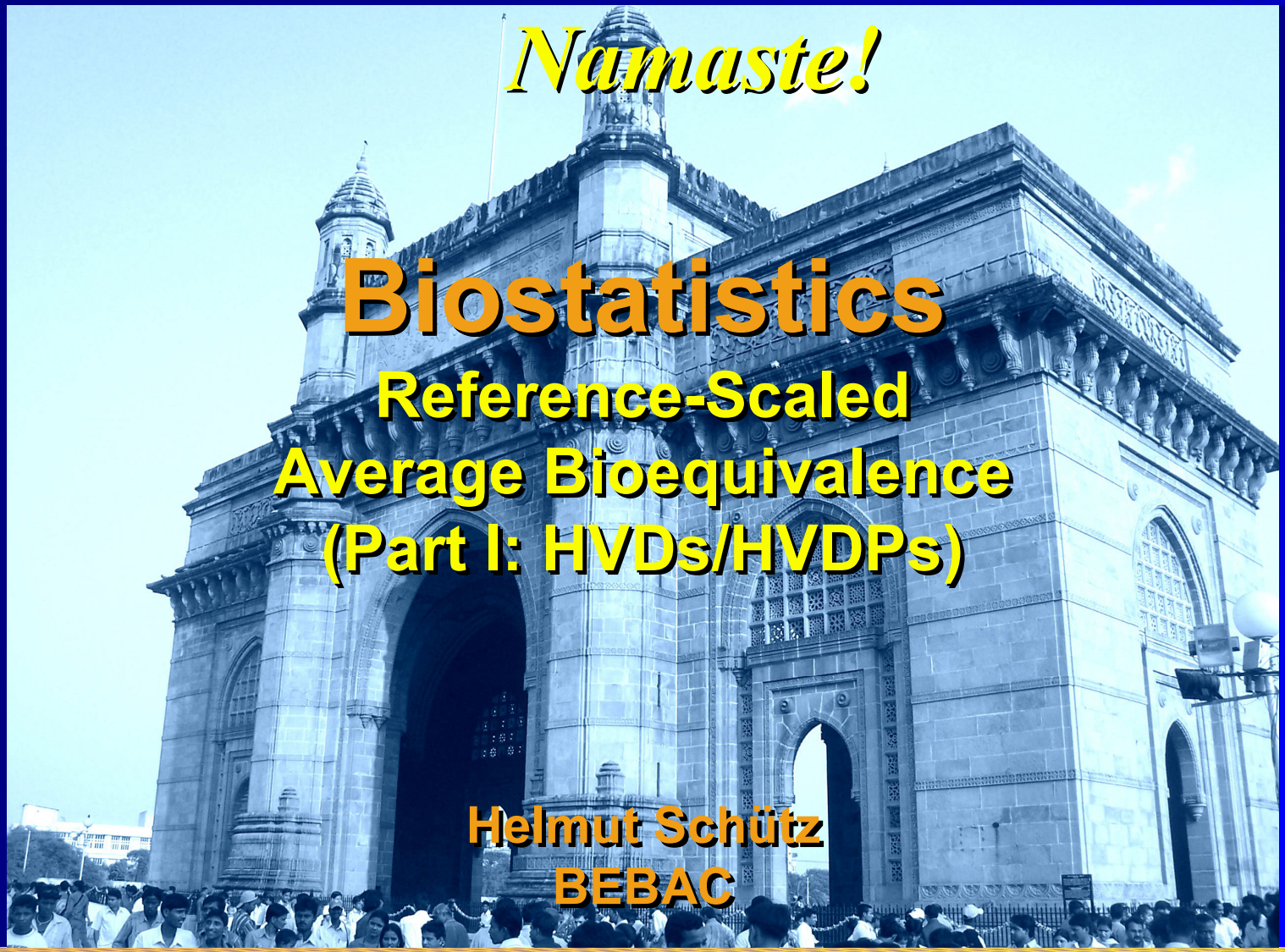


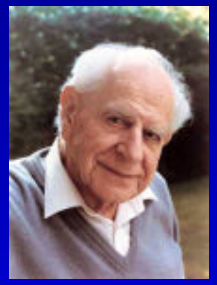
Biostatistics

Reference-Scaled Average Bioequivalence (Part I: HVDs/HVDPs)

Helmut Schütz
BEBAC

To bear in Remembrance...

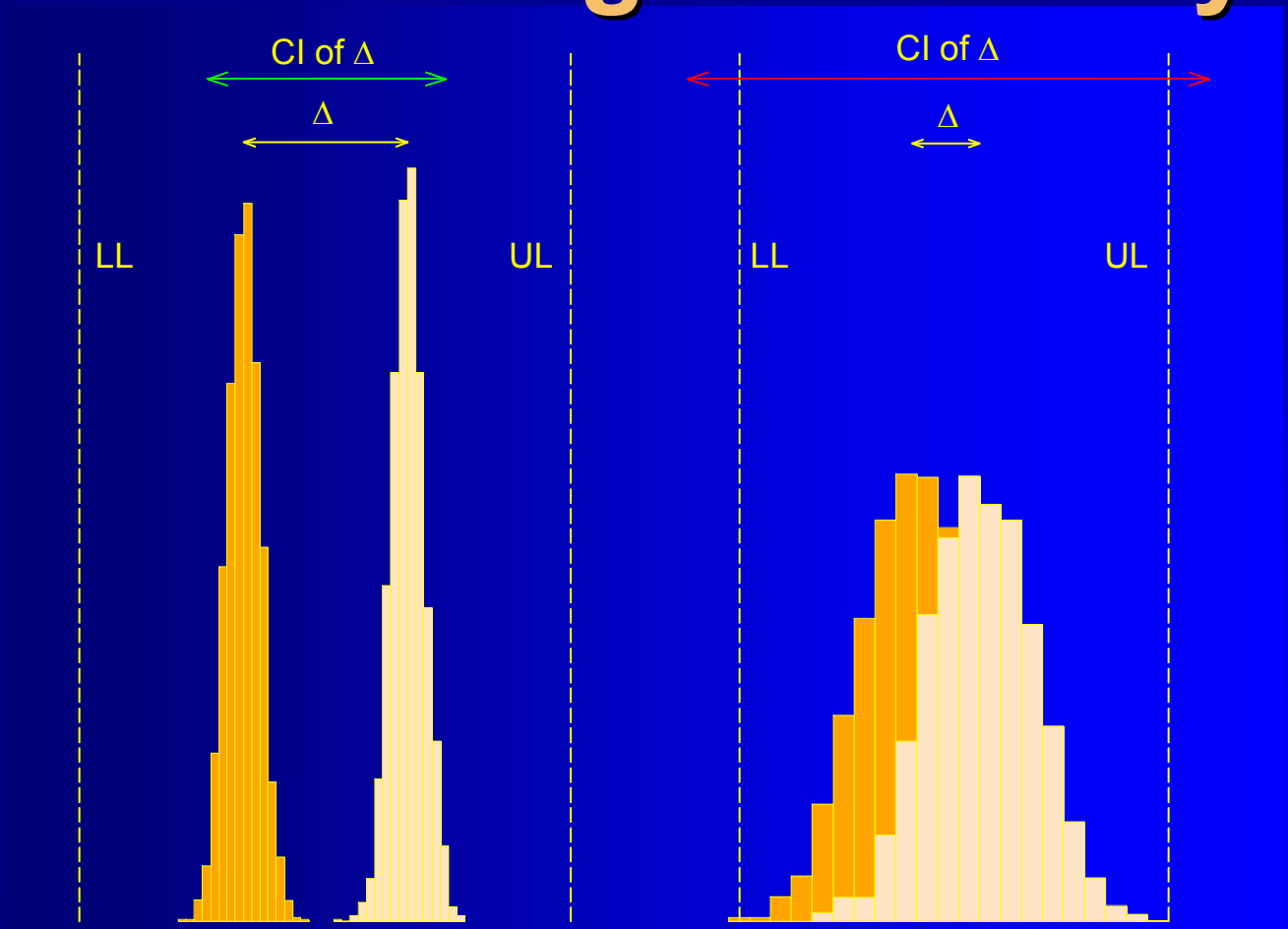
Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve. ***Karl R. Popper***



Even though it's *applied* science we're dealin' with, it still is – *science!*

Leslie Z. Benet

High variability



Modified from Fig. 1
Tothfálusi *et al.* (2009)

Counterintuitive concept of BE:

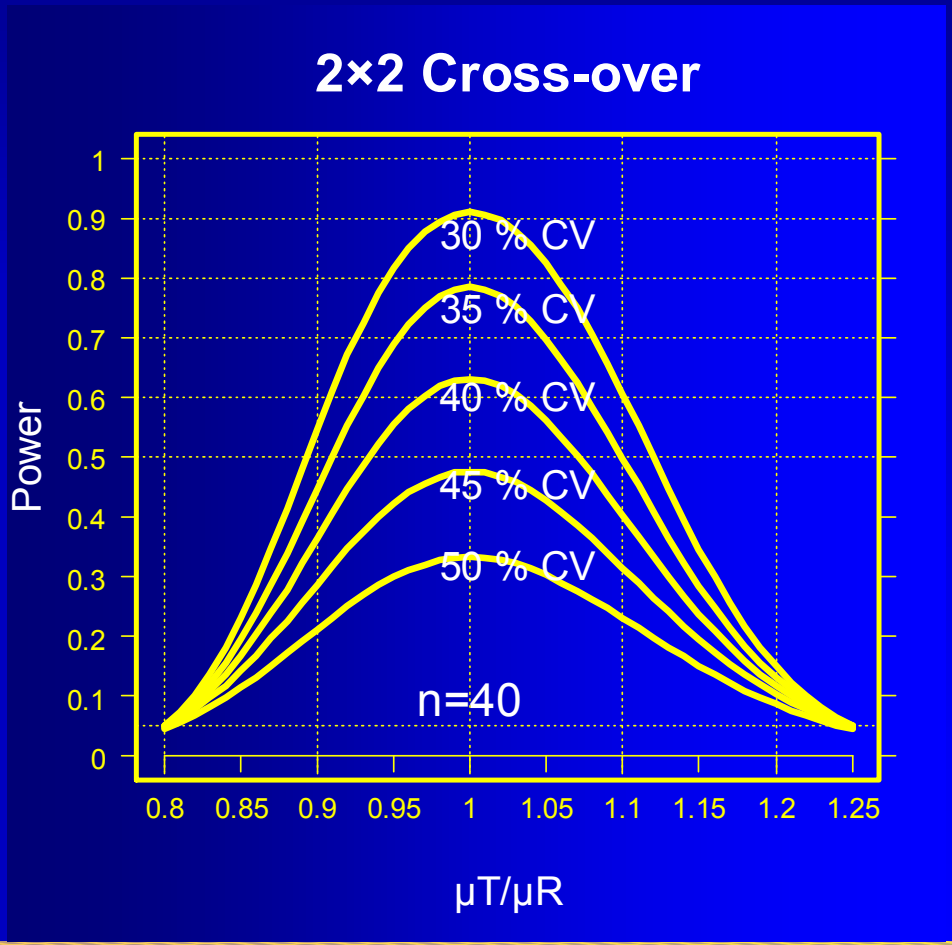
Two formulations with a large difference in means are declared bioequivalent if variances are low, but not bioequivalent – even if the difference is quite small – due to high variability.

High variability

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

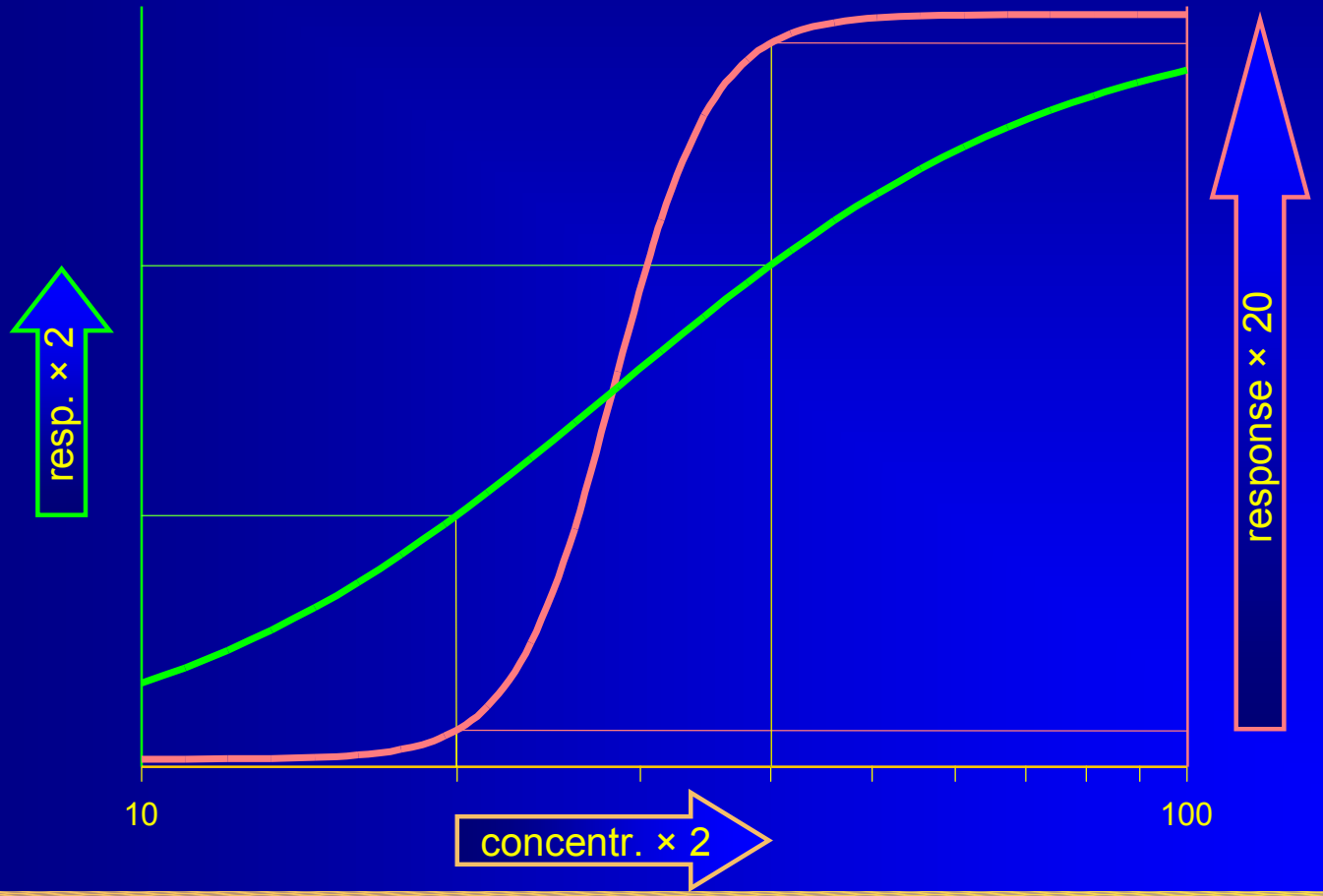
μ_T/μ_R 0.95, CV_{intra} 30%
→ power 0.816
μ_T/μ_R 1.00, CV_{intra} 45%
→ power 0.476 <
Roulette 0.486 (!)

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



HVDs/HVDPs are safe

steep/flat PK/PD-curves



HVDPs (FDA)

- 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 metabolism),
    - 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

HVDPs (FDA)

- 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].

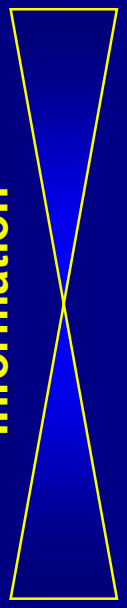
Haidar SH, Davit B, Chen M-L, Conner D, Lee LM, Li QH, Lionberger R, Makhlouf F, Patel D, Schuirmann DJ, and LX Yu
Bioequivalence Approaches for Highly Variable Drugs and Drug Products
Pharmaceutical Research 25/1, 237–41 (2008)
http://www.springerlink.com/content/u503p62056413677/fulltext.pdf
Haidar 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

High variability

- 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 design over 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.

Hierarchy of Designs

- The more ‘sophisticated’ a design is, the more information can be extracted
  - Hierarchy of designs:



Full replicate (TRTR | RTRT or TRT | RTR),
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)

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!

Replicate designs

- Any replicate design can be evaluated according to 'classical' (unscaled) Average Bioequivalence (ABE)
- ABE mandatory if scaling not allowed
  - FDA: s_{WR} <0.294 (CV_{WR} <30%); different models depend on design (*e.g.*, SAS **`Proc MIXED`** for full replicate and SAS **`Proc GLM`** for partial replicate).
  - EMA: CV_{WR} ≤30%; all fixed effects model according to 2011's Q&A-document preferred (*e.g.*, SAS **`Proc GLM`**).
  - Even if scaling is not intended, replicate design give more informations about formulation(s).

Application: HVDs/HVDPs

- CV_{WR} >30 %
  - ✓USA Recommended in API specific guidances. Scaling for AUC and/or C_{max} acceptable, GMR 0.80 – 1.25; ≥24 subjects.
  - ± EU Widening of acceptance range (only C_{max}) to maximum of 69.84% – 143.19%), GMR 0.80 – 1.25.
    Demonstration that CV_{WR} >30% is not caused by outliers.
    Justification that the widened acceptance range is clinically irrelevant.

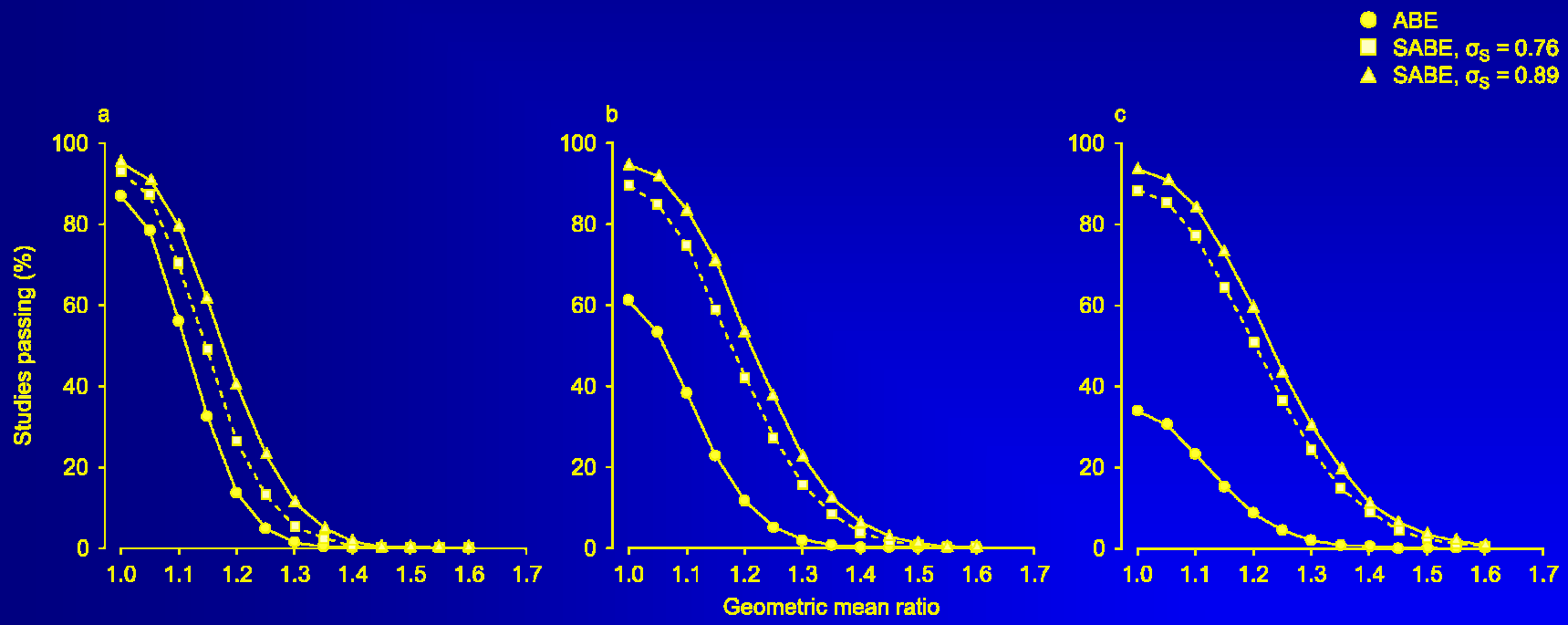
Replicate designs

- Two-sequence three-period
  - T R T
  - R T R
- Two-sequence four-period
  - T R T R
  - R T R T
- and many others…

  (FDA: TRR | RTR | RRT, aka ‘partial replicate’)
- The statistical model is complicated and depends on the actual design!

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

HVDPs (EMA *vs.* FDA)



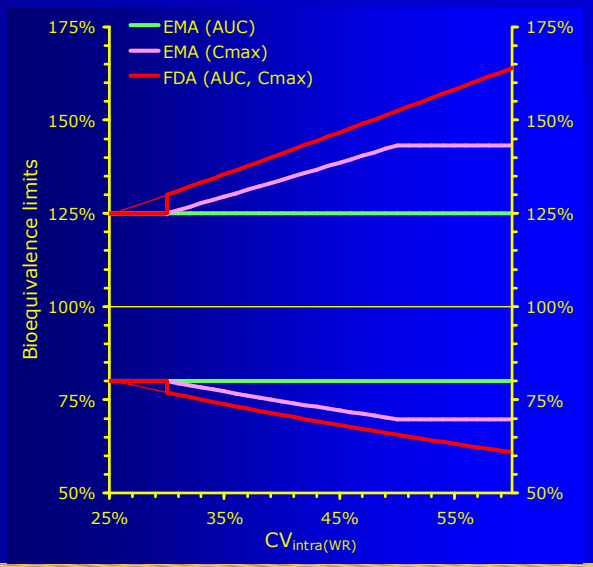
Tothfálusi *et al.* (2009), Fig. 3

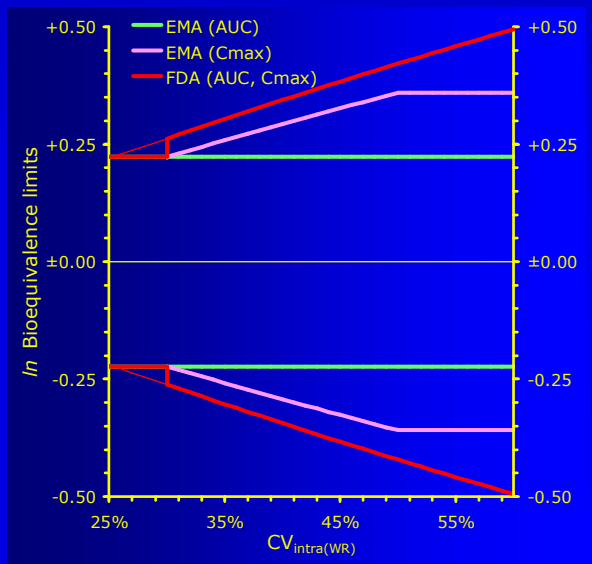
Simulated (n = 10 000) three-period full replicate design studies (TRT | RTR) in 36 subjects; GMR restriction 0.80–1.25. (a) CV = 35%, (b) CV = 45%, (c) CV = 55%.

ABE: Conventional Average Bioequivalence, SABE: Scaled Average Bioequivalence, 0.76: EMA criterion, 0.89: FDA criterion.

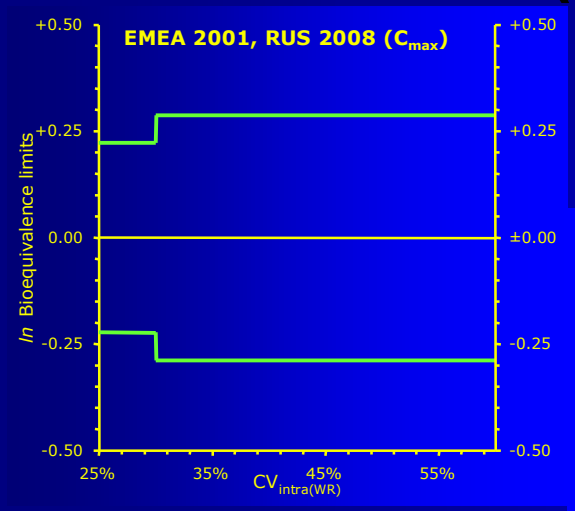
HVDPs (EMA *vs.* FDA)

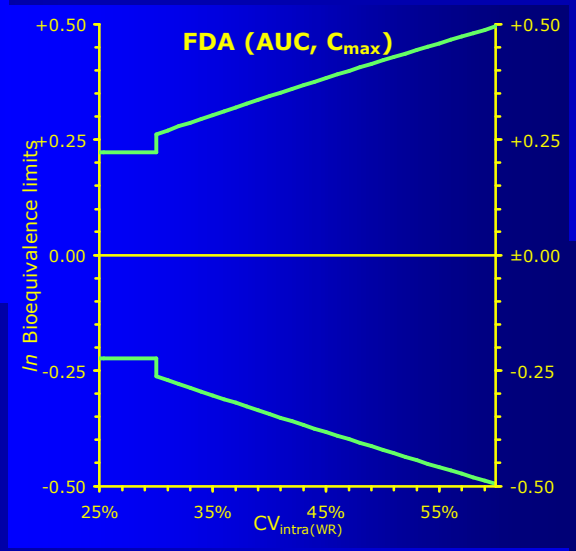
- EMA's and FDA's approaches differ; FDA's leads to a discontinuity of the acceptance range at CV 30%, because FDA's scaling CV is 25.83% (σ_{WR} 0.294) – but *applied* at $CV \geq 30\%$.

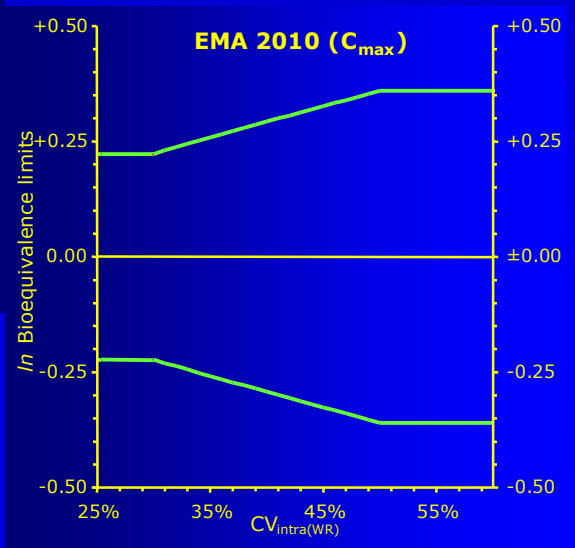




HVDPs (No Global Harmonization!)







Replicate designs

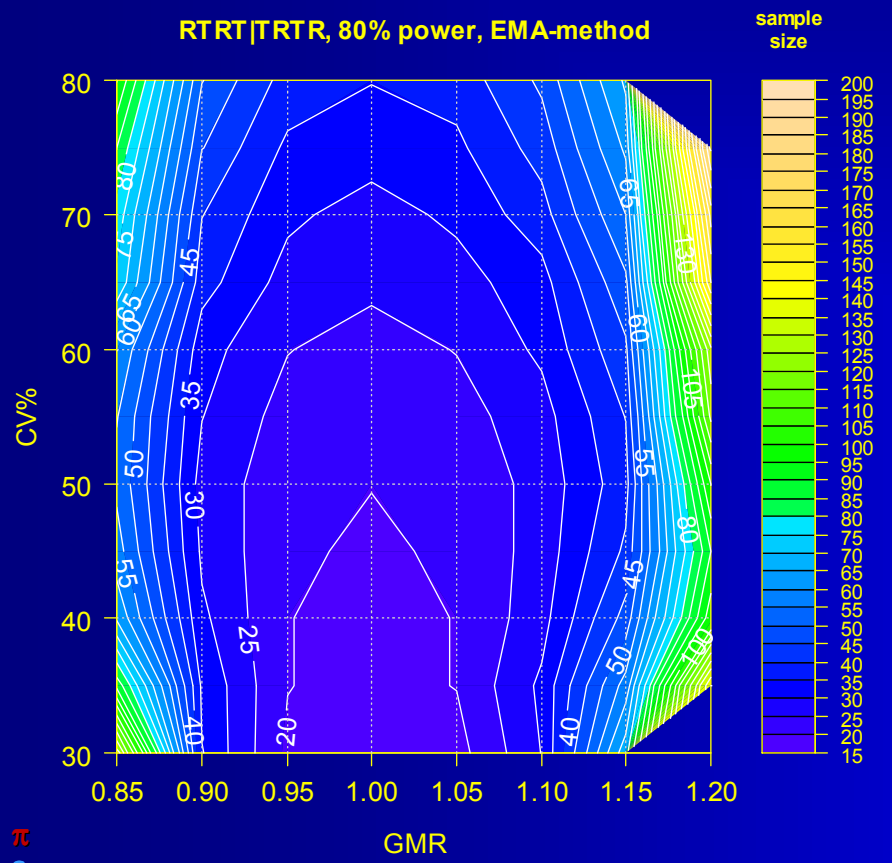
- Sample size and other issues
  - 4-period replicate designs:
    sample size = ~½ of 2×2 study's sample size.
  - 3-period replicate designs:
    sample size = ~¾ of 2×2 study's sample size.
  - Number of treatments (and biosamples) ~conventional 2×2 cross-over.
  - Allow for a safety margin – expect a higher number of drop-outs due to additional period(s).
  - Consider increased blood loss (ethics!); eventually improved bioanalytics required.

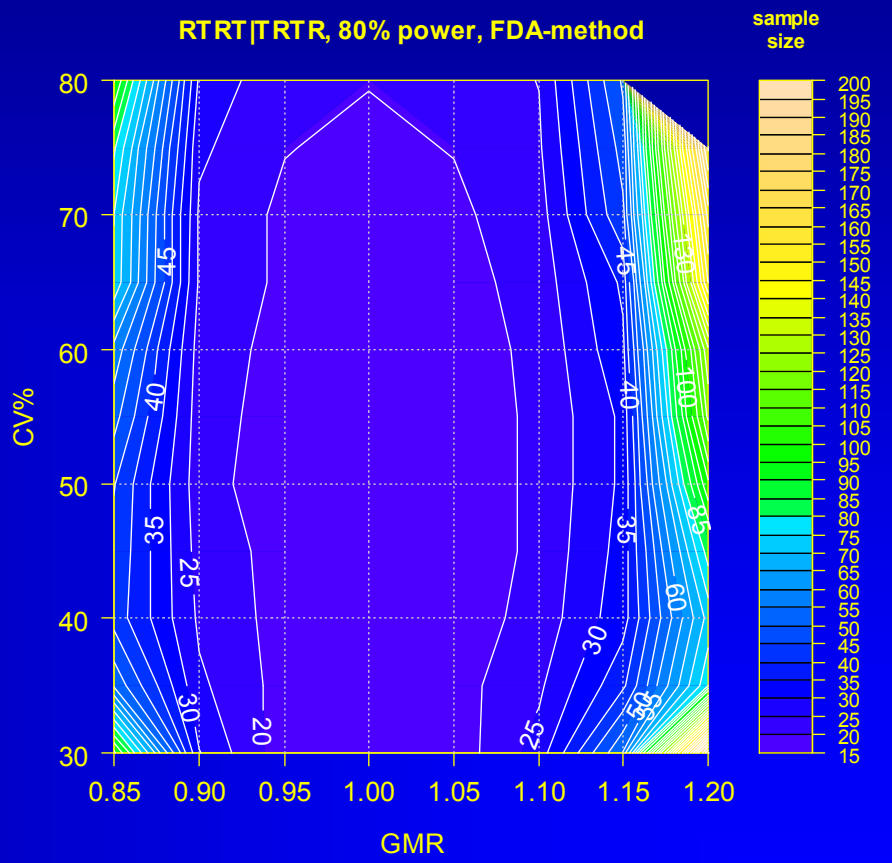
HVDPs (EMA *vs.* FDA)

- At higher CVs the GMR is of increasing importance!
- EMA: CV_{WR} >50% still requires large sample sizes.
- No algorithm for sample size estimation (based on α, β, GMR, and CV) can deal with the GMR restriction.
- Recently sample size tables based on simulations were published (for EMA's and FDA's methods, full and partial replicate designs, CV_{WR} 30–80%, power 80 and 90%).

L Tothfálusi and L Endrényi
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

HVDPs (EMA/FDA; sample sizes)





HVDPs (Regulatory models)

- Common to EMA and FDA

ABE model

$$-\theta_A \leq \mu_T - \mu_R \leq +\theta_A$$

SABE model

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

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).

Tothfálusi *et al.* (2009)

HVDPs (Regulary models)

- Differences between EMA and FDA

  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%.

HVDPs (Regulatory models)

- Differences between EMA and FDA

  EMA: Regulatory regulatory switching condition θ_S avoids the discontinuity.

$$CV_W = 0.30$$

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

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

HVDPs (FDA)

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

  Starting from the SABE model

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

  Rearrangement leads to a linear form

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

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

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

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

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

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

$$C_s = \frac{\theta_S^2 \cdot \left(N - S\right) \cdot s_W^2}{\chi^2_{\alpha,N-S}}$$

  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.

HVDPs (FDA)

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

  Howe method gets the CL from individual CIs

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

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

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

  The CL of the rearranged SABE criterion is evaluated at the 95% level. If the upper 95% is positive, RSABE is rejected, and accepted otherwise.

HVDPs (EMA)

- EU GL on BE (2010)
  - Average Bioequivalence with Expanding Limits (ABEL)
    - The regulatory switching condition θ_S at CV_{WR} 30% would be 0.760122829768**0**…
    - According to the GLs and the EMA's Q&A document (2011, 2012) use k ($\equiv\theta_S$) with 0.760 (*not* the exact value).

HVDPs (EMA)

- EU GL on BE (2010)
  - Average Bioequivalence (ABE) with Expanding Limits (ABEL)
    - Based on σ_{WR} (the *intra*-subject standard deviation of the reference formulation) calculate the scaled acceptance range based on the regulatory constant k (θ_s=0.760); limited at CV_{WR} 50%.

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

CV_{WR}	$L-U$
≤30	80.00 – 125.00
35	77.23 – 129.48
40	74.62 – 143.02
45	72.15 – 138.59
≥50	69.84 – 143.19

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

Example datasets (EMA)

- Q&A document (March 2011)
  - Data set I
    RTRT | TRTR full replicate, 77 subjects, imbalanced, incomplete
    - FDA
      s_{WR} 0.446 ≥0.294 → apply RSABE (CV_{WR} 46.96%)
      a. critbound –0.0921 ≤0 and
      b. PE 115.46% ⊂ 80.00–125.00% ✓
    - EMA
      - CV_{WR} 46.96% → apply ABEL (> 30%)
      - Scaled Acceptance Range: 71.23–140.40%
      - Method A: 90% CI 107.11–124.89% ⊂ AR; PE 115.66% ✓
      - Method B: 90% CI 107.17–124.97% ⊂ AR; PE 115.73% ✓

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 → apply ABE (CV_{WR} 11.43%)
      90% CI 97.05–107.76 ⊂ AR (CV_{intra} 11.55%) ✓
    - EMA
      - CV_{WR} 11.17% → apply ABE (≤30%)
      - Method A: 90% CI 97.32–107.46% ⊂ AR; PE 102.26% ✓
      - Method B: 90% CI 97.32–107.46% ⊂ AR; PE 102.26% ✓
      - A/B: CV_{intra} 11.86%

Outliers (EMA)

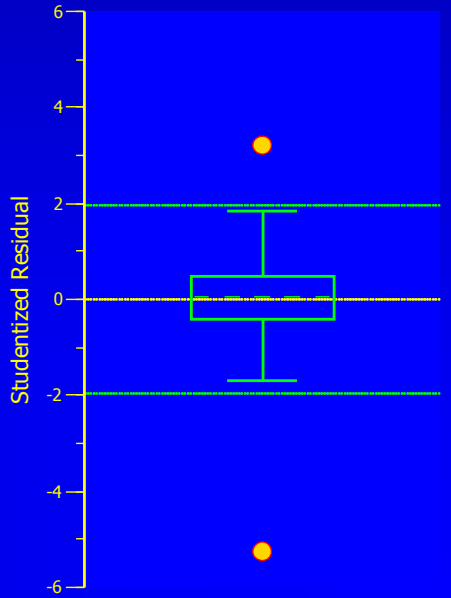
- EMA GL on BE (2010), Section 4.1.10
  - The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers.
- EGA/EMA Q&A (2010)
  - Question:
    How should a company proceed if outlier values are observed for the reference product in a replicate design study for a Highly Variable Drug Product (HVDP)?

Outliers (EMA)

- EGA/EMA Q&A (2010)
  - Answer:
    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.

Outliers (EMA)

- Data set I (full replicate)
  - CV_{WR} 46.96%
    EL 71.23–140.40%
    Method A: 107.11–124.89%
    Method B: 107.17–124.97%
  - But there *are* two outliers!
    By excluding subjects 45 and 52
    CV_{WR} drops to 32.16%.
    EL 78.79–126.93%
    Almost no more gain compared to conventional limits.



Thank You!

Reference-Scaled Average Bioequivalence (Part I)

Open Questions?

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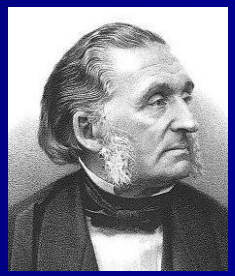
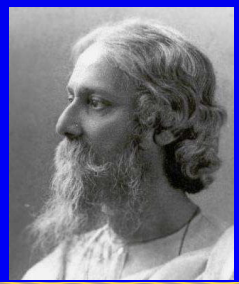
To bear in Remembrance...

The fundamental cause of trouble in the world today is that the stupid are cocksure
while the intelligent are full of doubt. *Bertrand Russell*



You should treat as many patients as possible with the new drugs while they still have the power to heal.
Armand Trousseau

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



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  The AAPS Journal 14/4, 915–24 (2012)
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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;
```

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;
```

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;
```

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 sWR $\geq$0.294

RSABE if

a. critbound $\leq$ 0 *and*

b. 0.8000 $\leq$pointest $\leq$1.2500

If sWR <0.294, apply conventional (unscaled ABE), mixed effects model.

ABE if 90% CI within 0.8000 and 1.2500.

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;
```

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;
```

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));
```

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;
```

Example datasets (EMA)

- Q&A document (Dec 2012, 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