# Development of a population PK model using NONMEM® - Case Study II

## Multiple oral dose

# TABLE OF CONTENTS

## Creating a data file

The comma delimited data file consists of data obtained from 100 individuals who were administered 500 mg dose orally. A sample NONMEM data file for this study looks the following:

```
C          Multiple dose oral study
C          No.of subjects = 100,  Dose = 500mg tid for 5 days
C          II - drug dosing every 8 hrs, ADDL = 14 more doses to be administered
C          CONC = plasma concentrations in ug/ml, TIME in hrs
CID        TIME        CONC        AMT      ADDL     II          MDV
      1          0           0         500          14           8           1
      1         0.5      4.5799           0           0           0           0
      1           1      8.5717           0           0           0           0
      1           3      10.979           0           0           0           0
      1           4      11.347           0           0           0           0
      1           6      8.7705           0           0           0           0
      1           8      7.0155           0           0           0           0
      1         8.5      10.889           0           0           0           0
      1          16      9.7015           0           0           0           0
      1        16.5      14.115           0           0           0           0
      1          24      10.809           0           0           0           0
      1        24.5      14.217           0           0           0           0
      1          32      11.412           0           0           0           0
      1        32.5      16.441           0           0           0           0
      1          40      11.038           0           0           0           0
      1        40.5      16.612           0           0           0           0
```

*Explanation of the data file columns*

| Column name | Description | Required or optional |
|---|---|---|
| ID | subject identification number. It is written as CID, where C = default NONMEM recognized symbol for ignoring any data from data file. | Required item |
| TIME | Blood sampling time. Should be chronologically arranged. | Required |
| CONC = DV | Plasma concentration in this case, could be any dependant variable i.e., biomarker concentration or tissue concentration | Required |
| AMT | Dose administered at dosing time or zero for observation records | Required |
| ADDL | Additional identical doses given (ex: if dose administered for 5 days, at 3 three times a day, ADDL will be 14) | Additional, if required |
| II | Interdose interval (ex: Dosing every 8 hrs) | Additional, if required |
| MDV | Missing dependant variable, takes value as 1, when observation is missing, otherwise zero. | Optional |

The data file created is stored as .csv file in any working directory for the project or in the same folder as the control stream.

Click here for link to the data file

## Control stream for the PK model

The control stream (with explanations) for the structural PK model, which is chosen as a two-compartment oral absorption model based on preliminary data analysis, is given below. Analysis in NONMEM® was performed by using a first order (FO) estimation method. Results from other estimation methods namely, first order conditional estimation (FOCE) and FOCE with interaction are also provided in the end for comparison.

Click here for the control stream. (Download the control stream, copy the contents in Notepad and save it in the working directory with a .ctl extension)

## Performing the NONMEM run

- NONMEM execution was done using Wings for NONMEM (WFN) developed by Dr.Nick Holford, available at http://wfn.sourceforge.net/ WFN is a set of DOS batch command files and awk scripts. The various features of WFN are described at the above mentioned website.
- Click the command prompt icon configured for WFN (This could be done when installing WFN) and open the working directory (The path could also be stored).
    - When using WFN, Type nmgo XXXX (The name of the control stream, No need to type the .ctl extension) to perform the NONMEM run.

## Viewing and interpreting the output file

- When each control stream is run, an output folder is created in the same working directory from where the NONMEM run was performed.

- In the output folder, there is a summary file with a ***.smr*** extension, a detailed output file with ***.lst*** extension and the table output in a ***.fit*** extension.

The output from the ***.smr*** file is explained and interpreted.
Diagnostic plots are created using the table output with a ***.fit*** extension

## FINAL PARAMETER ESTIMATE

THETA: POPCL POPV2 POPQ POPV3 POPKA
ETA: BSVCL BSVV2 BSVQ BSVV3 BSVKA
ERR: ERRCV ERRSD

cs2_oralestaddl.lst 1309.117 eval=541 sig=+3.2 sub=100 obs=4200

**Objective function value**

**Population PK parameter estimate**

THETA = 1.89 3.54 1.38 12.1 0.229

$POP_{VC}$ = 3.93L $POP_{VP}$ = 12L

**Population BSV estimate on parameters**

ETASD = 0.298831 0.389872 0.193391 0.394968 0.247386

$BSV_{CL}$ = 30% $BSV_{Q}$ = 35% $BSV_{ka}$ = 25%

**Residual variability estimates**

ERRSD = 0.0514782 0.104881

Proportional error = 5.1% Additive error = 0.10ug/ml

## PRECISION (STANDARD ERRORS) OF PARAMETER ESTIMATES

THETA:se% = 3.1 5.5 7.1 4.7 6.6

OMEGA:se% = 15.1 19.3 47.3 23.4 18.0

SIGMA:se% = 4.8 60.4

Diagnostic plots for structural model and interpretation

The first plot to look at would be a plot of concentration (observed (DV), individual predicted (IPRED) and population predicted (PRED)) versus time for all the individuals. A representative plot of few individuals is provided below. This plot would give an overall trend of fitted concentrations. NONMEM obtains IPRED values by the Bayesian POSTHOC option. Using the population mean estimate of parameters (prior) and each individual data (likelihood), NONMEM obtains the individual parameter estimates (posterior). From the individual parameter estimates, individual predicted concentrations (IPRED) are obtained.

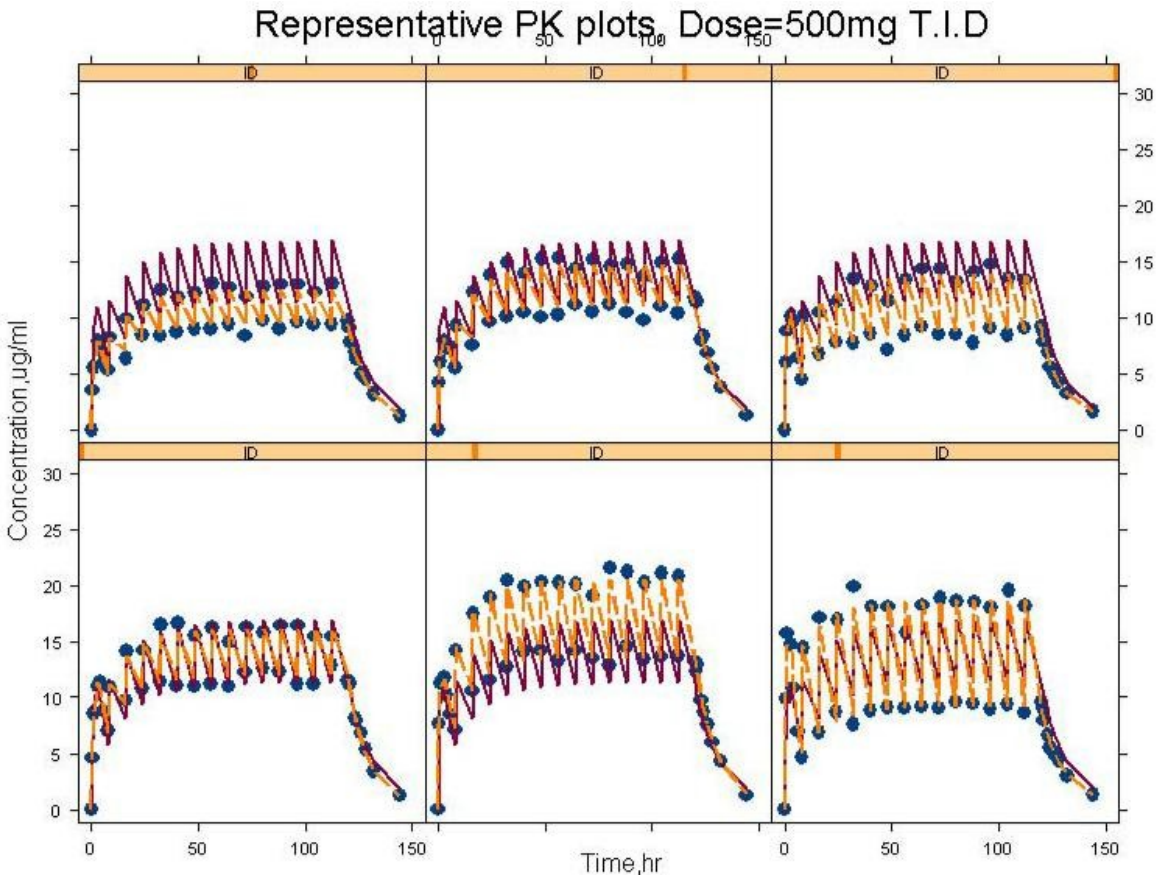

**Figure 1: Plot of observed (•), individual predicted (-----) and population predicted (-----) concentration versus time.**

The second set of diagnostic plots would be the following.

- DV vs IPRED and DV vs PRED: These graphs could be looked for any bias in the predictions. Ideally the points should be uniformly distributed along the line of identity.

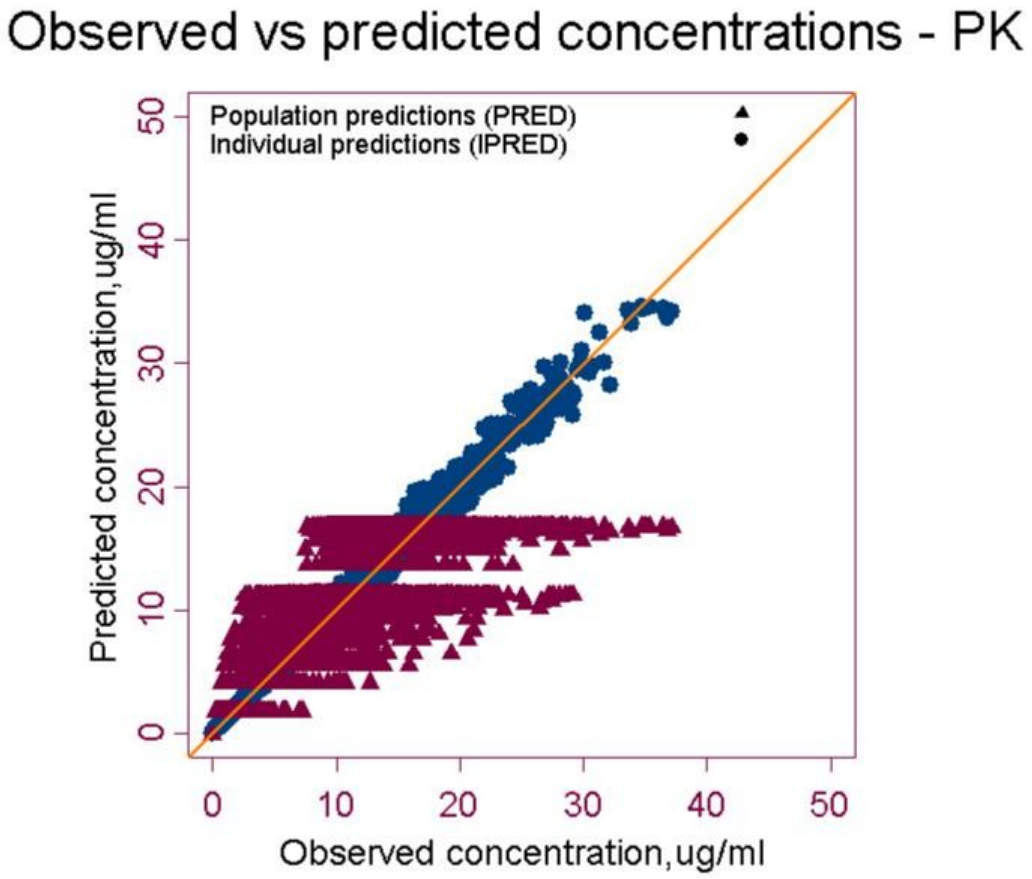


**Figure 2A: Goodness of fit plots (• - Observed vs individual predicted concentration, ▲- Observed vs population predicted)**

- RES vs PRED and WRES vs PRED: Residual plots are looked for any unaccounted heterogenity in the data.

- Note: Though residual plots are some of the goodness of fits plot explored, the utility of these residual plots is not well documented.

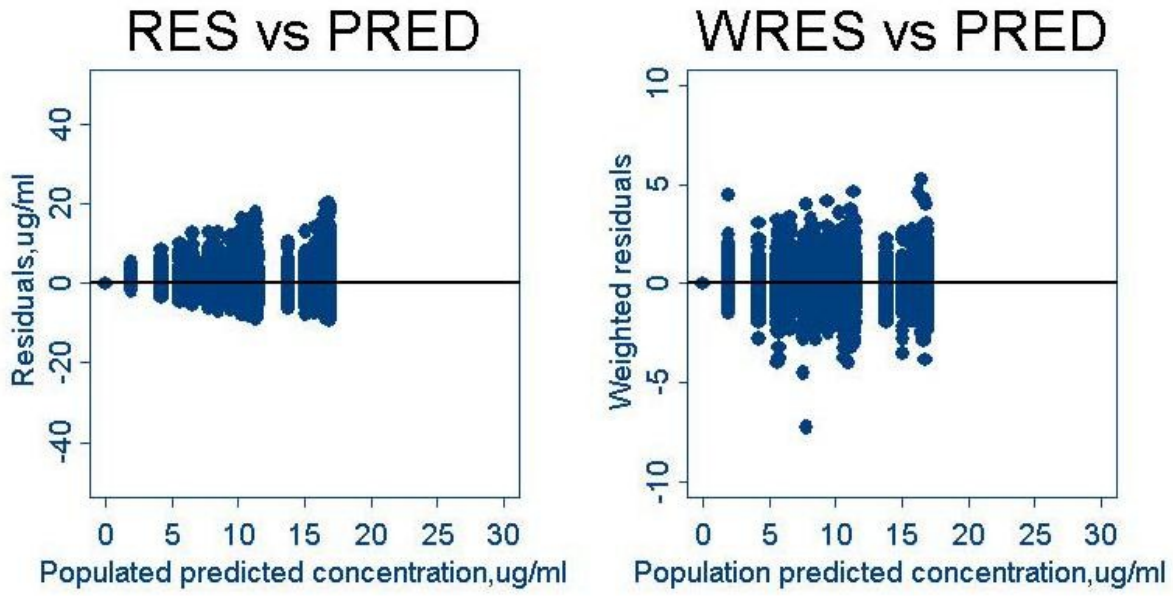


**Figure 2B: Goodness of fit plots (Residuals & Weighted residuals vs Population predicted concentration)**

## Compilation of results

The results obtained could be compiled and documented according to the user's documentation procedure. Following is a way of summarizing the results. The results below are from first order estimation method.

OFV = 1309.21

| **Parameter estimates** | **Population estimate (%SE)** | **Between subject variability (%SE)** |
|---|---|---|
| CL (L/hr) | 1.89 (3) | 30 % (15) |
| Vc (L) | 3.84 (6) | 39 % (19) |
| Q (L/hr) | 1.38 (7) | 19 % (47) |
| ka ($hr^{-1}$) | 0.229 (7) | 25%(18) |
| Vp (L) | 12.1 (5) | 39 % (23) |
| **Residual variability** | | |
| Proportional error | 5.1% (5) | |
| Additive error | 0.10 ug/ml (60) | |

These are the results obtained using FOCE method.

OFV = 1195.91

| Parameter estimates | Population estimate (%SE) | Between subject variability (%SE) |
|---|---|---|
| CL (L/hr) | 1.95 (3.4) | 29% (14.5) |
| Vc (L) | 5.3 (7.4) | 42% (13.3) |
| Q (L/hr) | 1.92 (6.9) | 41% (14) |
| ka ($hr^{-1}$) | 0.32 (7.1) | NE |
| Vp (L) | 10.9 (3.3) | 30% (15.8) |
| **Residual variability** | | |
| Proportional error | 5.4 % (5.2) | |
| Additive error | 0.08 ug/ml (120.2) | |