Validation of Bioequivalence Test Performed by BE R package

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Contents

1 Introduction

BE R package (Bae 2018) can conduct a noncompartmental analysis as similar as possible to the most widely used commercial software for pharmacokinetic analysis, i.e. Phoenix® WinNonlin®. This document provides validation of noncompartmental analysis performed by BE R package version 0.1.1 as compared to the results from the commercial software, SAS® version 9.4.

2 Results

A function, `Equal()` will return `TRUE` if there is no difference between results from NonCompart and WinNonlin.

```
library(BE) # install.packages("BE", repos="http://r.acr.kr")
```

```
## Loading required package: rtf
```

```
library(tidyverse)
```

```
## -- Attaching packages ---------------------------------- tidyverse 1.2.1 --
```

```
## v ggplot2 3.0.0     v purrr   0.2.5
## v tibble  1.4.2     v dplyr   0.7.6
## v tidyr   0.8.1     v stringr 1.3.1
## v readr   1.1.1     v forcats 0.3.0
```

```
## -- Conflicts ------------------------------------- tidyverse_conflicts() --
## x dplyr::filter() masks stats::filter()
## x dplyr::lag()    masks stats::lag()
```

```
library(knitr)
knitr::opts_chunk$set(message = FALSE)
```

2.1 AUClast

```
BE::test2x2(NCAResult4BE, "AUClast")
```

```
## $`Analysis of Variance (log scale)`
##                            SS DF           MS           F            p
## SUBJECT        2.875497e+00 32 8.985928e-02 3.183942248 0.0008742828
## GROUP          1.024607e-01  1 1.024607e-01 1.145416548 0.2927731856
## SUBJECT(GROUP) 2.773036e+00 31 8.945279e-02 3.169539016 0.0009544080
## PERIOD         3.027399e-05  1 3.027399e-05 0.001072684 0.9740824428
## DRUG           3.643467e-02  1 3.643467e-02 1.290972690 0.2645764201
## ERROR          8.749021e-01 31 2.822265e-02          NA           NA
## TOTAL          3.786834e+00 65           NA          NA           NA
##
## $`Between and Within Subject Variability`
##                                  Between Subject Within Subject
## Variance Estimate                     0.03061507     0.02822265
## Coefficient of Variation, CV(%)      17.63193968    16.91883011
##
## $`Least Square Means (geometric mean)`
##                  Reference Drug Test Drug
## Geometric Means        5092.098  4858.245
##
## $`90% Confidence Interval of Geometric Mean Ratio (T/R)`
##                   Lower Limit Point Estimate Upper Limit
## 90% CI for Ratio     0.889436      0.9540753    1.023412
##
## $`Sample Size`
##                         True Ratio=1 True Ratio=Point Estimate
## 80% Power Sample Size              6                        7
```

2.2 Cmax

```
BE::test2x2(NCAResult4BE, "Cmax")
```

```
## $`Analysis of Variance (log scale)`
##                            SS DF           MS           F          p
## SUBJECT        2.861492e+00 32 8.942162e-02 2.237604579 0.01367095
## GROUP          9.735789e-05  1 9.735789e-05 0.001054764 0.97429977
## SUBJECT(GROUP) 2.861394e+00 31 9.230304e-02 2.309706785 0.01131826
## PERIOD         4.717497e-03  1 4.717497e-03 0.118046317 0.73348258
## DRUG           6.837756e-03  1 6.837756e-03 0.171101730 0.68198228
## ERROR          1.238856e+00 31 3.996310e-02          NA         NA
## TOTAL          4.112258e+00 65           NA          NA         NA
##
## $`Between and Within Subject Variability`
##                                  Between Subject Within Subject
## Variance Estimate                     0.02616997      0.0399631
## Coefficient of Variation, CV(%)      16.28355371     20.1921690
##
```

```
## $`Least Square Means (geometric mean)`
##                  Reference Drug Test Drug
## Geometric Means       825.5206  808.8778
##
## $`90% Confidence Interval of Geometric Mean Ratio (T/R)`
##                   Lower Limit Point Estimate Upper Limit
## 90% CI for Ratio   0.9013625      0.9798396    1.065149
##
## $`Sample Size`
##                         True Ratio=1 True Ratio=Point Estimate
## 80% Power Sample Size            8                         8
```

```
results_Cmax <- BE::test2x2(NCAResult4BE, "Cmax")
ls(results_Cmax)
```

```
## [1] "90% Confidence Interval of Geometric Mean Ratio (T/R)"
## [2] "Analysis of Variance (log scale)"
## [3] "Between and Within Subject Variability"
## [4] "Least Square Means (geometric mean)"
## [5] "Sample Size"
```

```
results_Cmax$`90% Confidence Interval of Geometric Mean Ratio (T/R)` %>%
  as.tibble(rownames = row.names(.))
```

90% CI for Ratio	Lower Limit	Point Estimate	Upper Limit
90% CI for Ratio	0.9013625	0.9798396	1.065149

2.2.1 PROC GLM

```
gather_sas <- function(df){
  df %>%
    gather('parameter', 'value')
}
read_csv('sas/proc-glm.csv') %>%
  gather_sas()
```

parameter	value
Obs	1.000000
LNPE	-0.020366
DF	31.000000
SE	0.049236
LNLM	0.083481
LNLL	-0.103850
LNUL	0.063115
PE	0.979840
LL	0.901360
UL	1.065150
WD	0.163790

2.2.2 PROC MIXED

```
read_csv('sas/proc-mixed.csv') %>%
  gather_sas()
```

parameter	value
Obs	1
Label	T VS R
Estimate	-0.02037
StdErr	0.04924
DF	31
tValue	-0.41
Probt	0.682
Alpha	0.1
Lower	-0.1038
Upper	0.06311
MSE	0.039963
LNLM	0.083481
PE	0.97984
LL	0.90136
UL	1.06515
WD	0.16379

2.3 Tmax

```
BE::test2x2(NCAResult4BE, "Tmax")
```

```
## $`Analysis of Variance (log scale)`
##                           SS DF         MS         F          p
## SUBJECT          7.52334340 32 0.23510448 1.6924313 0.07317245
## GROUP            0.01395806  1 0.01395806 0.0576212 0.81187628
## SUBJECT(GROUP)   7.50938534 31 0.24223824 1.7437846 0.06351437
## PERIOD           0.48117922  1 0.48117922 3.4638334 0.07223183
## DRUG             0.10288377  1 0.10288377 0.7406227 0.39606886
## ERROR            4.30637210 31 0.13891523        NA         NA
## TOTAL           12.42781245 65         NA        NA         NA
##
## $`Between and Within Subject Variability`
##                                   Between Subject Within Subject
## Variance Estimate                       0.0516615      0.1389152
## Coefficient of Variation, CV(%)      23.0259070     38.6039754
##
## $`Least Square Means (geometric mean)`
##                  Reference Drug Test Drug
## Geometric Means         1.15244    1.0649
##
## $`90% Confidence Interval of Geometric Mean Ratio (T/R)`
##                   Lower Limit Point Estimate Upper Limit
## 90% CI for Ratio     0.790851      0.9240393    1.079658
##
## $`Sample Size`
##                         True Ratio=1 True Ratio=Point Estimate
## 80% Power Sample Size             25                        43
```

3 SAS

```
cat sas/sas-be-model-2.sas
```

```
## DATA BE; /* It will load 91 records. */
##   INFILE 'c:\Users\mdlhs\asancpt\BEreport\sas\NCAResult4BE.csv' FIRSTOBS=2 DLM=",";
##   INPUT SUBJ $ SEQ $ PRD $ TRT $ AUClast Cmax Tmax;
##   IF CMAX =< 0 THEN DELETE;
##   LNCMAX = LOG(Cmax);
##   LNAUCL = LOG(AUClast );
##
## PROC PRINT; RUN;
##
## PROC GLM DATA=BE OUTSTAT=STATRES; /* GLM use only complete subjects. */
##   CLASS SEQ PRD TRT SUBJ;
##   MODEL LNCMAX = SEQ SUBJ(SEQ) PRD TRT;
##   RANDOM SUBJ(SEQ)/TEST;
##   LSMEANS TRT /PDIFF=CONTROL('R') CL ALPHA=0.1 COV OUT=LSOUT;
## RUN;
##
## PROC PRINT DATA=STATRES; RUN;
## PROC PRINT DATA=LSOUT; RUN;
##
## DATA STATRES;
##   SET STATRES;
##   IF _TYPE_='ERROR' THEN CALL SYMPUT('DF', DF);
##
## DATA LSOUT;
##   SET LSOUT;
##   IF TRT='R' THEN CALL SYMPUT('GMR_R', LSMEAN);
##   IF TRT='T' THEN CALL SYMPUT('GMR_T', LSMEAN);
##   IF TRT='R' THEN CALL SYMPUT('V_R', COV1);
##   IF TRT='T' THEN CALL SYMPUT('V_T', COV2);
##   IF TRT='T' THEN CALL SYMPUT('COV', COV1);
##
## DATA LSOUT2;
##   LNPE = &GMR_T - &GMR_R;
##   DF = &DF;
##   SE = SQRT(&V_R + &V_T - 2*&COV);
##   LNLM = TINV(0.95, DF)*SE;
##   LNLL = LNPE - LNLM ;
##   LNUL = LNPE + LNLM;
##   PE = EXP(LNPE);
##   LL = EXP(LNLL);
##   UL = EXP(LNUL);
##   WD = UL - LL;
##
## PROC PRINT DATA=LSOUT2; RUN;
##
## PROC MIXED DATA=BE; /* MIXED  uses all data. */
##   CLASS SEQ TRT SUBJ PRD;
##   MODEL LNCMAX = SEQ PRD TRT;
##   RANDOM SUBJ(SEQ);
##   ESTIMATE 'T VS R' TRT -1 1 /CL ALPHA=0.1;
##   ODS OUTPUT ESTIMATES=ESTIM COVPARMS=COVPAR;
## RUN;
##
## DATA COVPAR;
```

```
##   SET COVPAR;
##   IF CovParm = 'Residual' THEN CALL SYMPUT('MSE', Estimate);
##
## DATA ESTIM;
##   SET ESTIM;
##   MSE = &MSE;
##   LNLM = (Upper - Lower)/2;
##   PE = EXP(Estimate);
##   LL = EXP(Lower);
##   UL = EXP(Upper);
##   WD = UL - LL;
##
## PROC PRINT Data=ESTIM; RUN;
```

A Raw

Table 1: Description of settings for the noncompartmental analysis performed in WinNonlin and links to the raw data

SUBJ	GRP	PRD	TRT	AUClast	Cmax	Tmax
1	RT	1	R	5018.927	1043.13	1.04
1	RT	2	T	6737.507	894.21	1.03
2	TR	1	T	4373.970	447.26	1.01
2	TR	2	R	6164.276	783.92	1.98
4	TR	1	T	5592.993	824.42	1.97
4	TR	2	R	5958.160	646.31	0.97
5	TR	1	T	3902.590	803.70	0.80
5	TR	2	R	4620.156	955.30	0.74
6	RT	1	R	3735.274	995.34	1.02
6	RT	2	T	4257.802	816.33	1.00
7	RT	1	R	4314.993	608.99	0.95
7	RT	2	T	5030.372	806.57	0.74
8	RT	1	R	6053.098	1283.67	0.72
8	RT	2	T	5790.067	822.95	1.03
9	RT	1	R	4602.582	679.39	0.74
9	RT	2	T	6042.462	556.55	0.98
10	RT	1	R	8848.988	1136.91	1.03
10	RT	2	T	7349.822	1082.79	0.97
11	TR	1	T	3054.096	547.73	2.02
11	TR	2	R	4719.175	984.69	0.54
13	RT	1	R	4828.682	615.17	1.00
13	RT	2	T	4175.434	692.26	0.97
14	RT	1	R	4566.275	864.56	1.03
14	RT	2	T	5042.649	1122.75	0.75
15	TR	1	T	4950.980	719.40	0.97
15	TR	2	R	4959.554	660.17	0.96
16	RT	1	R	4577.432	609.64	3.01
16	RT	2	T	4773.723	807.65	1.01
17	RT	1	R	6462.652	861.56	2.02
17	RT	2	T	5246.032	1187.75	0.73
18	TR	1	T	4754.625	919.87	0.77
18	TR	2	R	3214.809	1042.84	0.53
19	TR	1	T	7619.304	1089.84	3.00
19	TR	2	R	5210.569	1127.94	2.04
20	TR	1	T	5063.471	1191.46	0.71
20	TR	2	R	6406.634	1069.19	1.00
21	RT	1	R	5580.289	742.67	0.97
21	RT	2	T	6304.119	447.85	0.99
22	RT	1	R	4398.887	682.73	2.02
22	RT	2	T	3760.359	669.01	1.04
23	TR	1	T	5141.165	937.02	0.51
23	TR	2	R	5835.275	894.72	1.04
24	TR	1	T	4343.439	713.57	1.03
24	TR	2	R	2848.448	811.83	0.71
25	TR	1	T	3983.260	1160.32	0.73
25	TR	2	R	3476.389	769.63	0.78
27	TR	1	T	5772.972	1219.56	0.99
27	TR	2	R	7673.260	1063.29	1.03

SUBJ	GRP	PRD	TRT	AUClast	Cmax	Tmax
28	RT	1	R	5679.039	650.24	1.00
28	RT	2	T	5160.875	891.63	1.05
29	TR	1	T	4800.455	770.63	2.02
29	TR	2	R	5772.925	738.17	1.04
30	RT	1	R	4722.324	1034.11	0.77
30	RT	2	T	2896.939	569.22	1.03
31	RT	1	R	8032.393	1043.82	1.98
31	RT	2	T	6076.359	1141.43	0.96
32	TR	1	T	4245.372	608.93	2.97
32	TR	2	R	4745.770	539.66	2.04
33	TR	1	T	3648.195	856.18	0.76
33	TR	2	R	3356.777	647.95	0.98
34	TR	1	T	5015.499	739.42	0.96
34	TR	2	R	6325.746	682.41	1.99
35	RT	1	R	6259.347	1020.55	1.96
35	RT	2	T	5802.468	835.87	2.04
36	RT	1	R	4669.384	682.87	3.01
36	RT	2	T	3783.584	729.63	1.00

B Session Information

```
devtools::session_info()
```

```
##  setting  value
##  version  R version 3.5.1 (2018-07-02)
##  system   x86_64, mingw32
##  ui       RTerm
##  language (EN)
##  collate  Korean_Korea.949
##  tz       Asia/Seoul
##  date     2018-10-10
##
##  package     * version date       source
##  assertthat    0.2.0   2017-04-11 CRAN (R 3.5.0)
##  backports     1.1.2   2017-12-13 CRAN (R 3.5.0)
##  base        * 3.5.1   2018-07-02 local
##  BE          * 0.1.1   2018-07-19 CRAN (R 3.5.1)
##  bindr         0.1.1   2018-03-13 CRAN (R 3.5.0)
##  bindrcpp      0.2.2   2018-03-29 CRAN (R 3.5.0)
##  bookdown      0.7     2018-02-18 CRAN (R 3.5.0)
##  broom         0.5.0   2018-07-17 CRAN (R 3.5.1)
##  cellranger    1.1.0   2016-07-27 CRAN (R 3.5.0)
##  cli           1.0.1   2018-09-25 CRAN (R 3.5.1)
##  colorspace    1.3-2   2016-12-14 CRAN (R 3.5.0)
##  compiler      3.5.1   2018-07-02 local
##  crayon        1.3.4   2018-06-08 Github (gaborcsardi/crayon@3e751fb)
##  datasets    * 3.5.1   2018-07-02 local
##  devtools      1.13.6  2018-06-27 CRAN (R 3.5.0)
##  digest        0.6.17  2018-09-12 CRAN (R 3.5.1)
##  dplyr       * 0.7.6   2018-06-29 CRAN (R 3.5.0)
##  evaluate      0.12    2018-10-09 CRAN (R 3.5.1)
```

```
##  forcats     * 0.3.0   2018-02-19 CRAN (R 3.5.0)
##  ggplot2     * 3.0.0   2018-07-03 CRAN (R 3.5.1)
##  glue          1.3.0   2018-07-17 CRAN (R 3.5.1)
##  graphics    * 3.5.1   2018-07-02 local
##  grDevices   * 3.5.1   2018-07-02 local
##  grid          3.5.1   2018-07-02 local
##  gtable        0.2.0   2016-02-26 CRAN (R 3.5.0)
##  haven         1.1.2   2018-06-27 CRAN (R 3.5.0)
##  highr         0.7     2018-06-09 CRAN (R 3.5.0)
##  hms           0.4.2   2018-03-10 CRAN (R 3.5.0)
##  htmltools     0.3.6   2017-04-28 CRAN (R 3.5.0)
##  httr          1.3.1   2017-08-20 CRAN (R 3.5.0)
##  jsonlite      1.5     2017-06-01 CRAN (R 3.5.0)
##  knitr       * 1.20    2018-02-20 CRAN (R 3.5.0)
##  lattice       0.20-35 2017-03-25 CRAN (R 3.5.0)
##  lazyeval      0.2.1   2017-10-29 CRAN (R 3.5.0)
##  lubridate     1.7.4   2018-04-11 CRAN (R 3.5.0)
##  magrittr      1.5     2014-11-22 CRAN (R 3.5.0)
##  memoise       1.1.0   2017-04-21 CRAN (R 3.5.0)
##  methods     * 3.5.1   2018-07-02 local
##  modelr        0.1.2   2018-05-11 CRAN (R 3.5.0)
##  munsell       0.5.0   2018-06-12 CRAN (R 3.5.0)
##  nlme          3.1-137 2018-04-07 CRAN (R 3.5.1)
##  pillar        1.3.0   2018-07-14 CRAN (R 3.5.1)
##  pkgconfig     2.0.2   2018-08-16 CRAN (R 3.5.1)
##  plyr          1.8.4   2016-06-08 CRAN (R 3.5.0)
##  purrr       * 0.2.5   2018-05-29 CRAN (R 3.5.0)
##  R.methodsS3   1.7.1   2016-02-16 CRAN (R 3.5.0)
##  R.oo          1.22.0  2018-04-22 CRAN (R 3.5.0)
##  R6            2.3.0   2018-10-04 CRAN (R 3.5.1)
##  Rcpp          0.12.19 2018-10-01 CRAN (R 3.5.1)
##  readr       * 1.1.1   2017-05-16 CRAN (R 3.5.0)
##  readxl        1.1.0   2018-04-20 CRAN (R 3.5.0)
##  rlang         0.2.2   2018-08-16 CRAN (R 3.5.1)
##  rmarkdown     1.10    2018-06-11 CRAN (R 3.5.0)
##  rprojroot     1.3-2   2018-01-03 CRAN (R 3.5.0)
##  rstudioapi    0.8     2018-10-02 CRAN (R 3.5.1)
##  rtf         * 0.4-13  2018-05-17 CRAN (R 3.5.1)
##  rvest         0.3.2   2016-06-17 CRAN (R 3.5.0)
##  scales        1.0.0   2018-08-09 CRAN (R 3.5.1)
##  stats       * 3.5.1   2018-07-02 local
##  stringi       1.2.4   2018-07-20 CRAN (R 3.5.1)
##  stringr     * 1.3.1   2018-05-10 CRAN (R 3.5.0)
##  tibble      * 1.4.2   2018-01-22 CRAN (R 3.5.0)
##  tidyr       * 0.8.1   2018-05-18 CRAN (R 3.5.0)
##  tidyselect    0.2.4   2018-02-26 CRAN (R 3.5.0)
##  tidyverse   * 1.2.1   2017-11-14 CRAN (R 3.5.0)
##  tools         3.5.1   2018-07-02 local
##  utils       * 3.5.1   2018-07-02 local
##  withr         2.1.2   2018-03-15 CRAN (R 3.5.0)
##  xfun          0.3     2018-07-06 CRAN (R 3.5.1)
##  xml2          1.2.0   2018-01-24 CRAN (R 3.5.0)
##  yaml          2.2.0   2018-07-25 CRAN (R 3.5.1)
```

References

Bae, Kyun-Seop. 2018. *BE: Bioequivalence Study Data Analysis*. https://CRAN.R-project.org/package=BE.