Phi_l \cdot s_{ij} \cdot e_{ijkl}$$

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Application: HVDs/HVDPs

● Highly Variable Drugs / Drug Products (CV_{WR} >30 %)

✓ USA Recommended in product specific guidances. GMR 0.80 – 1.25. Minimum sample size 24?

✓ CAN 2010 draft GL. Scaling for AUC only. No restriction on GMR.

± EU Widening of acceptance range (for C_{max} only: to maximum 69.84% – 143.19%), if CV_{WR} in the study >30%. GMR 0.80 – 1.25. Demonstration that CV_{WR} >30% not caused by outliers.

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Application: HVDs/HVDPs

- All (!) ANDAs submitted to FDA/OGD 2003 – 2005 (1010 studies, 180 drugs)
  - 31% (57/180) highly variable (CV $\geq$30%)
  - of these HVDs/HVDPs,
    - 60% due to PK (*e.g.*, first pass metabol.)
    - 20% formulation performance
    - 20% unclear

Davit BM, Conner DP, Fabian-Fritsch B, Haidar SH, Jiang X, Patel DT, Seo PR, Suh K, Thompson CL, and LX Yu
Highly Variable Drugs: Observations from Bioequivalence Data Submitted to the FDA for New Generic Drug Applications
The AAPS Journal 10/1, 148–56 (2008)
http://www.springerlink.com/content/51162107w327883r/fulltext.pdf

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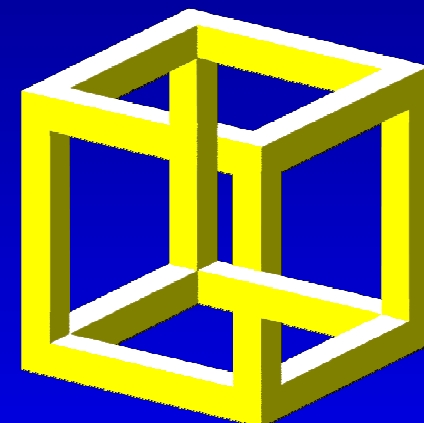11 • 29

Application: HVDs/HVDPs

- Ways out?
  - Nonparametric methods
    A non-parametric analysis is **not acceptable**. (BE GL, Section 4.1.8)
  - Compartmental methods
    (Population PK)
    The use of compartmental methods for the estimation of parameters is **not acceptable**. (BE GL, Section 4.1.5)
  - Replicate designs could be considered e.g. for substances with highly variable pharmacokinetic characteristics. (EU BE GL, Section 4.1.1, 4.1.10)

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HVDPs (US/EU)

- **Advisory Committee for Pharmaceutical Sciences (ACPS) to FDA (10/2006) on HVDs**
- **Follow-up papers in 2008 (ref. in API-GLs)**
  - **Replicate study design [TRR–RTR–RRT]**
  - **Reference Scaled Average Bioequivalence (RSABE)**
  - **Minimum sample size 36 (?) subjects**
  - **Point estimate restricted to [0.80,1.25]**

Haidar SH, Davit B, Chen M-L, Conner D, Lee LM, Li QH, Lionberger R, Makhlouf F, Patel D, Schuirmann DJ, and LX Yu
Bioequivalence Approaches for Highly Variable Drugs and Drug Products
Pharmaceutical Research 25/1, 237-241 (2008)
http://www.springerlink.com/content/u503p62056413677/fulltext.pdf
Haidar SH, Makhlouf F, Schuirmann DJ, Hyslop T, Davit B, Conner D, and LX Yu
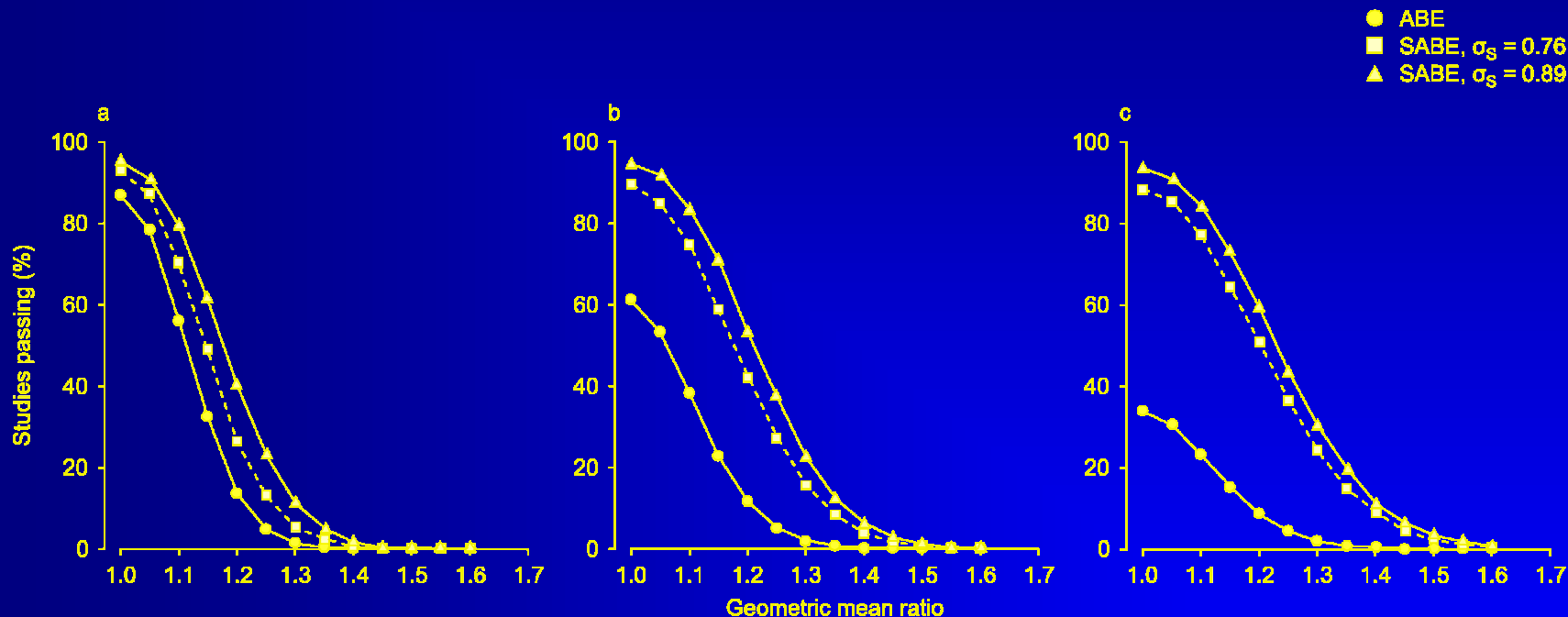*Evaluation of a Scaling Approach for the Bioequivalence of Highly Variable Drugs*
The AAPS Journal, 10/3, (2008) DOI: 10.1208/s12248-008-9053-4

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HVDs/HVDPs

- Replicate designs
  - 4-period replicate designs:
    sample size = ½ of 2×2 study's sample size
  - 3-period replicate designs:
    sample size = ¾ of 2×2 study's sample size
  - Reminder: number of treatments (and biosamples) identical to the conventional 2×2 cross-over.
  - Allow for a safety margin – expect a higher number of drop-outs due to the additional period(s).
  - Consider increased blood loss (ethics!) Eventually bioanalytics has to be improved.

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HVDPs (US/EU)

Tóthfalusi *et al.* (2009), Fig. 3
Simulated (n=10000) three-period replicate design studies (TRT-RTR) in 36 subjects;
GMR restriction 0.80–1.25. (a) CV=35%, (b) CV=45%, (c) CV=55%.
ABE: Conventional Average Bioequivalence, SABE: Scaled Average Bioequivalence,
0.76: EU criterion, 0.89: FDA criterion.

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HVDPs (US/EU)

- FDA's and EMA's approaches differ; FDA's leads to a discontinuity of the acceptance range at CV=30%, because FDA's scaling CV is 25.396% (σ_{WR} 0.25) – but *applied* at CV >30%.

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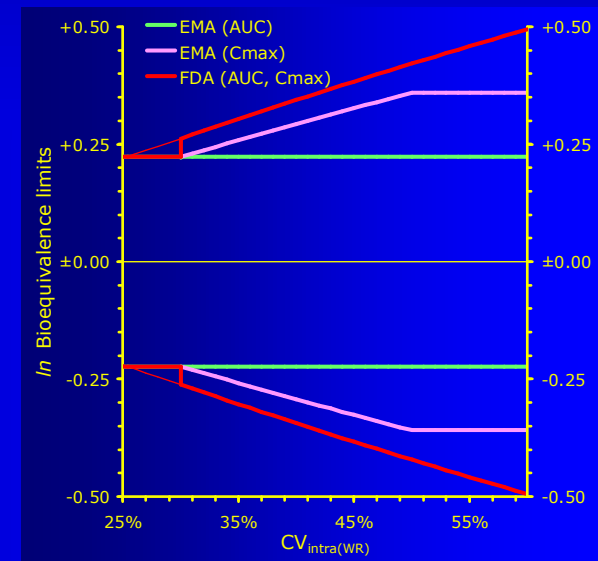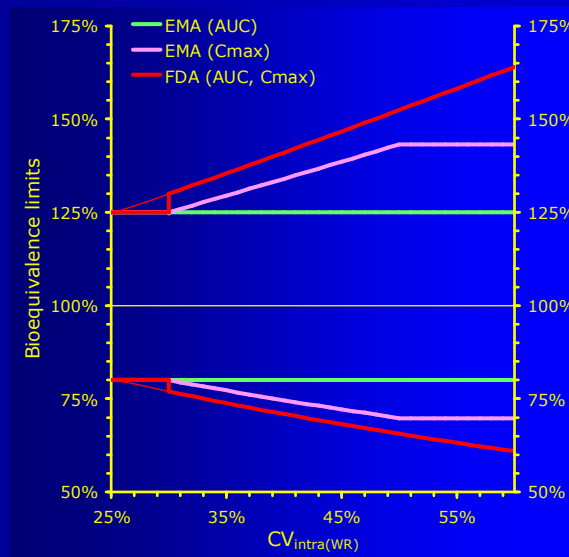
HVDPs (Global Harmonization?)

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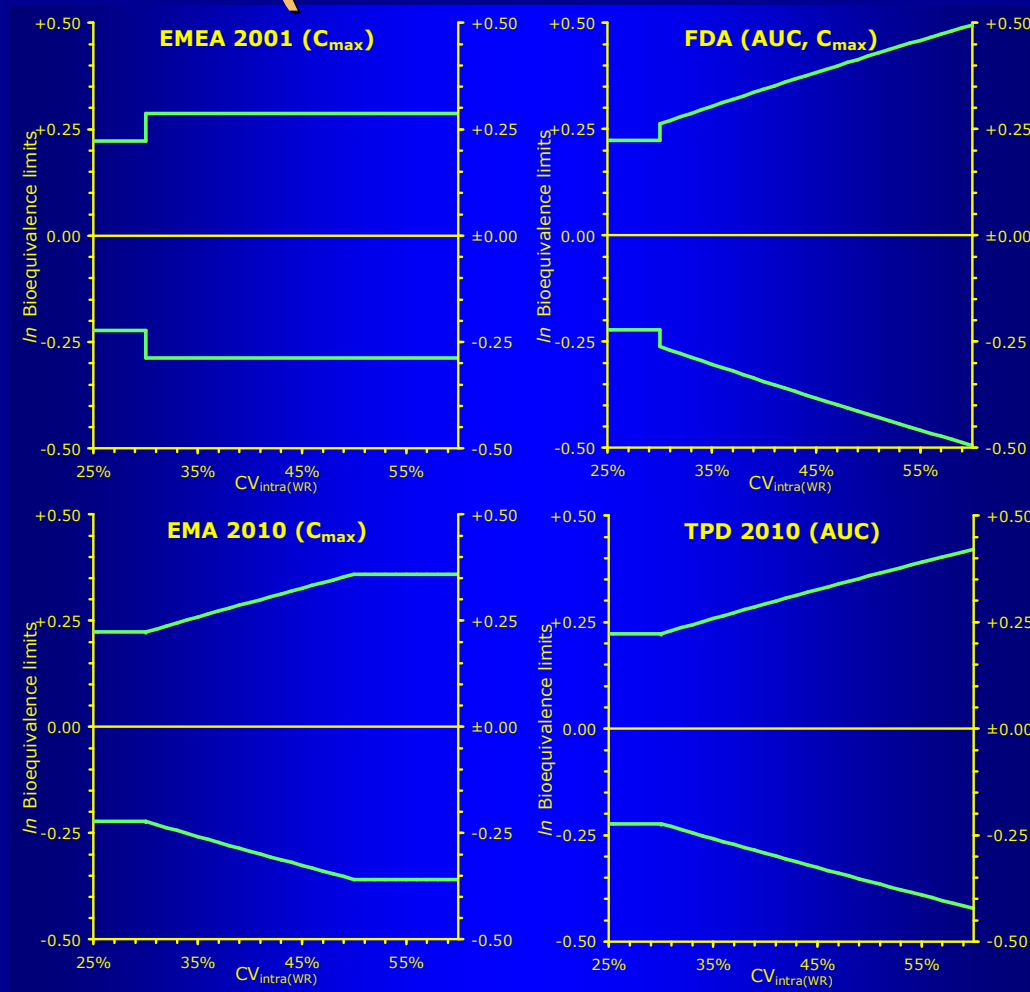
Application: HVDs/HVDPs

- Is suggested EU-method of any good?
  - Replicate designs *without scaling* (AUC)
    - reduce the number of subjects (to 75% for a 3-period design and to 50% for a 4-period design as compared to a conventional 2×2),
    - but keep the *theoretical* number of treatments constant:
      - ➢ The potentional drop-out rate increases.
      - ➢ Practically *more* treatments must be administered in order to maintain the desired power!

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Application: HVDs/HVDPs

- Example
  - AR [0.80,1.25], CV_{intra} 49.5%, T/R 0.95%, power 80%, $n_{2×2}$ 96
  - expected dropout rate of 10% per washout
    - 2×2 study: 96+10=106 subjects, 212 treatments
    - 4×2 study: 48+16=64 subjects, 256 treatments

    Ethical?

  - Proposed FDA Scaling-Method:
    AR [0.7006,1.4273], PE [0.80,1.25], n 34 (!)

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HVDs/HVDPs

- ## EU GL on BE (2010)
  - ### The regulatory switching condition θ_s is derived from the regulatory standardized variation σ_0. For CV_{WR} 30% one gets

$$\sigma_0 = \sqrt{\ln(0.30^2 + 1)} = 0.29356{\scriptstyle 03792085\ldots}$$

and

$$\theta_s = \frac{\ln(1.25)}{\sigma_0} = -\frac{\ln(0.80)}{\sigma_0} = 0.76012{\scriptstyle 28297680\ldots}$$

Tóthfalusi *et al.* (2009)

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HVDs/HVDPs

- EU GL on BE (2010)
    - The regulatory switching condition θ_s at CV_{WR} 30% is 0.76012$_{28297680...}$ But the GL gives k as 0.760. Backcalculating the switching CV_{WR} we get

$$CV_{WR} = \sqrt{\left(\exp^{\left(\frac{\ln(1.25)}{0.760} \right)^2} - 1 \right)} = 0.30005_{28579179...}$$

Which one should we use? The *exact* one – or the (wrong!) *rounded* one?

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HVDs/HVDPs

- EU GL on BE (2010)
  - Average Bioequivalence (ABE) with Expanding Limits (ABEL)
    - If you have σ_{WR} (the intra-subject standard deviation of the reference formulation) go to the next step; if not, calculate it from CV_{WR}

    $$\sigma_{WR} = \sqrt{\ln(CV_{WR}^2 + 1)}$$

    - Calculate the scaled acceptance range based on the regulatory constant k (θ_s=0.760)

    $$[L, U] = e^{\mp k \cdot \sigma_{WR}}$$

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HVDs/HVDPs

- ●EU GL on BE (2010)
  - ■Scaling allowed for C_{max} only (*not* AUC!) – based on CV_{WR} >30% in the actual study (no reference to previous studies).
  - ■Limited to a maximum of CV_{WR} 50% (*i.e.*, higher CVs are treated *as if* CV = 50%).
  - ■GMR restricted within 80.00% – 125.00% in any case.
  - ■At higher CVs only the GMR is of importance!
  - ■No commercial software for sample size estimation can handle the GMR restriction.
  - ■Expect a solution from the community soon…

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Example ABEL

- RTR–TRT Replicate Design, n=18 (imbalanced!)

Subj	Seq	Per	Trt	Cmax
1	1	1	R	209.91
1	1	2	T	111.05
1	1	3	R	116.36
2	1	1	R	101.16
2	1	2	T	100.31
2	1	3	R	31.71
3	1	1	R	14.83
3	1	2	T	57.10
3	1	3	R	21.47
4	1	1	R	118.71
4	1	2	T	37.34
4	1	3	R	52.29
5	1	1	R	36.11
5	1	2	T	83.95
5	1	3	R	17.76
6	1	1	R	146.44
6	1	2	T	40.45
6	1	3	R	38.34

Subj	Seq	Per	Trt	Cmax
7	1	1	R	58.49
7	1	2	T	62.80
7	1	3	R	123.23
8	1	1	R	105.34
8	1	2	T	103.32
8	1	3	R	43.67
9	1	1	R	59.73
9	1	2	T	169.03
9	1	3	R	48.26
10	1	1	R	38.34
10	1	2	T	31.19
10	1	3	R	19.43
11	2	1	T	51.95
11	2	2	R	195.71
11	2	3	T	65.87
12	2	1	T	18.72
12	2	2	R	20.63
12	2	3	T	7.45

Subj	Seq	Per	Trt	Cmax
13	2	1	T	92.76
13	2	2	R	59.54
13	2	3	T	56.84
14	2	1	T	159.20
14	2	2	R	155.50
14	2	3	T	165.31
15	2	1	T	162.41
15	2	2	R	47.31
15	2	3	T	88.23
16	2	1	T	19.44
16	2	2	R	42.80
16	2	3	T	18.93
17	2	1	T	90.58
17	2	2	R	42.39
17	2	3	T	54.57
18	2	1	T	42.96
18	2	2	R	171.86
18	2	3	T	59.15

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Example ABEL

- σ_{WR} (Phoenix/PBE)

Dependent	Statistic	Value
Ln(Cmax)	Difference(Delta)	-0.001061229
Ln(Cmax)	Ratio(%Ref)	99.893933
Ln(Cmax)	SigmaR	0.73185177
Ln(Cmax)	SigmaWR	0.46277444

Calculate the scaled acceptance range based on the regulatory con-stant k (0.760) and the limiting CV_{WR}.

$$CV_{WR} = \sqrt{e^{\sigma_{WR}^2} - 1} \qquad [L, U] = e^{\mp k \cdot \sigma_{WR}}$$

Dependent	SigmaWR	CVWR	L	U	Delta
Ln(Cmax)	0.46277444	0.48869324	0.7034851	1.4214942	0.2965149

σ_{WR}	0.4628
CV_{WR}	0.4887
L	0.7035
U	1.4215

Scaling applicable since 30% $< CV_{WR} \leq$ 50% and PE within 80% – 125%.

Example ABEL

```
Bioequivalence Statistics

User-Specified Confidence Level for CI's = 90.0000
Percent of Reference to Detect for 2-1 Tests = 20.0%
A.H.Lower =  0.800   A.H.Upper =  1.250


Formulation variable: Trt
Reference: R   LSMean=     4.069159  SE=    0.173739  GeoLSM=    58.507730
----------------------------------------------------------------------
Test:       T   LSMean=     4.068098  SE=    0.174718  GeoLSM=    58.445673

    Difference =     -0.0011,   Diff_SE=     0.1876,  df= 16.5
    Ratio(%Ref) =     99.8939


                    Classical                 Westlake
CI  80% = (    77.7639,  128.3217) (   75.1692,  124.8308)
CI  90% = (    72.0378,  138.5217) (   67.3124,  132.6876)
CI  95% = (    67.1817,  148.5344) (   59.4138,  140.5862)
Failed to show average bioequivalence
for confidence=90.00 and percent=20.0.

              Two One-Sided T-tests
 Prob(< 80%)=0.1266  Prob(> 125%)=0.1244  Max=0.1266  Total=0.2510

              Anderson-Hauck Procedure
 A.H. p-value = 0.002164
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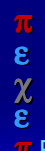
ABE
72.04 – 138.52
failed 80 – 125
failed 75 – 133

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Example ABEL

```
Bioequivalence Statistics

User-Specified Confidence Level for CI's = 90.0000
Percent of Reference to Detect for 2-1 Tests = 29.6%
A.H.Lower =  0.703   A.H.Upper =  1.421


Formulation variable: Trt
Reference: R    LSMean=     4.069159  SE=     0.173739  GeoLSM=    58.507730
--------------------------------------------------------------------------
Test:       T   LSMean=     4.068098  SE=     0.174718  GeoLSM=    58.445673


   Difference =     -0.0011,  Diff_SE=     0.1876,  df= 16.5
   Ratio(%Ref) =     99.8939


                   Classical                 Westlake
CI  80% = (   77.7639,  128.3217) (   75.1692,  124.8308)
CI  90% = (   72.0378,  138.5217) (   67.3124,  132.6876)
CI  95% = (   67.1817,  148.5344) (   59.4138,  140.5862)
Average bioequivalence shown
for confidence=90.00 and percent=29.6.


                Two One-Sided T-tests
 Prob(< 70%)=0.0397  Prob(> 142%)=0.0389  Max=0.0397  Total=0.0786


                Anderson-Hauck Procedure
 A.H. p-value = 0.000820
```

RSABE
72.04 – 138.52
passed ABEL
70.35 – 142.15
PE 99.89
within
80.00 – 125.00

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Part III: Advanced Designs for BE Studies

Helmut Schütz
BEBAC
Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria
helmut.schuetz@bebac.at

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To bear in Remembrance...

The fundamental cause of trouble in the world today is that the stupid are cocksure
while the intelligent are full of doubt. *Bertrand Russell*
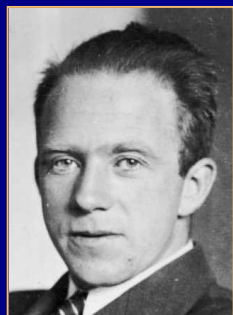
An expert is someone who knows some
of the worst mistakes that can be made in his subject,
and how to avoid them.

Werner Heisenberg

If you shut your door to all errors
truth will be shut out.

Rabindranath Tagore

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