Supplementary Material 1
Example NONMEM code used in the model-integrated bioequivalence method

1. Example NONMEM code for estimation step

```
$PROBLEM    PK estimation
$INPUT      REP=DROP ID TIME AMT EVID DV TRT SEQ PER
$DATA       be_data.csv IGNORE=@
$SUBROUTINE ADVAN2 TRANS2
$PK
FTRT = 1
IF(TRT.EQ.2) FTRT = THETA(5)

KATRT = 1
IF(TRT.EQ.2) KATRT = THETA(6)

FSEQ = 1
IF(SEQ.EQ.2) FSEQ = THETA(7)

KASEQ = 1
IF(SEQ.EQ.2) KASEQ = THETA(8)

FPER = 1
IF(PER.EQ.2) FPER = THETA(9)

KAPER = 1
IF(PER.EQ.2) KAPER = THETA(10)

IF (PER.EQ.1)  IOVF = ETA(4)
IF (PER.EQ.2)  IOVF = ETA(5)

CL = THETA(1)* EXP(ETA(1))
V = THETA(2)*EXP(ETA(2))
F1 = THETA(3) * EXP(IOVF) * FTRT * FSEQ * FPER
KA = THETA(4) * EXP(ETA(3)) * KATRT * KASEQ * KAPER

$ERROR
IPRED = A(2)/V
IRES  = DV-IPRED
PROP  = SQRT(SIGMA(1,1))*IPRED
W     = PROP
IF (W.EQ.0) W=1
IWRES = IRES/W
Y     = IPRED + IPRED*EPS(1)

$THETA
(0,46)    ; 1.CL
 (0,400)  ; 2.V
 1 FIX.   ; 3.F
 (0, 1.2) ; 4.KA
 (0,1.25) ; 5.FTRT
 (0, 1.1) ; 6. KATRT
 (0, 1.1) ; 7.FSEQ
 (0, 1.1) ; 8. KASEQ
 (0, 1.1) ; 9.FPER
```

```
   (0, 1.1) ; 10. KAPER

$OMEGA
 0.03. ;     1. CL
 0.02  ;     2. V
 0.03  ;     3. KA
$OMEGA BLOCK(1)  0.0025 ;IOVF
$OMEGA BLOCK(1) SAME   ;IOVF

$SIGMA
 0.01 ;PROP



;;; estimation step
$ESTIMATION PRINT=1 MAXEVAL=9999 METHOD=1 INTER NOABORT SADDLE_RESET=1

;;; uncertainty: covariance matrix
$COVARIANCE UNCONDITIONAL

;;; uncertainty: SIR method
$COV SIRSAMPLE=2000 SIRNITER=6 SIRDF=30 IACCEPT=0.4 FILE=output_sir.ext

;;; uncertainty: bootstrap method
$SIML (101) BOOTSTRAP=-1 SUBP=1000 STRAT=SEQ
```

2. Example NONMEM code for the simulation step of a more complicated model (non-linear elimination) defined using ordinary differential equations

The input dataset (simdata.csv) includes:
- Dosing records for the 2-period BE study design with the doses the same as in the original BE data
- Observation records
  - at the last sampling time of the original BE dataset to calculate AUC_{last}
  - at an extended time point (5 times of the last sampling time) to calculate AUC_{inf}
- treatment covariate (TRT) of 1 and 2 for each period, respectively
- Period covariate (PER) and sequence covariate (SEQ) set to 1 for both periods

AUC_{inf} is extracted from the output table file sim_result.txt at the extended time point and AUC_{last} is extracted from the value reported at the last sampling time of the original BE dataset.

```
$PROBLEM    PK simulation
$INPUT      ID TIME DV AMT EVID CMT PER SEQ TRT DOSE
$DATA       simdata.csv IGNORE=@
$SUBROUTINE ADVAN13 TOL=6
$MODEL
   COMP=(DEPOT)            ;1. Depot compartment
   COMP=(CENTRAL)          ;2. Central compartment
   COMP=(AUC NODOSE)       ;3. AUC calculation

$PK
```

```
IF(NEWIND.NE.2) THEN
    TDOS = 0
    TAD  = 0
ENDIF

IF(EVID.EQ.1.OR.EVID.EQ.4) THEN
    TDOS = TIME
ENDIF

TAD = TIME - TDOS

FTRT = 1
IF(TRT.EQ.2) FTRT = THETA(5)

KATRT = 1
IF(TRT.EQ.2) KATRT = THETA(6)

IF (PER.EQ.1)  IOVF = ETA(4)
IF (PER.EQ.2)  IOVF = ETA(5)

VM = THETA(1)* EXP(ETA(1))
V = THETA(2)*EXP(ETA(2))
F1 = THETA(3)  * EXP(IOVF) * FTRT
KA = THETA(4)  * EXP(ETA(3)) * KATRT
KM = THETA(11)

AUCI = F1*DOSE/CL  ;for linear PK

$DES
DADT(1) = - KA*A(1)
DADT(2) =   KA*A(1) -  A(2)*VM/(V*(A(2)/V + KM))
CP  =  A(2)/V
DADT(3) = CP
AUCL = A(3)    ;AUClast theoretical value

IF(T.EQ.TDOS) THEN
    CMAX = 0
    TMAX = 0
ENDIF

IF(CP.GT.CMAX) THEN
    CMAX = CP
    TMAX = T-TDOS
ENDIF

; Nonlinear pk
;A very large last time needs to be set for AUCinf (Note: different
from the last time of the study design, where AUClast is measured)

$ERROR
IPRED = A(2)/V
IRES  = DV-IPRED
PROP  = SQRT(SIGMA(1,1))*IPRED
W     = PROP
IF (W.EQ.0) W=1
IWRES = IRES/W
Y     = IPRED + IPRED*EPS(1)
```

```
$THETA
(0,46)    ; 1.VM
 (0,400)  ; 2.V
 1 FIX    ; 3.F
 (0, 1.2) ; 4.KA
 (0,1.25) ; 5.FTRT
 (0, 1) ; 6. KATRT
 (0, 1) ; 7.FSEQ
 (0, 1) ; 8. KASEQ
 (0, 1) ; 9.FPER
 (0, 1) ; 10. KAPER
(0, 5) ; 11. KM

$OMEGA
 0.03 ;     1. VM
 0.02  ;     2. V
 0.03  ;     3. KA
$OMEGA BLOCK(1)  0.0025 ;IOVF
$OMEGA BLOCK(1) SAME  ;IOVF

$SIGMA
 0 FIX ;PROP

$SIMULATION (12345) ONLYSIM NSUBPROBS=1

$TABLE ID TIME TAD CP AUCI AUCL CMAX TMAX
      ONEHEADER NOPRINT FILE=sim_result.txt
```