Statistical aspects of reference-scaled studies
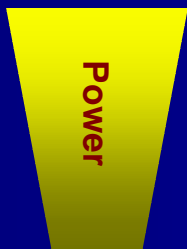
Helmut Schütz
BEBAC

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1 • 42

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Hierarchy of Designs

- The more 'sophisticated' a design is , the more information (in terms of σ^2) we may obtain.
  - Hierarchy of designs:
    Full replicate (TRTR | RTRT) ⇗
     Partial replicate (TRR | RTR | RRT) ⇗
       Standard 2×2 cross-over (RT | RT) ⇗
         Parallel (R | T)

Power

  - 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 Xover assumes Independent Identically Distributions (IID), 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.
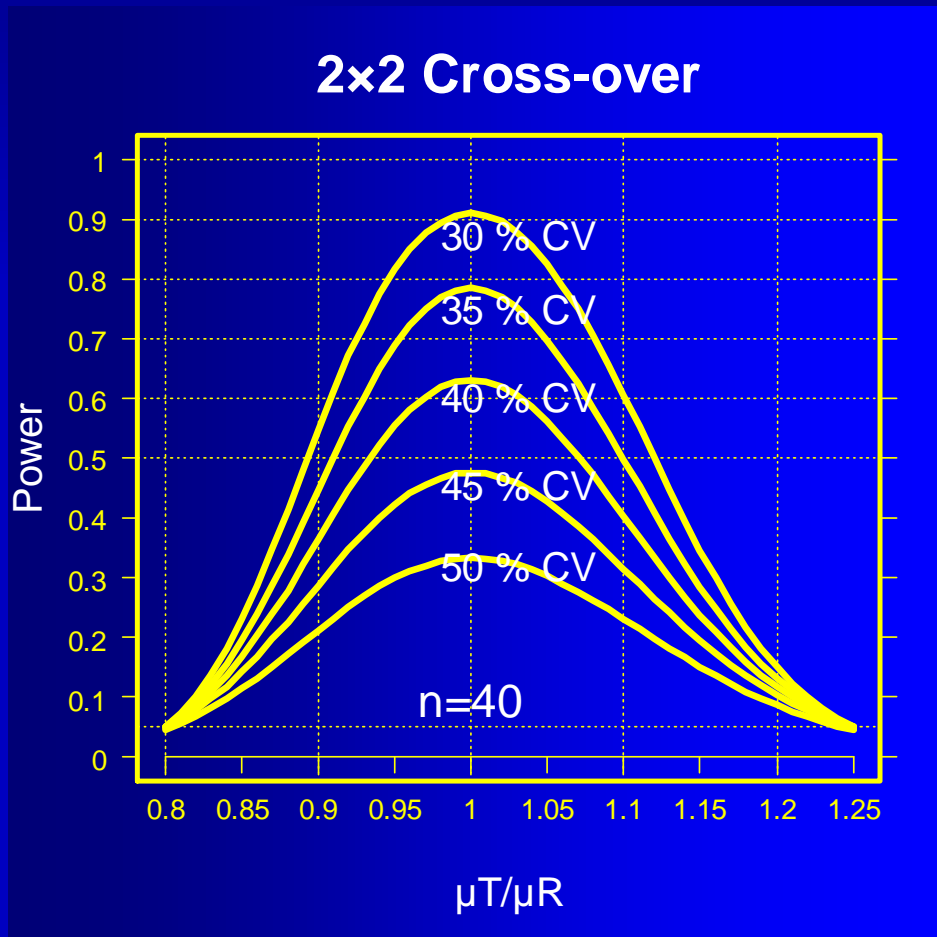
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Variances

2×2 Cross-over

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)

30 % CV
35 % CV
40 % CV
45 % CV
50 % CV
n=40

Power

μT/μR

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4 • 42

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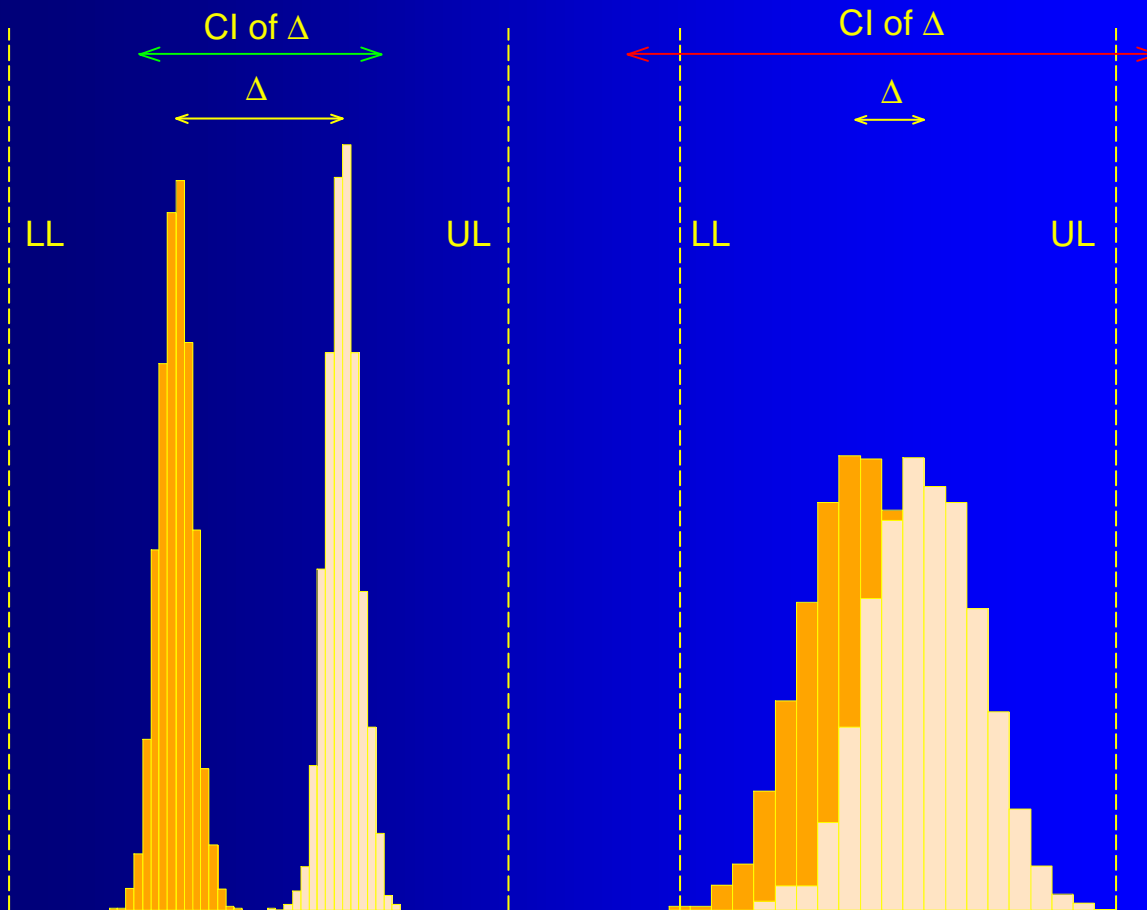
Modified from Fig. 1
L Tóthfalusi, L Endrenyi and A García Arieta
Evaluation of Bioequivalence for Highly Variable Drugs with Scaled Average Bioequivalence
Clin Pharmacokinet 48, 725–743 (2009)

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 treat-ments 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).

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7 • 42

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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 (!)
  - SAS-code published by the FDA in April 2010: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf
  - Handling of outliers. For the EMA it has to be shown that $CV_{WR} > 30\%$ is not caused by outliers. Method?
  - SAS-code and two example datasets published by the EMA in March 2011: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002963.pdf

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Replicate designs

- ■ Designs
    - ■ 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 ≥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 • 42

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 24 subjects
  - GMR 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
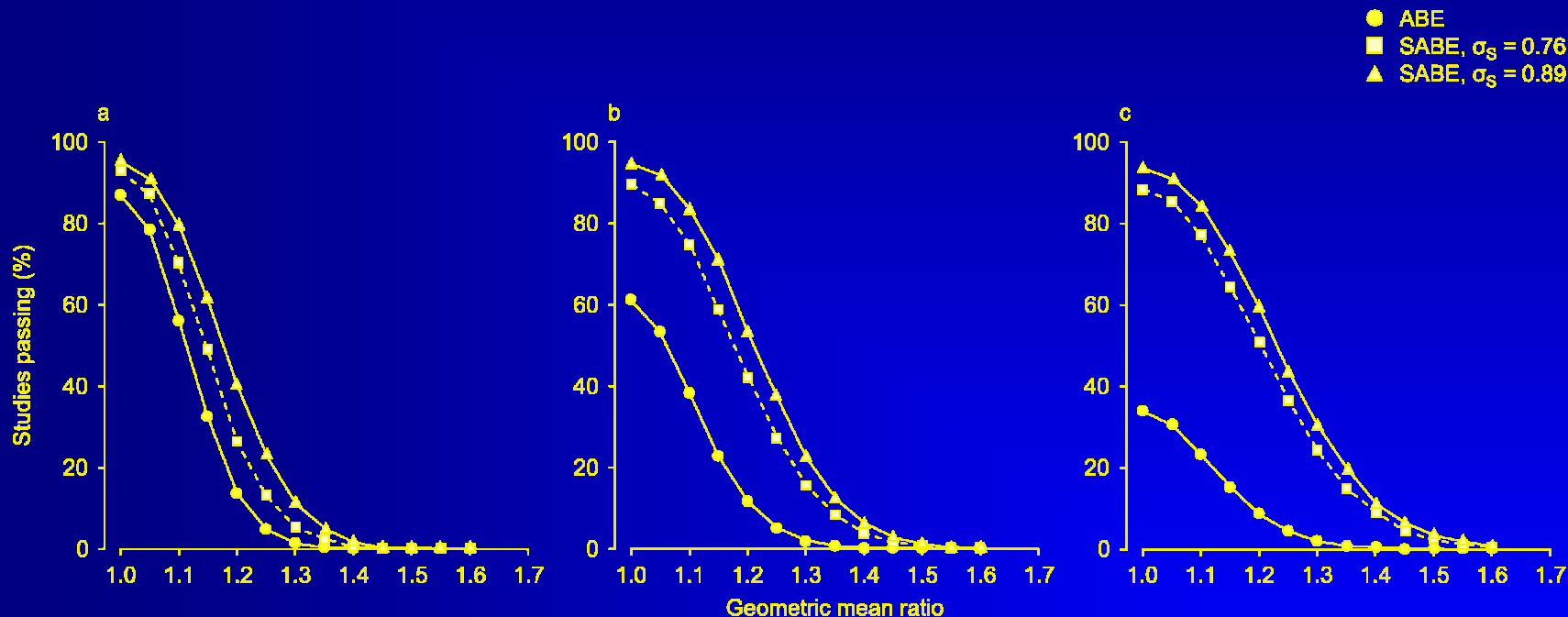The AAPS Journal, 10/3, (2008) DOI: 10.1208/s12248-008-9053-4

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12 • 42

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 25.83% (σ_{WR} 0.294) – but to be *applied* at CV≥30%.

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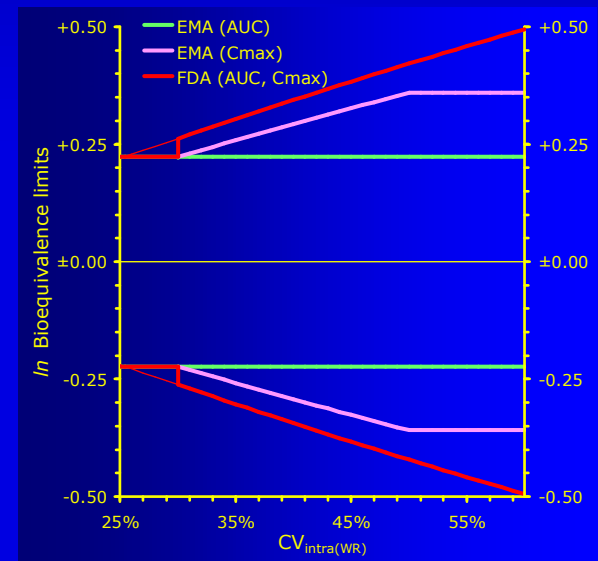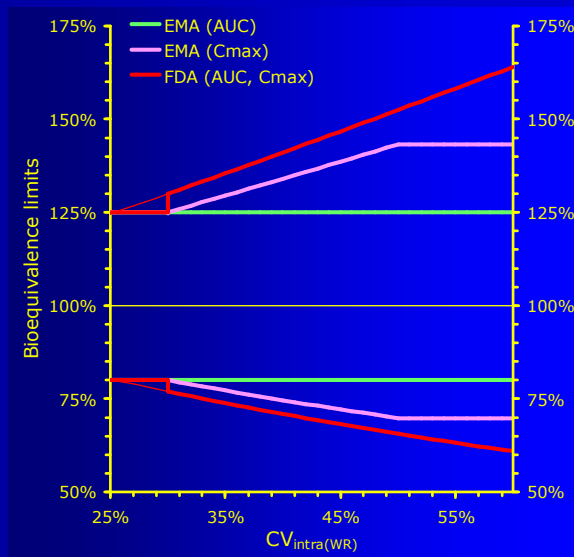
HVDPs (No Global Harmonization!)

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16 • 42
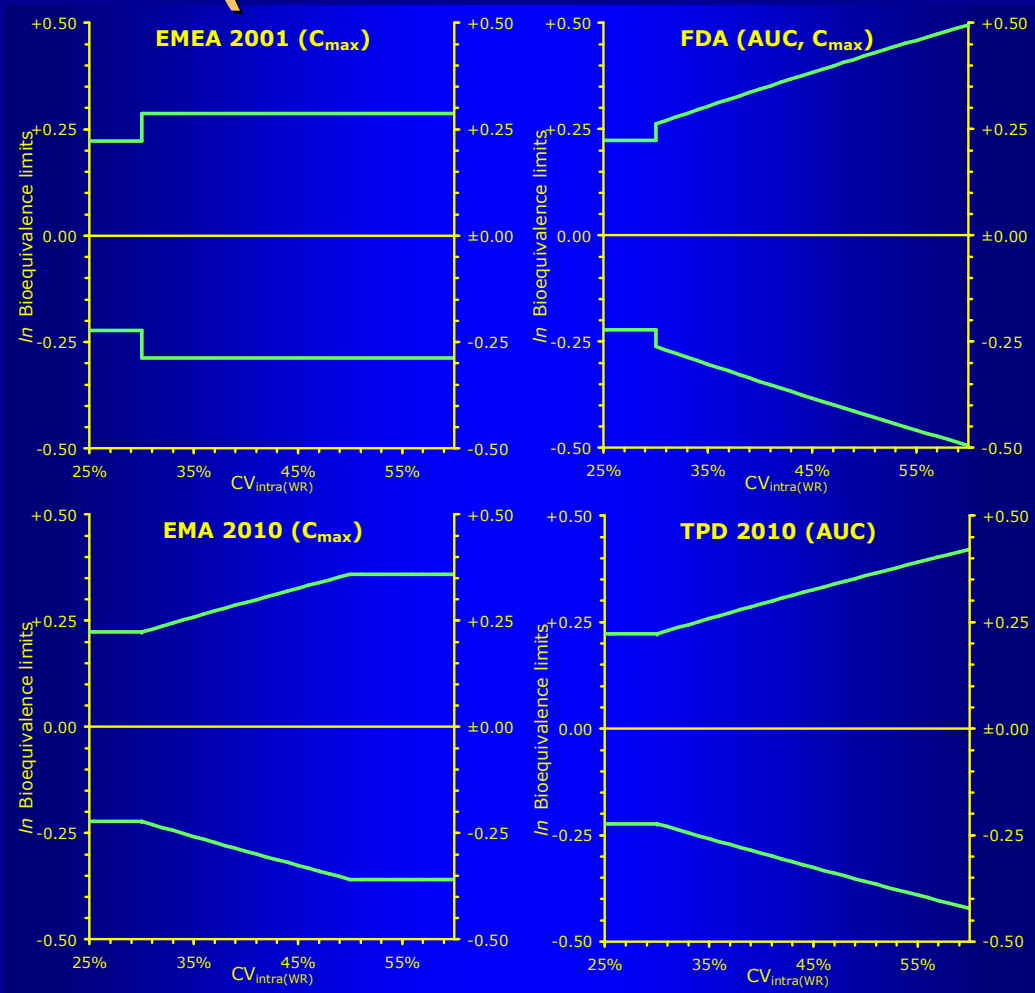
HVDs/HVDPs (Reg. models)

● Common to FDA and EMA

ABE model

$$-\theta_A \le \mu_T - \mu_R \le +\theta_A$$

SABE model

$$-\theta_S \le \frac{\mu_T - \mu_R}{\sigma_W} \le +\theta_S$$

Regulatory regulatory switching condition θ_S is derived from the regulatory standardized variation σ_0 (proportionality between acceptance limits in ln-scale and σ_W in the highly variable region).

Tóthfalusi *et al.* (2009)

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17 • 42

HVDs/HVDPs (Reg. models)

- Differences between FDA and EMA

  FDA: Regulatory regulatory switching condition θ_S is set to 0.893, which would translate into

  $$CV_{WR} = 100\sqrt{e^{\left(\frac{\ln(1.25)}{0.893}\right)^2} - 1} \approx 25.83\%$$

  RSABE is allowed only if $CV_{WR} \geq 30\%$ ($s_{WR} \geq 0.294$), which explains to the discontinuity at 30%.

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18 • 42

HVDs/HVDPs (Reg. models)

- Differences between FDA and EMA

  EMA: Regulatory regulatory switching condition θ_S avoids the discontinuity.

$$CV_W = 0.30$$

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

$$\theta_S = \frac{\ln(1.25)}{\sigma_0} = -\frac{\ln(0.80)}{\sigma_0} \approx 0.760$$

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19 • 42

HVDs/HVDPs (FDA)

- Haidar *et al.* (2008), progesterone guid. (2010)

Starting from the SABE model

$$-\theta_S \leq \frac{\mu_T - \mu_R}{\sigma_W} \leq +\theta_S$$

Rearrangement leads to a linear form

$$\left(\mu_T - \mu_R\right)^2 - \theta_S^2 \cdot \sigma_W^2 \leq 0$$

Since we don't have the true parameters, we use estimates

$$E_m = \left(\mu_T - \mu_R\right)^2$$

$$E_s = \theta_S^2 \cdot \sigma_W^2$$

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HVDs/HVDPs (FDA)

- Haidar *et al.* (2008), progesterone guid. (2010)

  Distributions of E_m and E_s are known and their upper confidence limits can be calculated

  $$C_m = \left(\left| m_T - m_R \right| + t_{\alpha, N-S} \cdot SE \right)^2$$

  $$C_s = \frac{\theta_S^2 \cdot (N-S) \cdot s_W^2}{\chi_{\alpha, N-S}^2}$$

  t and χ^2 are the inverse cumulative distribution functions at α 0.05 and $N-S$ degrees of freedom (N subjects, S sequences). SE is the standard error of the difference between means.

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21 • 42

HVDs/HVDPs (FDA)

- Haidar *et al.* (2008), progesterone guid. (2010)

  Howe method gets the CI from individual CIs

  $$L_m = \left(C_m - E_m \right)^2$$

  $$L_s = \left(C_s - E_s \right)^2$$

  $$CI = E_m - E_s + \sqrt{L_m + L_s}$$

  The CI of the rearranged SABE criterion (slide 20) is evaluated at the 95% level. If the upper 95% is positive RSABE is rejected, and accepted otherwise.

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22 • 42

HVDs/HVDPs (EMA)

- EU GL on BE (2010)
  - Average Bioequivalence (ABE) with Expanding Limits (ABEL)
    - The regulatory switching condition θ_S at CV_{WR} 30% would be 0.7601228297680…
    - According to the GL (2010) and the Q&A document (2011) use k ($\equiv\theta_S$) with 0.760 (not the exact value).

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23 • 42

HVDs/HVDPs (EMA)

- **EU GL on BE (2010)**
  - ■ 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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24 • 42

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HVDs/HVDPs (EMA)

- Q&A document (March 2011)
  - Two methods proposed (Method A preferred)
    - Method A: All effects fixed; assumes equal variances of test and reference, and no subject-by-formulation interaction; only a common within (*intra*-) subject variance is estimated
    - Method B: Similar to A, but random effects for subjects. Common within (*intra*-) subject variance and between (*inter*-) subject variance are estimated.
  - Outliers: Boxplots (of model residuals?) suggested.

Questions & Answers on the Revised EMA Bioequivalence Guideline
Summary of the discussions held at the 3rd EGA Symposium on Bioequivalence
June 2010, London
http://www.egagenerics.com/doc/EGA_BEQ_Q&A_WEB_QA_1_32.pdf

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HVDs/HVDPs (EMA)

- At higher CVs only the GMR is of importance!
- At CVs > 50% still large sample sizes required.
- No commercial software for sample size estimation can handle the GMR restriction.
- Recently sample size tables were published.
- Expect a solution from the ® community soon…

L Tóthfalusi and L Endrenyi
Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs
J Pharm Pharmaceut Sci 15(1), 73 – 84 (2011)
http://ejournals.library.ualberta.ca/index.php/JPPS/article/download/11612/9489

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26 • 42

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Example datasets (EMA)

- Q&A document (March 2011)
  - Data set I
    RTRT | TRTR full replicate, 77 subjects, imbalanced, incomplete
    - FDA
      s_{WR} 0.446 $\geq$ 0.294 $\rightarrow$ apply RSABE (CV_{WR} 46.96%)
      a. critbound -0.0921 $\leq$ 0 and
      b. 80.00% $\leq$ pointest 115.46% $\leq$ 125.00% ✔
    - EMA
      - CV_{WR} 46.96% $\rightarrow$ apply RSABE (> 30%)
      - Scaled Acceptance Range: 71.23% − 140.40%
      - A: 71.23% $\leq$ 107.11% − 124.89% $\leq$ 140.40%, PE 115.66% ✔
      - B: 71.23% $\leq$ 107.17% − 124.97% $\leq$ 140.40%, PE 115.73% ✔

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27 • 42

Example datasets (EMA)

- Q&A document (March 2011)
  - Data set II
    TRR | RTR | RRT partial replicate, 24 subjects, balanced, complete
    - FDA
      s_{WR} 0.114 $<$ 0.294 $\rightarrow$ apply ABE (CV_{WR} 11.43%)
      80.00% $\leq$ 97.05 $-$ 107.76 $\leq$ 125.00% (CV_{intra} 11.55%) ✔
    - EMA
      - CV_{WR} 11.17% $\rightarrow$ apply ABE ($\leq$ 30%)
      - A: 90% CI 97.32% $-$ 107.46%, PE 102.26% ✔
      - B: 90% CI 97.32% $-$ 107.46%, PE 102.26% ✔
      - A/B: CV_{intra} 11.86%

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Outliers (EMA)

- EU GL on BE (2010), Section 4.1.10
  - The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers.

- EGA/EMA Q&A (2010)
  - Q: How should a company proceed if outlier values are observed for the reference product in a replicate design study for a Highly Variable Drug Product (HVDP)?

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29 • 42

Outliers (EMA)

- EGA/EMA Q&A (2010)
  - A: The outlier cannot be removed from evaluation […] but should not be taken into account for calculation of within-subject variability and extension of the acceptance range.
  An outlier test is not an expectation of the medicines agencies but outliers could be shown by a box plot. This would allow the medicines agencies to compare the data between them.

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30 • 42

Outliers (EMA)

● Data set I (full replicate)

■ CV_{WR} 46.96%
ABEL 71.23% − 140.40%
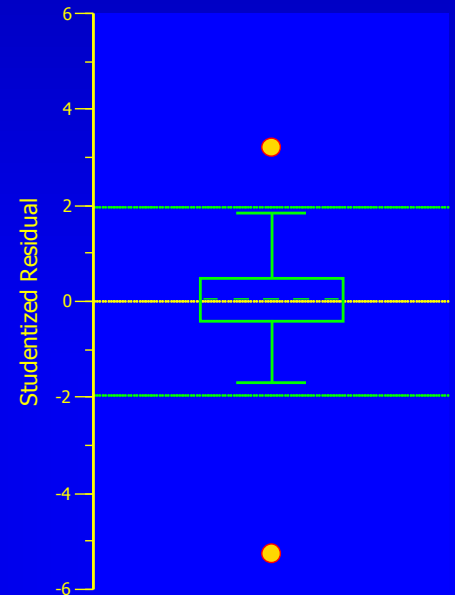Method A: 107.11% − 124.89%
Method B: 107.17% − 124.97%

■ But there are two outliers!
Excluding subjects 45 and 52
CV_{WR} drops to 32.16%.
ABEL 78.79% − 126.93%
Almost no more gain compared
to conventional limits.

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31 • 42

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Thank You!

Statistical aspects of reference-scaled studies

Open Questions?

*(EMA's and FDA's SAS code and EMA's datasets in the handouts)*

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32 • 42

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*
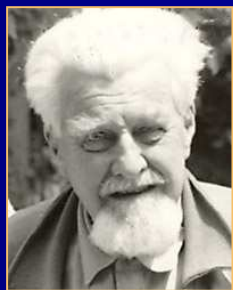
It is a good morning exercise for a research scientist
to discard a pet hypothesis every day before
breakfast.
It keeps him young.   *Konrad Lorenz*

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

Rabindranath Tagore

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33 • 42

SAS code (EMA)

Method A

```
proc glm data=replicate;
   class formulation subject period sequence;
   model logDATA= sequence subject(sequence) period formulation;
   estimate "test-ref" formulation -1+1;
   test h=sequence e=subject(sequence);
   lsmeans formulation / adjust=t pdiff=control("R") CL alpha=0.10;
run;
```

Method B

```
proc mixed data=replicate;
   class formulation subject period sequence;
   model logDATA= sequence period formulation;
   random subject(sequence);
   estimate "test-ref" formulation -1 1 / CL alpha=0.10;
run;
```

CV_{WR} (both methods)

```
data var;
   set replicate;
   if formulation='R';
run;
proc glm data=var;
   class subject period sequence;
   model logDATA= sequence subject(sequence) period;
run;
```

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34 • 42

SAS code (FDA)

Partial reference-replicated 3-way design

```
data test;
  set pk;
  if trt='T';
  latt=lauct;
run;

data ref1;
  set ref;
  if (seq=1 and per=2) or (seq=2 and per=1) or (seq=3 and per=1);
  lat1r=lauct;
run;

data ref2;
  set ref;
  if (seq=1 and per=3) or (seq=2 and per=3) or (seq=3 and per=2);
  lat2r=lauct;
run;

data ref2;
  set ref;
  if (seq=1 and per=3) or (seq=2 and per=3) or (seq=3 and per=2);
  lat2r=lauct;
run;
```

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SAS code (FDA)

Partial reference-replicated 3-way design (cont'd)

```
proc glm data=scavbe;
  class seq;
  model ilat=seq/clparm alpha=0.1;
  estimate 'average' intercept 1 seq 0.3333333333 0.3333333333 0.3333333333;
  ods output overallanova=iglm1;
  ods output Estimates=iglm2;
  ods output NObs=iglm3;
  title1 'scaled average BE';
run;

pointest=exp(estimate);
x=estimate**2-stderr**2;
boundx=(max((abs(LowerCL)),(abs(UpperCL))))**2;

proc glm data=scavbe;
  class seq;
  model dlat=seq;
  ods output overallanova=dglm1;
  ods output NObs=dglm3;
  title1 'scaled average BE';
run;

dfd=df;
s2wr=ms/2;
```

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36 • 42

SAS code (FDA)

Partial reference-replicated 3-way design (cont'd)

```
theta=((log(1.25))/0.25)**2;
y=-theta*s2wr;
boundy=y*dfd/cinv(0.95,dfd);
sWR=sqrt(s2wr);
critbound=(x+y)+sqrt((((boundx-x)**2)+((boundy-y)**2));
```

Apply RSABE if $\text{sWR} \geq 0.294$

RSABE if

a. `critbound` ≤ 0 *and*

b. $0.8000 \leq$ `pointest` ≤ 1.2500

If $\text{sWR} < 0.294$, apply conventional (unscaled ABE), mixed effects model.

ABE if 90% CI within 0.8000 and 1.2500.

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37 • 42

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SAS code (FDA)

Fully replicated 4-way design

```
data test1;
  set test;
  if (seq=1 and per=1) or (seq=2 and per=2);
  lat1t=lauct;
run;

data test2;
  set test;
  if (seq=1 and per=3) or (seq=2 and per=4);
  lat2t=lauct;
run;

data ref1;
  set ref;
  if (seq=1 and per=2) or (seq=2 and per=1);
  lat1r=lauct;
run;

data ref2;
  set ref;
  if (seq=1 and per=4) or (seq=2 and per=3);
  lat2r=lauct;
run;
```

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in Drug Product Development | Mumbai, 29 January 2012

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38 • 42

SAS code (FDA)

Fully replicated 4-way design (cont'd)

```
data scavbe;
  merge test1 test2 ref1 ref2;
  by seq subj;
  ilat=0.5*(lat1t+lat2t-lat1r-lat2r);
  dlat=lat1r-lat2r;
run;

proc mixed data=scavbe;
  class seq;
  model ilat =seq/ddfm=satterth;
  estimate 'average' intercept 1 seq 0.5 0.5/e cl alpha=0.1;
  ods output CovParms=iout1;
  ods output Estimates=iout2;
  ods output NObs=iout3;
  title1 'scaled average BE';
  title2 'intermediate analysis - ilat, mixed';
run;

pointest=exp(estimate);
x=estimate**2-stderr**2;
boundx=(max((abs(lower)),(abs(upper))))**2;
```

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39 • 42

SAS code (FDA)

Fully replicated 4-way design (cont'd)

```
proc mixed data=scavbe;
  class seq;
  model dlat=seq/ddfm=satterth;
  estimate 'average' intercept 1 seq 0.5 0.5/e cl alpha=0.1;
  ods output CovParms=dout1;
  ods output Estimates=dout2;
  ods output NObs=dout3;
  title1 'scaled average BE';
  title2 'intermediate analysis - dlat, mixed';
run;

  s2wr=estimate/2;
  dfd=df;

  theta=((log(1.25))/0.25)**2;
  y=-theta*s2wr;
  boundy=y*dfd/cinv(0.95,dfd);
  sWR=sqrt(s2wr);
  critbound=(x+y)+sqrt(((boundx-x)**2)+((boundy-y)**2));
```

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40 • 42

SAS code (FDA)

Unscaled 90% BE confidence intervals (applicable if critbound>0)

```
PROC MIXED
   data=pk;
   CLASSES SEQ SUBJ PER TRT;
   MODEL LAUCT = SEQ PER TRT/ DDFM=SATTERTH;
   RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
   REPEATED/GRP=TRT SUB=SUBJ;
   ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
   ods output Estimates=unsc1;
   title1 'unscaled BE 90% CI - guidance version';
   title2 'AUCt';
run;

data unsc1;
   set unsc1;
   unscabe_lower=exp(lower);
   unscabe_upper=exp(upper);
run;
```

Note: Lines marked with an arrow are missing in FDA's code!

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in Drug Product Development | Mumbai, 29 January 2012**

41 • 42

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Example datasets (EMA)

- Q&A document (March 2011)
  - Data set I
    4-period 2-sequence (RTRT | TRTR) full replicate, imbalanced (77 subjects), incomplete (missing periods: two periods in two cases, one period in six cases).
  - Data set II
    3-period 3-sequence (TRR | RTR | RRT) partial replicate, balanced (24 subjects), complete (all periods).
  - Download in Excel 2000 format:
    http://bebac.at/downloads/Validation Replicate Design EMA.xls

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42 • 42