Evaluation of Replicate Designs for (Reference Scaled) Average Bioequivalence according to FDA's Guidances with Phoenix™ WinNonlin®

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Consultancy Service for
Bioequivalence and Biovailability Studies
Vienna, August 2012

Version 1.1

Content

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2 Introduction

FDA published SAS-code for Reference Scaled Average Bioequivalence (RSABE) in the drafted Guidance on progesterone (2010, 2011).[1,2] For background on different scaling methods see Haidar *et al.* (2008a, 2008b),[3,4] Endrényi and Tóthfalusi (2009),[5] and Tóthfalusi *et al.* (2009).[6] This white paper demonstrates the implementation of FDA's methods based on two data sets provided by the EMA in a Q&A document (Rev. 4, March 2012)[7] in Phoenix/WinNonlin (PHX/WNL):

- data set I: 4-period 2-sequence (RTRT | TRTR) full replicate, imbalanced (77 subjects), incomplete (missing periods: one period in six cases, two periods in two cases).
- data set II: 3-period 3-sequence (TRR | RTR | RRT) partial replicate, balanced (24 subjects), complete (no missing periods).

Results reported by EMA for 'Method C' – which is identical to the code for ABE given by the FDA already in 2001[8] and also in the progesterone guidance – were compared to ones obtained in PHX/WNL. The OS was Windows XP Professional, Service Pack 3, all patches (German environment; set during runtime to EN-US for Phoenix) on a DELL Precision 670 Workstation (2 × 2.8 GHz Xeon, 4 GB RAM). Workflows

were initially developed in Phoenix 1.1 and modified to incorparate the new Data Wizard available in the latest version Phoenix/WinNonlin 6.3 (build 6.3.0.395, released 26 March 2012).

EMA's data sets are available for download at BEBAC's site in Excel and Phoenix 6.2 format:

- http://bebac.at/downloads/Validation Replicate Design EMA.xls
- http://bebac.at/downloads/EMA Replicate Data Sets.phxproj

3 Procedures

3.1 Data Import

Open the project file, or – alternatively – import the Excel file into a new project. Complete steps are given for data set I (full replicate), but are applicable to data set II (partial replicate) as well. Difference in the setup is given in Section 3.4.

3.2 Preliminary check of pointest and CV_{WR}

The PE and CV_{WR} can be obtained from PHX's standard model for Population/Individual Bioequivalence. If CV_{WR} <30% RSABE is not applicable and only the standard model for ABE may be applied (*i.e.*, PHX's Bioequivalence Wizard can be used). Below as an example the steps for the full replicate design.

data set I ➔ Send To ➔ NCA and Toolbox ➔ Bioequivalence

Keep the default mappings; map logData to Dependent. Set Type of Bioequivalence ➔ ○ Population/Individual. Set the Reference Formulation to R. Change Dependent Variables Transformation ➔ Already Ln-transformed

Bioequivalence | **Output Data** ➔ Population/Individual ➔ Send To ➔ Data ➔ Data Wizard

Add a series of Filters and Transformations:

1. Filter: Include where [Statistic] = 'Difference(Delta)'
2. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: Title
   Formula: 'PBE/IBE'
3. Transformation Type: Functions
   Transformation: e^x
   New Column Name: pointest
   Map Value to x Column
4. Filter: Exclude: Statistic and Value
   Rename Data Wizard to pointest.

Bioequivalence | **Output Data** ➔ Population/Individual ➔ Send To ➔ Data ➔ Data Wizard

Add a series of Filters and Transformations:

1. Filter: Include where [Statistic] = 'SigmaWR', Exclude: Units, Statistic, Upper_CI, and Conclusion
2. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: CVwr
   Formula: round(100*sqrt(exp(Value^2)-1),2)
3. Filter: Exclude: Value
   Rename Data Wizard to CVwr.

Set up a merge.

Worksheet 1: pointest.Results; map Dependent to Sort, include Title and pointest

Worksheet 2: CVwr.Results; map Dependent to Sort, include CVwr

Rename Merge Worksheets to Merge.

Merge | **Output Data** ➔ Result ➔ Send To ➔ Data ➔ Data Wizard

Add a Filter and Transformation:

1. Filter: Exclude: Dependent
2. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: Assessment
   Formula: if((pointest <0.8) | (pointest >1.25), 'PE outside AR: not BE, if(CVwr<30,'PE within 0.8-1.25 and CV<30%: perform ABE', 'PE within 0.8-1.25 and CV>=30%: try RSABE'))
   Rename Data Wizard to Preliminary.

data set	pointest	Title	CVwr	Assessment
I	1.1546132	PBE/IBE	47.57	PE within 0.8-1.25 and CV >= 30%: try RSABE
II	1.0226439	PBE/IBE	11.43	PE within 0.8-1.25 and CV < 30%: perform ABE

Note The CV_{WR} from PBE/IBE *may* differ from the one obtained by FDA's RSABE model (for data set I 47.57% *vs.* 46.96% and for data set II 11.43% *vs.* 11.55%)* whereas the PEs are identical. If the CV_{WR} in the preliminary check is already *substantially* smaller than 30% setting up the full RSABE workflow might well be futile (scaling not applicable). If the PE is outside 0.8–1.25 BE cannot be demonstrated.

3.3 Fully replicate 4-way design

Since in FDA's guidance some lines are missing – or formated in white on a white background – in the following the complete SAS-code.†

Note PK metrics must be ln-transformed beforehand (here `lauct`). In the example data sets use logData.

```
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=4);
  lat2r=lauct;
run;
data scavbe;
  merge test1 test2 ref1 ref2;
  by seq subj;
  ilat=0.5*(lat1t+lat2t-lat1r-lat2r);
run;
```

* This difference is due to imbalanced sequences and/or missing data. For the complete and balanced data set in `Pharsight\Phoenix\application\Examples\Data 2x4.CSV` CV_{WR} from IBE/PBE with 52.15% is identical to the one from FDA's model.

† Lines missing in FDA's code are formated in *darkred ialics*.

```
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;
```

IOUT2:

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

```
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;
```

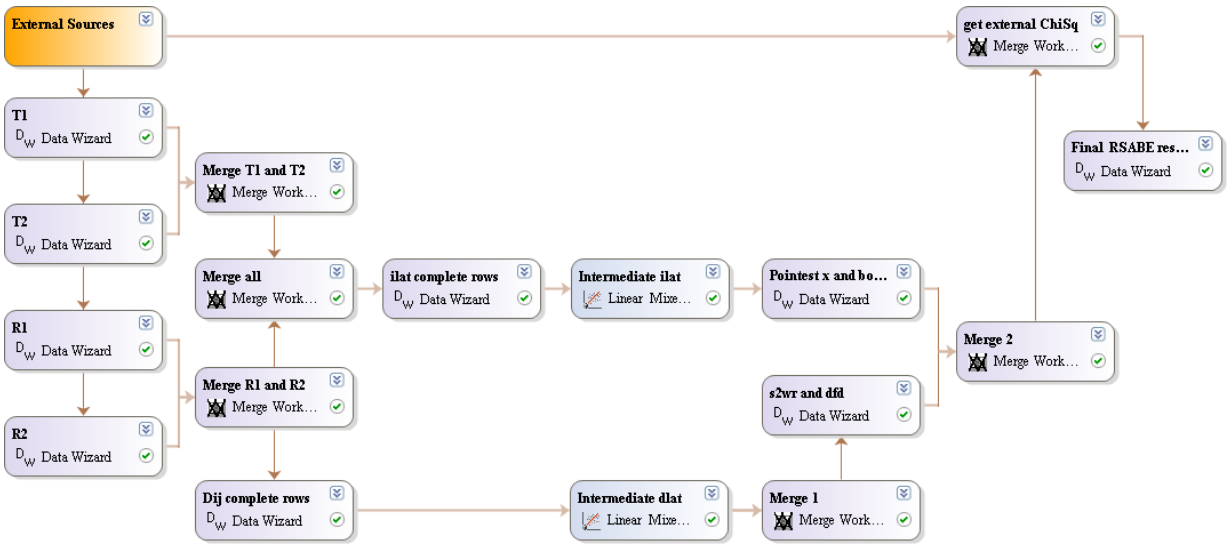
DOUT1:

```
s2wr=estimate/2;
```

DOUT2:

```
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));
```



data set I ➔ Send To ➔ Data ➔ Data Wizard

Set up four separate Custom inclusion filters (first and second occasions of test and reference, respectively). Exlude the Data variable. Set up properties.

1. Formulation='T' and ((Sequence='1' and Period=1) or (Sequence='2' and Period=2))
   Property: logData ➔ [New Column Name]: lat1t
   Rename Data Wizard to T1.

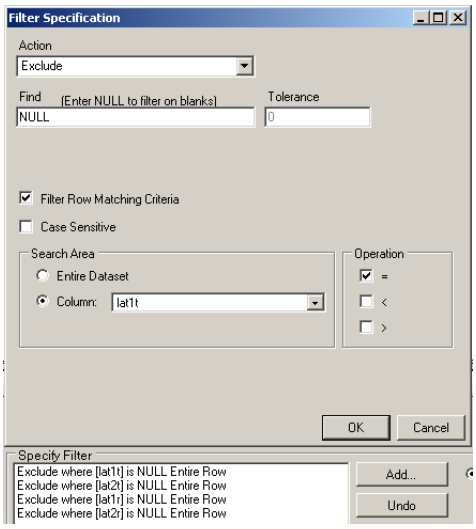
2. Formulation='T' and ((Sequence='1' and Period=3) or (Sequence='2' and Period=4))
   Property: logData ➔ [New Column Name]: lat2t
   Rename Data Wizard to T2.
3. Formulation='R' and ((Sequence='1' and Period=2) or (Sequence='2' and Period=1))
   Property: logData ➔ [New Column Name]: lat1r
   Rename Data Wizard to R1.
4. Formulation='R' and ((Sequence='1' and Period=4) or (Sequence='2' and Period=3))
   Property: logData ➔ [New Column Name]: lat2r
   Rename Data Wizard to R2.

Since – unlike to SAS – only *two* data sets can be merged in PHX, set up a series of three merges; first both tests, then both references, followed by a merge of the two intermediate results.

1. Worksheet 1: T1.Result; map Subject and Sequence to Sort, include lat1t
   Worksheet 2: T2.Result; map Subject and Sequence to Sort, include lat2t
   Rename Merge Worksheets to Merge T1 and T2.
2. Worksheet 1: R1.Result; map Subject and Sequence to Sort, include lat1r
   Worksheet 2: R2.Result; map Subject and Sequence to Sort, include lat2r
   Rename Merge Worksheets to Merge R1 and R2.
3. Worksheet 1: Merge T1 and T2.Result; map Subject and Sequence to Sort, include lat1t and lat2t
   Worksheet 2: Merge R1 and R2.Result; map Subject and Sequence to Sort, include lat1r and lat2r
   Rename Merge Worksheets to Merge all.

Merge all.Results ➔ Send To ➔ Data ➔ Data Wizard

Specify four Built in filters to exclude any incomplete data of lat1t, lat2t, lat1r, and lat2r (this is an important step, because SAS drops missing values in the following analysis, whereas PHX would calculate a maximum likelihood estimate instead).



Add a Custom Transformation:

New Column Name: ilat

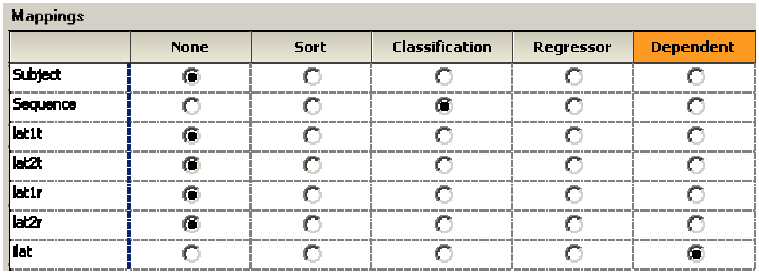
Formula: 0.5*(t1 + t2) - 0.5*(r1 + r2), Map lat1t to t1, lat2t to t2, lat1r to r1,: lat2r to r2.*

Rename Data Wizard to ilat complete rows.

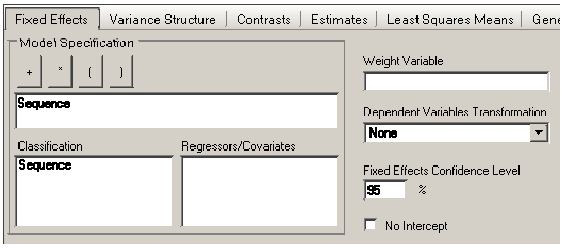
* This is a workaround, since direct input of variables in the formula field does not work (PHX does not accept non-numeric characters after a number).

Final Results ➔ Result ➔ Send To ➔ NCA and Toolbox ➔ Linear Mixed Effects

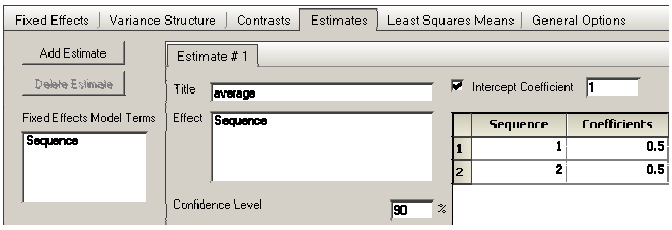
Map ilat as Dependent and Sequence as Classification



Drag Sequence to the Model Specification, change Dependent Variables Transformation ➔ Already Ln-transformed:



Specify Estimate #1, Title average, Effect Sequence, Confidence Level 90%, Confidence Level 90%, Intercept Coefficient 1, Coefficients of both Sequences 0.5:



Rename Linear Mixed Effects to Intermediate ilat.

Intermediate ilat | **Output Data** ➔ Estimates ➔ Send To ➔ Data ➔ Data Wizard

Add Transformations and a Filter

1. Transformation Type: Functions
   Transformation: e^x
   New Column Name: pointest
   Map Estimate to x Column
2. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: x
   Formula: Estimate^2 - StdError^2
3. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: boundx
   Formula: if(abs(Lower_CI)>=abs(Upper_CI), (abs(Lower_CI))^2, (abs(Upper_CI))^2)*
4. Replace where [Dependent] = '1' with 'dlat'
   Rename Data Wizard to Pointest x and boundx.

* This is a workaround, since max() is not available as a function.

Merge all.Results ➔ Send To ➔ Data ➔ Data Wizard

Specify two Built in filters to exclude any incomplete data of lat1r, and lat2r (similar to the one above). Add a Transformation:

Transformation Type: Arithmetic
Transformation: x - y
New Column Name: dlat
Map lat1r to x Column and lat2r to y Column
Rename Data Wizard to Dij complete rows.

Final Results ➔ Result ➔ Send To ➔ NCA and Toolbox ➔ Linear Mixed Effects

Set up the model as above for ilat (except specifying an estimate)
Rename Linear Mixed Effects to Intermediate dlat.

Set up a merge.

Worksheet 1: Intermediate dlat.Estimates; map Dependent to Sort, include Denom_DF
Worksheet 2: Intermediate dlat.Final Variance Parameters; map Dependent to Sort, include Estimate
Rename Merge Worksheets to Merge 1.

Merge 1 | **Output Data** ➔ Result ➔ Send To ➔ Data ➔ Data Wizard

Add a Transformation, Filter, and Property:

1. Transformation Type: Arithmetic
   Transformation: x / n
   New Column Name: s2wr
   n: 2
   Map Estimate to x Column
2. Exclude: Estimate
3. Property: rename Denom_DF to dfd
   Rename Data Wizard to s2wr and dfd.

Set up a two merges.

1. Worksheet 1: s2wr and dfd.Result; map Dependent to Sort, include s2wr and dfd
   Worksheet 2: Pointest x and boundx.Result; map Dependent to Sort, include pointest, x, and boundx
   Rename Merge Worksheets to Merge 2.
2. Worksheet 1: Merge 2.Result; map dfd to Sort, include all other variables
   Worksheet 2: ChiSq; map dfd to Sort, include Cinv*
   Rename Merge Worksheets to get external ChiSq.

get external ChiSq | **Output Data** ➔ Result ➔ Send To ➔ Data ➔ Data Wizard

Set up a Filter Include where [Dependent] = 'dlat'

Add Filters and Transformations:

1. Include where [Dependent] = 'dlat'
2. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: theta
   Formula: ((ln(1.25)) / 0.25)^2

---

* Critical values of $\chi^2_{0.05,df}$ are not available in PHX. They can be obtained by a simple R[9]-code (see below) and pasted into a worksheet (name ChiSq) in the data section (variable names: dfd, Cinv).

```
options(digits=16)
for (dfd in seq(1, 200, by=1)){
  cinv=qchisq(0.95, df=dfd)
  cat(paste(dfd, "\t", cinv, "\n"))
  }
```

Alternatively use one of the many online calculators, *e.g.*, the one from DanielSoper.com.

3. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: y
   Formula: -theta*s2
   Map s2wr to s2
4. Transformation Type: Functions
   Transformation: Square root(x)
   New Column Name: sWR
   Map s2wr to x Column
5. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: boundy
   Formula: y*dfd/Cinv
6. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: critbound
   Formula: (x+y)+sqrt(((boundx-x)^2)+((boundy-y)^2))
7. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: CVwr
   Formula: round(100*sqrt(exp(s2)-1),2)
8. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: Assessment
   Formula: if(sWR<0.294, 'sWr<0.294: use unscaled ABE', if((pointest>=0.8) & (pointest<1.25) & (critbound<=0), 'RSABE', 'not RSABE'))
9. Exclude dfd, Dependent, boundx, x, Cinv, theta, y

pointest	Title	sWR	boundy	critbound	CVwr	Assessment
1.1546132	average	0.44644551	-0.12298597	-0.092076336	46.96	RSABE

3.4 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 scavbe;
  merge test ref1 ref2;
  by seq subj;
  ilat=latt-(0.5*(lat1r+lat2r));
  dlat=lat1r-lat2r;
run;
```

```
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;
```

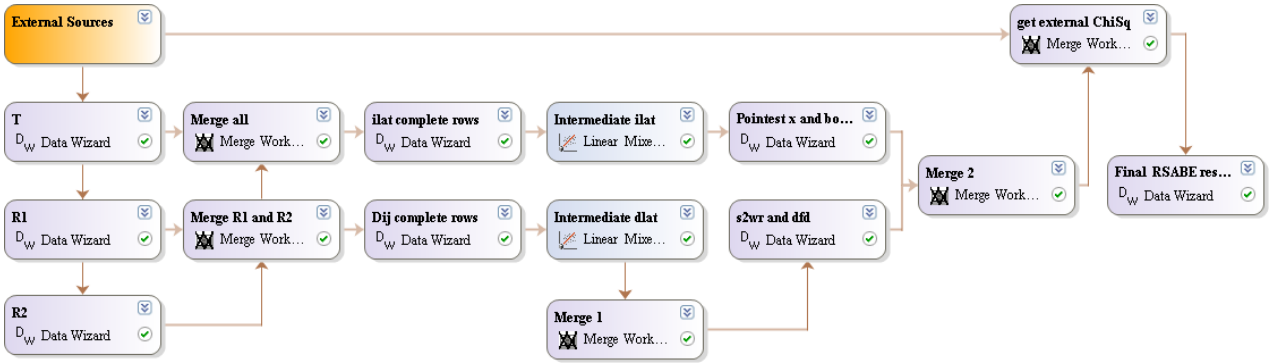
IGLM2:

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

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

DGLM1:

```
Dfd=df;
s2wr=estimate/2;
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));
```



data set II ➔ Send To ➔ Data ➔ Data Wizard

Set up three separate Custom inclusion filters (the test and first and second occasions of the reference, respectively). Exlude the Data variable. Set up properties.

1. Formulation='T'
   Property: logData ➔ [New Column Name]: latt
   Rename Data Wizard to T.
2. Formulation='R' and ((Sequence='1' and Period=2) or (Sequence='2' and Period=1) or (Sequence='3' and Period=1))
   Property: logData ➔ [New Column Name]: lat1r
   Rename Data Wizard to R1.
3. Formulation='R' and ((Sequence='1' and Period=3) or (Sequence='2' and Period=3) or (Sequence='3' and Period=2))
   Property: logData ➔ [New Column Name]: lat2r
   Rename Data Wizard to R2.

Set up two merges; first both references, then the test.

1. Worksheet 1: R1.Result; map Subject and Sequence to Sort, include lat1r
   Worksheet 2: R2.Result; map Subject and Sequence to Sort, include lat2r
   Rename Merge Worksheets to Merge R1 and R2.
2. Worksheet 1: Merge R1 and R2.Result; map Subject and Sequence to Sort, include lat1r and lat2r
   Worksheet 2: T.Result; map Subject and Sequence to Sort, include latt
   Rename Merge Worksheets to Merge all.

Merge all.Results ➔ Send To ➔ Data ➔ Data Wizard

Specify three Built in filters to exclude any incomplete data of latt, lat1r, and lat2r.

Add a Custom Transformation:

New Column Name: ilat

Formula: latt - (0.5 * (lat1 + lat2)), Map latt to latt, lat1r to lat1,: lat2r to lat2.

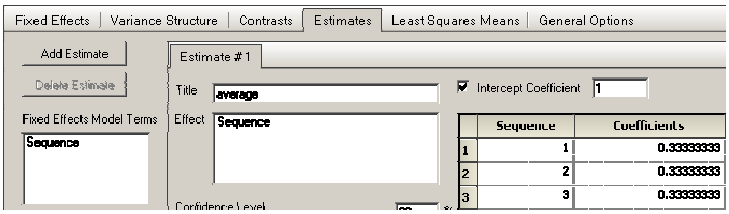
Rename Data Wizard to ilat complete rows.

Final Results ➔ Result ➔ Send To ➔ NCA and Toolbox ➔ Linear Mixed Effects

Map ilat as Dependent and Sequence as Classification

Drag Sequence to the Model Specification, change Dependent Variables Transformation ➔ Already Ln-transformed.

Specify Estimate #1, Title average, Effect Sequence, Confidence Level 90%, Intercept Coefficient 1, Coefficients of all Sequences 0.33333333:



Rename Linear Mixed Effects to Intermediate ilat.

The remainder of the workflow follows the steps given above for the full replicate design.

pointest	Title	sWR	boundy	critbound	CVwr	Assessment
1.0226439	average	0.11397294	-0.0066520374	-0.0039728893	11.43	sWr < 0.294: use unscaled ABE

3.5 Calculation of unscaled 90% bioequivalence 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=0.10;
 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;
```

data set II ➔ Send To ➔ NCA and Toolbox ➔ Linear Mixed Effects

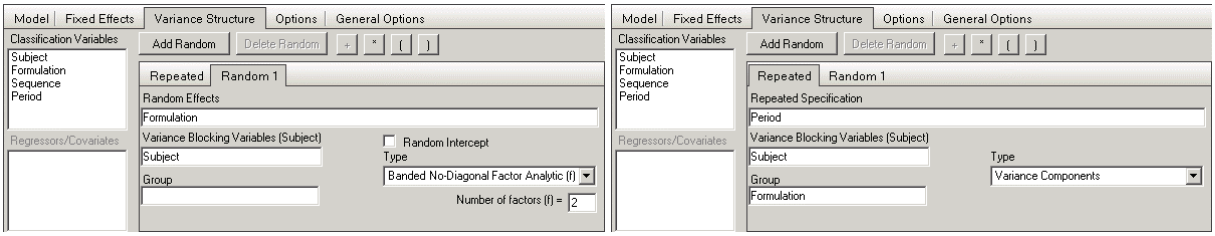
Map Subject, Period, Sequence, and Formulation to Classification and logData to Dependent.

Note Sometimes (*i.e.*, with other datasets) Phoenix fails in 'recognizing' the underlying design. If this happens, specify the model as:

[Fixed Effects]: Sequence+Formulation+Period

Variance Structure [Random 1]: Random Effects = Formulation, Variance Blocking Variables (Subject) = Subject, Type = Banded No-Diagonal Factor Analytic (f), Number of factors (f) = 2

Variance Structure [Repeated]: Repeated Specification = Period, Variance Blocking Variables (Subject) = Subject, Group = Formulation, Type = Variance Components



Linear Mixed Effects | **Output Data** ➔ Estimates ➔ Send To ➔ Data ➔ Data Wizard

Add Transformations

1. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: unscabe_pointest
   Formula: round(100*exp(Estimate),2)
2. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: unscabe_lower
   Formula: round(100*exp(Lower_CI),2)
3. Transformation Type: Custom
   Transformation: Custom Function
   New Column Name: unscabe_upper
   Formula: round(100*exp(Upper_CI),2)
   Rename Data Wizard to back transform.

Linear Mixed Effects | **Output Data** ➔ Final Variance Parameters ➔ Send To ➔ Data ➔ Data Wizard

Add a Filter Include where [Parameter] = 'Var(Period*Formulation*Subject)_21'

Add a Transformation

Transformation Type: Custom
Transformation: Custom Function
New Column Name: CVwr
Formula: round(100*sqrt(exp(Estimate)-1),2)
Rename Data Wizard to CVwr.

Merge Woksheets.

Worksheet 1: CVwr.Result; map Dependent to Sort, include CVwr

Worksheet 2: back transform.Result; map Dependent to Sort, include Title, Conf_Level, unscabe_pointest, unscabe_lower, and unscabe_upper.

Merge | **Output Data** ➔ Result ➔ Send To ➔ Data ➔ Data Wizard

Add a Transformation

Transformation Type: Custom

Transformation: Custom Function

New Column Name: Assessment

Formula: if((unscabe_lower > 125) | (unscabe_upper <80),'BioINequivalence shown', if((unscabe_lower >= 80) & (unscabe_upper <=125), 'Average Bioequivalence shown',' Failed to show Average BE'))

CVwr	Conf_Level	uncabe_pointest	uncabe_lower	uncabe_upper	Title	Assessment
11.55	90	102.26	97.05	107.76	T vs. R	Average Bioequivalence shown

4 Results

4.1 RSABE: Point Estimate, boundy/critbound, CV_{WR}

data set I (full replicate)										
SAS 9.2 (BEBA-Forum[10])					PHX					
PE	s_{WR}	boundy	critbound	CV_{WR}	PE	s_{WR}	boundy	critbound	CV_{WR}	Assessment
115.46	0.44645	-0.12299	-0.09208	NA	115.46	0.44645	-0.12299	-0.09208	46.96	RSABE
data set II (partial replicate)										
SAS 9.2 (BEBA-Forum[10])					PHX					
PE	s_{WR}	boundy	critbound	CV_{WR}	PE	s_{WR}	boundy	critbound	CV_{WR}	Assessment
102.26	0.11397	-0.00665	-0.00397	NA	102.26	0.11397	-0.00665	-0.00397	11.43	s_{WR} < 0.294: use unscaled ABE

4.2 Unscaled ABE: Point Estimate, Confidence Interval, CV_{WR}

data set I (full replicate)							
SAS 9.1 (EMA Q&A[7])				PHX			
PE	90% CI		CV_{WR}	PE	90% CI		CV_{WR}
115.66	107.10	124.89	47.3	115.66	107.10	124.89	47.33
data set II (partial replicate)							
SAS 9.1 (EMA Q&A[7])				PHX			
PE	90% CI		CV_{WR}	PE	90% CI		CV_{WR}
102.26	97.05	107.76	10.71	102.26	97.05	107.76	10.71

5 Discussion and Conclusions

The workflow in Phoenix/WinNonlin validated against results reported by EMA[7] in the unscaled analysis and against SAS 9.2 (RSABE).[10]

In the full replicate data set I (unscaled method) additionally to CV_{WR} the intra-subject CV of the test CV_{WT} can be obtained from 'Var(Period*Formulation*Subject)_22'.

Evaluation of data set II by the unscaled method indicates an over-specified model. A warning is issued:

```
Newton's algorithm converged with modified Hessian. Output is suspect.
Model may be over-specified. A simpler model could be tried.
```

A similar statement is obtained in SAS 9.21.

```
Convergence criteria met but final hessian is not positive definite.
```

These problems in convergence (due to non-replicated test treatments) explains the difference in estimated CV_{WT} from PHX and SAS. However, the method should provide reliable estimates for other 3-period designs (*e.g.*, TRT | RTR | TRR | RTT).

We suggest to calculate in routine use CV_{WR} from PHX's standard model of PBE/IBE first (see Section 3.2). This value is similar to the one obtained by FDA's full code. If CV_{WR} <30% setting up RSABE likely is futile. See also the project file in PHX 1.3 format at:

- http://bebac.at/downloads/FDA_RSABE_PHX63.phxproj

6 Acknowledgments

Members Shuange and Jean-Michel Cardot of the BEBA-Forum for in-depth discussions and cross-validating the workflow against SAS 9.2.

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