

CDISC Compliant NCA PK Parameter Analysis When Using Phoenix WinNonlin

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ABSTRACT

Mapping the Non-Compartmental Analysis (NCA) PK parameter defaulted names when using Phoenix WinNonlin to CDISC compliant PK parameter names needs to involve the pharmacokineticist to avoid confusion and incorrect report on PK parameter analysis.

In meeting the compliance with CDISC data standards and obtaining PK parameters submission ready domains, PP and ADPP, Pharmacokinetics group at Celgene has developed a process to ensure that NCA (Non-Compartment Analysis) PK parameter analysis using WinNonlin, the NCA defaulted PK parameter names are accurately mapped and compliant to the PK parameter codelist and controlled terminology defined by CDISC. PK scientists use their Pharmacokinetics expertise along with the knowledge of CDISC data standards, the PK scientists have carefully mapped the entire mapping worksheet between NCA defaulted PK parameter names and CDISC compliant PK parameter codes. This PK parameter mapped EXCEL worksheet is finally put into production for when working on the CDISC compliant NCA PK parameter analysis using WinNonlin.

INTRODUCTION

CDISC mission statement -

“CDISC is a global, open, multidisciplinary, non-profit organization that has established standards to support the acquisition, exchange, submission and archive of clinical research data and metadata. The CDISC mission is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare.”

Like any other healthcare companies, we are working diligently for meeting the CDISC standards submission requirements. Pharmacokinetics group has come up with a process to enhance such requirements while programming team is working on PK parameters related data domains.

Following you are going to see the changes in process while working on NCA PK parameter analysis – the comparison between the prior and current CDISC compliant PK parameter analysis process.

PRIOR AND CURRENT NCA PK PARAMETER ANALYSIS PROCESSES

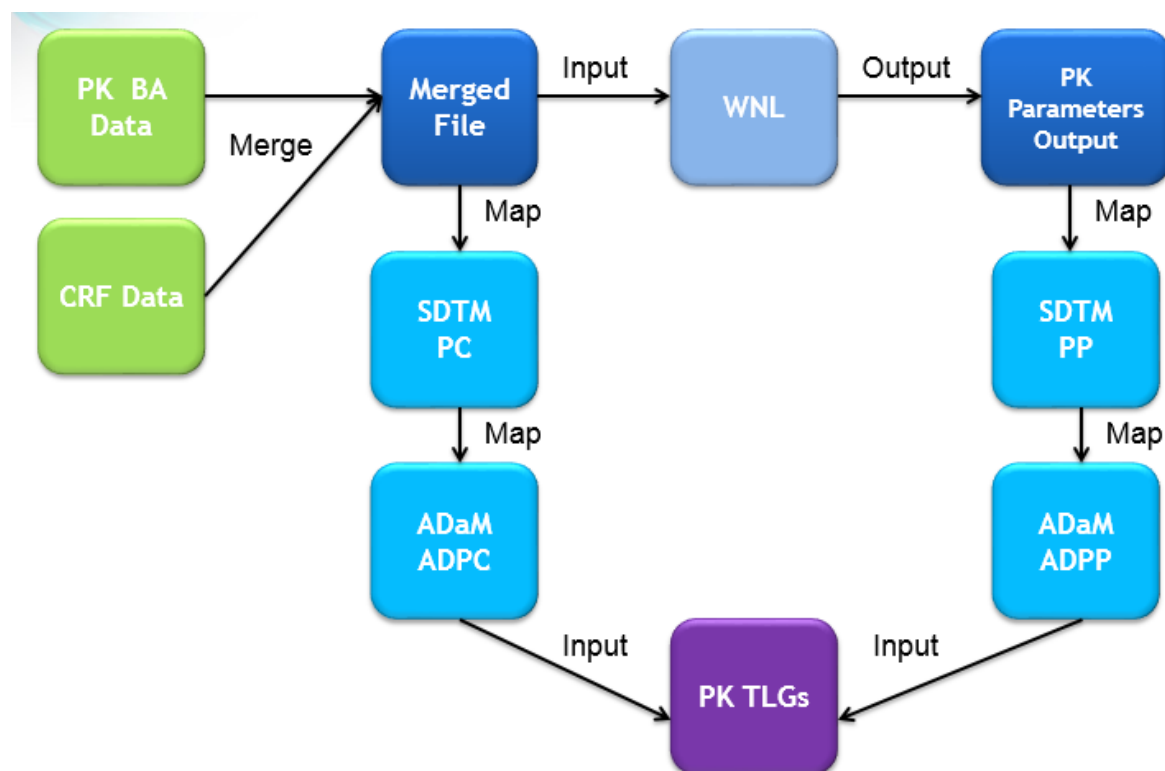
PRIOR NON-CDISC COMPLIANT NCA PK PARAMETER ANALYSIS PROCESS

- Merged PK concentration file received by Pharmacokineticist.
- Pharmacokineticist uses this merged PK concentration file to do the NCA PK parameter analysis using Phoenix WinNonlin.
- When NCA PK analysis is done, the protocol defined and study needed PK parameters are calculated and output with the defaulted NCA PK parameter names along with other study information
- This output is used to build PK parameter source dataset.
- Analysis ready PK parameter dataset hence is built based on the provided PK parameter source dataset.

CURRENT AND CDISC COMPLIANT NCA PK PARAMETER ANALYSIS PROCESS (ALSO SEE CURRENT PK DATA FLOW ON NEXT PAGE)

- Merged PK concentration received by Pharmacokineticist.
- Pharmacokineticist uses this merged PK concentration file as input file and does the NCA PK parameter analysis using Phoenix WinNonlin.
- When NCA PK parameter analysis is done, the protocol defined and study needed PK parameters are calculated and output with CDISC compliant NCA PK parameter names along with other study information.
- This output hence is used to build PK parameter CDISC compliant PP domain
- CDISC compliant Analysis Data Module, PK parameter dataset ADPP hence is built for the outputs of Tables, Listings and Figures.

PK Data Flow



PHARMACOKINETICIST LEADS THE NCA CDISC COMPLIANT PK PARAMETER NAMES MAPPING PROCESS

While the setup of PK parameter domains of PP and ADPP is the responsibility of data management area, the accuracy of the PK parameter names used and their compliance to CDISC controlled terminology need Pharmacokineticist's expertise. WinNonlin often implements specific calculation methods for certain PK parameters calculation and Pharmacokineticist understands such calculation implementation best. Therefore (s)he is able to perform the NAC defaulted PK parameter names mapping to those defined in CDISC controlled terminology/codelist.

At the end the Pharmacokineticists at Clinical Pharmacology have come up with 4 mapped EXCEL sheets due to three for data from different dose administration routes and one for urine data.

- Extravascular Administration (see example on next page)
- IV Bolus Administration
- IV Infusion Administration
- Urine Data

1	For Extravascular Administration		
2	WNL Defaulted Parameter Name	CDISC Compliant PK Parameter Codes	Include
3	Rs _q	R2	yes
4	Rs _q _adjusted	R2ADJ	no
5	Corr_XY	CORRXY	no
6	No_points_lambda_z	LAMZNPT	no
7	Lambda_z	LAMZ	no
8	Lambda_z_lower	LAMZLL	no
9	Lambda_z_upper	LAMZUL	no
10	HL_Lambda_z	LAMZHL	yes
11	Tlag	TLAG	no
12	Tmax	TMAX	yes
13	Cmax	CMAX	yes
14	Cmax_D	CMAXD	yes
15	Tlast	TLST	no
16	Clast	CLST	yes
17	AUClast	AUCLST	yes
18	AUCall	AUCALL	yes
19	AUCINF_obs	AUCIFO	yes
20	AUCINF_D_obs	AUCIFOD	yes
21	AUC_%Extrap_obs	AUCPEO	no
22	AUCINF_pred	AUCIFP	no
23	AUCINF_D_pred	AUCIFPD	no
24	AUC_%Extrap_pred	AUCPEP	no
25	Tmin	TMIN	no
26	Cmin	CMIN	no
27	Cavg	CAVG	no
28	Fluctuation%	FLUCP	no

ESSENTIAL STEPS – BUILDING CDISC COMPLIANT PK PARAMETER NAMES IN WINNONLIN

1. Import the mapped EXCEL sheet to project Data folder and open the excel sheet to include (by typing yes in the include column) the needed PK parameters according to study protocol

The screenshot displays the Phoenix WinNonlin interface. On the left is the Object Browser showing a project structure for 'CP034'. The main window shows a table with 15 rows of PK parameters. Below the table is a 'Columns' panel with 'Data Type' and 'Unit' settings, and a 'Display Format' panel with 'Custom' and 'Numeric' options.

	Parameter_Name	Preferred_Name	Include
1	Rsq	R2	yes
2	Rsq_adjusted	R2ADJ	yes
3	Corr_XY	CORRXY	no
4	No_points_lambda_z	LAM2NPT	no
5	Lambda_z	LAMZ	no
6	Lambda_z_lower	LAMZLL	no
7	Lambda_z_upper	LAMZUL	no
8	HL_Lambda_z	LAMZHL	yes
9	Tlag	TLAG	yes
10	Tmax	TMAX	yes
11	Cmax	CMAX	yes
12	Cmax_D	CMAXD	no
13	Tlast	TLST	no
14	Clast	CLST	no
15	AUClast	AUCLST	yes

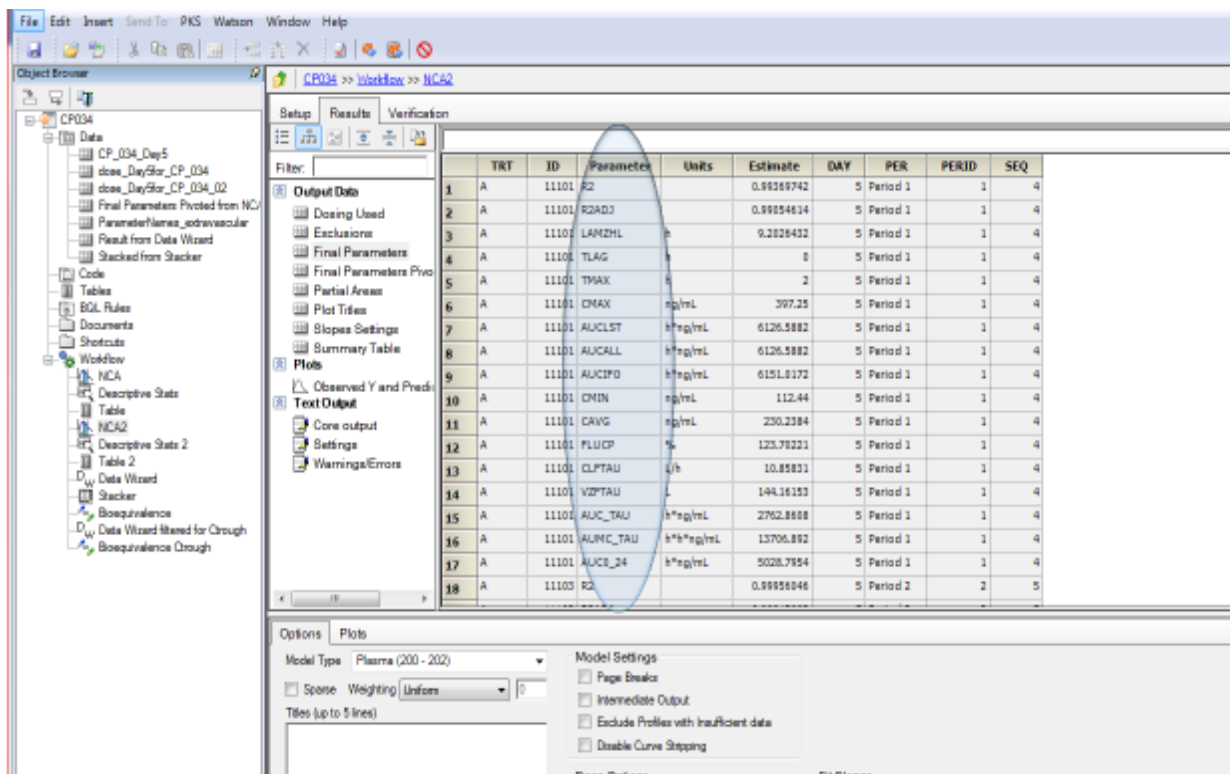
- At the Setup → Parameter Names, drag the EXCEL sheet (ParameterNames_extravascular) from Data folder to the Source area and make the selection as below

The screenshot displays the Phoenix WinNonlin software interface. The 'Object Browser' on the left shows a project structure for 'CP034' with a 'Workflow' folder containing 'NCA2'. The main window is in the 'Setup' tab, showing a list of parameters including 'Parameter Names (ParameterNames_extravascular)'. The 'Source' area is set to 'CP034.Data.ParameterNames_extravascular'. The 'Mappings' table is as follows:

	None	Parameter Name	Preferred	Include in Workbook
Parameter_Name	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Preferred_Name	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Include	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>

The 'Options' tab is also visible, showing 'Model Type' as 'Plasma (200 - 202)', 'Dose Options' as 'Extravascular', and 'Fit Slopes' checked. The 'Unit' is set to 'mg' and 'Normalization' is set to 'None'.

3. Execute after completing the other needed setups, and the results are as follows (next page).



Now the PK parameter analysis results contain the CDISC compliant PK parameter names (PK parameter Code, to be more precise per CDISC). Please note, the PK units of measure and PK parameter long names are not CDISC compliant at this stage. The downstream programming team will need to merge accordingly, based on the PK parameter codes pharmacokineticist provides, with the file from CDISC that contains CDISC compliant PK units and PK parameter long name codelist and controlled terminology.

The following CDISC SDTM controlled terminology for PK parameter codes, PK parameter long names and units of measures are for your reference.

CDISC Controlled Terminology for PK parameter Codes (short names) example (partially displayed)

Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)	CDISC Definition
C85839		Yes	PK Parameters Code	PKPARAMCD	PK Parameters Code	Parameter codes used to describe the time-concentration curve.
C114234	C85839		PK Parameters Code	AILAMZ	Accumulation Index using Lambda z	Predicted accumulation ratio for area under the curve (AUC) calculated using the Lambda z estimated from single dose data.
C102356	C85839		PK Parameters Code	ARAUC	Accumulation Ratio AUCTAU	The area under the curve (AUCTAU) at steady state divided by the area under the curve from T1 to T2 during the initial dosing interval.
C122329	C85839		PK Parameters Code	ARAUCINT	Accumulation Ratio AUC from T1 to T2	The area under the curve from T1 to T2 at steady state divided by the area under the curve from T1 to T2 during the initial dosing interval.
C102357	C85839		PK Parameters Code	ARCMAX	Accumulation Ratio Cmax	The maximum concentration at steady state divided by the maximum concentration during the initial dosing interval.
C102358	C85839		PK Parameters Code	ARCMIN	Accumulation Ratio Cmin	The minimum concentration at steady state divided by the minimum concentration during the initial dosing interval.
C102426	C85839		PK Parameters Code	ARCTROUG	Accumulation Ratio Ctrough	The trough concentration at steady state divided by the trough concentration during the initial dosing interval.
C85564	C85839		PK Parameters Code	AUCALL	AUC All	The area under the curve (AUC) from the time of dosing to the time of the last observation, regardless of whether the last concentration is measurable or not.
C92362	C85839		PK Parameters Code	AUCALLB	AUC All Norm by BMI	The area under the curve (AUC) from the time of dosing to the time of the last observation divided by the body mass index, regardless of whether the last concentration is measurable or not.
C92306	C85839		PK Parameters Code	AUCALLD	AUC All Norm by Dose	The area under the curve (AUC) from the time of dosing to the time of the last observation divided by the dose, regardless of whether the last concentration is measurable or not.

CDISC Controlled Terminology for PK Parameter Names (long names) example (partially displayed)

Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)	CDISC Definition
C85493		Yes	PK Parameters	PKPARAM	PK Parameters	Parameters used to describe the time-concentration curve.
C114234	C85493		PK Parameters	Accumulation Index using Lambda z	Accumulation Index using Lambda z	Predicted accumulation ratio for area under the curve (AUC) calculated using the Lambda z estimated from single dose data.
C122329	C85493		PK Parameters	Accumulation Ratio AUC from T1 to T2	Accumulation Ratio AUC from T1 to T2	The area under the curve from T1 to T2 at steady state divided by the area under the curve from T1 to T2 during the initial dosing interval.
C102356	C85493		PK Parameters	Accumulation Ratio AUCTAU	Accumulation Ratio AUCTAU	The area under the curve (AUCTAU) at steady state divided by the area under the curve (AUCTAU) over the initial dosing interval.
C102357	C85493		PK Parameters	Accumulation Ratio Cmax	Accumulation Ratio Cmax	The maximum concentration at steady state divided by the maximum concentration during the initial dosing interval.
C102358	C85493		PK Parameters	Accumulation Ratio Cmin	Accumulation Ratio Cmin	The minimum concentration at steady state divided by the minimum concentration during the initial dosing interval.
C102426	C85493		PK Parameters	Accumulation Ratio Ctrough	Accumulation Ratio Ctrough	The trough concentration at steady state divided by the trough concentration during the initial dosing interval.
C102359	C85493		PK Parameters	Amt Rec from T1 to T2	Amt Rec from T1 to T2	The cumulative amount recovered from the specimen type specified in PPSPEC over the interval from T1 to T2.
C102360	C85493		PK Parameters	Amt Rec from T1 to T2 Norm by BMI	Amt Rec from T1 to T2 Norm by BMI	The cumulative amount recovered from the specimen type specified in PPSPEC over the interval from T1 to T2 divided by body mass index.
C102361	C85493		PK Parameters	Amt Rec from T1 to T2 Norm by SA	Amt Rec from T1 to T2 Norm by SA	The cumulative amount recovered from the specimen type specified in PPSPEC over the interval from T1 to T2 divided by surface area.
C102362	C85493		PK Parameters	Amt Rec from T1 to T2 Norm by WT	Amt Rec from T1 to T2 Norm by WT	The cumulative amount recovered from the specimen type specified in PPSPEC over the interval from T1 to T2 divided by weight.
C112032	C85493		PK Parameters	Amt Rec Infinity Obs	Amt Rec Infinity Obs	The cumulative amount recovered from the specimen type specified in PPSPEC extrapolated to infinity, calculated using the observed value of the last non-zero concentration.

CDISC Controlled Terminology for PK units of measure example (partially displayed)

Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)	CDISC Definition
C85494		Yes	PK Units of Measure	PKUNIT	PK Units of Measure	Units of measure for pharmacokinetic data and parameters.
C25613	C85494		PK Units of Measure	%	Percentage	A fraction or ratio with 100 understood as the denominator. (NCI)
C120727	C85494		PK Units of Measure	(L/day)/(kg/m ²)		Liters per day (flow rate), divided by kilograms per meter squared (body mass index).
C120728	C85494		PK Units of Measure	(L/day)/(mg/day)		Liters per day (flow rate), divided by milligrams per day (daily dose).
C120729	C85494		PK Units of Measure	(L/day)/(mg/kg)		Liters per day (flow rate), divided by milligrams per kilogram (dose normalized by body weight).
C120730	C85494		PK Units of Measure	(L/day)/(mg/kg/day)		Liters per day (flow rate), divided by milligrams per kilogram per day (daily dose normalized by body weight).
C120731	C85494		PK Units of Measure	(L/day)/(mg/m ²)		Liters per day (flow rate), divided by milligrams per meter squared (dose normalized by surface area).
C120732	C85494		PK Units of Measure	(L/day)/(mg/m ² /day)		Liters per day (flow rate), divided by milligrams per meter squared per day (daily dose normalized by surface area).
C120733	C85494		PK Units of Measure	(L/day)/(ug/day)		Liters per day (flow rate), divided by micrograms per day (daily dose).
C120734	C85494		PK Units of Measure	(L/day)/(ug/kg)		Liters per day (flow rate), divided by micrograms per kilogram (dose normalized by body weight).
C120735	C85494		PK Units of Measure	(L/day)/(ug/kg/day)		Liters per day (flow rate), divided by micrograms per kilogram per day (daily dose normalized by body weight).
C120736	C85494		PK Units of Measure	(L/day)/(ug/m ²)		Liters per day (flow rate), divided by micrograms per meter squared (dose normalized by surface area).
C120737	C85494		PK Units of Measure	(L/day)/(ug/m ² /day)		Liters per day (flow rate), divided by micrograms per meter squared per day (daily dose normalized by surface area).
C85657	C85494		PK Units of Measure	(L/day)/g		Liters per day (flow rate), divided by grams (weight).

CONCLUSION

Pharmacokineticist plays an important role in mapping the defaulted Non CDISC compliant PK parameter names directly coming out of Phoenix WinNonlin when working on Non-Compartmental Analysis. Without pharmacokineticist’s inputs and guidance, the CDISC compliant PK parameter names mapping will easily get confused and results in an incorrect CDISC compliant PK parameter name reported and explained.

REFERENCES

CDISC SDTM Controlled Terminology. Available at <https://www.cancer.gov/research/resources/terminology/cdisc>

Phoenix® WinNonlin® - The Industry Standard for NCA, Non-Compartment Analysis – Certara L.P.

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CONTACT INFORMATION

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