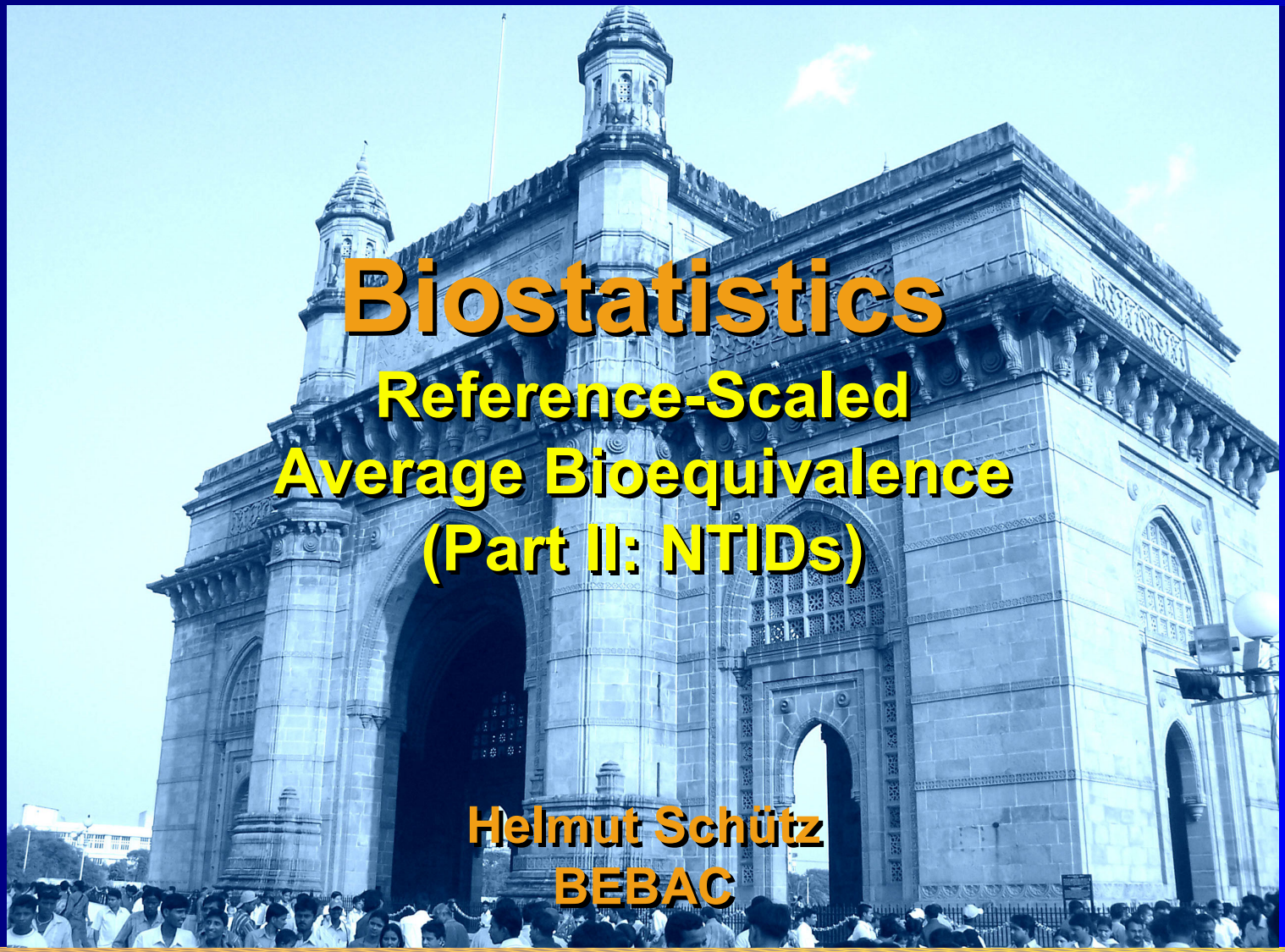
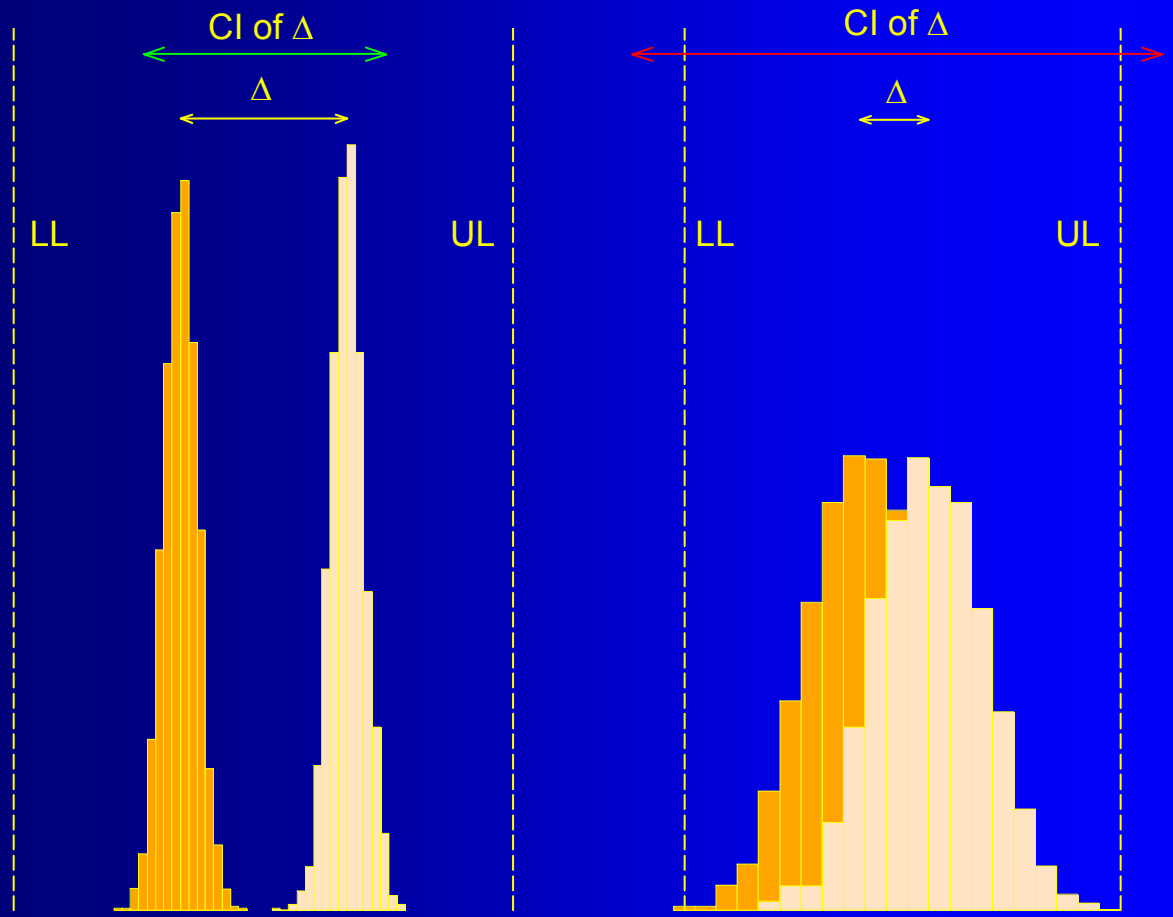


# Biostatistics

## Reference-Scaled Average Bioequivalence (Part II: NTIDs)

Helmut Schütz
BEBAC

# Low variability



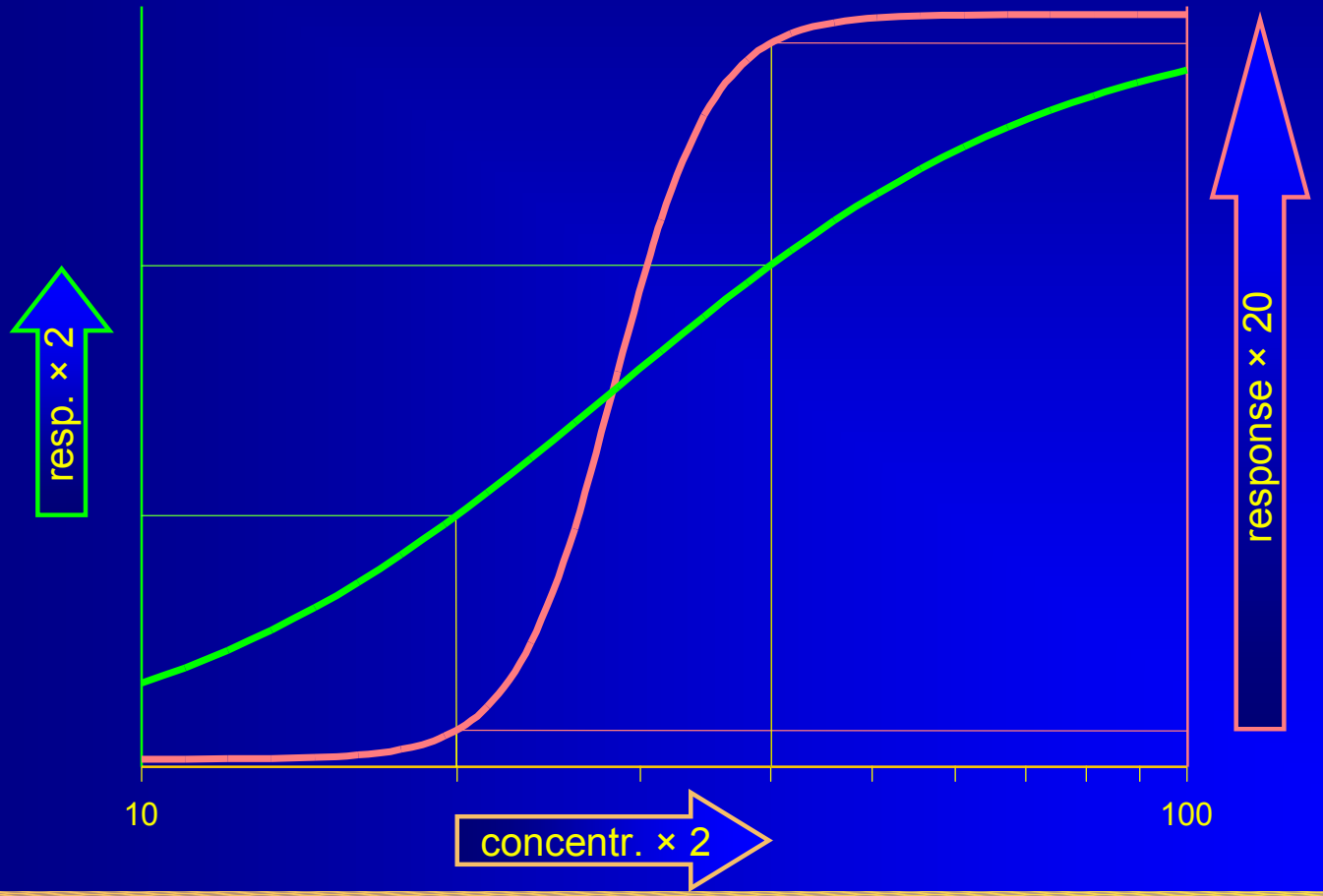

Modified from Fig. 1
Tothfálusi *et al.* (2009)

Conventional concept of BE:

Two formulations with a large difference in means are declared bioequivalent if variances are low.

# NTIDs might be problematic

steep/flat PK/PD-curves



# NTIDs (FDA)

- NTIDs from ANDAs reviewed by FDA/OGD within 1996 – 2008 (89 studies)

| Drug | Studies | $AUC_{0-t}$ | | $C_{max}$ | |
|---|---|---|---|---|---|
| | | Mean | Range | Mean | Range |
| Warfarin | 29 | 5.7 | 3.3 – 11.0 | 12.7 | 7.7 – 20.1 |
| Levothyroxine | 9 | 9.3 | 3.8 – 15.5 | 9.6 | 5.2 – 18.6 |
| Carbamazepine | 15 | 8.0 | 4.4 – 19.4 | 8.7 | 5.2 – 17.6 |
| Lithium carbonate | 16 | 7.8 | 4.5 – 14.0 | 13.5 | 6.4 – 24.4 |
| Digoxin | 5 | 21.7 | 13.1 – 32.2 | 21.0 | 14.3 – 26.1 |
| Phenytoin | 12 | 9.2 | 4.1 – 18.6 | 14.9 | 7.4 – 20.0 |
| Theophylline | 3 | 17.9 | 12.8 – 24.2 | 18.2 | 11.8 – 25.8 |

**LX Yu**
*Approaches to Demonstrate Bioequivalence Critical Dose Drugs*
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, April 13, 2010
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM209319.pdf

# NTIDs (FDA)

- For NTIDs 20% fluctuation in plasma concentrations might be clinically relevant
- NTIDs often have low variability; CIs of two generics might be 85–90% and 115–120%. Switchability? Potential Approaches:
  - AUC: PE $\subset$ 90–111%
  - AUC: PE $\subset$ 95–105%
  - AUC: CI $\subset$ 90–111% (like EMA)
  - AUC: CI $\subset$ 90–111% and includes 100% (like Denmark)
  - AUC: CI $\subset$ 95–105%
  - Reference Scaled Average Bioequivalence (RSABE)

# NTIDs (FDA)

- Percentage of ANDAs passing tighter criteria (89 studies)

| Method | $AUC_{0-t}$ | $C_{max}$ |
|---|---|---|
| CI includes 100% | 84.3 | 69.7 |
| CI ⊂ 90–111% | 86.5 | 60.7 |
| CI ⊂ 90–111% and includes 100% | 77.5 | 50.6 |
| PE ⊂ 90–111% | 100.0 | 95.5 |
| RSABE | not assessed | |

  - Tighter AR ensures smaller differences in mean BA
  - Differences in variability between products are not addressed
  - RSABE suggested

LX Yu 2010

# Statistical model

- Fully replicated TRTR | RTRT design
  - 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 $\theta$ based on regulatory constant $\sigma_0$ 0.1 and $\Delta$ 1.11111 (=1/0.9, the upper BE limit)

$$\theta \equiv \left( \frac{\ln \Delta}{\sigma_0} \right)^2$$

# Evaluation

- SABE
  - Mixed effects model (SAS **`Proc MIXED`**, Phoenix **`Linear Mixed Effects`**).
  - Determine 95% upper confidence limit for

    $$\left(\overline{Y}_T - \overline{Y}_R\right)^2 - \theta \cdot s_{WR}^2$$

    by Howe's method (like in SABE for HVDPs).
  - Bioequivalent if 95% upper CL ≤0.
- ABE
  - Mixed effects model.
  - Bioequivalent if 90% CI ⊂ 80.00–125.00%.

# Evaluation

- Comparison of $\sigma_{WT}$ with $\sigma_{WR}$
  - Mixed effects model of intra-subject contrast $T_1–T_2$ and $R_1–R_2$ by sequence.
    Comparison based on $s_{WT}$ and $s_{WR}$ (the estimates of $\sigma_{WT}$ and $\sigma_{WR}$).
    $s_{WR}$ is already available from SABE ($R_1–R_2$); similar setup for $T_1–T_2$ to obtain $s_{WT}$.
  - Determine 90% confidence interval of $\sigma_{WT}/\sigma_{WR}$ as

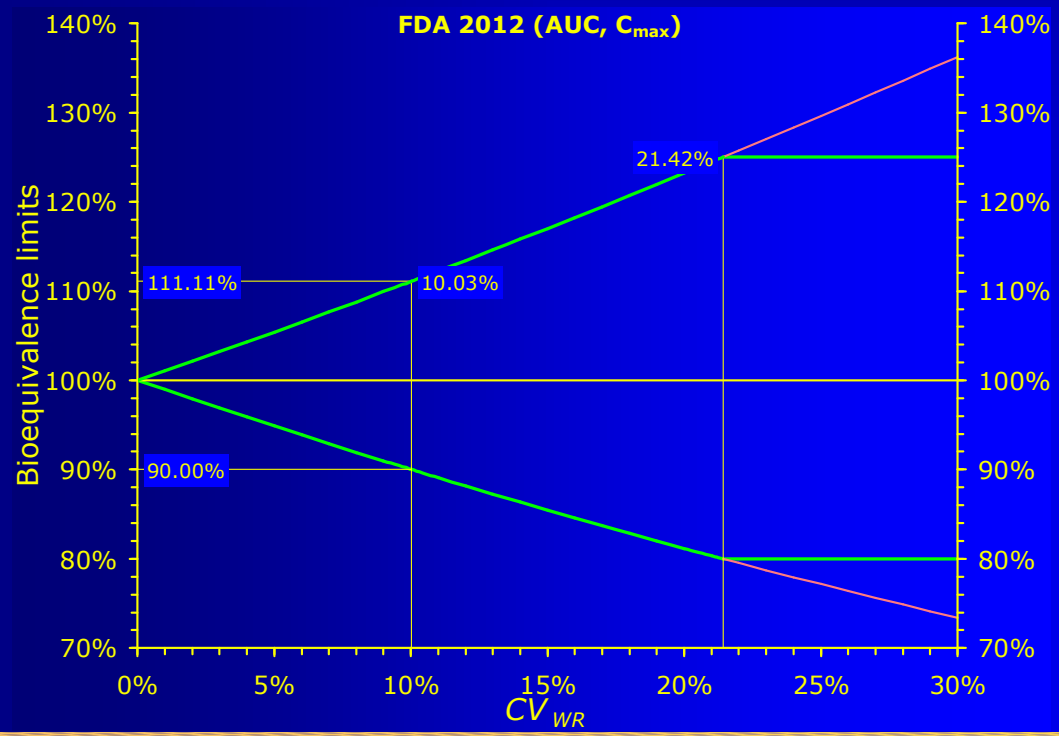
$$\frac{s_{WT}/s_{WR}}{\sqrt{F_{\alpha/2(\nu_1,\nu_2)}}}, \frac{s_{WT}/s_{WR}}{\sqrt{F_{1-\alpha/2(\nu_1,\nu_2)}}}$$

# Evaluation

- Comparison of $\sigma_{WT}$ with $\sigma_{WR}$
  - $s_{WT}$ is the estimate $\sigma_{WT}$ with $\nu_1$ degrees of freedom ($\nu_1 = n_1 - 2$ in the fully replicate).
  - $s_{WR}$ is the estimate $\sigma_{WR}$ with $\nu_2$ df.
  - Probability of risk type I $\alpha = 0.1$.
  - $F_{\alpha/2(\nu_1,\nu_2)}$ is the value of the $F$-distribution with $\nu_1$ (numerator) and $\nu_2$ (denominator) degrees of freedom and a probability of $\alpha/2$.
  - $F_{1-\alpha/2(\nu_1,\nu_2)}$ is the value of the $F$-distribution with $\nu_1$ and $\nu_2$ df and a probability of $1 - \alpha/2$.
  - Bioequivalent if 95% upper CL of $\sigma_{WT}/\sigma_{WR} \leq 2.5$.

# Consequences of Scaling

- At $\sigma_{WR}$ 0.1 ($CV$ 10.03%) the expanded AR is 90.00–111.11%




| $CV_{WR}$ | $L - U$ |
|---|---|
| 5 | 94.87 – 105.41 |
| 10 | 90.02 – 111.08 |
| 15 | 85.35 – 117.02 |
| 20 | 81.17 – 123.20 |
| 25 | 77.15 – 129.62 |
| 30 | 73.40 – 136.25 |

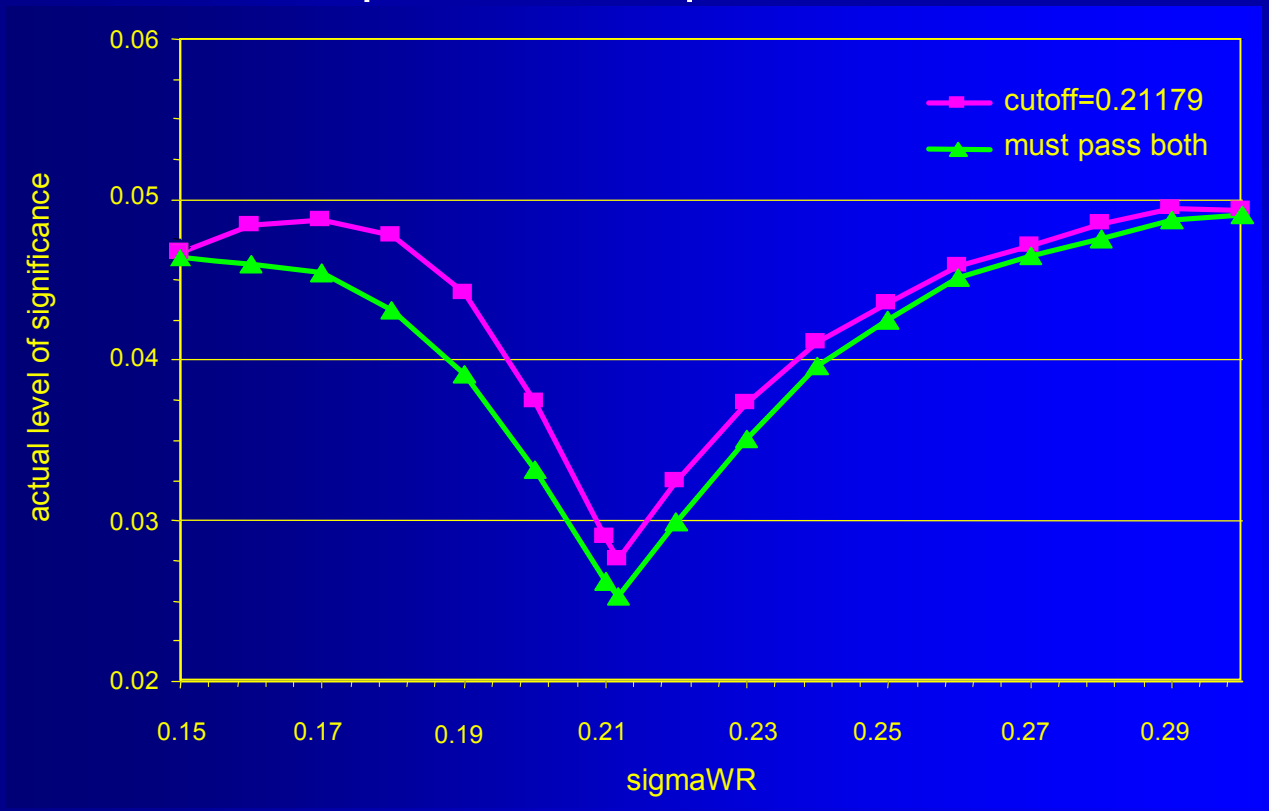
# NTIDs (FDA)

- As a consequence of scaling the AR for $s_{WR}$ >0.21179 ($CV_{WR}$ >21.42%) will be *wider* than the conventional 80.00–125.00%.
- Possible 'ways out'
  1. Cutoff on $s_{WR}$ and switch to conventional unscaled ABE
  2. A "Must Pass Both" criterion: RSABE + ABE
     - Both methods maintain the patient's risk <5%.
       Method 2 slightly more conservative.
       Power essentially identical.

**DJ Schuirmann**
*Evaluation of Scaling Approaches to Demonstrate BE of NTI Drugs – OGD Simulation Efforts*
Advisory Committee for Pharmaceutical Science and linical Pharmacology, July 26, 2011
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM266777.pdf

# NTIDs (FDA)

- Both methods preserve the patient's risk

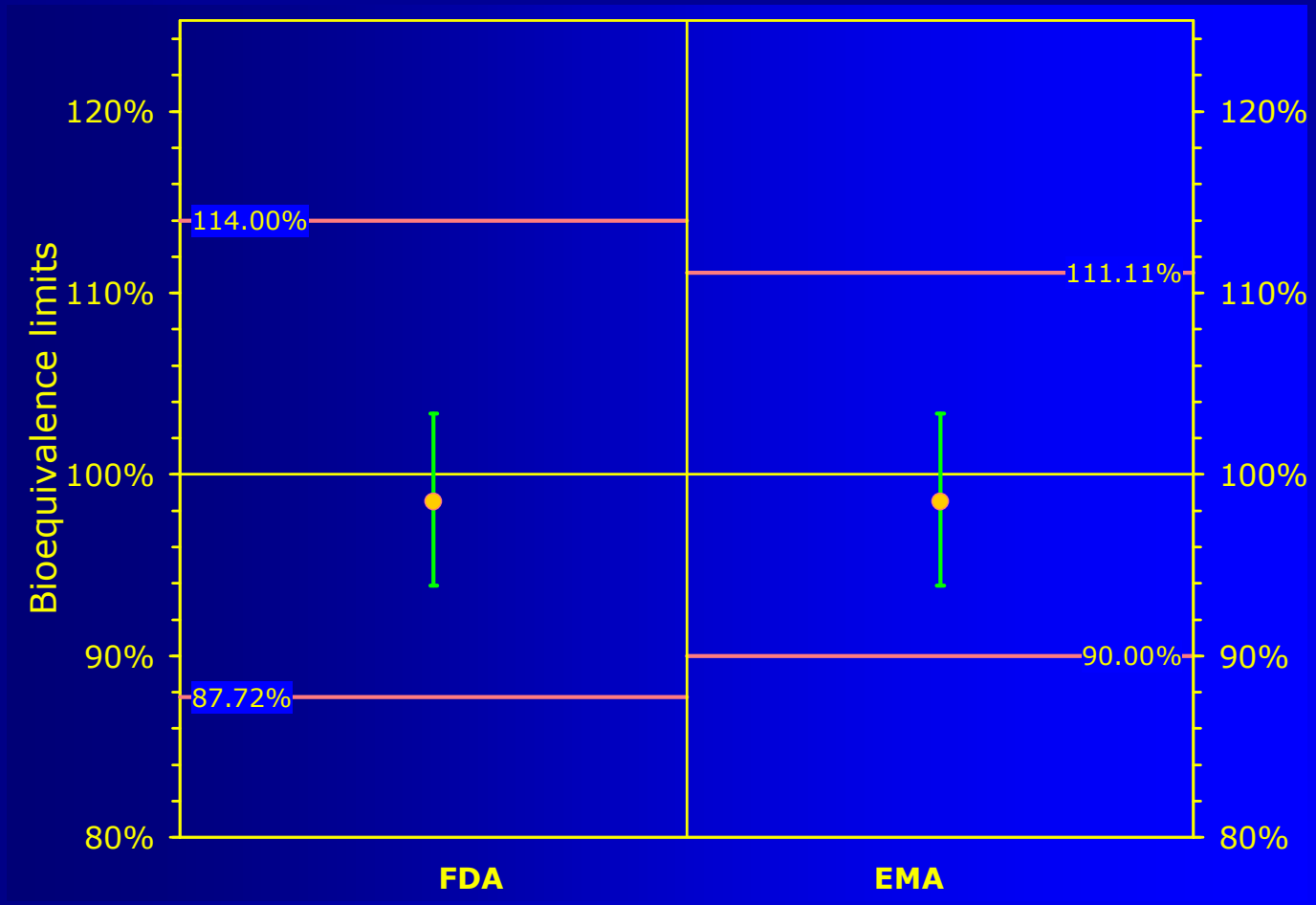



**DJ Schuirmann** 2011

# Example

- CNS drug from BEBAC's files
  - RTRT | TRTR full replicate, 18 subjects, balanced, complete
    - FDA
      1. critbound: –0.0098283 ≤0 ($CV_{WR}$ 12.49%, $CV_{WT}$ 5.58%)
      2. ✓ ABE: 90% CI 93.90–103.35% ⊂ AR
      3. upper 95% CL of $s_{WT}/s_{WR}$ 0.68427 ≤2.5
    - EMA
      - AR 90.00–111.11%
      - ✓ ABE: 90% CI 93.90–103.35% ⊂ AR ($CV_{WR}$ 15.86%, $CV_{WT}$ 5.73%)
  - Data set in Excel 2000 format: http://bebac.at/downloads/NTID.xls

# Example


120%
110%
100%
90%
80%
Bioequivalence limits
114.00%
87.72%
111.11%
90.00%
FDA
EMA

*Thank You!*

# Reference-Scaled Average Bioequivalence (Part II)

*Open Questions?*

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helmut.schuetz@bebac.at

# References


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  - E9: Statistical Principles for Clinical Trials (1998)
- EMA-CPMP/CHMP/EWP
  - Guideline on the Investigation of BE (2010)
  - Questions & Answers: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics (2011, 2012)
- US-FDA
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    - Statistical Approaches Establishing Bioequivalence (2001)
    - Bioequivalence Recommendations for Specific Products (2007–2012):
      Draft Guidance on Progesterone (Feb 2011)
      Draft Guidance on Warfarin (Dec 2012)
- LX Yu
  *Approaches to Demonstrate Bioequivalence Critical Dose Drugs*
  ACPSCP-Meeting, April 13, 2010
  http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM209319.pdf
- DJ Schuirmann
  *Evaluation of Scaling Approaches to Demonstrate BE of NTI Drugs – OGD Simulation Efforts*
  ACPSCP-Meeting, July 26, 2011
  http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM266777.pdf
- Davit BM *et al.*
  *Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration*
  The AAPS Journal 14/4, 915–24 (2012)
  DOI: 10.1208/s12248-012-9406-x

# 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(1.11111))/0.1)**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

```
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;
```

RSABE *if*

1. critbound ≤0 *and*
2. 90% CI of ABS within 0.8000 and 1.2500 *and*
3. 95% upper CL of sWT/sWR ≤2.5.