Appendix 1. The example of NONMEM control file of semi-compartmental model.

```
$PROBLEM PD with Ke0 fit
$DATA
$INPUT
$PRED
   E0 = THETA(1);Baseline
   EMAX = THETA(2);Max Effect
   CE50 = THETA(3)*EXP(ETA(1));C50, only parameter with
                               ;interindividual variability
   GAM = THETA(4); Gamma - don't add an ETA to this - very hard to fit
   KE0 = THETA(5)*EXP(ETA(2)); Ke0

   IF (TIME.EQ.0) THEN
     CE = 0
     PTIME = 0
     PCP = 0
     PCE = 0
   ENDIF

   DT = TIME-PTIME;

   IF (DT.EQ.0) THEN; Fighting with problem of nested if statements
     DT1 = 1
   ELSE
     DT1 = DT
   ENDIF

   IF (CP.GE.PCP) THEN
     SLOPE = (CP-PCP)/DT1
     DELTA = DT1*SLOPE+(KE0*PCP-SLOPE)*(1-EXP(-KE0*DT1))/KE0
   ELSE
     SLOPE = (LOG(CP)-LOG(PCP))/DT1
     DELTA = PCP*KE0/(KE0+SLOPE)*(EXP(DT1*SLOPE)-EXP(-KE0*DT1))
   ENDIF

   IF (DT.GT.0) THEN
     CE = PCE*EXP(-KE0*DT)+DELTA
   ELSE
     CE = PCE
   ENDIF

   ; Full sigmoidal Emax PD model with simple additive error
   Y = E0+(EMAX-E0)*CE**GAM/(CE**GAM+C50**GAM) + EPS(1)

   ; Variables for NONMEM to remember at the next iteration
   PTIME = TIME; Prior Time
   PCP = CP; Prior plasma concentration
   PCE = CE; Prior effect site concentration

$ESTIMATION SIG=3 MAX=2000 PRINT=1 METHOD = 1; FOCE method
```

KSAP