NCA Guideline

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# Purpose

This guideline describes the methods used during the non-compartmental analysis (NCA) of clinical pharmacokinetic (PK) study data within qPharmetra.

# Scope

This guideline applies to all personnel who is involved with the execution of non-compartmental analyses. This guidance does not cover compartmental and/or population PK analyses.

# Data Set Requirements

At a minimum, the input data set must contain the variables:

- subject ID;  
- nominal time after dose;  
- actual time after dose;  
- dependent variable (i.e. drug concentration)  
- administered dose  
- LOQ information

# General Rules for NCA PK Parameter Calculation

## Sampling time deviations

Actual sampling times should be used for all calculations of individual pharmacokinetic parameters when available. On critical time points like t=0 or t=τ (tau), concentrations on deviating time points should be corrected to the nominal time where possible by interpolation or extrapolation.

## Missing drug concentrations

Missing drug concentrations will not be imputed except if these occur on critical time points. In that case drug concentrations will be imputed where possible by interpolation, extrapolation or substitution.

## Anomalous drug concentrations

Concentrations with apparently anomalous values on an individual profile generally can be excluded from the analysis. Anomalous concentrations in the terminal log-linear part of the concentration vs. time profile could be excluded from the calculation of λz. In both cases the value will be identified in the relevant tables of the study report.

## Estimation of AUC∞

The % of the AUC∞ that is extrapolated should be ≤ 20% (i.e. ≤ 0.2). Otherwise, AUC∞ is unreliable and therefore not estimated.

# Methods

## LOQ handling

For AUC determination as part of non-compartmental analyses, below limit of quantification (LOQ) values should be imputed by applying one of the following rules:

|  |  |  |  |
| --- | --- | --- | --- |
| **LOQ rule number** | **LOQ value occurs before the first measurable concentration** | **LOQ value occurs after the first measurable concentration** | |
| **First of consecutive LOQ values** | **Other consecutive  LOQ values** |
| **1** | 0 | Set to missing | Set to missing |
| **2** | 0 | 0 | 0 |
| **3** | 0 | 0.5 \* LOQ | Set to missing |
| **4** | 0 | 0.5 \* LOQ | 0 |

In case a single LOQ value lies between two quantifiable concentrations the user decides on how to impute the LOQ value.

## Elimination rate constant estimation

Estimation of the elimination rate constant (z)is performed by log-linear regression of the last three time points with measurable and non-missing concentrations. The regression is repeated using the last four, five, etc. time points until Cmax is. The z value resulting from the regression with the highest adjusted R2will be chosen. The user decides whether the regression including Cmax is included in this choice.

## Interpolation / extrapolation rules

In cases where concentrations must be calculated by interpolation or extrapolation (e.g. to correct time deviations and/or impute missing concentrations) the following rules will be applied:

Linear interpolation rule:

Log-linear interpolation rule:

Extrapolation rule using z:

Back-extrapolation rule (IV bolus administration only):

Back-extrapolation will only be applied if 1) *c*1 and *c*2 are non-missing and above LOQ and 2) *c*1 is larger than *c*2. If this is not the case, then *c*0 will get the value of *c*1. If the PK curve clearly shows one-compartmental kinetics, the user can consider applying log-linear regression to the complete curve to estimate c0. On the other hand, if the curve shows two distinct phases (bi-exponential, two compartments) the user can decide to apply curve stripping to estimate c0 (Gabrielsson and Weiner, p. 388).

## Trapezoidal rules and AUC calculation

Trapezoidal rules are used to calculate partial areas for AUC and AUMC estimation. Different rules can be applied to different parts in the PK curve:

|  |  |
| --- | --- |
| **Method No.** | **Method description** |
| **1** | Calculate all partial areas with the linear trapezoidal rule |
| **2** | Calculate areas between increasing concentrations with the linear trapezoidal rule, areas between decreasing concentrations with the log-linear trapezoidal rule |
| **3** | Calculate areas before the first tmax with the linear trapezoidal rule, areas after the first tmax with the log-linear trapezoidal rule. |

*Observed versus predicted C­last*

The calculation of AUC∞ can be done using the observed Clast (Clast,obs) or the predicted value for *C*last (Clast,pred), which is defined as: *C*last,pred= exp(intercept - z x tlast) where intercept and z result from the estimation of the elimination rate constant. In paragraph 6, parameters based on AUC∞ will have the notation ‘*(obs,pred)’* in the description to indicate that the parameter can be calculated using both values of Clast.

The method used for AUC and /or AUMC calculation as well as the type of Clast used in the calculations should be described in the study protocol and/or the NCA Analysis Plan.

Linear trapezoidal rule:

Log-linear trapezoidal rule:

# PK Parameters

The following PK parameters can be estimated if data are sufficient. A list of preferred variable names for coding and reporting as well as CDISC/SDTM variable short and long names is given in Appendix 1.

## Parameters that do not need z for estimation

**Cmax**

The value of the maximum plasma concentration is directly obtained from the experimental data without interpolation.

When identical maximum concentrations occur at different time points in the same individual concentration vs. time profile, the first occurrence will be considered for Cmax.

**tmax**

The time of the maximum plasma concentration is directly obtained from the experimental data without interpolation.

When identical maximum concentrations occur at different time points in the same individual concentration vs. time profile, the first occurrence will be considered for tmax.

**tlast**

The time of the last sample with a measurable concentration (>LOQ).

**Clast,obs**

The observed concentration at t=tlast.

**C0**

The back-extrapolated concentration at t=0 after IV bolus administration.

**AUClast**

The area under the concentration vs. time curve from time=0 (pre-dose) to the time of the last measurable concentration (tlast).

**AUCall**

The area under the concentration vs. time curve from time=0 (pre-dose) to the time of the last sample, after application of the LOQ rules.

**AUMClast**

The area under the first moment curve from the time=0 (pre-dose) to the time of the last measurable concentration (tlast).

**AUMCall**

The area under the moment curve from the time=0 (pre-dose) to the time of the last sample, including after application of the LOQ rules.

**AUCτ**

The area under the concentration vs. time curve during one dosing interval (tau).

**AUMCτ**

The area under the moment curve during one dosing interval (tau).

**MRTlast**

The mean residence times, based on AUClast,calculated as follows:

**MRTall**

The mean residence times, based on AUCall,calculated as follows:

**z**

The first order rate constant associated with the terminal portion of the concentration vs. time curve is estimated by linear regression of the natural logarithmic transformed concentration concentrations vs. time using the procedure described in paragraph 5.2.

## Parameters that do need z for estimation

**t1/2**

The apparent terminal elimination half-life is calculated as follows:

**Clast.pred**

The concentration at t=tlast estimated using the linear regression performed to estimate z (see paragraph 5.2).

**AUC∞** *(obs,pred)*

The area under the concentration vs. time curve from time=0 (pre-dose) to infinite time is calculated as follows:

where Clast is the last observed (Clast,obs) or predicted (Clast,pred) quantifiable concentration.

**%AUCextrap** *(obs,pred)*

The percentage of AUC obtained by extrapolation is calculated as follows:

where Clast is the last observed (clast,obs) or predicted (clast,pred) quantifiable concentration.

**%AUCbackextrap** *(obs,pred)*

The percentage of AUC obtained by back-extrapolation is calculated as follows (only after IV bolus administration):

**AUMC***(obs,pred)*

The area under the first moment curve from the time=0 (pre-dose) to infinite time.

**MRT***(obs,pred)*

The mean residence time, based on AUC**** is calculated as follows:

**CL** *(obs,pred)*

Systemic clearance following an i.v. administration is calculated as follows:

**CL/F** *(obs,pred)*

Apparent systemic clearance following an extravascular (e.v.) administration is calculated as follows:

**Vz** *(obs,pred)*

Volume of distribution is calculated as follows:

**Vz/F** *(obs,pred)*

Apparent volume of distribution is calculated as follows:

**F** *(obs,pred)*

The absolute bioavailability following an extravascular administration is calculated as follows:

## Additional parameters and changes in parameter calculations if steady-state has been reached

**Cmin**

The minimum concentration is obtained directly from the concentration vs. time profile as the minimum concentration observed during the dosing interval.

**Cavg**

The average steady-state concentration during the dosing interval is calculated as follows:

**CLss**

Systemic clearance at steady state following an i.v. administration is calculated as follows:

**CLss/F**

Apparent systemic clearance at steady state following an extravascular administration is calculated as follows:

**Vss** *(obs,pred)*

Volume of distribution at steady state:

Note: Vss/F cannot be calculated following extravascular administration as MRT**** for oral models includes Mean Input Time as well as time in systemic circulation and therefore is not appropriate to use in calculating Vss.

**MRT***(obs,pred)*

The mean residence time at steady state is calculated as follows:

**%PTF**

The peak to through fluctuation is calculated as follows:

## Urine parameters

**Aet**

Cumulative urinary excretion from time= 0 to time= t is calculated as the sum of the products of the volumes of the urine fraction collected from 0 up to time t and the corresponding drug concentrations.

**ClR**

The renal clearance is calculated as follows:

# PP domain

For regulatory purposes, clients often want to have the pharmacokinetic parameters delivered as a CDISC SDTM PP domain. For that reason, template documents (DTAs, Data Transfer Agreements) have been added to this guideline (Appendix 2) which contain information about what variables should be in the domain and which label, type and length these variables should have. Proper PK parameter names (to be placed in the PPTESTCD and PPTEST variables) can be found in Appendix 1. At the moment, DTAs are available for two CDISC SDTM versions (CDISC SDTM version 3.1.3 and CDISC SDTM version 3.2).

# References:

Rowland and Tozer (2011). *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and applications*, 4th ed. Wolters Kluwer, Philadelphia.

Gabrielsson and Weiner (1997). *Pharmacokinetic and Pharmacodynamic Data Analysis:*

*Concepts and Applications*, 2nd ed. Swedish Pharmaceutical Press, Stockholm.

Gibaldi and Perrier (1982). *Pharmacokinetics*, 2nd ed. Marcel Dekker, New York.

SDTM Implementation guide v3.2, <https://www.cdisc.org/standards/foundational/sdtmig>.

# Appendix 1

| **Parameter** | **observed / predicted / route** | **CDISC short name (PPTESTCD)** | **CDISC long name (PPTEST)** | **qPNCA variable name** |
| --- | --- | --- | --- | --- |
| Cmax |  | CMAX | Max Conc | cmax |
| tmax |  | TMAX | Time of CMAX | tmax |
| tlast |  | TLST | Time of Last Nonzero Conc | tlast |
| Clast,obs |  | CLST | Last Nonzero Conc | clast.obs |
| C0 |  | C0 | Initial Conc | c0 |
| AUClast |  | AUCLST | AUC to Last Nonzero Conc | auclast |
| AUCall |  | AUCALL | AUC All | aucall |
| AUMClast |  | AUMCLST | AUMC to Last Nonzero Conc | aumclast |
| AUMCall |  | - | - | aumcall |
| AUCτ |  | AUCTAU | AUC Over Dosing Interval | auctau |
| AUMCτ |  | AUMCTAU | AUMC Over Dosing Interval | aumctau |
| MRTlast | Extravascular | MRTEVLST | MRT Extravasc to Last Nonzero Conc | - |
|  | Intravascular | MRTIVLST | MRT Intravasc to Last Nonzero Conc | - |
| MRTall |  | - | - | - |
| λz |  | LAMZ | Lambda z | lambda\_z |
| t1/2 |  | LAMZHL | Half-Life Lambda z | thalf |
| Clast.pred |  | CLST | Last Nonzero Conc | clast.pred |
| AUC∞ | Observed | AUCIFO | AUC Infinity Obs | aucinf.obs |
| Predicted | AUCIFP | AUC Infinity Pred | aucinf.pred |
| %AUCextrap | Observed | AUCPEO | AUC %Extrapolation Obs | pctextr.obs |
| Predicted | AUCPEP | AUC %Extrapolation Pred | pctextr.pred |
| %AUCbackextrap | Observed | AUCPBEO | AUC %Back Extrapolation Obs | pctback.obs |
| Predicted | AUCPBEP | AUC %Back Extrapolation Pred | pctback.pred |
| AUMC∞ | Observed | AUMCIFO | AUMC Infinity Obs | aumcinf.obs |
| Predicted | AUMCIFP | AUMC Infinity Pred | aumcinf.pred |
| MRT∞ | Observed, Extravascular | MRTEVIFO | MRT Extravasc Infinity Obs | mrt.obs |
| Observed, Intravascular | MRTIVIFO | MRT Intravasc Infinity Obs | mrt.obs |
| Predicted, Extravascular | MRTEVIFP | MRT Extravasc Infinity Pred | mrt.pred |
| Predicted, Intravascular | MRTIVIFP | MRT Intravasc Infinity Pred | mrt.pred |
| CL | Observed | CLO | Total CL Obs | cl.f.obs |
| Predicted | CLP | Total CL Pred | cl.f.pred |
| CL/F | Observed | CLFO | Total CL Obs by F | cl.f.obs |
| Predicted | CLFP | Total CL Pred by F | cl.f.pred |
| Vz | Observed | VZO | Vz Obs | vz.f.obs |
| Predicted | VZP | Vz Pred | vz.f.pred |
| Vz/F | Observed | VZFO | Vz Obs by F | vz.f.obs |
| Predicted | VZFP | Vz Pred by F | vz.f.pred |
| F | Observed | - | - | - |
| Predicted | - | - | - |
| Cmin |  | CMIN | Min Conc | - |
| Cavg |  | CAVG | Average Concentration | - |
| CLss |  | - | - | cl.f.obs |
| CLss/F |  | - | - | cl.f.pred |
| Vss | Observed | VSSO | Vol Dist Steady State Obs | vss.obs |
| Predicted | VSSP | Vol Dist Steady State Pred | vss.pred |
| %PTF |  | FLUCP | Fluctuation% | - |

# Appendix 2

## CDISC SDTM version 3.1.3

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Seq #** | **SDTM Field Name** | **Plain Language Field Name** | **Field Type** | **Field Length** | **Field Description (Codelist)** | **Core** | **Example of Possible Values** |
| 1 | STUDYID | Study Identifier | Char |  | Unique identifier for a study. | Req |  |
| 2 | DOMAIN | Domain Abbreviation | Char | 2 | Two-character abbreviation for the domain. | Req | PP |
| 3 | USUBJID | Unique Subject Identifier | Char |  | Unique subject identifier within the submission. | Req |  |
| 4 | PPSEQ | Sequence Number | Num |  | Sequence Number given to ensure uniqueness of subject records within a domain. | Req | 1, 2, 3, … |
| 5 | PPGRPID | Group ID | Char |  | Used to tie together a block of related records in PC and PP domain. | Perm |  |
| 6 | PPTESTCD | Parameter Short Name | Char |  | Short name of the pharmacokinetic parameter. (PKPARAMCD) | Req |  |
| 7 | PPTEST | Parameter Name | Char |  | Name of the pharmacokinetic parameter. (PKPARAM) | Req |  |
| 8 | PPCAT | Parameter Category | Char |  | For PP, this should be the name of the analyte in PCTEST whose profile the parameter is associated with. | Exp |  |
| 9 | PPORRES | Result or Finding in Original Units | Char |  | Result of the measurement or finding as originally received or collected. (PKUNIT) | Exp |  |
| 10 | PPORRESU | Original Units | Char |  | Original units in which the data were collected. | Exp | ng.h/mL |
| 11 | PPSTRESC | Character Result/Finding in Std Format | Char |  | Contains the result value for all findings, copied or derived from PPORRES in a standard format or standard units. | Exp |  |
| 12 | PPSTRESN | Numeric Result/Finding in Standard Units | Num |  | Used for continuous or numeric results or findings in standard format; copied in numeric format from PPSTRESC. | Exp |  |
| 13 | PPSTRESU | Standard Units | Char |  | Standardized unit used for PPSTRESC and PPSTRESN. (PKUNIT) | Exp | ng.h/mL |
| 14 | PPSPEC | Specimen Material Type | Char |  | Defines the type of specimen used for a measurement. If multiple specimen types are used for a calculation (e.g., serum and urine for renal clearance), then this field should be left blank. Examples: SERUM, PLASMA, URINE. (SPECTYPE) | Exp | PLASMA |
| 15 | PPRFTDTC | Date/Time of Reference Point | Char | 16 | The values in PPRFTDTC should be the same as that in PCRFTDTC for related records. | Exp | 01-04-2012T08:00 |

## CDISC SDTM version 3.2

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Seq #** | **SDTM Field Name** | **Plain Language Field Name** | **Field Type** | **Field Length** | **Field Description (Codelist)** | **Core** | **Example of Possible Values** |
| 1 | STUDYID | Study Identifier | Char |  | Unique identifier for a study. | Req |  |
| 2 | DOMAIN | Domain Abbreviation | Char | 2 | Two-character abbreviation for the domain. | Req | PP |
| 3 | USUBJID | Unique Subject Identifier | Char |  | Unique subject identifier within the submission. | Req |  |
| 4 | PPSEQ | Sequence Number | Num |  | Sequence Number given to ensure uniqueness of subject records within a domain. | Req | 1, 2, 3, … |
| 5 | PPGRPID | Group ID | Char |  | Used to tie together a block of related records in PC and PP domain. | Perm |  |
| 6 | PPTESTCD | Parameter Short Name | Char |  | Short name of the pharmacokinetic parameter. (PKPARAMCD) | Req |  |
| 7 | PPTEST | Parameter Name | Char |  | Name of the pharmacokinetic parameter. (PKPARAM) | Req |  |
| 8 | PPCAT | Parameter Category | Char |  | For PP, this should be the name of the analyte in PCTEST whose profile the parameter is associated with. | Exp |  |
| 9 | PPORRES | Result or Finding in Original Units | Char |  | Result of the measurement or finding as originally received or collected. (PKUNIT) | Exp |  |
| 10 | PPORRESU | Original Units | Char |  | Original units in which the data were collected. | Exp | ng.h/mL |
| 11 | PPSTRESC | Character Result/Finding in Standard Format | Char |  | Contains the result value for all findings, copied or derived from PPORRES in a standard format or standard units. | Exp |  |
| 12 | PPSTRESN | Numeric Result/Finding in Standard Units | Num |  | Used for continuous or numeric results or findings in standard format; copied in numeric format from PPSTRESC. | Exp |  |
| 13 | PPSTRESU | Standard Units | Char |  | Standardized unit used for PPSTRESC and PPSTRESN. (PKUNIT) | Exp | ng.h/mL |
| 14 | PPSPEC | Specimen Material Type | Char |  | Defines the type of specimen used for a measurement. If multiple specimen types are used for a calculation (e.g., serum and urine for renal clearance), then this field should be left blank. Examples: SERUM, PLASMA, URINE. (SPECTYPE) | Exp | PLASMA |
| 15 | PPRFTDTC | Date/Time of Reference Point | Char | 16 | The values in PPRFTDTC should be the same as that in PCRFTDTC for related records. | Exp | 01-04-2012T08:00 |