# Validation of Bioequivalence Test Performed by BE R package

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## Contents



# 1 Introduction

`BE` R package (Bae 2018) can analyze bioequivalence study data with industrial strength. The current version `BE` performs bioequivalency tests for several variables of a 2x2 crossover study in a data file. To establish BE, the calculated confidence interval should fall within a BE limit, usually 80-125% for the ratio of the product averages. (Drug Evaluation et al. 2001; Chow and Liu 2008; Hauschke, Steinijans, and Pigeot 2007) In this document, the author performed validation of bioequivalence test performed by `BE` R package.

# 2 Methods

The required packages are following.

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

## 2.1 Calculation BE

BE::test2x2() function was used to calculated the 90% confidence interval.

```
Cmax_R_BE <- BE::test2x2(NCAResult4BE, "Cmax")[[4]] %>%
  as.tibble() %>%
  mutate(Analysis = 'R: BE package') %>%
  select(Analysis, everything())

AUClast_R_BE <- BE::test2x2(NCAResult4BE, "AUClast")[[4]] %>%
  as.tibble() %>%
  mutate(Analysis = 'R: BE package') %>%
  select(Analysis, everything())
```

## 2.2 Calculation SAS

SAS PROC GLM and SAS PROC MIXED in SAS version 9.0 with SEQ (sequence), TRT (treatment), SUBJ (subject), PRD (period) variables, and LNAUCL or LNCMAX denoting the response measure.
A part of examplary SAS program statement is following and the full SAS scripts are appended in Appendix A.

```
PROC GLM DATA=BE OUTSTAT=STATRES; /* GLM use only complete subjects. */
CLASS SEQ PRD TRT SUBJ;
MODEL LNAUCL = SEQ SUBJ(SEQ) PRD TRT;
RANDOM SUBJ(SEQ)/TEST;
LSMEANS TRT /PDIFF=CONTROL('R') CL ALPHA=0.1 COV OUT=LSOUT;
```

```
PROC MIXED DATA=BE; /* MIXED uses all data. */
CLASS SEQ TRT SUBJ PRD;
MODEL LNAUCL = SEQ PRD TRT;
RANDOM SUBJ(SEQ);
ESTIMATE 'T VS R' TRT -1 1 /CL ALPHA=0.1;
ODS OUTPUT ESTIMATES=ESTIM COVPARMS=COVPAR;
```

A function, tab_sas_proc_results() reads SAS analysis results exported to Microsoft Excel files (.xls) and converted to comma separated version file (.csv). It returns a data frame of 90% confidence interval calculated either PROC GLM or PROC MIXED in SAS version 9.0.

```
tab_sas_proc_results <- function(filename, skip_no, analysis_name){
  read_lines(filename, skip = skip_no, n_max = 2) %>%
  paste(collapse='\n') %>% read_csv() %>%
  mutate(Analysis = analysis_name) %>%
  select(Analysis, `Lower Limit` = LL, `Point Estimate` = PE, `Upper Limit` = UL)
}
```

# 3 Results

## 3.1 $C_{max}$

Dataset, `NCAResult4BE` is shown in Appendix 1.

Comparison between BE and SAS is shown in Table 1.

```
Cmax_proc_glm <- tab_sas_proc_results('sas/SAS_results_Cmax.csv',
                                      skip = 206, 'SAS: PROC GLM')
Cmax_proc_mixed <- tab_sas_proc_results('sas/SAS_results_Cmax.csv',
                                        skip = 278, 'SAS: PROC MIXED')

bind_rows(Cmax_R_BE, Cmax_proc_glm, Cmax_proc_mixed) %>%
  kable(longtable = TRUE, booktabs = TRUE, caption = 'Cmax', digits = 5)
```

Table 1: Cmax

| Analysis | Lower Limit | Point Estimate | Upper Limit |
|---|---|---|---|
| R: BE package | 0.90136 | 0.97984 | 1.06515 |
| SAS: PROC GLM | 0.90136 | 0.97984 | 1.06515 |
| SAS: PROC MIXED | 0.90136 | 0.97984 | 1.06515 |

## 3.2 $AUC_{last}$

Comparison between BE and SAS is shown in Table 2.

```
AUClast_proc_glm <- tab_sas_proc_results('sas/SAS_results_AUClast.csv',
                                         skip = 206, 'SAS: PROC GLM')
AUClast_proc_mixed <- tab_sas_proc_results('sas/SAS_results_AUClast.csv',
                                           skip = 278, 'SAS: PROC MIXED')

bind_rows(AUClast_R_BE, AUClast_proc_glm, AUClast_proc_mixed) %>%
  kable(longtable = TRUE, booktabs = TRUE, caption = 'AUClast', digits = 5)
```

Table 2: AUClast

| Analysis | Lower Limit | Point Estimate | Upper Limit |
|---|---|---|---|
| R: BE package | 0.88944 | 0.95408 | 1.02341 |
| SAS: PROC GLM | 0.88944 | 0.95408 | 1.02341 |
| SAS: PROC MIXED | 0.88944 | 0.95408 | 1.02341 |

# 4 Conclusion

*There is no discrepancy* between results from BE and SAS. We also performed multiple analyses with the real clinical trial datasets and have found no differences (data not shown: confidential). Noncompartmental analysis performed by the open-source R package, NonCompart can be **qualified and validated** enough to acquire the identical results of the commercial software, WinNonlin.

*Please report issues regarding validation of the R package to https://github.com/asancpt/NonCompart-tests/issues.*

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# A Raw

Table 3: 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 SAS Scripts and results

To run these scripts, the dataset `NCAResult4BE` should be exported from R by `write.csv()`.

## B.1 $C_{max}$

```
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;
```

```
read_csv('sas/SAS_results_Cmax.csv') %>%
  knitr::kable(longtable = TRUE, booktabs = TRUE, # format = "latex",
                caption = 'Cmax')
```

## B.2 $\text{AUC}_{\text{last}}$

```
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 LNAUCL = 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 LNAUCL = 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;
```

# C Session Information

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

```
## - Session info ---------------------------------------------------------------
##  setting  value
##  version  R version 3.5.1 (2018-07-02)
##  os       Windows 7 x64 SP 1
##  system   x86_64, mingw32
##  ui       RTerm
##  language (EN)
##  collate  Korean_Korea.949
##  ctype    Korean_Korea.949
##  tz       Asia/Seoul
##  date     2018-10-23
##
## - Packages -------------------------------------------------------------------
##  package     * version date       lib source
##  assertthat    0.2.0   2017-04-11 [1] CRAN (R 3.5.0)
##  backports     1.1.2   2017-12-13 [1] CRAN (R 3.5.0)
##  base64enc     0.1-3   2015-07-28 [1] CRAN (R 3.5.0)
##  BE          * 0.1.1   2018-07-19 [1] CRAN (R 3.5.1)
##  bindr         0.1.1   2018-03-13 [1] CRAN (R 3.5.0)
##  bindrcpp      0.2.2   2018-03-29 [1] CRAN (R 3.5.0)
##  bookdown      0.7     2018-02-18 [1] CRAN (R 3.5.0)
##  broom         0.5.0   2018-07-17 [1] CRAN (R 3.5.1)
##  callr         3.0.0   2018-08-24 [1] CRAN (R 3.5.1)
##  cellranger    1.1.0   2016-07-27 [1] CRAN (R 3.5.0)
##  cli           1.0.1   2018-09-25 [1] CRAN (R 3.5.1)
##  colorspace    1.3-2   2016-12-14 [1] CRAN (R 3.5.0)
##  crayon        1.3.4   2018-06-08 [1] Github (gaborcsardi/crayon@3e751fb)
##  debugme       1.1.0   2017-10-22 [1] CRAN (R 3.5.0)
##  desc          1.2.0   2018-05-01 [1] CRAN (R 3.5.0)
##  devtools      2.0.0   2018-10-19 [1] CRAN (R 3.5.1)
##  digest        0.6.18  2018-10-10 [1] CRAN (R 3.5.1)
##  dplyr       * 0.7.7   2018-10-16 [1] CRAN (R 3.5.1)
##  evaluate      0.12    2018-10-09 [1] CRAN (R 3.5.1)
##  forcats     * 0.3.0   2018-02-19 [1] CRAN (R 3.5.0)
##  fs            1.2.6   2018-08-23 [1] CRAN (R 3.5.1)
##  ggplot2     * 3.0.0   2018-07-03 [1] CRAN (R 3.5.1)
##  glue          1.3.0   2018-07-17 [1] CRAN (R 3.5.1)
##  gtable        0.2.0   2016-02-26 [1] CRAN (R 3.5.0)
##  haven         1.1.2   2018-06-27 [1] CRAN (R 3.5.0)
##  highr         0.7     2018-06-09 [1] CRAN (R 3.5.0)
##  hms           0.4.2   2018-03-10 [1] CRAN (R 3.5.0)
##  htmltools     0.3.6   2017-04-28 [1] CRAN (R 3.5.0)
##  httr          1.3.1   2017-08-20 [1] CRAN (R 3.5.0)
##  jsonlite      1.5     2017-06-01 [1] CRAN (R 3.5.0)
##  knitr       * 1.20    2018-02-20 [1] CRAN (R 3.5.0)
##  lattice       0.20-35 2017-03-25 [1] CRAN (R 3.5.0)
##  lazyeval      0.2.1   2017-10-29 [1] CRAN (R 3.5.0)
##  lubridate     1.7.4   2018-04-11 [1] CRAN (R 3.5.0)
##  magrittr      1.5     2014-11-22 [1] CRAN (R 3.5.0)
##  memoise       1.1.0   2017-04-21 [1] CRAN (R 3.5.0)
```

```
##  modelr        0.1.2   2018-05-11 [1] CRAN (R 3.5.0)
##  munsell       0.5.0   2018-06-12 [1] CRAN (R 3.5.0)
##  nlme          3.1-137 2018-04-07 [2] CRAN (R 3.5.1)
##  pillar        1.3.0   2018-07-14 [1] CRAN (R 3.5.1)
##  pkgbuild      1.0.2   2018-10-16 [1] CRAN (R 3.5.1)
##  pkgconfig     2.0.2   2018-08-16 [1] CRAN (R 3.5.1)
##  pkgload       1.0.1   2018-10-11 [1] CRAN (R 3.5.1)
##  plyr          1.8.4   2016-06-08 [1] CRAN (R 3.5.0)
##  prettyunits   1.0.2   2015-07-13 [1] CRAN (R 3.5.0)
##  processx      3.2.0   2018-08-16 [1] CRAN (R 3.5.1)
##  ps            1.2.0   2018-10-16 [1] CRAN (R 3.5.1)
##  purrr       * 0.2.5   2018-05-29 [1] CRAN (R 3.5.0)
##  R.methodsS3   1.7.1   2016-02-16 [1] CRAN (R 3.5.0)
##  R.oo          1.22.0  2018-04-22 [1] CRAN (R 3.5.0)
##  R6            2.3.0   2018-10-04 [1] CRAN (R 3.5.1)
##  Rcpp          0.12.19 2018-10-01 [1] CRAN (R 3.5.1)
##  readr       * 1.1.1   2017-05-16 [1] CRAN (R 3.5.0)
##  readxl        1.1.0   2018-04-20 [1] CRAN (R 3.5.0)
##  remotes       2.0.1   2018-10-19 [1] CRAN (R 3.5.1)
##  rlang         0.2.2   2018-08-16 [1] CRAN (R 3.5.1)
##  rmarkdown     1.10    2018-06-11 [1] CRAN (R 3.5.0)
##  rprojroot     1.3-2   2018-01-03 [1] CRAN (R 3.5.0)
##  rstudioapi    0.8     2018-10-02 [1] CRAN (R 3.5.1)
##  rtf         * 0.4-13  2018-05-17 [1] CRAN (R 3.5.1)
##  rvest         0.3.2   2016-06-17 [1] CRAN (R 3.5.0)
##  scales        1.0.0   2018-08-09 [1] CRAN (R 3.5.1)
##  sessioninfo   1.1.0   2018-09-25 [1] CRAN (R 3.5.1)
##  stringi       1.2.4   2018-07-20 [1] CRAN (R 3.5.1)
##  stringr     * 1.3.1   2018-05-10 [1] CRAN (R 3.5.0)
##  testthat      2.0.1   2018-10-13 [1] CRAN (R 3.5.1)
##  tibble      * 1.4.2   2018-01-22 [1] CRAN (R 3.5.0)
##  tidyr       * 0.8.1   2018-05-18 [1] CRAN (R 3.5.0)
##  tidyselect    0.2.5   2018-10-11 [1] CRAN (R 3.5.1)
##  tidyverse   * 1.2.1   2017-11-14 [1] CRAN (R 3.5.0)
##  usethis       1.4.0   2018-08-14 [1] CRAN (R 3.5.1)
##  withr         2.1.2   2018-03-15 [1] CRAN (R 3.5.0)
##  xfun          0.3     2018-07-06 [1] CRAN (R 3.5.1)
##  xml2          1.2.0   2018-01-24 [1] CRAN (R 3.5.0)
##  yaml          2.2.0   2018-07-25 [1] CRAN (R 3.5.1)
##
## [1] C:/Users/mdlhs/Rlib
## [2] C:/Program Files/R/R-3.5.1/library
```

# References


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

Chow, Shein-Chung, and Jen-pei Liu. 2008. *Design and Analysis of Bioavailability and Bioequivalence Studies (Chapman & Hall/Crc Biostatistics Series).* Chapman; Hall/CRC.

Drug Evaluation, Center for, Food Research (CDER), U.S. Department of Health Drug Administration, and Human Services. 2001. *Guidance for Industry Statistical Approaches to Establishing Bioequivalence.* https://www.fda.gov/downloads/drugs/guidances/ucm070244.pdf.

Hauschke, Dieter, Volker Steinijans, and Iris Pigeot. 2007. *Bioequivalence Studies in Drug Development: Methods and Applications*. Wiley.