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Macro library that implements non-compartmental analysis of pharmacokinetics and generates the outputs in CDISC SDTM format

Sujin Seo, OakPil Han, Hanmi Pharma. Co., Ltd.

ABSTRACT

This paper provides a macro library, consisting of multiple macro functions, which conducts PK non-compartmental analysis (NCA) with one command line and gives the result in SDTM format. It describes about key options and criteria for NCA comparing our macro with WinNonlin® or R. The main feature is that PK NCA can be automatically implemented even in the case where the threshold is not met unlike R or WinNonlin®. Besides, the functions calculate all the pharmacokinetic parameters (PP) defined in TESTCD of CDISC SDTM and the output format is compatible with CDISC SDTM. A macro function embedded in the developed library provides summary statistics for each parameter as well.

INTRODUCTION

PK non-compartmental analysis (NCA) contributes to facilitate of drug discovery process. Non-compartmental parameters are required and to submit NCA dataset to FDA, the data format should be compatible with CDISC SDTM which requires specific knowledge on it. Usually, NCA is conducted by commercial software. The developed library is expected to help users of SAS®, predominant software widely used in pharmaceutical industry, carry out PK NCA in SDTM format or utilize the output for validating the results derived from other software.

MACRO LIBRARY

Following macro functions are implemented in SAS® and can accept a set of input arguments that allow for generation of NCA output. The input parameters for each function are explained in below. The macro library has two main functions, PKNCA and CalcStat, which calculates PK parameters for each individual and summarizes the calculated parameters, respectively.

SPKNCA

sPKNCA calculates PK NCA parameters of a single subject. Below functions, AUC, SLOPE, BESTSLOPE, and UNIT, are embedded in sPKNCA. The rules depicted in BestSlope function are as similar as possible to widely used PK analysis software, such as WinNonlin® or R. The one big difference is that the developed SAS® code gives the output even the adjusted R^2 is less than the given threshold, usually 0.9. In WinNonlin® or {NonCompart} package of R, users should manually select the points to be analyzed while our macro will be able to provide automatically the optimal output with the largest adjusted R^2 along with the note of “R2ADJ is less than the threshold. The output is the largest R2ADJ”. Thus, it is expected to reduce human error and time but generate consistent result with the manual work. The required input parameters are listed in the following bullet points with descriptions.

- dsn : Dataset which contains time, dose, and concentration.
- time : Column name for time in the dsn.
- conc : Column name for concentration in the dsn.
- dose : Dose. Default is *0*.
- R2ADJ : Lowest threshold of adjusted R^2. Default is *0.9*.
- adm : Indicates drug administration type. Default is *Extravascular.*

- *Bolus*
- *Extravascular*
- *Infusion*

- timeUnit : Unit of time. Default is *h*.
- concUnit : Unit of concentration. Default is *ng/mL*.
- doseUnit : Unit of dose. Default is *mg*.
- down : Indicates the way to calculate AUC and AUMC. Default is *Linear*.
  - *Linear* : Linear trapezoidal rule
  - *Log* : Linear-up and log-down method
- MW : Molecular weight of drug. Default is *0.*

PKNCA

PK NCA calculates PK NCA parameters of multiple subjects at once. The only difference with sPKNCA is that an input parameter for identifier is added and dsn should contain the variable. The required input parameters are listed in the following bullet points with descriptions.

- dsn : Dataset which contains subject, time, dose, and concentration.
- subject : Column name for identifier in the dsn.
- time : Column name for time in the dsn.
- conc : Column name for concentration in the dsn.
- dose : Dose. Default is *0*.
- R2ADJ : Lowest threshold of adjusted R^2. Default is *0.9*.
- adm : Indicates drug administration type. Default is *Extravascular.*
  - *Bolus*
  - *Extravascular*
  - *Infusion*
- timeUnit : Unit of time. Default is *h*.
- concUnit : Unit of concentration. Default is *ng/mL*.
- doseUnit : Unit of dose. Default is *mg*.
- down : Indicates the way to calculate AUC and AUMC. Default is *Linear*.
  - *Linear* : Linear trapezoidal rule
  - *Log* : Linear-up and log-down method
- MW : Molecular weight of drug. Default is *0.*

CALCSTAT

In general, based on the derived PK NCA parameters of individuals, summary statistics are computed. CalcStat calculates the summary statistics for each variable at once: number of observation, min, max, median, mean, geometrics mean, standard deviation, standard error, coefficient of variance, geometric

coefficient of variance and confidence interval. The required input parameters are listed in the following bullet points with descriptions.

- dsn : Dataset which to be summarized.
- var : Variable names to be summarized in dsn. Multiple variables should be separated by blank.

AUC

AUC calculates AUC and AUMC in two ways; log rule and linear rule. Log rule calculates AUC by sum the linear trapezoidals up to T_{max} and the log trapezoidal after T_{max}, while linear rule sums linear trapezoidal for both of duration. The required input parameters are listed in the following bullet points with descriptions.

- dsn : Dataset with x(independent variable, usually time) and y(dependent variable, usually concentration)
- down : Indicates the way to calculate AUC and AUMC. Default is *Linear*.

  - Linear : Linear trapezoidal rule

  - Log : Linear-up and log-down rule

SLOPE

Slope gives slope calculated via linear regression of given x and y in dsn. This function is used in BestSlope function, which is explained in following section. The required input parameters are listed in the following bullet points with descriptions.

- dsn : Dataset with x(independent variable, usually time) and y(dependent variable, usually log concentration)

BESTSLOPE

BestSlope is for the first order rate constant associated with the terminal portion of the curve. Terminal phase is defined differently depending on the administration type. For Bolus, the terminal portion includes from T_{max} to the last time point but for others, it does not include T_{max}. In addition, minimum of three points is needed to define the terminal portion of the curve.

The function fits linear regression of log concentration versus time repeatedly by excluding one point one by one from T_{max} until at least three points are remained. Among the results, the slope which has the largest adjusted R^2 is chosen as the final output. However, if there are longer slope with the adjusted R^2 within tolerance, i.e. the largest adjusted R^2-tolerance, the longer slope is chosen.

There are three cases where the output is not available.
1. The case where there are less than three points in the terminal portion.
2. The case where all the concentrations are the same except for the 0 concentration.
3. The case where the estimated final slope is positive.

The required input parameters are listed in the following bullet points with descriptions.

- dsn : Dataset with x(independent variable, usually time) and y(dependent variable, usually concentration)
- adm : Indicates drug administration type. Default is *Extravascular.*

  - *Bolus*

  - *Extravascular*

- Infusion

- tol : Tolerance. Default it *1e04*.

UNIT

Unit converts the unit of PK parameters into CDIDSC PP output based on the input units of time, concentration and dose. The required input parameters are listed in the following bullet points with descriptions.

- timeUnit : Unit of time. Default is *h*.
- concUnit : Unit of concentration. Default is *ng/mL*.
- doseUnit : Unit of dose. Default is *mg*.
- MW : Molecular weight of drug. Default is *0*.

EXAMPLE

We used Theoph dataset obtained from R software. The Theoph dataset has 132 observations from 12 subjects.

Prior to the calculations, call macro library.

```
/* Specify the location where the macro library is stored. */
FILENAME PKNCA 'C:\PKNCA\Macro' ;`
OPTIONS MAUTOSOURCE SASAUTOS = PKNCA ;
```

Once all the functions are called, then calculate PK NCA parameters as follows.

```
%PKNCA(dsn = Theoph, subject = Subject, time = Time, conc = conc,
       dose = Dose, adm = Extravascular, doseUnit = mg, timeUnit = h,
       concUnit = mg/mL, down = Linear) ;
```

Once the code is completed, the table named Result and Unit_result would be created in Work folder. The Result table contains the calculated parameters for each subject. The greatest advantage of this function is that the outputs are compatible with those of pharmacokinetic parameter TESTCD of CDISC SDTM. Besides, when you look at the column attributes, you can find the label with its unit. For convenience, the corresponding unit is also listed in a separate table, Unit_result.

The summary statistics can be performed by following example code and the output will be shown as in Fingure 1.

```
%CalcStat(dsn = result, var = CMAX TMAX LAMZ AUCLST)
```

VIEWTABLE: Work.Summary_result

	Parameter	CMAX	TMAX	LAMZ	AUCLST
1	Ntot	12	12	12	12
2	Nunique	12	12	12	12
3	Min	6,44	0,63	0,048457	73,77555
4	Max	11,4	3,55	0,110259	148,923
5	Mean	8,7591666667	1,7883333333	0,0884678333	103,80677083
6	Median	8,465	1,135	0,0880665	95,40665
7	SD	1,4729590399	1,1124079805	0,0163834815	23,645206926
8	SE	0,4252066491	0,3211245235	0,0047295037	6,8257832919
9	CVp	16,816200627	62,203614941	18,519139527	22,778096974
10	CI95l	7,823293142	1,0815430226	0,0780582658	88,783323102
11	CI95u	9,6950401913	2,4951236441	0,0988774008	118,83021856
12	gMean	8,6462167929	1,5151505042	0,0867886183	101,48234461
13	gCVp	16,977760542	64,668107732	21,854342007	22,25384164

Figure 1. Summary Statistics Calculated by "CalcStat"

CONCLUSION

These macro functions can help statisticians performing PK NCA efficiently and conveniently in respect of diverse input parameters and separated functions which could be modified easily. We tried to reduce a burden when implementing PK NCA in one line code, even in the case where the threshold is not met unlike R or WinNonlin®. In addition, conversion of the output format to SDTM is another effort. One does not need to re-name or re-format the output in our macro, so the inconvenience and time consuming of changing variable names would be alleviated. The library is expected to help users of SAS®, predominant software widely used in pharmaceutical industry, carry out PK NCA in SDTM format or utilize the output for validating the results derived from other software.

REFERENCES

Bae, K. S. " NonCompart: Noncompartmental Analysis for Pharmacokinetic." Accessed July 29,2019. https://cran.r-project.org/web/packages/NonCompart/index.html

Certara. "Phoenix WinNonLin." Accessed July 29, 2019. https://www.certara.com/software/pkpd-modeling-and-simulation-2.

Clinical Data Interchange Standards Consortium (CDISC). "Study data Tabulation Model Implementation Guide." Accessed July 29,2019. https://www.cdisc.org/standards/foundational/sdtmig.

R. "The R Project for Statistical Computing." Accessed July 29,2019. https://www.r-project.org.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Sujin Seo
sujin.seo@hanmi.co.kr

OakPil Han
ophan@hammi.co.kr