

SAS-based Method for PK Noncompartmental Analysis and Validation

Hui Mao, BioPier Inc.

Lixin Gao, BioPier Inc.

ABSTRACT

Pharmacokinetics (PK) analysis is an important part of clinical trials that explores drug effects in humans. Noncompartmental analysis (NCA) is a model-independent and cost-effective method as the industry consensus. PK commercial software WinNonlin™ and open-source tools are traditional approaches for such analyses. This paper presents an alternative SAS®-based PK NCA method that derives and validates PK parameters like C_{max} , t_{max} , λ_z , $t_{1/2}$, AUC_{last} , AUC_{inf} , CL , V_z , etc. The key benefit of such a method is to promote operational efficiency and compliance because no intermediate software is needed. It can be directly embedded in the statistical programming to create CDISC SDTM PP datasets, PK summary tables, and figures. The SAS code can be directly used for regulatory submission.

INTRODUCTION

Pharmacokinetics (PK) is a fundamental branch of pharmacology that is concerned with the study of how drugs move through the body. It involves investigating the journey of a drug from its point of administration to its elimination from the body. The processes involved in pharmacokinetics include absorption, distribution, metabolism, and excretion of drugs. The study of pharmacokinetics is essential in the field of medicine, as it provides crucial information about how drugs interact with the body and how they can be used to treat various diseases and conditions.

Pharmacokinetic Noncompartmental Analysis (NCA) is a widely used method for analyzing pharmacokinetic data in clinical trials. NCA is a mathematical approach that allows researchers to quantify drug exposure and evaluate the pharmacokinetic behavior of a drug over time. NCA is particularly useful in clinical trials because it provides a way to evaluate the safety and efficacy of a drug. By analyzing the pharmacokinetic data from a clinical trial, researchers can determine the optimal dosage of a drug, identify any potential safety concerns, and compare the pharmacokinetic profile of the drug to that of other drugs in the same class.

SDTM (Study Data Tabulation Model)¹ and ADaM² (Analysis Data Model) are two commonly used data standards in clinical trials. Both ADaM and SDTM are important components of the FDA's data submission requirements for clinical trials. Our SAS-based NCA method reads in the ADaM.ADPC dataset and outputs the SDTM.PP dataset following the process proposed by Implementation of CDISC ADaM in the Pharmacokinetics Department³. One of the main advantages of using SAS-based PK NCA is that it is a self-contained software, meaning that it does not require other intermediated commercial software to operate. This can significantly reduce costs and streamline the data analysis process. Using SAS-based PK NCA can also promote operational efficiency and compliance. With its streamlined workflows and integrated reporting capabilities, SAS-based PK NCA can help to reduce the time and resources required for data analysis, while also ensuring that results meet regulatory requirements and industry standards. This can help to accelerate the drug development process and improve overall operational efficiency.

WORKFLOW

Our process follows CDISC standards by utilizing compliant terms (Figure 1). Initially, SDTM PC and ADPC are generated, followed by the calculation of PK parameters based on ADPC. Finally, PP and ADPP are created, and PK parameters are calculated using SAS. By following protocol and statistical analysis plan (SAP), programmers can develop SDTM PC/PP and ADaM ADPC/ADPP with specifications, as well as TLFs. This approach enables the programmatic generation of parameters using SAS, thereby reducing the overall review time, and promoting the operational efficiency.

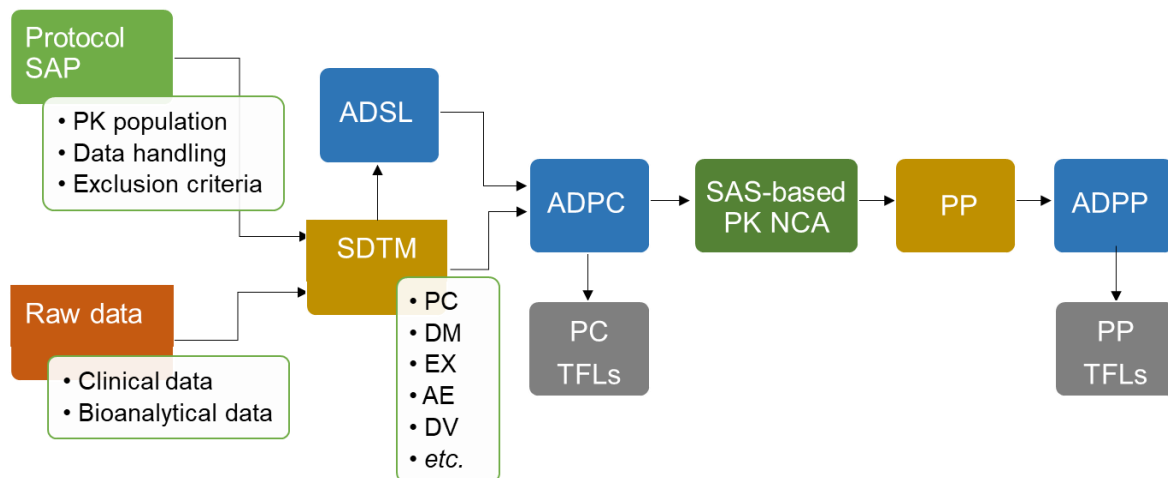


Figure 1. SAS-based PK NCA Process.

SAS-BASED PK NONCOMPARTMENTAL ANALYSIS

The following main features are available in SAS-based PK NCA method: 1) Observed (C_{max} , t_{max} , C_{last} , t_{last}) and derived (λ_z , $t_{1/2}$, AUC_{last} , AUC_{inf} , CL , V_z , *etc.*) PK parameters can be estimated. 2) The terminal elimination rate constant λ_z can be estimated based on the best adjusted R^2 . 3) AUCs can be estimated by linear trapezoidal rule and log-linear trapezoidal rule. 4) Concentrations are supported to be calculated by interpolation. 5) Partial area can be estimated with interpolation method.

OBSERVED PK PARAMETERS

The following PK parameters are observed, which do not need any computation. Sort the data by concentration or time for each subject, these parameters can be obtained.

- C_{max} : The maximum concentration
- t_{max} : The time of the maximum concentration
- C_{last} : The last measurable concentration
- t_{last} : The time of the last measurable concentration

TERMINAL ELIMINATION RATE CONSTANT

This macro calculates elimination rate constant λ_z based on best fitting regression method. This involves fitting a linear regression to the terminal portion of the log-transformed concentration-time curve. The slope of the terminal phase corresponds to the λ_z value. The slope can be obtained by calculating the negative of the regression coefficient (b) from the linear regression equation: $y = a - b \cdot x$, where y is the natural logarithm of the concentration values, x is the time, a is the intercept, and b is the slope. At least three observed values are required. The λ_z value obtained from the best fitted regression with the highest adjusted R^2 is selected. If the difference of adjusted R^2 values among different regressions less than 0.0001, the regression with most observed points is chosen⁴. The parameters $t_{1/2}$, $\lambda_{z \text{ Lower}}$, and $\lambda_{z \text{ upper}}$ which are depended on λ_z are also calculated by this macro `lambdaz`. You just need to specify the input data set with `inds`;

```
%macro lambdaz (inds= );
```

- $t_{1/2}$: The terminal elimination half-life. Calculated as follows: $t_{1/2} = \ln(2) / \lambda_z$
- $\lambda_{z \text{ Lower}}$: The lower limit on time for values to be included in the calculation of λ_z
- $\lambda_{z \text{ upper}}$: The upper limit on time for values to be included in the calculation of λ_z

AREA UNDER CURVE

Area under curve (AUC) is the region enclosed by the concentration versus time curve. To calculate this area, two methods are typically employed: the linear trapezoidal rule and the log-linear trapezoidal rule⁵. Both methods involve dividing the region into trapezoids and computing the sum of their individual areas. The linear trapezoidal method calculates the AUC by dividing the curve into trapezoids with straight-line segments and then summing their areas. In the log-linear trapezoidal rule, the descending part of the curve is divided into trapezoids using a logarithmic transformation. Both methods are supported in the macro `aucs`. The option `trpzrule=linear` indicates the linear trapezoidal method and `trpzrule=loglinear` is the log-linear trapezoidal method.

```
%macro aucs (inds=, trpzrule=);
```

There are several types of AUCs in PK analysis. Some are derived from observed values; others are need predicted parameters λ_z . The following are a few examples related to AUC are supported in SAS-based PK NCA method. Partial AUC is discussed in the later section.

- AUC_{last} : Area under the concentration versus time curve from time 0 to the time of the last measurable concentration (t_{last})
- AUC_{inf} : Area under the concentration versus time curve from time 0 extrapolated to infinity. Calculated as follows: $AUC_{inf} = AUC_{last} + C_{last} / \lambda_z$
- $\%AUC_{extrap}$: The percentage of AUC obtained by extrapolation. Calculated as follows: $\%AUC_{extrap} = 100 * (C_{last} / \lambda_z) / AUC_{inf}$

INTERPOLATION

Interpolates concentration with a corresponding new time point.

In PK NCA analysis of clinical trial data, concentration-time profiles of a drug are typically generated by measuring drug concentrations at discrete time points. However, in some cases, it may be necessary to estimate the drug concentration at a specific time point that was not actually measured in the study. This is where interpolation comes into play.

Interpolation is a mathematical technique that allows estimation of values between measured data points. It can be performed using different mathematical methods. Both linear interpolation rule and logarithmic interpolation rule are supported. Linear interpolation is a method of estimating the concentration at a specific time point by drawing a straight line between two adjacent concentration values and calculating the concentration at the desired time point based on the position of that time point on the line. Logarithmic interpolation, on the other hand, is a method of estimating the concentration at a specific time point by drawing a curved line on a semi-logarithmic plot and calculating the concentration at the desired time point based on the position of that time point on the curve. In macro `interpolc`. The option `trpzrule=linear` is the linear interpolation rule and `trpzrule=log` is the logarithmic interpolation rule. `Tnew` is the missing new time point. By default, if t_{new} is less than t_{max} or the adjacent concentration is less or equal to zero, linear interpolation rule is implemented, otherwise, use logarithmic interpolation rule.

```
%macro interpolc(inds=, Tnew=, trpzrule=);
```

Partial AUC

Partial area under the concentration-time curve (partial AUC) is a pharmacokinetic parameter that measures the exposure to a drug over a specified period of time, rather than the entire duration of the study. Partial AUC is typically calculated for a portion of the AUC that is of particular interest, such as the AUC_{24} , the area under the concentration-time curve of a drug over the 24-hour dosing interval. It is commonly used in pharmacokinetic studies to assess the overall exposure to a drug following a single dose. To calculate partial AUC both linear trapezoidal rule and the log-linear trapezoidal rule are supported. If the specific interested time point is missing, the above interpretation method is used. You just need to specify the two interested time points in t_1 and t_2 , the partial AUC will be calculated.

```
%macro ptauc(inds=, t1=, t2=, trpzrule=);
```

OTHER DERIVED PK PARAMETERS

There are several other PK parameters can be derived in SAS-based PK NCA method. The following are few examples:

- CL: Total body clearance. Calculated as follows: $CL = DOSE / AUC_{inf}$. CL is the rate at which the drug is eliminated from the body. It is important to know the clearance rate because it determines the dosing regimen required to maintain therapeutic drug levels in the body.
- V_z : Volume of distribution. Calculated as follows: $V_z = CL / \lambda_z$. It is the apparent volume of the body that is available to distribute the drug.
- Extrapolation rules using λ_z and back-extrapolation rule to estimate concentration are also supported.

VALIDATION AND OUTPUT

The performance and validity of the program were evaluated by comparing it to WinNonlin™, one of the most widely used commercial software packages. To assess the accuracy of the program, we used SAS PROC COMPARE. Our analysis showed that the results of the program were in agreement with those of WinNonlin™.

The output from SAS-based PK NCA method is compliant with CDISC SDTM Implementation guide v3.2. Examples of the values and terms for PK parameters from specification are presented in Table 1.

PK Parameter	PTESTCD	PTEST
C_{max}	CMAX	Max Conc
t_{max}	TMAX	Time of CMAX
C_{last}	CLST	Last Nonzero Conc
t_{last}	TLST	Time of Last Nonzero Conc
AUC_{last}	AUCLST	AUC to Last Nonzero Conc
λ_z	LAMZ	Lambda z
$t_{1/2}$	LAMZHL	Half-Life Lambda z
AUC_{inf}	AUCIFO	AUC Infinity Obs
% AUC_{extrap}	AUCPEO	AUC %Extrapolation Obs
CL	CLO	Total CL Obs
V_z	VZO	V_z Obs

Table 1. CDISC Parameter Short Name and Parameter Name for example PK Parameters.

CONCLUSION

This paper presents a SAS-based PK NCA method that is self-contained, meaning it does not require intermediate commercial software to operate. It can significantly reduce costs, streamline the data analysis process, and promote operational efficiency and compliance. By following protocol and statistical analysis plan, SAS programmers can develop SDTM PC/PP and ADaM ADPC/ADPP with specifications. The SAS-based PK NCA method can estimate both observed and derived PK parameters. It can estimate the terminal elimination rate constant based on the best fitted regression. Moreover, this method supports the calculation of concentrations by interpolation and partial area with the interpolation method. Only several most common PK parameters in single ascending dose study are discussed in this paper. Since the SAS-based PK NCA method can calculate a wide range of pharmacokinetic parameters, including C_{max} , t_{max} , λ_z , $t_{1/2}$, AUC_{last} , AUC_{inf} , CL, V_z , etc, it can be applied to multiple ascending dose studies with

steady-state to derive additional parameters. However, further research and validation may be needed to confirm the applicability and accuracy of the method. Using this SAS-based PK NCA method can ensure that the results meet regulatory requirements and industry standards and help to advance the drug development process.

REFERENCES

1. CDISC SDTM Implementation Guide (Version 3.2).
2. CDISC ADaM Implementation Guide (Version 1.1).
3. Joanna Magielse. 2014. "Implementation of CDISC ADaM in the Pharmacokinetics department". PhUSE, Paper CD06.
4. Arturo Soto Matos-Pita. "Noncompartmental Pharmacokinetics and Bioequivalence Analysis". Paper SP07
5. Gabrielsson J, Weiner D. 2017. Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications. 5th ed.

CONTACT INFORMATION

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

Hui Mao
BioPier Inc.
hmao@biopier.com

Lixin Gao
BioPier Inc.
lgao@biopier.com

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