Parameter Guidelines

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NCA Guideline

Contents

1 Purpose

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

2 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.

3 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

4 General Rules for NCA PK Parameter Calculation

4.1 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.

4.2 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.

4.3 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 λ_z. In both cases the value will be identified in the relevant tables of the study report.

4.4 Estimation of AUC_∞

The % of the AUC_∞ that is extrapolated should be $\leq$ 20% (i.e. $\frac{C_{last}/\lambda_z}{AUC_\infty} \leq 0.2$). Otherwise, AUC_∞ is unreliable and therefore not estimated.

5 Methods

5.1 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.

5.2 Elimination rate constant estimation

Estimation of the elimination rate constant (λ_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 C_{max} is. The λ_z value resulting from the regression with the highest adjusted R^2 will be chosen. The user decides whether the regression including C_{max} is included in this choice.

5.3 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:

$$c_i = c_{i-1} + \frac{(t_i - t_{i-1})}{(t_{i+1} - t_{i-1})} \times (c_{i+1} - c_{i-1})$$

Log-linear interpolation rule:

$$c_i = \exp(\ \ln(c_{i-1}) + \frac{(t_i - t_{i-1})}{(t_{i+1} - t_{i-1})} \times (\ \ln(c_{i+1}) - \ln(c_{i-1})\ ))$$

Extrapolation rule using λ_z:

$$c_t = c_{last} \times \exp(-\lambda_z \times (t_t - t_{last}))$$

Back-extrapolation rule (IV bolus administration only):

$$c_0 = \exp(\ln(c_1) + \frac{(0 - t_1)}{(t_2 - t_1)} \times (\ln(c_2) - \ln(c_1)))$$

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 c_0. 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 c_0 (Gabrielsson and Weiner, p. 388).

5.4 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 t_{max} with the linear trapezoidal rule, areas after the first t_{max} with the log-linear trapezoidal rule.

Observed versus predicted C_{last}

The calculation of AUC_∞ can be done using the observed C_{last} ($C_{last,obs}$) or the predicted value for C_{last} ($C_{last,pred}$), which is defined as: $C_{last,pred}$ = exp(intercept - λ_z x t_{last}) where intercept and λ_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 C_{last}.

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

Linear trapezoidal rule:

$$AUC_{(t_{i+1}-t_i)} = (t_{i+1} - t_i) \times \frac{c_{i+1} + c_i}{2}$$

$$AUMC_{(t_{i+1}-t_i)} = (t_{i+1} - t_i) \times \frac{(t_{i+1} \times c_{i+1}) + (t_i \times c_i)}{2}$$

Log-linear trapezoidal rule:

$$AUC_{(t_{i+1}-t_i)} = (t_{i+1} - t_i) \times \frac{c_{i+1} - c_i}{\ln(\frac{c_{i+1}}{c_i})}$$

$$AUMC_{(t_{i+1}-t_i)} = (t_{i+1} - t_i) \times \frac{(t_{i+1} \times c_{i+1}) - (t_i \times c_i)}{\ln(\frac{c_{i+1}}{c_i})} - (t_{i+1} - t_i)^2 \times \frac{c_{i+1} - c_i}{\ln(\frac{c_{i+1}}{c_i})^2}$$

6 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.

6.1 Parameters that do not need λ_z for estimation

C_{max}

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 C_{max}.

t_{max}

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 t_{max}.

t_{last}

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

$C_{last,obs}$

The observed concentration at $t=t_{last}$.

C_0

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

AUC_{last}

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

AUC_{all}

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.

$AUMC_{last}$

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

$AUMC_{all}$

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.

AUC_{τ}

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

$AUMC_{\tau}$

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

MRT_{last}

The mean residence times, based on AUC_{last}, calculated as follows:

$$MRT_{last} = \frac{AUMC_{last}}{AUC_{last}}$$

MRT_{all}

The mean residence times, based on AUC_{all}, calculated as follows:

$$MRT_{all} = \frac{AUMC_{all}}{AUC_{all}}$$

λ_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.

6.2 Parameters that <u>do</u> need λ_z for estimation

$t_{1/2}$

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

$$t_{½} = \frac{\mathrm{LN}\ (2)}{\lambda_z}$$

$C_{last.pred}$

The concentration at $t=t_{last}$ estimated using the linear regression performed to estimate λ_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:

$$AUC_{\infty} = AUC_{last} + \frac{C_{last}}{\lambda_z}$$

where C_{last} is the last observed ($C_{last,obs}$) or predicted ($C_{last,pred}$) quantifiable concentration.

$\%AUC_{extrap}$ *(obs,pred)*

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

$$\%AUC_{extrap} = 100 \times \frac{C_{last}/\lambda_z}{AUC_{\infty}}$$

where C_{last} is the last observed ($c_{last,obs}$) or predicted ($c_{last,pred}$) quantifiable concentration.

$\%AUC_{backextrap}$ *(obs,pred)*

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

$$\%AUC_{backextrap} = 100 \times \frac{AUC_{0-first\ measurable}}{AUC_{\infty}}$$

$AUMC_{\infty}$ *(obs,pred)*

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

$$AUMC_{\infty} = AUMC_{last} + \frac{t_{last} \times C_{last}}{\lambda_z} + \frac{C_{last}}{\lambda_z^2}$$

MRT_{∞} *(obs,pred)*

The mean residence time, based on AUC_{∞}, is calculated as follows:

$$MRT_{\infty} = \frac{AUMC_{\infty}}{AUC_{\infty}}$$

CL *(obs,pred)*

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

$$CL = \frac{DOSE_{i.v.}}{AUC_{\infty}}$$

CL/F *(obs,pred)*

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

$$\frac{CL}{F} = \frac{DOSE_{e.v.}}{AUC_{\infty}}$$

V_z *(obs,pred)*

Volume of distribution is calculated as follows:

$$V_z = \frac{CL}{\lambda_z}$$

V_z/F *(obs,pred)*

Apparent volume of distribution is calculated as follows:

$$\frac{V_z}{F} = \frac{CL/_F}{\lambda_z}$$

F *(obs,pred)*

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

$$F = \frac{AUC_{\infty,e.v.}}{AUC_{\infty,i.v.}} \times \frac{DOSE_{i.v.}}{DOSE_{e.v.}}$$

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

C_{min}

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

C_{avg}

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

$$C_{avg} = \frac{AUC_\tau}{\tau}$$

CL_{ss}

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

$$CL_{ss} = \frac{DOSE_{i.v.}}{AUC_\tau}$$

CL_{ss}/F

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

$$\frac{CL}{F} = \frac{DOSE_{e.v.}}{AUC_\tau}$$

V_{ss} *(obs,pred)*

Volume of distribution at steady state:

$$V_{ss} = MRT_\infty \times CL_{ss}$$

Note: V_{ss}/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 V_{ss}.

MRT_∞ *(obs,pred)*

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

$$MRT_\infty = \frac{AUMC_\tau + \tau \times (AUC_\infty - AUC_\tau)}{AUC_\tau}$$

%PTF

The peak to through fluctuation is calculated as follows:

$$\%PTF = 100 \times \frac{(C_{max} - C_{min})}{C_{avg}}$$

6.4 Urine parameters

Ae_t

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.

$$Ae_{(t_{i+1}-t_i)} = V_{urine(t_{i+1}-t_i)} \times C_{urine(t_{i+1}-t_i)}$$

$$Ae_{(t_0-t_{last})} = \sum_{i=1}^{n} Ae_{(t_{i+1}-t_i)}$$

Cl_R

The renal clearance is calculated as follows:

$$CL_R = \frac{\mathrm{Ae}_t}{AUC_t}$$

7 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).

8 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
C_{max}		CMAX	Max Conc	cmax
t_{max}		TMAX	Time of CMAX	tmax
t_{last}		TLST	Time of Last Nonzero Conc	tlast
$C_{last,obs}$		CLST	Last Nonzero Conc	clast.obs
C_0		C0	Initial Conc	c0
AUC_{last}		AUCLST	AUC to Last Nonzero Conc	auclast
AUC_{all}		AUCALL	AUC All	aucall
$AUMC_{last}$		AUMCLST	AUMC to Last Nonzero Conc	aumclast
$AUMC_{all}$		-	-	aumcall
AUC_{τ}		AUCTAU	AUC Over Dosing Interval	auctau
$AUMC_{\tau}$		AUMCTAU	AUMC Over Dosing Interval	aumctau
MRT_{last}	Extravascular	MRTEVLST	MRT Extravasc to Last Nonzero Conc	-
	Intravascular	MRTIVLST	MRT Intravasc to Last Nonzero Conc	-
MRT_{all}		-	-	-
λ_z		LAMZ	Lambda z	lambda_z
$t_{1/2}$		LAMZHL	Half-Life Lambda z	thalf
$C_{last.pred}$		CLST	Last Nonzero Conc	clast.pred
AUC_{∞}	Observed	AUCIFO	AUC Infinity Obs	aucinf.obs
	Predicted	AUCIFP	AUC Infinity Pred	aucinf.pred
$\%AUC_{extrap}$	Observed	AUCPEO	AUC %Extrapolation Obs	pctextr.obs
	Predicted	AUCPEP	AUC %Extrapolation Pred	pctextr.pred
$\%AUC_{backextrap}$	Observed	AUCPBEO	AUC %Back Extrapolation Obs	pctback.obs
	Predicted	AUCPBEP	AUC %Back Extrapolation Pred	pctback.pred
$AUMC_{\infty}$	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
V_z	Observed	VZO	Vz Obs	vz.f.obs
	Predicted	VZP	Vz Pred	vz.f.pred
V_z/F	Observed	VZFO	Vz Obs by F	vz.f.obs
	Predicted	VZFP	Vz Pred by F	vz.f.pred
F	Observed	-	-	-
	Predicted	-	-	-
C_{min}		CMIN	Min Conc	-
C_{avg}		CAVG	Average Concentration	-
CL_{ss}		-	-	cl.f.obs
CL_{ss}/F		-	-	cl.f.pred
V_{ss}	Observed	VSSO	Vol Dist Steady State Obs	vss.obs
	Predicted	VSSP	Vol Dist Steady State Pred	vss.pred

Parameter	observed / predicted / route	CDISC short name (PPTESTCD)	CDISC long name (PPTEST)	qPNCA variable name
%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