Appendix 1. NONMEM control streams of one- and two-volume kinetic models.

< One-volume model >

```
$PROB RUN# 100 (One-volume kinetic model)
$INPUT ID OID TIME DUR RATE AMT DV MDV EVENT HB HCT SEX AGE WT HT BSA LBM IBW BMI CO CI SVV SV SVI HR
SBP DBP MBP
; DV (dilution, unitless) = (BHB/HB-1)/(1-BHCT) = (expandable plasma volume - baseline plasma volume)/(baseline plasma volume)
= (V(t) - BV)/BV
$DATA 05_06_NONMEM_data_OID_ID25.csv IGNORE=#
$SUBROUTINE ADVAN13 TRANS=1 TOL=6
$MODEL COMP (VOLUME)
$PK
  TH1 = THETA(1)
  TH2 = THETA(2)
  TH3 = THETA(3)

KB = TH1 ; basal elimination rate (ml/min, 0.8 at Anesthesiology 1997; 87: 204-12)
KR = TH2 ; renal clearance (ml/min)
V0 = TH3 ; baseline plasma volume (ml)

KB = TH1*EXP(ETA(1))
KR = TH2*EXP(ETA(2))
V0 = TH3*EXP(ETA(3))

$DES
 DADT(1) = RATE - KB - KR*(A(1)/V0)
  ; A: volume expansion (V(t) - V0); V(t) and V0 mean plasma volume at any time and at baseline, respectively.

$ERROR
 A1 = A(1)
 TA = A1/V0

 IPRED = TA
 W = 1
 IRES = DV - IPRED
 IWRES = IRES / W
 Y = IPRED + W * EPS(1)

$THETA ; #2
 0.8 FIX ; KB
 (0 200) ; KR
 (0, 3000) ; V0

$OMEGA ; #2
 0 FIX ; IIV_KB
 0.3 ; IIV_KR
```


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 0.3 ; IIV_V0

$SIGMA ; #1
 0.01

$ESTIMATION MAXEVAL = 9999 SIGL = 6 NSIG = 2 PRINT = 5 METHOD = 1 INTER NOABORT MSFO = 100.MSF
$COVARIANCE PRINT = E

< Two-volume model >
$PROB RUN# 200 (Two-volume kinetic model)
$INPUT ID OID TIME DUR RATE AMT DV MDV EVENT HB HCT SEX AGE WT HT BSA LBM IBW BMI CO CI SVV SV SVI HR
SBP DBP MBP
; DV (dilution, unitless) = (BHB/HB-1)/(1-BHCT) = (expandable plasma volume - baseline plasma volume)/(baseline plasma volume)
= (V(t) - BV)/BV
$DATA 05_06_NONMEM_data_OID_ID25.csv IGNORE = #
$SUBROUTINE ADVAN13 TRANS = 1 TOL = 6
$MODEL COMP (VOLUME1) COMP (VOLUME2)
$PK
  TH1 = THETA(1)
  TH2 = THETA(2)
  TH3 = THETA(3)
  TH4 = THETA(4)
  TH5 = THETA(5)

  KB = TH1 ; basal elimination rate (ml/min, 0.8 at Anesthesiology 1997; 87: 204-12)
  KR = TH2 ; renal clearance (ml/min)
  VC0 = TH3 ; baseline plasma volume (ml)
  VT0 = TH4 ; baseline interstitial volume (ml)
  KT = TH5 ; distributional clearance (ml/min)

  KB = TH1*EXP(ETA(1))
  KR = TH2*EXP(ETA(2))
  VC0 = TH3*EXP(ETA(3))
  VT0 = TH4*EXP(ETA(4))
  KT = TH5*EXP(ETA(5))

$DES
  DADT(1) = RATE - KB - KR*(A(1)/VC0) - KT*(A(1)/VC0) + KT*(A(2)/VT0)
  DADT(2) = KT*(A(1)/VC0) - KT*(A(2)/VT0)

  ; A1: plsam volume expansion at central compartment (VC(t) - VC0); VC(t) and VC0 mean plasma volume at any time and at baseline,
respectively.
  ; A2: interstitial volume expansion at tissue compartment (VT(t) - VT0); VT(t) and VT0 mean interstitial volume at any time and at
baseline tissue compartment, respectively.

$ERROR
  A1 = A(1)
```

```
A2 = A(2)
TA = A1/VC0
TB = A2/VT0

IPRED = TA
W = 1
IRES = DV - IPRED
IWRES = IRES / W
Y = IPRED + W * EPS(1)

$THETA ; #4
0.8 FIX ; KB
(0, 100) ; KR
(0, 2000) ; VC0
(0, 3000) ; VT0
(0, 100) ; KT

$OMEGA ; #4
0 FIX ; IIV_KB
0.2 ; IIV_KR
0.2 ; IIV_VC0
0.2 ; IIV_VT0
0.2 ; IIV_KT

$SIGMA ; #1
 0.01

$ESTIMATION NOTBT NOOBT NOSBT MAXEVAL=9999 SIGL=6 NSIG=2 PRINT=5 METHOD=1 INTER NOABORT
MSFO=200.MSF
$COVARIANCE PRINT=E
```


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