ECP 8506
Clinical Trial Simulations

The Nomenclature of Population Pharmacokinetics

Richard C. Brundage, PharmD, PhD

1

ECP 8506
Simulation Sciences

- Introduce basic concepts and nomenclature of nlme modeling
- The reason why is mrgsolve relies on many of the same concepts, and uses many of the same terms
- Simulations often take off where the model estimation process ends
- With modeling, we start with data and fit a model to the data
- With simulation, we start with the model and generate predictions for model qualification or for what-if scenarios

2

Model = Equation = Function

- A MODEL → equation that produces a family of lines
  - y = mx + b
  - Cp = D/V exp (-kt)
  - E = Emax * C/(EC50 + C)
- PARAMETERS (m, b, k, V, Emax, EC50) impose a unique shape

3

To start…
…we'll make it simple

- Consider the model for a straight line

4

y = mx+b

5

How Does This All Work?

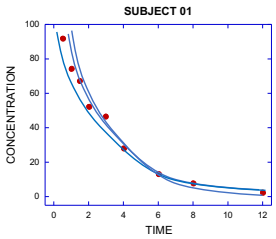
- We start with data
  - From an EXPERIMENT
- Then we need a model that plausibly goes through the data
  - Up to the modeling scientist, guided by EXPERIENCE
  - (and there a lot of models to choose from)
- Then we need parameters for that model to specify a particular shape to best fit the model predictions to observed data
  - We most often turn parameter estimation over to ELECTRONS in a computer program
  - (and there are a lot of them to choose from)

6

We start with data

Then we propose a MODEL that might reasonably predict the data

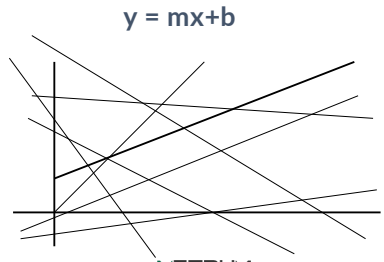
Then we need to think about which parameters to choose to match the data



Confidential

METRUM RESEARCH GROUP

7



Confidential

METRUM RESEARCH GROUP

8

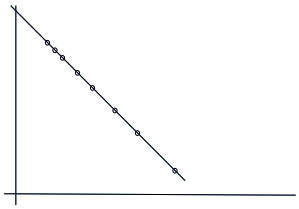
Getting Parameters

- Model
- Parameters
- What does it mean to have a line go through the data?

Confidential

METRUM RESEARCH GROUP

9



Confidential

METRUM RESEARCH GROUP

10

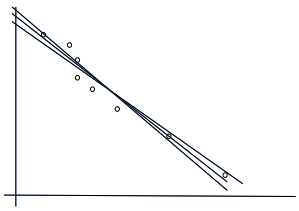
Getting Parameters

- Model
- Parameters
- What does it mean to have a line go through the data?
- Make the line go as close to as many of the data points as possible

Confidential

METRUM RESEARCH GROUP

11

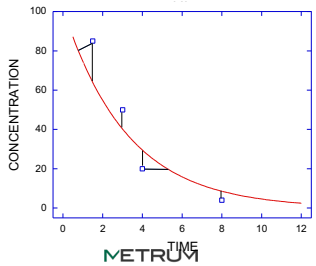


Confidential

METRUM RESEARCH GROUP

12

Now time to get more quantitative

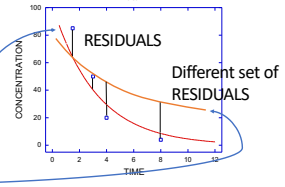


13

What you need

- Observed data
- Model
  Cp=D/V exp$^{(-Kt)}$
- Model parameters
  V=48L
  K=0.412 hr^{-1}

Predicted data
V=42L
K=0.356 hr^{-1}



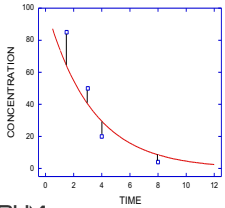
14

Nonlinear Regression
Time to get more mathematical

$$\begin{aligned}&(\text{Cobs} - \text{Cpred})\\ &\sum(\text{Cobs} - \text{Cpred})\\ &\sum(\text{Cobs} - \text{Cpred})\,2\\ \text{SSQ} = &\sum(\text{Cobs} - \text{Cpred})\,2\end{aligned}$$

where

Cobs are the data
Cpred = D/V * exp$^{(-kt)}$
D is dose
t is time
k is a first-order rate constant
V is volume of distribution



15

Nonlinear Regression Algorithm

1. You must give initial starting values for each parameter in your model
2. Computer calculates the SSQ
3. Search for another parameter set (i.e., new pair of CL, V)
4. Compute new SSQ
5. If new SSQ is lower; loop back to 3, or
6. Stop when a lower SSQ cannot be found

16

Terms from estimation you need for Simulation

- Model
- Parameters
- Observed data
- Predicted data (i.e., simulated under the model)
- Residuals

17

Objective Function Value

$$OFV_{ols} = \sum_{j} (C_{ij,obs} - C_{ij,pred})^2$$

where

in individual i, at time j

$$C_{ij,pred} = \frac{D_i}{V_i} \exp^{(-CL/V_i \times t_{ij})}$$

18

Analytical Variability

- With most analytical systems, the noise of the response increases in proportion to the signal
- Constant S/N ratio
- Constant Coefficient of Variation (CV)

  CV = SD/mean
- Analytical variability is usually 5-10%; acceptable up to 20% (FDA)

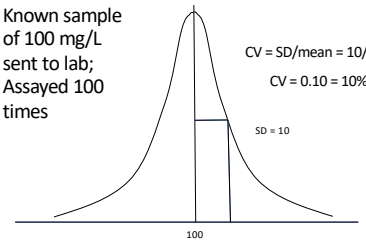
Confidential METRUM RESEARCH GROUP

19

Known sample of 100 mg/L sent to lab; Assayed 100 times

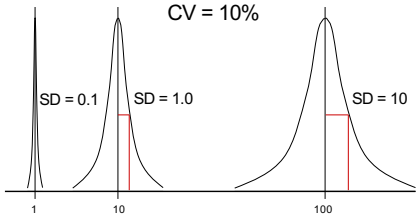
CV = SD/mean = 10/100

CV = 0.10 = 10%



Confidential METRUM RESEARCH GROUP

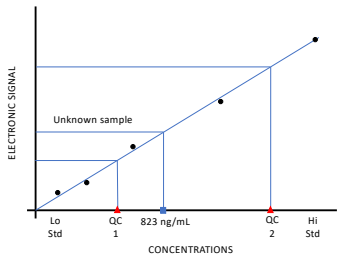
20



Confidential METRUM RESEARCH GROUP

21

22



Confidential METRUM RESEARCH GROUP

22

23

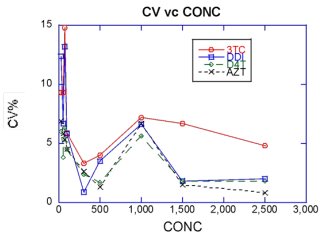
ZIDOVUDINE
QCs

Sample	75	300	1500
1	75.3	306	1567
2	78.2	299	1553
3	72.6	305	1532
4	69.1	302	1525
5	69.4	287	1510
mean	72.9	300	1537
SD	3.89	7.66	22.66
CV%	**5.30%**	**2.60%**	**1.50%**

Confidential METRUM RESEARCH GROUP

23

24



Confidential METRUM RESEARCH GROUP

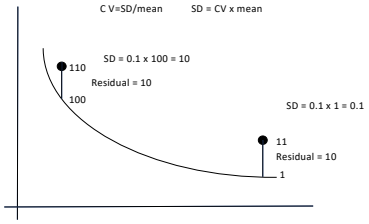
24

So why is all this important?

- An assumption of nonlinear regression is that the variance at all observations is equal
- Homoschedasticity
- Clearly not what we have in PK systems

25

Heteroscedasticity



26

Objective Function Value (WLS)

$$OFV_{WLS} = \sum_{j} \frac{(C_{ij,obs} - C_{ij,pred})^2}{W_{ij}}$$

Residuals (RES) are now Weighted Residuals (WRES)

where

in individual i, at time j

$$C_{ij,pred} = \frac{D_i}{V_i} \exp^{(-CL_i/V_i \times t_{ij})}$$

$$W_{ij} = \text{weight} = \text{variance} = SD^2 = (CV \times Cp)^2$$

27

Terms from estimation you need for Simulation

- Model
- Parameters
- Observed data
- Predicted data (i.e., simulated under the model)
- Residuals
- Weighted residuals (WRES)

28

NLME Population Pharmacokinetics

- Experimental unit is the population, not the individual
- The PK parameters of interest are POPULATION means and variances, not those in any individual subject
- Pool ALL data from ALL subjects and analyze them simultaneously

29

PopPK Modeling four models

- PK model
- Covariate model
- Between subject variability (BSV)
  - Interindividual variability
- Residual unexplained variability (RUV)
  - Intraindividual variability

ALL FOUR MODELS ALSO APPLY TO SIMULATION

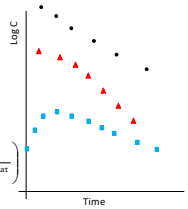
30

PK Model

$Cp = D/V \exp^{-kt}$

Rate of elim=Vmax x C / (Km + C)

$$Cp = \frac{F \times D \times Ka}{V \times (Ka - K)} \times \left(\frac{\exp^{-Kt}}{1 - \exp^{-Kt}} - \frac{\exp^{-Kat}}{1 - \exp^{-Kat}} \right)$$



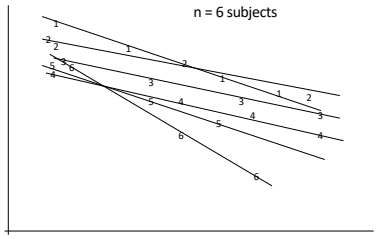
31

Covariate Model

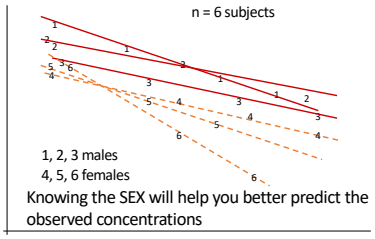
- Covariates help us understand what patient-specific characteristics are important determinants of PK parameters
- The covariate model specifies a mathematical relationship between a PK parameter and the covariate *(fixed effects)*
- usually requires the addition of another parameter in the model

32

Categorical Covariates



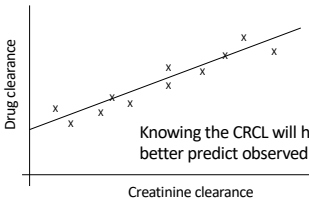
33



Knowing the SEX will help you better predict the observed concentrations

34

Continuous Covariates



Knowing the CRCL will help you better predict observed concentrations

35

NONMEM "Typical Value" notation

- TVCL, TVV, TVEmax, TVEC50
- Typical values of PK/PD parameters in the population
- Population-level values (not individual values)
- Think about it like a population average

36

Regression Parameters

- THETAs are the labels used for the regression parameters
- y = mx + b

y = THETA(1) * x + THETA(2)

- USING NONMEM TV notation

TVslope = THETA(1)
TVintercept = THETA(2)
y = TVslope * x + TVintercept

Confidential METRUM RESEARCH GROUP

37

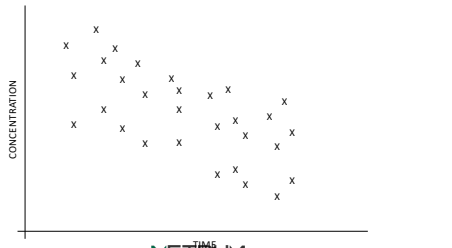
NONMEM Typical Value notation

- PK parameters vs. Regression parameters
- PK/PD models can get complex, and each "PK parameter" might have multiple regression parameters

TVCL = THETA(1) + THETA(2)*CLCR
TVV = THETA(3) if male, or
TVV =THETA(4) if female

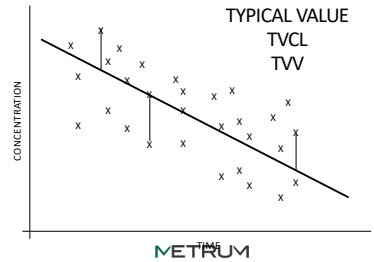
Confidential METRUM RESEARCH GROUP

38



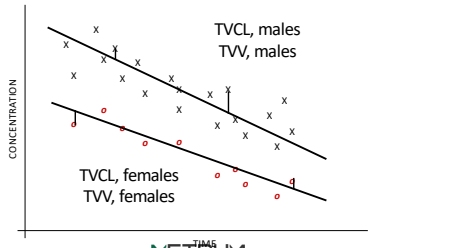
Confidential METRUM RESEARCH GROUP

39



Confidential METRUM RESEARCH GROUP

40



Confidential METRUM RESEARCH GROUP

41

Categorical Covariates

- Often modeled as a fractional multiplier

TVCL = THETA(1)
IF (SEX.EQ.0) TVCL = TVCL * THETA(2)

- THETA(1) is the TVCL for males
- THETA(2) is the fraction by which the male TVCL is multiplied to get the female TVCL
- THETA(1)=4.0; THETA(2)=0.75
- TVCLmale = 4.0; TVCLfemale = 4.0 x 0.75 = 3.0

Confidential METRUM RESEARCH GROUP

42

Continuous Covariates

- TVCL = THETA(1)*(WT/70)**THETA(2)
  - Allows a bend in the relationship
  - Usually a more stable parameterization
  - THETA(1) is the TVCL for a standard 70kg subject
  - THETA(2) ~ 0 ➔ no relationship with WT
  - THETA(2) ~ 1 ➔ CL proportional with WT
- You might choose the denominator as a reference value
- Often chosen as the median, or the mean of the covariate

43

Terms from estimation you need for Simulation

- Model
- Parameters
- Observed data
- Predicted data (i.e., simulated under the model)
- Residuals
- Weighted residuals
- Typical Value notation (TVCL, TVV, etc.)
- Fixed effects
- Covariate models

44

Limitation to Fixed-effects

- Not all 32 yo, 6'4", 84 kg, *1*3 males with a CRCL of 93 mL/min will have the same actual CL that is being predicted by the regression equation
- PopPK is interested in means and variances
- How can we formalize the notion that not everyone is at the mean?

RANDOM EFFECTS

45

More NONMEMese

- ETA (η)
- The difference between an individual's true parameter (e.g., CLi) and that predicted by the regression equation (TVCLi)

  e.g., TVCLi = THETA(1)*WTi

  CLi = TVCLi + ETAi

46

Between Subject Variability (BSV) Model

- TVCL = THETA(1) + THETA(2)*WT + …

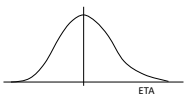
  CL = TVCL + ETA(1)
- An individual may have a CL different from the TV, even AFTER that TVCL has been adjusted for WT, SEX, RACE, AGE, etc.
- Similar for V, etc.

  V = TVV + ETA(2)

47

Random Variable

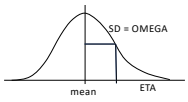
- Not really interested in individual ETAs
- We really want the variance of the distribution of ETAs



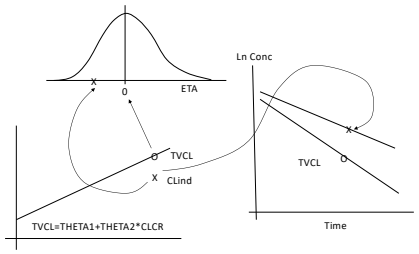
48

Random Variable

- ETAs are a RANDOM variable because they are defined ONLY as a distribution with a mean and estimable variance (OMEGA^2)
- The variance of the ETAs relates directly to the variance of the PK parameter



49



50

BSV: Additive Model CL = TVCL + ETA(1)

- In this additive model, the SD of the ETAs (OMEGA) is the SD of the parameter in the population
- OMEGA(1)^2 = 16
  SD of CL is 4.0

51

BSV Model

- However, biological parameters are often right (positively) skewed because they are bounded by zero at the low end
- Better approximated using a log normal distribution
- Normal distribution in the log world

52

BSV: Exponential Model CL = TVCL * EXP(ETA(1))

log CL = log TVCL + ETA(1)

- In this exponential model, OMEGA is the variability expressed as the CV in the population
- If OMEGA(1)^2 = 0.09
  CV of CL is 30% (SQRT 0.09 = 0.30)

53

Terms from estimation you need for Simulation

- Model
- Parameters
- Observed data
- Predicted data
- Residuals
- Weighted residuals
- Typical Value notation
- Fixed effects
- Covariate models
- Random effects
- BSV/IIV
- ETA
- Omega

54

Residual Unexplained Variability (RUV) Model

- Even after you get the right PK model
- and even after you take into account all the covariates that are predictive,
- and even after you allow BSV to account for differences in PK parameters
- You still cannot perfectly predict most concentrations

55

Sources of RUV

- Analytical errors
- Model misspecification
- Errors in recording time of dose
- Errors in recording time of blood draws
- Compliance issues
- Content uniformity of dosage forms

56

More NONMEMese

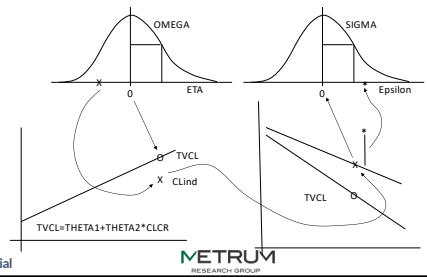
- Epsilon (ε)
- The difference between the observed concentration and the concentration predicted by the model
- Cobs = Cpred + ε

57

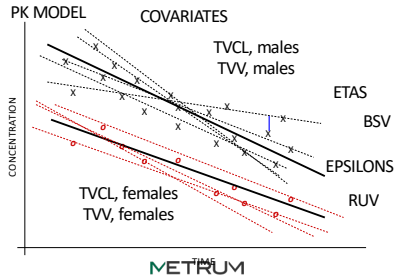
RUV

- We don't have an interest in any particular difference, only the collection of them
- Epsilon is another RANDOM variable
- Defined by a mean and a variance ($SIGMA^2$)
- The estimated variance of the Epsilons is an estimate of how much variability remains in the system after you take into account the PK, covariate, and BSV models

58



59



60

RUV: Additive Error Model

$$Y = F + EPS(1)$$

- Observation
- Prediction
- Error

Confidential METRUM RESEARCH GROUP

62

RUV: Additive Error Model

$$Y = F + EPS(1)$$

- Constant SD across all concentrations
- SD of the epsilons (SIGMA) is the SD of the residual unexplained errors
- $SIGMA^2 = 5.29$
- SD RUV = +/- 2.3 mg/L
- May be appropriate with concentrations over a limited range, such as TDM data

Confidential METRUM RESEARCH GROUP

63

RUV: Proportional Error Model

$$Y = F + F*EPS(1)$$

- Observation
- Prediction
- Error

Confidential METRUM RESEARCH GROUP

64

RUV: Proportional Error Model

$$Y = F + F*EPS(1)$$

- Constant CV model
- The SD of the epsilons (SIGMA) is the CV of the RUV
- $SIGMA^2 = 0.0234$
- CV% RUV = 15.3%
- Absolute error is usually smaller at lower concentrations, increases with observation

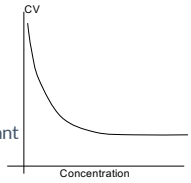
Confidential METRUM RESEARCH GROUP

65

Combined Error Model

$$Y = F + F*EPS(1) + EPS(2)$$

- Proportional component
- Additive component
- At low Cp, F*EPS(1) is insignificant and EPS(2) dominates
- At high Cp, EPS(2) is insignificant and F*EPS(1) dominates
- CV decreases and plateaus



Confidential METRUM RESEARCH GROUP

66

Terms from estimation you need for Simulation

- Model
- Parameters
- Observed data
- Predicted data
- Residuals
- Weighted residuals
- Typical Value notation
- Fixed effects
- Covariate models
- Random effects
- BSV/IIV
- ETA
- Omega
- RUV
- Epsilon
- Sigma

Confidential METRUM RESEARCH GROUP 67

67

PRED vs. IPRED

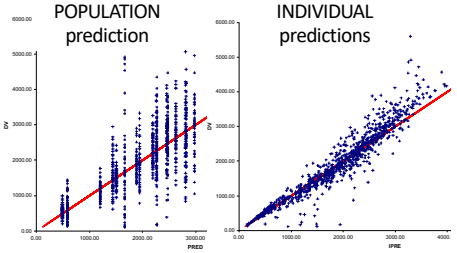
- **PRED** is the prediction based on the population-based (TV) regression equations
  TVCL = THETA(1)+THETA(2)*WT+.....
- All the ETAs are set to zero
  C_{pred} = D/TVV * exp[-(TVCL/TVV)*t]
- **IPRED** is the prediction based on CL_i, not $TVCL_i$, with individual ETAs calculated
  $CL_i = TVCL_i + ETA(1)$ $V_i = TVV_i + ETA(2)$
  C_{ipred} = D/V_i * exp[-(CL_i/V_i)*t]

Confidential METRUM RESEARCH GROUP

68

PRED is based on POPULATION prediction

IPREDs are from INDIVIDUAL predictions



Confidential METRUM RESEARCH GROUP

69

WRES vs CWRES

- **WRES** are calculated using the **PRED**, and then weighted
- It's a historical definition
- **CWRES** are calculated with the RES based on **IPREDs**, and then weighted
- You will usually see CWRES in plots rather than WRES

Confidential METRUM RESEARCH GROUP

70

```
;; 1. Based on: 001
;; 2. Description: 1-comp iv, linear elim
;; 3. Label:
;; x1. Author:

$PROBLEM PK

$INPUT C ID TIME DV AMT CMT MDV EVID WT CRCL AGE SEX CENT

$DATA demo.csv IGNORE=@

$SUBROUTINES ADVAN1 TRANS2

$PK
  CL = THETA(1) * EXP(ETA(1))
  V  = THETA(2) * EXP(ETA(2))
  S1 = V

$ERROR
IPRED = F
   W = F
   Y = IPRED + F*EPS(1) + EPS(2)
IRES = DV-IPRED
IWRES = IRES/W
```

Confidential METRUM RESEARCH GROUP

71

```
$THETA
  (0, 10)  ; CL
  (0, 100)  ; V

$OMEGA
  (0.1) ; IIV CL
  (0.1) ; IIV V1

$SIGMA
  0.01 ; PROP
  1    ; ADD

$EST METHOD=1 INTER MAXEVAL=2000 SIG=3 PRINT=1
$COV

; Xpose
$TABLE ID TIME DV MDV EVID IPRED IWRES CWRES ONEHEADER NOPRINT
FILE=sdtab001.tab
$TABLE CL V ONEHEADER NOPRINT FIRSTONLY FILE=patab001.tab
```

Confidential METRUM RESEARCH GROUP

72

NONMEM DATASETS
Rules and Structure

- Numbers only
- NO alpha characters
- No symbols

Confidential METRUM RESEARCH GROUP

73

NONMEM DATASETS
Rules and Structure

- EVENT RECORD: Each row of the data set
- Only one type of event can occur per record
  - AMT event (dose)
  - DV (observation) event
  - OTHER type occasionally used (e.g., covariate changes)
- Each AMT and DV (drug conc, metabolite conc, or PD effect) must EACH be on different rows
- EVEN IF AT THE SAME TIME!!!

74

NONMEM DATASETS
Rules and Structure

- All records from an individual MUST be contiguous
- Within each individual, all records must be in time order
  - But there is a way to reset the system back to TIME=0
  - Handy for multiple doses

75

Example Data Records

C	ID	TIME	DV	AMT	WT	AGE	CRCL	SMK	SEX
	1	0	0	500	58.4	51	4.49	1	1
	1	1	1.67	0	58.4	51	4.49	1	1
	1	4	2.79	0	58.4	51	4.49	1	1
	1	10	0.58	0	58.4	51	4.49	1	1
	1	24	0.14	0	58.4	51	4.49	1	1
	2	0	0	500	79.3	53	5.05	0	1
	2	1	1.32	0	79.3	53	5.05	0	1

76

IGNORE=@ IGNORE=C in $DATA

C	ID	TIME	DV	AMT	WT	AGE	CRCL	SMK	SEX
	1	0	0	500	58.4	51	4.49	1	1
	1	1	1.67	0	58.4	51	4.49	1	1
	1	4	2.79	0	58.4	51	4.49	1	1
	1	10	0.58	0	58.4	51	4.49	1	1
	1	24	0.14	0	58.4	51	4.49	1	1
	2	0	0	500	79.3	53	5.05	0	1
	2	1	1.32	0	79.3	53	5.05	0	1

77

An ID column is required for NONMEM

C	ID	TIME	DV	AMT	WT	AGE	CRCL	SMK	SEX
C		hr	mg/L	mg	kg	yr	L.hr	1=Y	1=M
	1	0	0	500	58.4	51	4.49	1	1
	1	1	1.67	0	58.4	51	4.49	1	1
	1	4	2.79	0	58.4	51	4.49	1	1
	1	10	0.58	0	58.4	51	4.49	1	1
	1	24	0.14	0	58.4	51	4.49	1	1
	2	0	0	500	79.3	53	5.05	0	1
	2	1	1.32	0	79.3	53	5.05	0	1

78

DV column is required for NONMEM

C	ID	TIME	DV	AMT	WT	AGE	CRCL	SMK	SEX
C		hr	mg/L	mg	kg	yr	L.hr	1=Y	1=M
	1	0	0	500	58.4	51	4.49	1	1
	1	1	1.67	0	58.4	51	4.49	1	1
	1	4	2.79	0	58.4	51	4.49	1	1
	1	10	0.58	0	58.4	51	4.49	1	1
	1	24	0.14	0	58.4	51	4.49	1	1
	2	0	.	500	79.3	53	5.05	0	1
	2	1	1.32	0	79.3	53	5.05	0	1

79

TIME column is required

C	ID	TIME	DV	AMT	WT	AGE	CRCL	SMK	SEX
C		hr	mg/L	mg	kg	yr	L.hr	1=Y	1=M
	1	0	0	500	58.4	51	4.49	1	1
	1	1	1.67	0	58.4	51	4.49	1	1
	1	4	2.79	0	58.4	51	4.49	1	1
	1	10	0.58	0	58.4	51	4.49	1	1
	1	24	0.14	0	58.4	51	4.49	1	1
	2	0	0	500	79.3	53	5.05	0	1
	2	1	1.32	0	79.3	53	5.05	0	1

Confidential METRUM RESEARCH GROUP

80

AMT column is required

C	ID	TIME	DV	AMT	WT	AGE	CRCL	SMK	SEX
C		hr	mg/L	mg	kg	yr	L.hr	1=Y	1=M
	1	0	0	500	58.4	51	4.49	1	1
	1	1	1.67	.	58.4	51	4.49	1	1
	1	4	2.79	.	58.4	51	4.49	1	1
	1	10	0.58	.	58.4	51	4.49	1	1
	1	24	0.14	.	58.4	51	4.49	1	1
	2	0	0	500	79.3	53	5.05	0	1
	2	1	1.32	0	79.3	53	5.05	0	1

$INPUT … DOSE=AMT …

Confidential METRUM RESEARCH GROUP

81

MUST be sequenced in TIME order

C	ID	TIME	DV	AMT	WT	AGE	CRCL	SMK	SEX
C		hr	mg/L	mg	kg	yr	L.hr	1=Y	1=M
	1	0	0	500	58.4	51	4.49	1	1
	1	1	1.67	0	58.4	51	4.49	1	1
	1	4	2.79	0	58.4	51	4.49	1	1
	1	10	0.58	0	58.4	51	4.49	1	1
	1	24	0.14	0	58.4	51	4.49	1	1
	2	0	0	500	79.3	53	5.05	0	1
	2	1	1.32	0	79.3	53	5.05	0	1

NMTRAM is going to check to make sure DV and AMT are not BOTH positive

Confidential METRUM RESEARCH GROUP

82

No covariates are required for NONMEM

C	ID	TIME	DV	AMT	WT	AGE	CRCL	SMK	SEX
C		hr	mg/L	mg	kg	yr	L.hr	1=Y	1=M
	1	0	0	500	58.4	51	4.49	1	1
	1	1	1.67	0	58.4	51	4.49	1	1
	1	4	2.79	0	58.4	51	4.49	1	1
	1	10	0.58	0	58.4	51	4.49	1	1
	1	24	0.14	0	58.4	51	4.49	1	1
	2	0	0	500	79.3	53	5.05	0	1
	2	1	1.32	0	79.3	53	5.05	0	1

As such, NO rule to use WT, WGT, SIZE, TBW, IBW etc.

Confidential METRUM RESEARCH GROUP

83

RATE column is recognized by PREDPP

C	ID	TIME	DV	AMT	RATE	AGE	CRCL	SMK	SEX
C		hr	mg/L	mg	mg/hr	yr	L.hr	1=Y	1=M
	1	0	0	500	500	51	4.49	1	1
	1	1	1.67	0	.	51	4.49	1	1
	1	4	2.79	0	.	51	4.49	1	1
	1	10	0.58	0	.	51	4.49	1	1
	1	24	0.14	0	.	51	4.49	1	1
	2	0	0	500	1000	53	5.05	0	1
	2	1	1.32	0	.	53	5.05	0	1

Confidential METRUM RESEARCH GROUP

84

C	ID	TIME	DV	AMT	WT	AGE	CRCL	SMK	SEX
C		hr	mg/L	mg	kg	yr	L/hr	1=Y	1=M
	1	0	.	500	58.4	51	4.49	1	1
	1	1	96	.	58.4	51	4.49	1	1
	1	12	55	.	58.4	51	4.49	1	1
	1	12	.	250	58.4	51	4.49	1	1
	1	24	9.3	.	57.1	51	4.49	1	1
	1	24	.	250	57.1	51	4.49	1	1
	1	48	5.1	.	57.5	51	5.05	1	1

Confidential METRUM RESEARCH GROUP

85

Multiple doses can be administered

Or give implicit doses using two new PREDPP-defined data items
ADDL item with Interdose Interval (II) item

C	ID	TIME	DV	AMT	ADDL	II	WT
	1	0	.	500	5	24	58.4
	1	132	67	.	.	.	57.1

ADDL will give 5 ADDITIONAL doses identical to the one on this record, given at the interval indicated on II.

NMTRAN keeps track of the elapsed time.

nb: May or may not be at SS by 132 hours

Confidential METRUM RESEARCH GROUP

86

C	ID	TIME	DV	AMT	SS	II	WT	AGE
C		hr	mg/L	mg			kg	yr
	1	0	.	500	.	.	58.4	51
	1	2	96	.	.	.	58.4	51
	1	12	55	.	.	.	58.4	51
	2	0	.	500	1	24	57.1	51
	2	0	34	.	.	.	57.1	51
	2	2	143	.	.	.	57.1	51
	2	12	67	.	.	.	57.1	51
	2	26	.	.	.	.	57.1	51

500mg has been given every 24h for a gazillion dose

BUT… 500mg at time=0 is the last dose given (without additional dosing recs)

Confidential METRUM RESEARCH GROUP

87

MDV

- Missing Dependent Variable
  - 1 = DV missing (i.e., usually a dose event)
  - 0 = DV not missing (i.e., an Observation record)
- Required by NONMEM
- NMTRAN will append this column in FDATA if you don't provide it

Confidential METRUM RESEARCH GROUP

88

EVID

- Event ID
  - 0 = observation event
  - 1 = dosing record
  - 2 = other record
  - 3 = resets time and zeroes out compartments
  - 4 = resets time and compartments, AND gives another dose, using the same event record
- Required by PREDPP
- NMTRAN will append it to FDATA

Confidential METRUM RESEARCH GROUP

89

EVID=4 zeroes out ALL compartments; resets TIME; AND…

C	ID	TIME	DV	AMT	SS	II	EVID	MDV	WT
C		hr	mg/L	mg					
	1	0	.	500	.	.	1	1	77
	1	1	96	.	.	.	0	0	77
	1	12	55	.	.	.	0	0	77
	1	0	.	500	1	24	4	1	81
	1	24	34	.	.	.	0	0	81
	1	24	.	1000	1	24	4	1	89
	1	36	67	.	.	.	0	0	89

AND gives the DOSE specified on the record

Confidential METRUM RESEARCH GROUP

90

This last dose could be months later

C	ID	TIME	DV	AMT	SS	II	EVID	MDV	WT
C		hr	mg/L	mg					
	1	0	.	500	.	.	1	1	77
	1	1	96	.	.	.	0	0	77
	1	12	55	.	.	.	0	0	77
	1	0	.	500	1	24	4	1	81
	1	24	34	.	.	.	0	0	81
	1	24	.	1000	1	24	4	1	89
	1	36	67	.	.	.	0	0	89

EVID=4 zeroes out ALL compartments; resets TIME=0 or TIME=24 (or whatever); AND with SS=1, puts the system at a NEW steady state

Confidential METRUM RESEARCH GROUP

91

Confidential

METRUM
RESEARCH GROUP

92