Analyses and Displays Associated to Non-Compartmental Pharmacokinetics – With a Focus on Clinical Trials

Final - Version 1.0
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A White Paper by the PhUSE CSS Development of Standard Scripts for Analysis and Programming Working Group

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List of Abbreviations

Abbreviation	Description
%SEM	Percent Standard Error of the Mean
ADaM	Analysis Data Model
Adj_RSq^2	Adjusted Coefficient of Determination
ADPC	ADaM Dataset containing the PK Concentrations
ADPP	ADaM Dataset containing the PK Parameters
ADSL	ADaM Dataset containing Subject-Level information
AGAH	Arbeitsgemeinschaft für Angewandte Humanpharmakologie
BA/BE	Bioavailability/Bioequivalence
BLQ	Below lower Limit of Quantification
CBER	Center for Biologics Evaluation and Research
CDASH	Clinical Data Acquisition. Standards Harmonization
CDER	Center for Drug Evaluation and Research
CI	Confidence Interval
CSR	Clinical Study Report
CSS	Computational Science Symposium
CV	Coefficient of Variation
D	Dose
DM	SDTM dataset containing the Demographic characteristics
EMA	European Medicines Agency
EX	SDTM dataset containing the Exposure information
FDA	Food and Drug Administration
Geo-mean	Geometric mean
ICH	International Conference on Harmonization of technical requirements for registration
ICH E3	ICH Efficacy guideline #3
IG	Implementation Guide
LLOQ	Lower Limit Of Quantification
LOQ	Limit Of Quantification
Min	Minimum value
Max	Maximum value
N.A.	Not Available
NCA	Non-Compartmental Analysis
NIHS	National Institute of Health Sciences
PD	Pharmacodynamic(s)
PhUSE	Pharmaceuticals Users Software Exhange
PC	SDTM dataset containing the PK concentrations

PK	Pharmacokinetic(s)
PKPARMCD	Variable name in the PP and ADPP datasets containing the PK Parameter Code
PP	SDTM dataset containing the PK parameters
PPSPEC	Specimen material type variable in the PP and ADPP datasets (matrix)
RELREC	SDTM dataset associating Related Records from other datasets
Q1	First Quartile
Q3	Third Quartile
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SOP	Standard Operating Procedure
τ	Dosing interval, scheduled time between two successive administrations
TFLs	Tables, Figures and Listings
Tinf	Actual duration of a constant rate infusion
TM	Trademark
ULOQ	Upper Limit Of Quantification
UOM	Unit Of Measurement

2. Revision History

Version 1.0 was finalized on 25 March 2014. As part of the PhUSE/CSS initiative, this white paper was a collective effort involving more than 26 key contributors from 15 different companies. It presents recommendations for the calculation of PK parameters, and for the analysis and display of PK data in clinical trials.

These resolutions are a good start but they are not final, by any means. As a living document, the white paper will be revised over time, in order to incorporate feedback on the current proposals and to address any additional topic not currently covered.

A subsequent version 2 is already planned to be released within a year. It will incorporate the following items, that were raised during the initial review but could not be addressed in Version 1:

- Templates for the most common statistical analyses of PK data
- Listings limited to noteworthy data points only (instead of all values)
- Additional derivations and rules for PK parameters

If you would like to contribute to the next release, feel free to contact the primary author Francois Vandenhende at francois@clinbay.com or any member of the PhUSE/CSS steering committee.

3. Purpose

Under CDISC, standards have been defined for data collection (Clinical Data Acquisition. Standards Harmonization - CDASH), tabulation (Study Data Tabulation Model - SDTM), and analysis (Analysis Data Model - ADaM) datasets. The next step is to develop standard tables, figures and listings. The Development of Standard Scripts for Analysis and Programming Working Group is leading an effort to create several white papers providing recommended analyses and displays for common measurements, and has developed a Script Repository as a place to store shared code.

The purpose of this white paper is to provide advice on displaying, summarizing, and/or analyzing measures of pharmacokinetic (PK) data in clinical trials. PK data is frequently given as drug concentration at different time points in a number of healthy volunteers or patients, collectively named subjects. The intent is to begin the process of developing industry standards with respect to analysis and reporting for PK concentrations and non-compartmental PK parameters that are common across clinical trials. In particular, this white paper provides recommended processes for:

- the calculation of PK parameters using non-compartmental analysis (NCA),
- the production of PK listings, tables and figures for inclusion in clinical study reports (CSR), and
- the definition of statistical analysis plans (SAP) for PK data

Separate white papers address other types of data.

Model-based (compartmental, population approach-type) PK analyses are considered out-of-scope for this white paper.

The content of this document can be used when developing the analysis plan for individual clinical trials in which PK data are of interest. Although the focus of this white paper pertains to clinical trials where intense PK sampling is made, some of the content may apply to trials where only sparse samples are collected. Similarly, although the focus of this white paper pertains to clinical trials, some of the content may apply to pre-clinical studies where PK is being assessed.

Development of standard Tables, Figures, and Listings (TFLs) and associated analyses will lead to improved standardization from collection through data storage, as it is necessary to determine how the results should be reported and analyzed before finalizing how to collect and store the data. The development of standard TFLs will also lead to improved product lifecycle management by ensuring reviewers receive the desired analyses for consistent and efficient evaluation of patient safety and drug exposure. Although having standard TFLs is an ultimate goal, this white paper reflects recommendations only and should not be interpreted as “required” by any regulatory agency.

Detailed specifications for TFL development are in the scope of this white paper. The hope is that code (utilizing SDTM and ADaM data structures) will be developed in any script language

such as SAS or R, consistent with the concepts outlined in this white paper, and placed in the publicly available PhUSE CSS Standard Scripts Repository.

4. Introduction

Industry standards have evolved over time for data collection (CDASH), observed data (SDTM), and analysis datasets (ADaM). There is now recognition that the next step in standardization should be to develop standard TFLs for common measurements across clinical trials and across therapeutic areas. Having industry standards for data collection and analysis datasets in place provides a good basis for creating standard TFLs.

The beginning of the effort leading to this white paper came from the FDA computational statistics groups (CBER and CDER). The FDA identified key priorities and teamed up with the Pharmaceuticals Users Software Exhange (PhUSE) to tackle various challenges using collaboration, crowd sourcing, and innovation (Rosario, et. al. 2012). The FDA and PhUSE created several working groups to address a number of these challenges. The working group entitled "Development of Standard Scripts for Analysis and Programming" has led the development of this white paper, along with the development of a platform for storing shared code. Most contributors and reviewers of this white paper are industry pharmacokineticists, statisticians, statistical programmers, and clinical pharmacologists with input from non-industry experts (e.g., FDA and academia). Hopefully additional input (e.g., other regulatory agencies) will be received for future versions of this white paper.

There are several existing documents that contain suggested TFLs for PK measurements. However, many of these documents are relatively outdated, and generally lack sufficient detail to be used as support for the entire standardization effort. Nevertheless, these documents were used as a starting point in the development of this white paper. The documents include:

- ICH E3: Structure and Content of Clinical Study Reports
- ICH E7: Studies in Support of Special Populations: Geriatrics
- FDA: Guideline for Industry: Structure and Content of Clinical Study Reports
- FDA: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations
- FDA: Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs
- FDA: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (draft)
- FDA: Pharmacokinetics in Patients with Hepatic Insufficiency: Study Design, Data Analysis and Impact on Dosing and Labeling
- FDA: Population Pharmacokinetics
- FDA: Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications
- FDA: Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis and Impact on Dosing and Labeling (draft)
- FDA: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (draft)
- NIHS (Japan): Clinical Pharmacokinetic Studies of Pharmaceuticals
- EMA: Pharmacokinetic Studies in Man

- EMA: Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party
- EMA: Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins

The listed guidance documents present high-level requirements for the collection, analysis and presentation of PK results in a variety of clinical trials. They do not provide, however, detailed information that would enable standardization of the calculation and presentation of PK results. The AGAH working group pharmacokinetics (2004) has released a glossary of terms and formula for common pharmacokinetic parameters. This white paper extends their work to provide a set of rules and checklists to standardize the production of PK TFLs in clinical trials.

5. General Considerations

5.1. Reporting workflow

The general workflow for the analysis and reporting of PK data in clinical trials involves two major steps, as outlined in Figure 5-1:

1. Calculation of PK parameters
2. Production of PK TFLs

For each step, we shall define, in subsequent sections, a checklist of standard rules that need to be followed. The SDTM to ADaM mapping for PK concentrations (PC) and parameters (PP) will also be discussed.

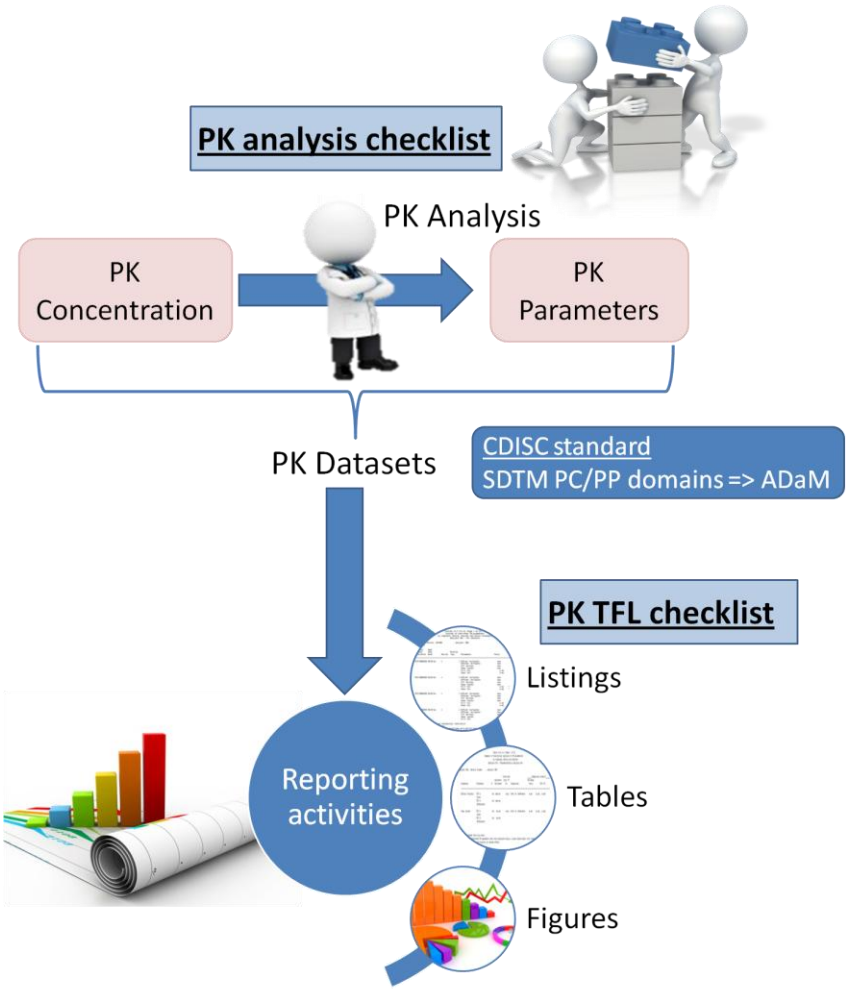


Figure 5-1 Reporting workflow for pharmacokinetic data

5.2. CDISC PK datasets creation workflow

According to the SDTM Implementation Guide (IG) (v3.2) and AdaM-IG (v1.0), SDTM Pharmacokinetic Concentration (PC) data, SDTM Pharmacokinetic Parameter (PP) data, ADaM Pharmacokinetic Concentration (ADPC) data and ADaM Pharmacokinetic Parameters (ADPP) datasets are created based on SDTM/ADaM metadata, clinical data, bioanalytical data and the derived PK parameters calculated by pharmacokineticists. Then, all of the related tables, figures, and listings can be generated based on ADPC and ADPP datasets.

An illustrative process for creating SDTM and ADaM PK-related datasets is summarized in Figure 5-2.

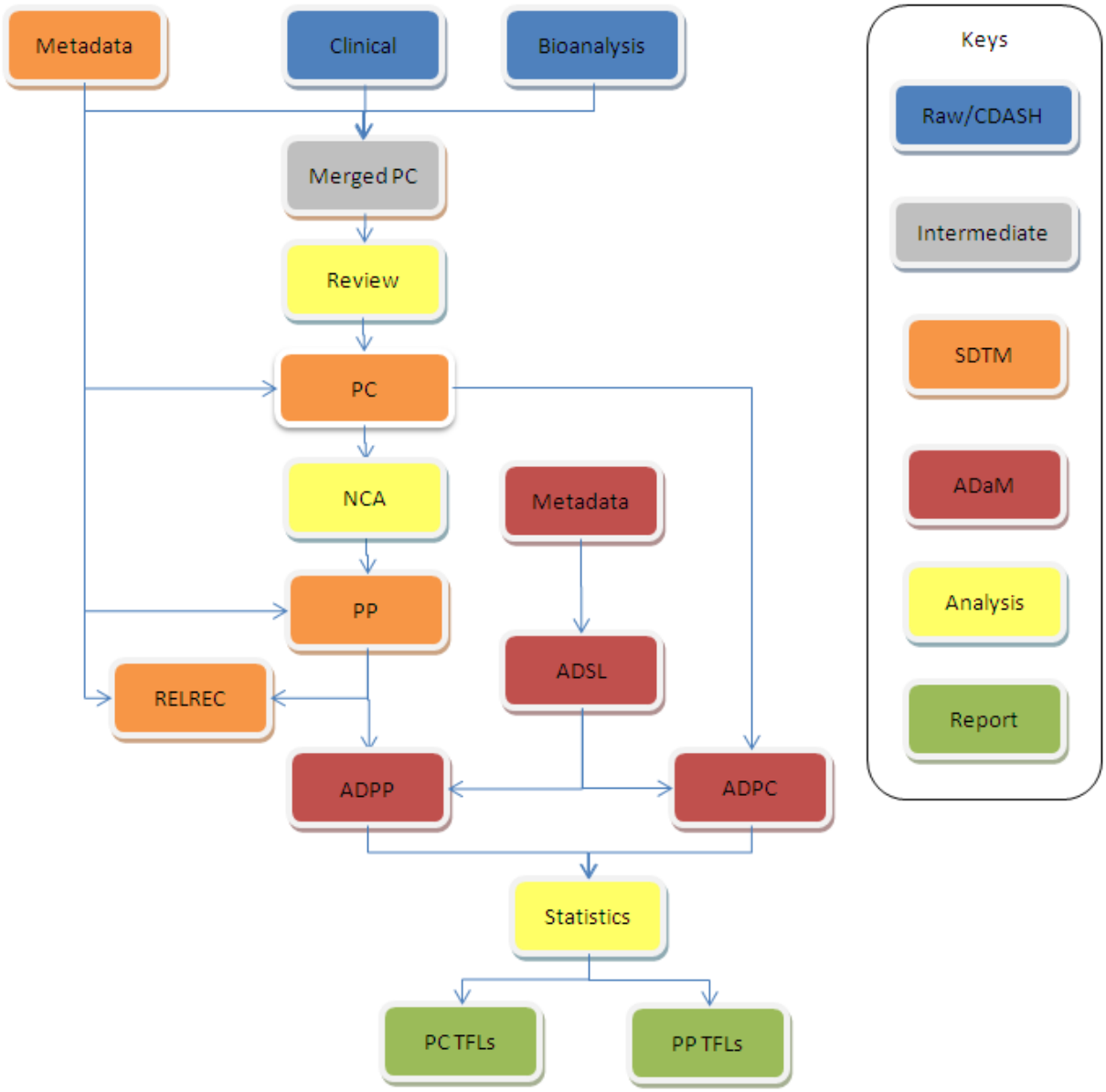


Figure 5-2 Process map for the creation of SDTM and ADaM PK datasets

This process works as follows:

1. An intermediate merged input dataset is created for PK concentrations based on the clinical (DM, EX) and bioanalytical datasets.
2. Individual concentration-time profiles are reviewed prior to NCA. Observations that need to be excluded from PK calculations or from summary statistics are flagged. The analysis time scale (actual vs. scheduled) is properly adjusted. BLQ and missing concentration values are adequately managed. Then, the SDTM PC dataset is created according to the SDTM implementation guide (IG).

3. Using specific software for non-compartmental analysis (NCA) such as SAS™ or WinNonlin/Phoenix™, PK parameters are calculated from PC. The SDTM PP dataset is created to store the PK parameters according to the SDTM IG. The SDTM RELREC dataset is also updated to provide the links between the PC and PP datasets.
4. The subject-level ADSL dataset is updated to contain the PK population flagging information.
5. The ADPC and ADPP ADaM datasets are created by combining the ADSL, PP and PC datasets, according to the ADaM-IG. As suitable, additional flagging information related to the study design, etc is created using programming statements. As necessary, additional variables are added to the ADPC and ADPP datasets from the other SDTM/ADaM datasets to enable subgroup or ad-hoc analyses.
6. PK concentration TFLs are generated from the ADPC dataset and PK parameter TFLs from the ADPP dataset.

6. Calculation of PK parameters

6.1. Main PK parameters

Table 6-1 presents the recommended labels and definitions for the main PK parameters calculated by non-compartmental analysis. We also present the standard variable labels for these PK parameters in the PP and ADPP datasets.

The first column of Table 6-1displays the parameter names. This is also the symbol recommended for use in the study documents (protocol, SAP, CSR), and in the PK TFLs. When the use of subscripts is not supported by the reporting programs, then normal line of type can be used. Likewise, the Greek letter τ may be replaced by its English counterpart (tau) in the TFL labels.

The third column provides the CDISC submission value for the corresponding variable (PKPARMCD) in PP and ADPP datasets. Indeed, CDISC has issued a controlled terminology for all SDTM variables. The correspondence between column 1 and 3 permits to create reporting formats for the main PK parameters stored in the CDISC datasets. Mapping was done according to CDISC terminology version 2013-12-20. We indicate N.A. (not available) when a standard value was not yet defined.

Table 6-1 Symbols and definition of terms used in single and multiple dose NCA

Symbol	Definition	CDISC submission value for PKPARMCD variable in PP (ADPP) dataset
Aa	Cumulative amount of drug excreted in expired air	N.A.
Ae	Cumulative amount of drug excreted in urine	N.A.
$Ae(t_1\text{-}t_2)$	Cumulative amount of drug excreted in urine from t_1 to t_2	RCAMINT determined for the specimen type specified in PPSPEC
$Ae\tau$	Cumulative amount of drug excreted in urine over a dosing interval	RCAMTAU determined for the specimen type specified in PPSPEC
A_f	Cumulative amount of drug excreted in feces	N.A.
$Af(t_1\text{-}t_2)$	Cumulative amount of drug excreted in feces from t_1 to t_2	RCAMINT determined for the specimen type specified in PPSPEC
At	Cumulative amount of drug excreted in expired air, feces and urine	N.A
AUC_{all}	Area Under the Curve from the time of dosing to the time of the last observation, regardless of whether the last concentration is measurable or not.	AUCALL

Symbol	Definition	CDISC submission value for PKPARMCD variable in PP (ADPP) dataset
AUC_{inf}	Area Under the Curve from 0 to infinity	AUCIFO when using C_{last} AUCIFP when using $C_{last,calc}$
AUC_{last}	Area Under the Curve from 0 to the time of the last quantifiable concentration	AUCLST
AUCextr	Extrapolated area under the curve from t_{last} to infinity, expressed as percentage of AUCINF	AUCPEO when using C_{last} AUCPEP when using $C_{last,calc}$
$AUC(t_1\text{-}t_2)$	Partial Area Under the Curve between t_1 and t_2	AUCINT
AUCτ	Area Under the Curve over a dosing interval	AUCTAU
AUMC	Area Under the first Moment Curve from time 0 to infinity	AUMCIFO when using C_{last} AUMCIFP when using $C_{last,calc}$
$AUMC_{last}$	Area Under the first Moment Curve from time 0 to the time of the last quantifiable concentration	AUMCLST
AUMCτ	Area Under the first Moment Curve over a dosing interval	AUMCTAU
AUMCextr	Extrapolated area Under the first Moment Curve from time t_{last} to infinity, expressed as percentage of AUMC	AUMCPEO when using C_{last} AUMCPEP when using $C_{last,calc}$
$AUMC(t_1\text{-}t_2)$	Partial Area Under the first Moment Curve between time t_1 and t_2	N.A.
C_0	Initial (or fictive) concentration at time zero for bolus iv administration	C0
C_{av}	Average concentration over a dosing interval	CAVG
C_{last}	Last observed (quantifiable) concentration	CLST
$C_{last,calc}$	Predicted concentration value at t_{last} by regression of terminal phase	N.A.
CL	Total body clearance following iv administration	CLO when using C_{last} CLP when using $C_{last,calc}$
CL/F	Apparent total body clearance following extravascular administration	CLFO when using C_{last} CLFP when using $C_{last,calc}$
CL_{NR}	Non-Renal Clearance	NRENALCL
CL_R	Renal Clearance	RENALCL – analyte defined separately
CL_{Rm}	Renal Clearance of a metabolite	RENALCL – analyte defined separately
CL_{ss}	Total body clearance at steady state following iv administration	N.A.

Symbol	Definition	CDISC submission value for PKPARMCD variable in PP (ADPP) dataset
CL_{ss}/F	Apparent total body clearance at steady state following extravascular administration	N.A.
C_{max}	Maximum observed concentration	CMAX
C_{min}	Minimum observed concentration over a dosing interval	CMIN
C(t)	Drug concentration at time t	CONC
C_{trough}	Observed concentration at the end of a dosing interval, immediately before next administration	CTROUGH
F	Absolute bioavailability, where the reference is an iv dose. F= the proportion of the administered dose which is systemically available	N.A.
F_{rel}	Relative bioavailability, where the reference is not an iv dose	N.A.
f_e	Cumulative fraction of the dose excreted (urine by default, add qualifier for other matrices)	RCPCTAU, RCPCINT determined for the specimen type specified in PPSPEC
f_u	Unbound fraction	N.A.
HVD	Half-value duration, i.e. time coverage of drug concentration in the plasma between half of C_{max} and C_{max}	N.A.
λ_z	First order terminal elimination rate constant or apparent first order terminal elimination rate constant, for compounds presenting release/absorption as limiting steps	LAMZ
LF	Linearity Factor	N.A.
MAT	Mean Absorption Time	N.A.
MRT	Mean Residence Time	MRTIFO when using C_{last} MRTIFP when using $C_{last,calc}$
PTF	Peak to Trough Fluctuation within a complete dosing interval at steady state	Peak Trough Ratio
R	Accumulation Ratio	ARAUC ARCMAX ARCMIN ARCTROUG
Swing	The degree of fluctuation over one dosing interval at steady state	N.A

Symbol	Definition	CDISC submission value for PKPARMCD variable in PP (ADPP) dataset
t_{lag}	Time delay between drug administration and the last time point prior to first observed concentration above the LLOQ (i.e. lag time to start of absorption).	TLAG
t_{last}	Time of C_{last}	TLST
t_{max}	Time of occurrence of C_{max}	TMAX
t_{min}	Time of occurrence of C_{min}	TMIN
$t_{½}$	Terminal elimination half-life or apparent terminal elimination half-life, for compounds presenting release/absorption as limiting steps	LAMZHL
V_{ss}	Volume of distribution at steady-state following iv administration	VSSO when using C_{last} VSSP when using $C_{last,calc}$
V_{ur}	Volume of urine	VOLPK
V_z	Volume of distribution following iv administration	VZO when using C_{last} VZP when using $C_{last,calc}$ VZTAU using AUCτ
V_z/F	Apparent Volume of distribution (up to bioavailability) following extravascular administration	VZFO when using C_{last} VZFP when using $C_{last,calc}$ VZFTAU using AUCτ

Additional qualifiers may be used when parameters need to be further defined for clarification purposes. These are often inserted as subscripts. By default, the matrix will in general be plasma. A non-exhaustive list of qualifiers is presented in Table 6-2.

Table 6-2. Main qualifiers for the determination of PK parameters.

Matrix (specimen type)		**Route of administration**	
bl	Blood	im	Intra-muscular
csf	Cerebrospinal fluid	nas	Intra-nasal
fcs	Feces	iv	Intravenous
mlk	Breast milk	po	Per os (by mouth)
p	Plasma		
rbc	Red Blood Cells	rec	Rectal
sal	Saliva	sc	Subcutaneous
ser	Serum	sbl	Sublingual
ur	Urine	top	Topical
Dosing interval		**Binding**	
ss	Steady-state	b	Bound
md	multiple dose in case that steady state has not been reached	u	Unbound
dayx	If multiple administration, this qualifier can be used to specify		

the day at which the parameter is calculated. It is typical to assume that the first dosing day is day1.	

The formulas used for the calculation of the main PK parameters by NCA are presented in Table 6-3, below.

Table 6-3 Main formulas for calculation for PK parameters

Parameters	Determination	
	Single Dose	Multiple Dose (if different)
Ae	$Ae = \sum C_{ur} * V_{ur}$, where C_{ur} is the concentration in urine.	
$Ae(t_1\text{-}t_2)$	$Ae(t_1 - t_2) = \sum_{t_1}^{t_2} C_{ur} * V_{ur}$	
AUC_{inf}	$AUC_{inf} = AUC(0 - t_{last}) + \frac{C(t_{last})}{\lambda_z}$, where $C(t_{last})$ is either the observed C_{last} or the predicted $C_{last,calc}$ value.	
AUC_{extr} (%)	$(C_{last}/\lambda_z)/AUCINF*100$	
$AUC(t_1\text{-}t_n)$	$AUC(t_1 - t_n) = \sum_{i=1}^{n-1} AUC(t_i - t_{i+1})$, with concentrations measured at times $t_1,\ldots t_n$, where according to the linear trapezoidal rule: $AUC(t_i - t_{i+1}) = \frac{C(t_i) + C(t_{i+1})}{2} * (t_{i+1} - t_i)$ or according to the log-linear trapezoidal rule: $AUC(t_i - t_{i+1}) = \frac{C(t_i) - C(t_{i+1})}{\ln C(t_i) - \ln C(t_{i+1})} * (t_{i+1} - t_i)$ (the logarithmic trapezoidal rule is used for the descending part of the concentration-time curve, i.e. if $C(t_i) > 1.001 * C(t_{i+1}) > 0$)	
AUMC	$AUMC = AUMC_{last} + \frac{C(t_{last}) * t_{last}}{\lambda_z} + \frac{C(t_{last})}{\lambda_z^2}$, where $C(t_{last})$ is either the observed C_{last} or the predicted $C_{last,calc}$ value.	
$AUMC(t_1\text{-}t_2)$	$AUMC(t_1 - t_n) = \sum_{i=1}^{n-1} AUMC(t_i - t_{i+1})$, with concentrations measured at times $t_1,\ldots t_n$, where according to the linear trapezoidal rule: $AUMC(t_i - t_{i+1}) = \frac{t_i * C(t_i) + t_{i+1} * C(t_{i+1})}{2} * (t_{i+1} - t_i)$.	

C_{av}		$C_{av,ss} = \frac{AUC_{\tau}}{\tau}$
CL	$CL = \frac{F * D}{AUC_{\inf}}$ NB: after iv, F=1	$CL_{ss} = \frac{F * D}{AUC\tau}$
CL/F	$CL/F = \frac{D}{AUC_{\inf}}$	$CL_{ss}/F = \frac{D}{AUC\tau}$
C_{last}	Directly obtained from the observed concentration vs. time curve.	
$C_{last,calc}$	Predicted concentration value at t_{last} by regression of terminal phase	
C_{max}	Directly obtained from the observed concentration vs. time curve	
C_{min}	Directly obtained from the observed concentration vs. time curve.	
CL_{NR}	$CL_{NR} = CL - CL_R$	
CL_R	$CL_R = \frac{Ae}{AUC_{\inf}}$	$CL_R = \frac{Ae\tau}{AUC\tau}$
CL_{Rm}	$CL_{Rm} = \frac{Ae_{metabolite}}{AUC_{\inf}} = f_e * \frac{D}{AUC_{\inf}}$	
C_{trough}	Directly obtained from the observed concentration vs. time curves.	
F	$F = \frac{AUC_{\inf,po} * D_{iv}}{AUC_{\inf,iv} * D_{po}}$	
F_{rel}	$F_{rel} = \frac{AUC_{po} * D_{ref}}{AUC_{ref} * D_{po}}$ $F_{rel} = \frac{AUC_{\inf,po} * D_{ref}}{AUC_{\inf,ref} * D_{po}}$	
f_e	$f_e = \frac{A_e}{D}$	
f_u	$f_u = \frac{C_u}{C}$	
LF		$LF = \frac{AUC_{\tau}}{AUC_{\inf,dose1}}$, Where $AUC_{inf,dose1}$ is the AUC_{inf} after first single dose.
λ_z	Estimated terminal slope of the linear regression of log-transformed concentration vs. time.	
MAT	MRT_{po} - MRT_{iv}	

MRT	After single dose oral or iv bolus: $MRT = \frac{AUMC}{AUC_{\inf}}$ For constant rate infusion : $MRT = \frac{AUMC}{AUC_{\inf}} - \frac{T\inf}{2}$, Where T_{inf} is the infusion time.	After multiple po or iv bolus: $\mathrm{MRT} = \frac{\mathrm{AUMC}\tau + \tau * (\mathrm{AUC} - \mathrm{AUC}\tau)}{\mathrm{AUC}\tau}$ After infusion: $MRT = \frac{AUMC\tau + \tau * (AUC - AUC\tau)}{AUC\tau} - \frac{T\inf}{2}$
PTF (%)		$PTF = 100 * \frac{C_{\max,ss} - C_{\min,ss}}{C_{av,ss}}$
R		After multiple dose administration: $\mathrm{R}_{\max} = \frac{\mathrm{C}_{\max,ss}}{\mathrm{C}_{\max,dose1}}$ $\mathrm{R}_{\min} = \frac{\mathrm{C}_{\min,ss}}{\mathrm{C}_{\min,dose1}}$ $\mathrm{R}_{\mathrm{AUC}} = \frac{\mathrm{AUC}\tau_{ss}}{\mathrm{AUC}\tau_{dose1}}$ $\mathrm{R}_{\mathrm{trough}} = \frac{\mathrm{C}_{\mathrm{trough},ss}}{\mathrm{C}_{\mathrm{trough},dose1}}$
Swing (%)		$Swing = 100 * \frac{C_{\max,ss} - C_{\min,ss}}{C_{\min,ss}}$
t_{lag}	Directly obtained from the observed concentrations: t_{lag}=argmin(t_i):C(t_{i+1}) > LLOQ	
t_{max}	Directly obtained from the observed concentration vs. time curve. If two identical values are recorded for C_{max}, the first one will be used for t_{max}.	
$t_{½}$	$\mathrm{t}_{1/2} = \frac{\ln 2}{\lambda_z}$	
V_{ss}	$V_{ss} = MRT * CL = \frac{F * D * AUMC}{AUC_{\inf}^{2}}$ For iv only	Vss = MRTss*CLss
V_z	$\mathrm{V}_z = \frac{\mathrm{CL}}{\lambda_z}$ For iv	Vz = CLss/λz
V_z/F	$\mathrm{V}_z / \mathrm{F} = \frac{\mathrm{CL}/\mathrm{F}}{\lambda_z}$ For extravascular	Vz/F = CLss/F/λz

6.2. NCA Checklist

A set of standard rules needs to be defined for the management of particular source data points in NCA. These include the following:

- Management of missing sampling or concentration data
- Management of concentration values below the lower limit of quantification
- Exclusion of outliers
- Use of actual vs. planned sampling timepoints
- Reporting of missing data and derived PK parameters

The standard rules are generally defined at the company level in standard operating procedures (SOP). When several alternatives are possible, or when deviating from the SOPs, the specific rules employed in a particular trial should be documented preferably in the SAP, or in the CSR. We list the most common rules for setting up the PC dataset for NCA in the following sub-sections.

6.2.1. Missing sampling or concentration data

Unless otherwise specified below, missing sampling or concentration values should not be imputed, but left missing in the calculation of derived PK parameters.

If the actual sampling time is missing, but a valid concentration value has been measured, the scheduled protocol time may be used for the calculation of derived PK parameters.

A missing predose value for single-dose study with extravascular administration is usually set to 0 for the PK calculations corresponding to an observation at dosing time (C_0).

6.2.2. Concentration values below the lower limit of quantification

Generally, only values above the LLOQ are used for the estimation of PK parameters (e.g. t1/2, AUC). Values below LLOQ are set to missing and ignored in the PK evaluation.

Exceptions are:

-Individual concentration values between the dosing time and the first time point above LLOQ (i.e. during lag-time) are often set to 0 and included in the PK evaluation.

-Pharmacokinetically plausible concentration value(s) below LLOQ at time points between two measurable concentration values or at trough may be replaced by the LLOQ or the LLOQ/2 value, flagged and included in the PK evaluation.

For urine, when calculating individual amounts and cumulative amounts excreted, BLQ urine levels are usually set to 0.

6.2.3. Exclusion of outliers

On a case by case basis, it may be necessary to exclude individual PK concentration values for the calculation of derived PK parameters because they are erroneous or abnormal. Any excluded

data should be flagged in the individual data listings and possibly on figures. The reason for exclusion should also be documented. Specifically, values may be erroneous due to a protocol violation, documented sample handling errors, vomiting episode during drug absorption, and/or analytical errors. They may also appear implausible to the pharmacokineticist in charge of the analysis. If the exclusion has a meaningful impact on the overall interpretation of the results, then it should be discussed. Note, however, that exclusion of abnormal concentrations should generally be avoided in relative bioavailability and in bioequivalence studies.

For exogenous entities, it may be necessary to exclude a subject from the pharmacokinetic population if the predose concentration prior to first day of dosing is significantly non-null. The FDA guidance (2003) for bioavailability/bioequivalence (BA/BE) studies recommends a maximum of 5% of the Cmax in the pre-dose sample for inclusion of the subject's data in the PK analysis without further adjustments.

6.2.4. Baseline adjustment for endogenous compounds

For entities with endogenous levels, positive predose concentrations are generally expected, and they should be included in all pharmacokinetic measurements and calculations.

Generally, several predose samples are collected to establish an accurate mean baseline value, particularly if a temporal rhythm is expected. Both baseline-adjusted and unadjusted concentrations can then be analysed. Negative concentration values after baseline-adjustment should be set to 0 prior to the calculation of adjusted PK parameters and for the presentation of the PK profile of the endogenous compounds.

6.2.5. Use of actual vs. planned sampling timepoints

In general, actual post-dose time should be used in calculation of PK parameters and in the generation of individual concentration-time profiles. As an alternative method, it is also acceptable to consider the planned sampling times where the timepoints deviating by more than 5% from the schedule are replaced by the actual sampling times.

Planned sampling times may be used as a replacement for unknown or missing actual times. In single dose studies, planned sampling times may be used for the predose values.

For urine, unless a gross deviation has occurred, planned sampling intervals may be used.

6.2.6. Reporting of missing PK parameters

The percentage of extrapolated AUC should not exceed 20% of AUC_{inf} for each individual profile. For i.v. bolus studies, the extrapolated AUC from time 0 to first data point should not exceed 20%. If the percentage of extrapolated AUC is more than 20%, the individual AUC_{inf} result and the parameters depending on AUC_{inf} will be listed but flagged as not reliably calculated. They will generally not be included in descriptive statistics and statistical testing procedures.

The terminal half-life should be determined over a time interval equal to at least 1.5 x t½. The regression analysis should contain data from at least 3 different time points in the terminal phase and as many data points as possible (always including the last quantifiable concentration but excluding the concentration at tmax), consistent with the assessment of a straight line on the log-

transformed scale. The coefficient of determination Adj_RSq^2 should be larger than or equal to 0.85. If at least one of these three conditions is not fulfilled, the terminal half-life and the parameters depending on t½ will be listed but flagged as not reliably calculated. They will generally be excluded from descriptive statistics and statistical testing procedures. However, if the reliability of estimated terminal half-life is judged by pharmacokineticists, who are in charge of PK analysis, the $t_{1/2}$ and related parameters would not be excluded.

7. PK Tables, Figures and Listings for Individual Studies

7.1. Standard List of Outputs

In individual studies where PK data is collected, the following list of PK outputs are commonly produced:

- Listing of individual PK concentrations
- Listing of individual PK parameters
- Summary table of PK concentrations
- Summary table of PK parameters
- Figures for PK concentration-time profiles:
  - Individual plots (separate and/or overlaying)
  - Mean plots with or without error bars

In addition, statistical TFLs are created in trials where a statistical analysis of PK data is planned.

Section 7.2 provides illustrative shells for the main types of PK TFLs and Section 7.3 presents a set of standard rules for the reporting of PK data in TFLs.

The proposed standard PK TFLs contain 3 parts: title, body, and footnote which can be adapted to match individual company standards and/or study-specific requirements.

In our standard templates, the title part contains the following pieces of information:

1. Protocol/Product information, such as the protocol number, and the compound name/code.
2. Listing/Table/Figure label to identify the type of output.
3. A unique reference number for all in-text and post-text outputs included into the CSR. According to the ICH E3 guidance document, the following section may be impacted:
   a. Section 11: A limited set of in-text PK tables and figures.
   b. Section 14.2: Any additional supportive PK tables and figures cross-referenced in the text of the CSR.
   c. Section 16.2.5: Appendix to the CSR dedicated to the additional PK TFLs.
4. The output title.
5. A page numbering indicator for the page number and the total number of pages. Please note that page numbers may appear in the footer or anywhere else in the title, as suitable.
6. The analysis population/set. Generally, summary tables and figures are produced on the PK analysis set and individual data listings and graphs are reported for all subjects.

The body part is broken up into 2 parts:

1. An optional headline defining the information displayed on any particular page (the by-lines).
2. The actual output content presented in a tabular grid.

The footnote contains the following pieces of information:

1. The definition of all abbreviations. Please note that, generally, PK parameters are not defined in the footnotes.
2. Annotations for flagged data values. Usually, flags are used for exclusion of individual data.
3. A description of how BLQ values are reported.
4. Information about the source dataset, program and output path.
5. Information about the data and program status (development/test/production).
6. Production date and time.

7.2. Annotated PK TFLs

7.2.1. Listings for PK parameters

Two templates are provided for the listing of PK parameters. Figure 7-2 presents the vertical display (one parameter per row) and Figure 7-3 the horizontal one (parameters in column). The vertical display is most suited for a comprehensive listing. The horizontal display is more concise and probably more easy to read, having parameters displayed in column.

PROTOCOL/PRODUCT INFO (page x of x)

Listing 16.2.5-x.x Individual pharmacokinetic parameters

by compound, matrix, analyte and [actual/randomized] [treatments/group]

Analysis Set: All subjects

Compound: XXX, Matrix: YYY, Analyte: ZZZ

[Actual/Randomized] [treatment/group] [sequence]: AAAAAA

			Treatment				
Country/ Site/ Subject	Age/ Sex/ Race	Period	Name [Dose (uom)]	Profile day	Parameter (unit)	Value	
CNTR/ ST1/ XXXXX	YY/ M/ Ca	1	xx mg	1	AUCinf (ng*h/mL)	xx	*
					Cmax (ng/mL)	xx	
					tmax (h)	xx.x	
					t1/2 (h)	xx	*

Age/Sex/Race: M=Male, F=Female, Ca=Caucasian, …
NV: No Value was calculated.
Value * was not considered for summary and inferential procedures.
PATH DATA/PROGRAM/OUTPUT
PRODUCTION STATUS/RUN DDMMMYYYY: HHMM

Figure 7-1. Shell for individual PK parameters listing – one parameter per row

Annotations:

- If the actual treatment is known, and it differs from the randomized treatment, reporting it according to actual treatment is recommended. Otherwise, the randomized treatment is reported.

- In some particular multi-arm trials, all groups receive the same treatment but they differ by other characteristics, such as gender, disease status or stage, administration with food, etc... In these cases, data are reported according to the group, and not the treatment.
- In sequential and cross-over trials, the sequence and period are reported. In parallel group or single arm trials, these data are usually skipped. In multi-part trials, the part is displayed either in the title, headline or column.
- This column is optional when there is only one day with PK profile data, such as in single dose trials.

Notes to programmer:

- If possible, order parameters to show first the primary, then the secondary PK endpoints.
- Align values to the decimal place.

PROTOCOL/PRODUCT INFO (page x of x)

Listing 16.2.5-x.x Individual pharmacokinetic parameters
by compound, matrix, analyte and [actual/randomized] [treatments/group]
Analysis Set: All subjects

Compound: XXX, Matrix: YYY, Analyte: ZZZ

[Actual/Randomized] [treatment/group] [sequence]: AAAAAA

Country/ Site/ Subject	Age/ Sex/ Race	Period	Treatment Name [Dose (uom)]	Profile day	AUCinf (ng*h/mL)	Cmax (ng/mL)	tmax (h)	[PKPARAM] (uom)
CNTR/ ST1/ XXXXX	YY/ M/ Ca	1	xx mg	1	xxx	xxx	xxx	xxx
					NV	xxx	xxx	xxx
					xx.x *	xx.x *	xxx *	xxx *

Age/Sex/Race: M=Male, F=Female, Ca=Caucasian, …
NV: Not Value was calculated.
Value * was not considered for summary and inferential procedures.
PATH DATA/PROGRAM/OUTPUT
PRODUCTION STATUS/RUN DDMMMYYYY: HHMM

Figure 7-2. Shell for individual PK parameters listing –parameters on column

Annotations:

- If the actual treatment is known, and it differs from the randomized treatment, reporting it according to actual treatment is recommended. Otherwise, the randomized treatment is reported.
- In some particular multi-arm trials, all groups receive the same treatment but they differ by other characteristics, such as gender, disease status or stage, administration with food, etc... In these cases, data are reported according to the group, and not the treatment.
- In sequential and cross-over trials, the sequence and period are reported. In parallel group or single arm trials, these data are usually skipped. In multi-part trials, the part is displayed either in the title, headline or column.
- This column is optional when there is only one day with PK profile data, such as in single dose trials.

Notes to programmer:

- If possible, order parameters to display first the primary, then the secondary PK endpoints. If necessary, the table can be split into 2 files: one for the primary, the other for the secondary PK endpoints.
- Align parameter values to the decimal place.
- Add columns, as necessary to list all PK parameters. When there are more parameters to display than the number of available columns in a page, continue the list over the next page. In that case, repeat the initial columns prior to the first PK parameter on all pages. Note that the list of parameters and their units may vary across analytes, profile days, etc… Therefore, the labels for the PK parameter columns need dynamic adaptations according to the actual data.

7.2.2. Listings for PK concentrations

Two templates are provided for the listings of PK concentrations. Figure 7-3 presents the shell for continuous concentration samples such as in plasma or blood, and Figure 7-4 for the sampling by interval, such as in urine.

PROTOCOL/PRODUCT INFO (page x of x)

Listing 16.2.5-x.x Individual pharmacokinetic concentrations
by compound, matrix, analyte and [actual/randomized] [treatments/group]
Analysis Set: PK analysis set

Compound: XXX, Matrix: YYY, Analyte: ZZZ

[Actual/Randomized] [treatment/group] [sequence]: AAAAAA

Country / Site/ Subject	Age/ Sex/ Race	Period	Treatment: Dose (uom)	Treatment: Date/Time of dosing	Profile day	Scheduled Sampling Time (uom)	Date/Time of collection	Actual Time (uom)	Concentration (uom)	Exclusion Comment
CNTR/ ST1/ XXXXX	YY/ M/ Ca	1	xx mg	2000-02-12Txx:xx	1	0.0	2000-02-12Txx:xx	- xx.x	xxx.xx +*	Predose >0
						1.0	2000-02-12Txx:xx	xx.x	xxx.xx +	Outlier
						1.5	2000-02-12Txx:xx	xx.x	0 (<1)	
						2.0	2000-02-12Txx:xx	xx.x	NV	Vomiting

Age/Sex/Race: M=Male, F=Female, Ca=Caucasian, …
NV : No Value collected.
Value * was not considered for summary and inferential procedures.
Value + was excluded from estimation of PK parameters.
For values <LLOQ, the reported (<LLOQ) values are presented.
PATH DATA/PROGRAM/OUTPUT
PRODUCTION STATUS/RUN DDMMMYYYY: HHMM

Figure 7-3. Shell for individual PK concentrations listing

Annotations:

- If the actual treatment is known and it differs from the randomized treatment, reporting it according to actual treatment is recommended. Otherwise, the randomized treatment is reported.
- In some particular multi-arm trials, all groups receive the same treatment but they differ by other characteristics, such as gender, disease status or stage, administration with food, etc… In these cases, data are reported according to the groups and not the treatment.
- In sequential and cross-over trials, the sequence and period are reported. In parallel group or single arm trials, these data are skipped. In multi-part trials, the part is displayed either in the title, headline or column.
- A footnote indicates the LLOQ value and how values <LLOQ are reported.

Note to programmer:

- Align the concentration values to the decimal place.
- The comment column is optional and can be dropped if there are no comments. Vomiting episodes are also generally recorded under this column.

PROTOCOL/PRODUCT INFO (page x of x)

Listing 16.2.5-x.x Individual pharmacokinetic concentrations in urine
by compound, matrix, analyte and [actual/randomized] [treatments/group]
Analysis Set: PK analysis set

Compound: XXX, Matrix: Urine, Analyte: ZZZ

[Actual/Randomized] [treatment/group] [sequence]: AAAAAA

				Collection					Cumulative amount excreted	
Country/ Site/ Subject	Age/ Sex/ Race	Period	Profile day	Planned Collection Interval (uom)	Start Date/Time	End Date/Time	Amount of urine collected (uom)	Concentration (uom)	Amount excreted (uom)	Absolute (uom)	Relative to dose (%)
CNTR/ ST1/ XXXXX	YY/ M/ Ca	1	1	0 - 1	2000-02-12Txx:xx	2000-02-12Txx:xx	xxx	xxx.xx	xxx.xx	xxx.xx	x.xx%
				1 - 2			NV	0	0 x	xxx.xx	x.xx%
				2 - 12	2000-02-12Txx:xx	2000-02-12Txx:xx	xxx	xxx.xx *	xxx.xx	xxx.xx	x.xx%

Age/Sex/Race: M=Male, F=Female, Ca=Caucasian, …
NV : No Value collected.
Value * was not considered for summary and inferential procedures.
Value x was <LLOQ (xxx uom) and considered as zero.
PATH DATA/PROGRAM/OUTPUT
PRODUCTION STATUS/RUN DDMMMYYYY: HHMM

Figure 7-4. Shell for listing of individual PK concentrations in urine

Annotations:

- If the actual treatment is known and it differs from the randomized treatment, reporting it according to actual treatment is recommended. Otherwise, the randomized treatment is reported.

- In some particular multi-arm trials, all groups receive the same treatment but they differ by other characteristics, such as gender, disease status or stage, administration with food, etc… In these cases, data are reported according to the groups and not the treatment.
- In sequential and cross-over trials, the sequence and period are reported. In parallel group or single arm trials, these data are skipped. In multi-part trials, the part is displayed either in the title, headline or column.
- A footnote indicates the LLOQ value and how values <LLOQ values are reported. The standard is to replace them by zero.

Note to programmer:

- Align the concentration values to the decimal place.
- If possible, report the cumulative amount excreted both in absolute value and in percentage of the administered dose.

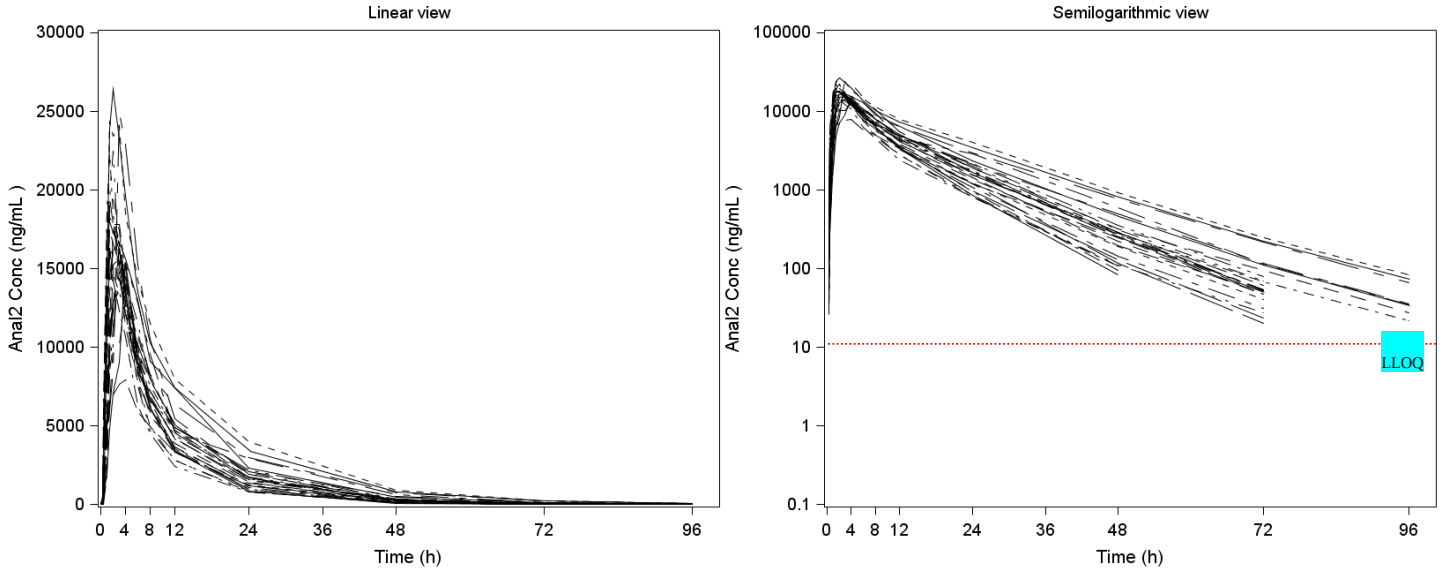
7.2.3. Figures for PK concentration-time profiles

Three templates are provided for the display of concentration-time profiles. Figure 7-5 presents the overlaying individual profiles, Figure 7-6 shows the individual profiles, and Figure 8-7, the mean profiles. The shells can be used for actual or dose-normalized concentrations, as appropriate.

PROTOCOL/PRODUCT INFO (page x of x)

Figure 16.2.5-x.x Overlaying individual [dose-normalized] concentration-time profiles
by compound, matrix, analyte and [actual/randomized] [treatments/group]
Analysis Set: PK analysis set

Compound: XXX, Matrix: YYY, Analyte: ZZZ
[Actual/Randomized] [treatment/group]: AAAAAA



Values <LLOQ (xxx uom) were considered as [zero;missing;LLOQ; LLOQ/2;…].
PATH DATA/PROGRAM/OUTPUT
PRODUCTION STATUS/RUN DDMMMYYYY: HHMM

Figure 7-5. Shell for overlaying PK concentration-time profiles

Annotations:

- Dose-normalized plots may be added in clinical trials testing several dose levels of a compound. The same template can be used as for non-adjusted plots. The same scale for the y-axis (concentration) can be used across multiple plots to enable a visual comparison of the dose-normalized profiles.
- If the actual treatment is known and it differs from the randomized treatment, reporting it according to actual treatment is recommended. Otherwise, the randomized treatment is reported.
- In some particular multi-arm trials, all groups receive the same treatment but they differ by other characteristics, such as gender, disease status or stage, administration with food, etc... In these cases, data are reported according to the groups and not the treatment.
- The LLOQ value is presented either in the footer or as a reference line on the plot. The footnote also indicates how values <LLOQ are reported.

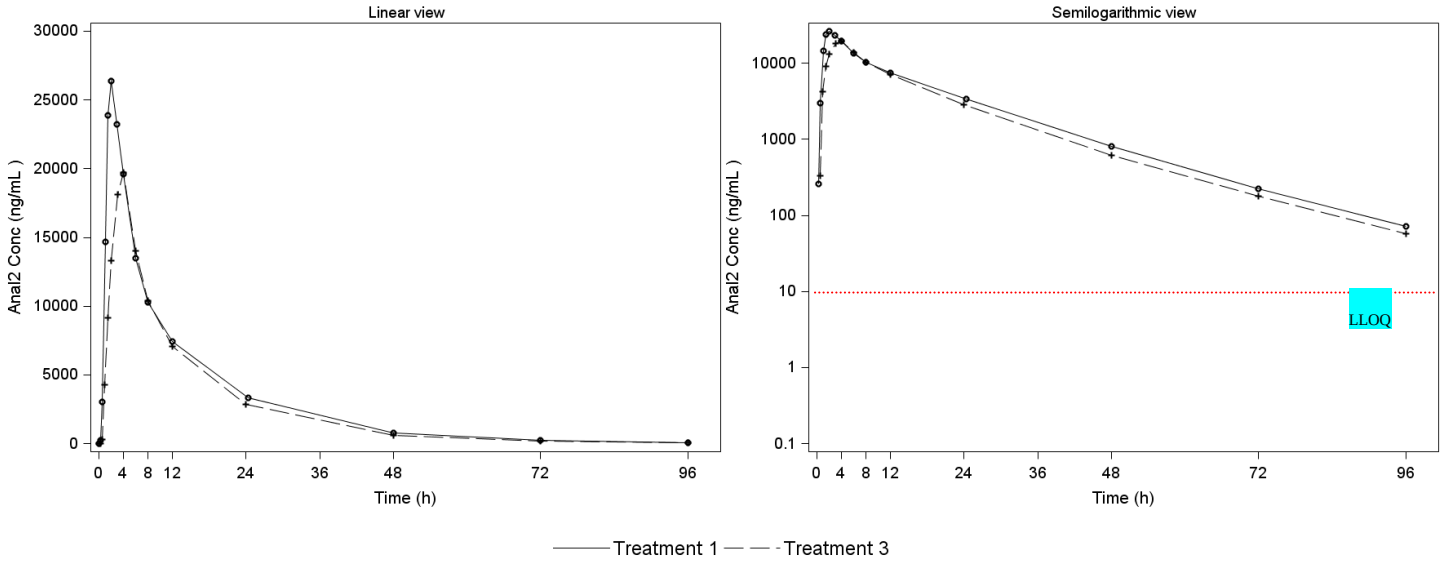
Notes to programmer:

- Plot against actual time since last dosing, if possible. Otherwise, use protocol times. As an alternative option, use protocol times unless actual times are more than 5% distant, then use actual times. Use the method that was chosen for PK parameters determination.
- Scale of y-axis may be either identical across all treatment groups or treatment-specific, as most relevant. This will generally depend if the purpose is to optimize the fit of individual groups or to enable a visual comparison of groups.
- As appropriate, scale of x-axis may be truncated to the first timepoint where all concentrations are <LLOQ to optimize the presentation. However, the scale of the x-axis should generally be identical across all treatment groups to enable a fair comparison of time courses.
- The LLOQ reference line is optional.

PROTOCOL/PRODUCT INFO (page x of x)

Figure 16.2.5-x.x Individual concentration-time profiles
by compound, matrix, analyte and [actual/randomized] [treatments/group]
Analysis Set: All subjects

Compound: XXX, Matrix: YYY, Analyte: ZZZ
Country/Site/Subject: CNTR/ST1/XXXXX



Values <LLOQ (xxx uom) were considered as [zero;missing;LLOQ; LLOQ/2;…].
PATH DATA/PROGRAM/OUTPUT
PRODUCTION STATUS/RUN DDMMMYYYY: HHMM

Figure 7-6. Shell for individual PK concentration-time profiles

Annotations:

- If the actual treatment is known and it differs from the randomized treatment, reporting it according to actual treatment is recommended. Otherwise, the randomized treatment is reported.

- In some particular multi-arm trials, all groups receive the same treatment but they differ by other characteristics, such as gender, disease status or stage, administration with food, etc… In these cases, data are reported according to the groups and not the treatment.
- The LLOQ value is presented either in the footer or as a reference line on the plot. The footnote also indicates how values<LLOQ are reported.

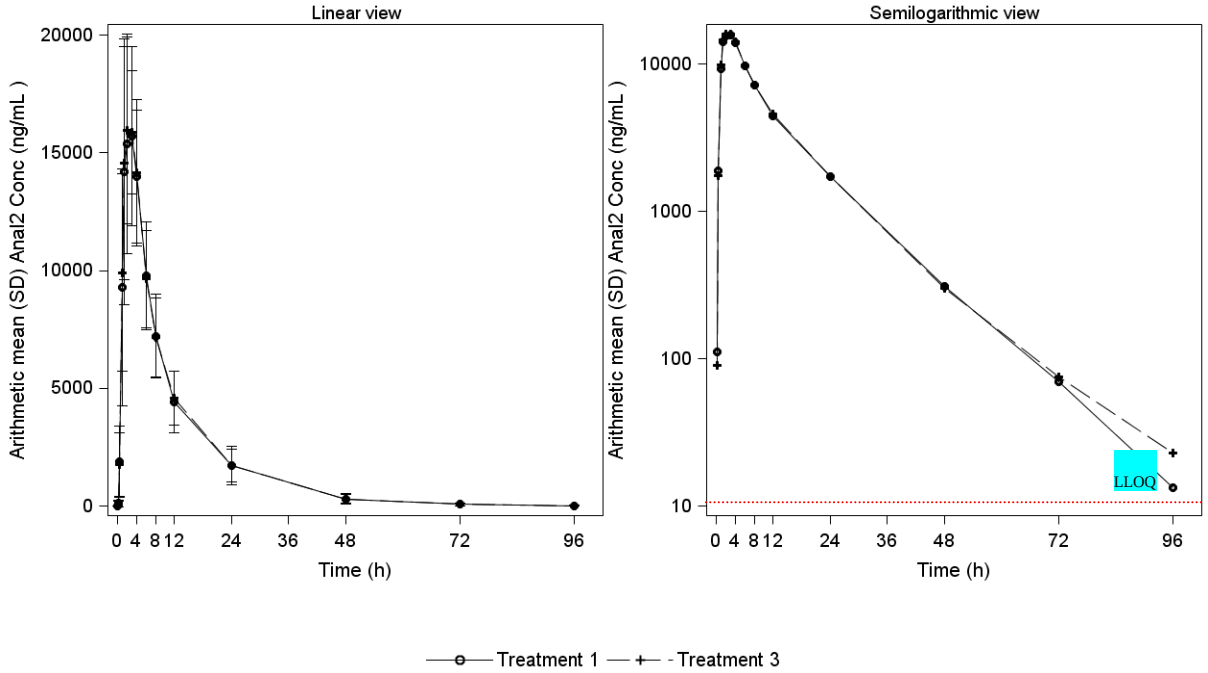
Notes to programmer:

- Plot against actual time since last dosing, if possible. Otherwise, use protocol times. As an alternative option, use protocol times unless actual times are more than 5% distant, then use actual times. Use the method that chosen for PK parameters determination.
- For multiple dose trials, display the entire time course or split into different panels by dosing occasion, as most appropriate.
- For multi-period trials, display overlaying treatments separately for each analyte.
- Scale of y-axis may be either identical across all subjects or subject-specific, as most relevant.
- The LLOQ reference line is optional.

PROTOCOL/PRODUCT INFO (page x of x)

Figure 14.2-x.x [Arithmetic mean/Geometric mean/Median] (SD) [dose-normalized] concentration-time plot per treatment (overlaying) and analyte (separately)
Analysis Set: PK analysis set

Compound: XXX, Matrix: YYY, Analyte: ZZZ



Values <LLOQ (xxx uom) were considered as [zero;missing;LLOQ; LLOQ/2;…].
PATH DATA/PROGRAM/OUTPUT
PRODUCTION STATUS/RUN DDMMMYYYY: HHMM

Figure 7-7. Shell for mean PK concentration-time profiles

Annotations:

- It is customary and computationally simple to produce arithmetic mean plots for PK data. Considering the inherently log-normal distribution of concentrations, plots of geometric mean concentration versus time may also be created. Median plots are another alternative to mean plots for robust displays in the presence of extreme values. They are simple to compute and can handle the case of zero concentration values.
- Dose-normalized plots may be added in clinical trials testing several dose levels of a compound. The same template can be used as for the non-adjusted plots. The same scale for the y-axis (concentration) can be used across multiple plots to enable a visual comparison of the dose-normalized profiles.
- Error bars may be added to the linear view to present the concentration standard deviation (SD) at each timepoint.
- In some particular multi-arm trials, all groups receive the same treatment but they differ by other characteristics, such as gender, disease status or stage, administration with food, etc… In these cases, data are reported according to the groups and not the treatment.
- A footnote indicates the LLOQ value and how values<LLOQ are managed for the computation of the statistics. The LLOQ value can also be displayed as an horizontal reference line on the plot.

Notes to programmer:

- Plot against protocol time since last dosing. Individual data may have been flagged for exclusion if actual time differs significantly from scheduled time. See rules in Section 7.3.5.
- A geometric mean is simply computing the arithmetic mean of the logarithm-transformed concentrations and then using the exponentiation to return the computation to the original scale. Please note that, in the presence of zero concentration values, geometric means cannot be calculated. So, a different approach to <LLOQ data (either impute to LLOQ or LLOQ/2 or consider as missing) may need to be adopted for the production of geometric mean plots.
- In geometric mean plots, error bars are computed after back transformation from the log-scale of the mean +/- SD log-concentrations. In that case, the upper and lower bars are calculated according to the following formula: upper bar=gmean*exp(SD_{logPK}); lower bar=gmean/exp(SD_{logPK}), where gmean is the geometric mean and SD_{logPK} is the standard deviation of the log-concentrations.
- One- or two-sided error bars may be used. For one-sided, either use the same side across all groups or choose the side depending on the mean values (upward for larger group means and downward for smaller group means).
- The y-axis should show only positive values. Error bars dipping below 0 should be truncated at 0.
- The LLOQ reference line is optional.

7.2.4. Tables for summary of PK parameters

PROTOCOL/PRODUCT INFO (page x of x)

Table 14.2-x.x Summary statistics for PK parameters

by compound, matrix, analyte and [actual/randomized] [treatments/group]

Analysis Set : PK analysis set

Compound: XXX, Matrix: YYY, Analyte: ZZZ

Actual treatment	Profile day	Statistic	<Parameter 1> <unit>	<Parameter 2> <unit>	<Parameter 3> <unit>
TRTA	1	N	xx	xx	xx
		Mean (SD)	xxx (xxx)	xxx (xxx)	xxx (xxx)
		CV% mean	xx.x	xx.x	xx.x
		Geo-mean	xxx	xxx	xxx
		CV% geo-mean	xx.x	xx.x	xx.x
		Median	xxx	xxx	xxx
		[Min; Max]	[xxx;xxx]	[xxx;xxx]	[xxx;xxx]

CV% = coefficient of variation (%)=sd/mean*100;

CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100

Geo-mean: Geometric mean.

Geo-mean and CV% geo-mean not presented when the minimum value for a parameter is zero.

PATH DATA/PROGRAM/OUTPUT

PRODUCTION STATUS/RUN DDMMMYYYY: HHMM

Figure 7-8. Shell for summary of PK parameters

Annotations:

- If the actual treatment is known and it differs from the randomized treatment, reporting it according to actual treatment is recommended. Otherwise, the randomized treatment is reported.

- In some particular multi-arm trials, all groups receive the same treatment but they differ by other characteristics (such as gender, disease status or stage, administration with food, etc…). In these cases, data are reported according to the groups and not the treatment.
- This column is optional when there is only one day with PK profile data, such as in single dose trials.

Notes to programmer:

- A geometric mean is simply computing the arithmetic mean of the logarithm-transformed concentrations and then using the exponentiation to return the computation to the original scale.
- The CV% of the geometric mean is calculated using the following formula: $CV\%\ geo-mean = 100 * \sqrt{e^{SD^2_{logPK}} - 1}$, where SD_{logPK} is the standard deviation of the log-concentrations.

7.2.5. Tables for summary of PK concentrations

Three shells are provided for the summary of PK concentrations. The first two present time in rows and treatment in columns. The last is the opposite display: time is in columns and treatment in rows. For one of these views (treatment in columns), we also provide statistical displays that depend on how values <LLOQ are managed. Figure 7-9 is when values < LLOQ are replaced by zero, LLOQ or LLOQ/2, or left missing. Figure 7-10 is when they are left-censored at LLOQ.

PROTOCOL/PRODUCT INFO (page x of x)

Table 14.2-x.x Summary statistics for PK concentrations

by compound, matrix, analyte and [actual/randomized] [treatments/group]

Analysis Set : PK analysis set

Compound: XXX, Matrix: YYY, Analyte: ZZZ, Unit : uom

Dose reference id	Profile day	Scheduled time point (h)	Statistic	TRTA	TRTB
1	1	0.0	N	xx	xx
			Mean (SD)	xxx (xxx)	xxx (xxx)
			CV% mean	xx.x	xx.x
			Geo-mean	xxx	xxx
			CV% geo-mean	xx.x	xx.x
			Median	xxx	xxx
			[Min; Max]	[xxx;xxx]	[xxx;xxx]

CV% = coefficient of variation (%)=sd/mean*100;

CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100

Geo-mean: Geometric mean.

Geo-mean and CV% geo-mean not presented when the minimum concentration is zero at respective timepoint.

Values <LLOQ (xxx uom) were considered as [missing; zero; LLOQ; LLOQ/2] in descriptive statistics calculation.

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PATH DATA/PROGRAM/OUTPUT
PRODUCTION STATUS/RUN DDMMMYYYY: HHMM
```

Figure 7-9. Shell for summary of PK concentration, when BLQ values are imputed or left missing.

Annotations:

- If the actual treatment is known and it differs from the randomized treatment, reporting it according to actual treatment is recommended. Otherwise, the randomized treatment is reported.
- In some particular multi-arm trials, all groups receive the same treatment but they differ by other characteristics such as gender, disease status or stage, administration with food, etc… In these cases, data are reported according to the groups and not the treatment.
- This column is optional when there is only one dosing day with PK data, such as in single dose trials.
- A footnote indicates the LLOQ value and how values<LLOQ are reported.

Note to programmer:

- In multi-part trials, the part is displayed either in the title, headline or column.

PROTOCOL/PRODUCT INFO (page x of x)

Table 14.2-x.x Summary statistics for PK concentration
by compound, matrix, analyte and [actual/randomized] [treatments/group]
Analysis Set : PK analysis set

Compound: XXX, Matrix: YYY, Analyte: ZZZ, Unit : uom

Dose reference id	Profile day	Scheduled time point (h)	Statistic	TRTA	TRTB
1	1	0.0	N	xx	xx
			<LLOQ – n (%)	xx (x%)	xx (x%)
			Mean (SD)	xxx (xxx)	xxx (xxx)
			CV% mean	xx.x	xx.x
			Geo-mean	xxx	xxx
			CV% geo-mean	xx.x	xx.x
			Median	xxx	xxx
			[Min; Max]	[xxx;xxx]	[xxx;xxx]

N = number of non-missing observations including values <LLOQ.
<LLOQ - n (%) number and percentage of values < LLOQ (xx uom).

CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100.

Geo-mean: Geometric mean.

In case of values <LLOQ ,the Mean, SD CV% mean, Geo-mean, CV% geo-mean are adjusted for left-censored data at the LLOQ. Otherwise, standard descriptive statistics are presented.
PATH DATA/PROGRAM/OUTPUT
PRODUCTION STATUS/RUN DDMMMYYYY: HHMM

Figure 7-10. Shell for summary of PK concentration, when BQL values are left censored.

Annotations:

- If the actual treatment is known and it differs from the randomized treatment, reporting it according to actual treatment is recommended. Otherwise, the randomized treatment is reported.
- In some particular multi-arm trials, all groups receive the same treatment but they differ by other characteristics such as gender, disease status or stage, administration with food, etc… In these cases, data are reported according to the groups and not the treatment.
- This column is optional when there is only one dosing day with PK data, such as in single dose trials.
- A footnote indicates the LLOQ value and how values<LLOQ are reported. See Section 7.3.3.1 for more details on how to report statistics in the presence of left censored values.

Notes to programmer:

- N must be the total number of non-missing values, including all values <LLOQ.
- Do not report the minimum value if there are values <LLOQ.
- In the presence of values <LLOQ, the summary statistics (mean, SD, geometric mean and CV% of the geometric mean) are the maximum likelihood estimates calculated using a parametric model for data that can be left censored. If there are no censored values, standard descriptive summary statistics are presented.
- For geometric means, results are calculated on the logarithm-transformed concentrations and then using the exponentiation to return the computation to the original scale.
- In multi-part trials, the part is displayed either in the title, headline or column.

PROTOCOL/PRODUCT INFO (page x of x)

Table 14.2-x.x Summary statistics for PK concentrations

by compound, matrix, analyte and [actual/randomized] [treatments/group]

Analysis Set : PK analysis set

Compound: XXX, Matrix: YYY, Analyte: ZZZ, Unit : uom

				Scheduled time (h)	
Treatment	Dose reference id	Profile day	Statistic	0.0	0.5
TRTA	1	1	N	xx	xx
			Mean (SD)	xxx (xxx)	xxx (xxx)
			CV% mean	xx.x	xx.x
			Geo-mean	xxx	xxx
			CV% geo-mean	xx.x	xx.x
			Median	xxx	xxx
			[Min; Max]	[xxx;xxx]	[xxx;xxx]

CV% = coefficient of variation (%)=sd/mean*100;

CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100

Geo-mean: Geometric mean.

Geo-mean and CV% geo-mean not presented when the minimum concentration is zero at respective timepoint.

Values <LLOQ (xxx uom) were considered as [missing; zero; LLOQ; LLOQ/2] in descriptive statistics calculation.

PATH DATA/PROGRAM/OUTPUT

PRODUCTION STATUS/RUN DDMMMYYYY: HHMM

Figure 7-11. Shell for summary of PK concentration, with time in columns.

Annotations:

- If the actual treatment is known and it differs from the randomized treatment, reporting it according to actual treatment is recommended. Otherwise, the randomized treatment is reported.
- In some particular multi-arm trials, all groups receive the same treatment but they differ by other characteristics such as gender, disease status or stage, administration with food, etc… In these cases, data are reported according to the groups and not the treatment.
- This column is optional when there is only one dosing day with PK data, such as in single dose trials.
- A footnote indicates the LLOQ value and how values<LLOQ are reported.

Notes to programmer:

- In multi-part trials, the part is displayed either in the title, headline or column.
- This shell can be adapted in a way similar to Figure 7-10 when BLQ values are left-censored.

7.2.6. Tables for summary of amount excreted in urine.

One shell is presented in Figure 7-12. The matrix is generally urine. But it can be adapted as appropriate.

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Table 14.2-x.x Summary statistics for (cumulative) amounts excreted by compound, matrix, analyte and [actual/randomized] [treatments/group]

Analysis Set : PK analysis set

Compound: XXX, Matrix: Urine, Analyte: ZZZ

Dose reference id	Profile day	Collection Interval (h)	Statistic	Amount excreted (uom) TRTA	Amount excreted (uom) TRTB	Cumulative amount excreted (uom) TRTA	Cumulative amount excreted (uom) TRTB
1	1	0 - 4	N	xx	xx	xx	xx
			Mean (SD)	xxx (xxx)	xxx (xxx)	xxx (xxx)	xxx (xxx)
			CV% mean	xx.x	xx.x	xx.x	xx.x
			Geo-mean	xxx	xxx	xxx	xxx
			CV% geo-mean	xx.x	xx.x	xx.x	xx.x
			Median	xxx	xxx	xxx	xxx
			[Min; Max]	[xxx;xxx]	[xxx;xxx]	[xxx;xxx]	[xxx;xxx]

CV% = coefficient of variation (%)=sd/mean*100;

CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100

Geo-mean: Geometric mean.

Geo-mean and CV% geo-mean not presented when the minimum amount is zero during the respective collection interval.

Values <LLOQ (xxx uom) were considered as zero in descriptive statistics calculation.

PATH DATA/PROGRAM/OUTPUT

PRODUCTION STATUS/RUN DDMMMYYYY: HHMM

Figure 7-12. Shell for summary of amounts excreted (in urine).

Annotations:

- If the actual treatment is known and it differs from the randomized treatment, reporting it according to actual treatment is recommended. Otherwise, the randomized treatment is reported.
- In some particular multi-arm trials, all groups receive the same treatment but they differ by other characteristics such as gender, disease status or stage, administration with food, etc… In these cases, data are reported according to the groups and not the treatment.
- This column is optional when there is only one dosing day with PK data, such as in single dose trials.
- A footnote indicates the LLOQ value and how values <LLOQ are reported. They are generally set to zero.

Notes to programmer:

- For geometric means, results are calculated on the logarithm-transformed concentrations and then using the exponentiation to return the computation to the original scale.
- Geometric mean and CV% are not presented when the minimum value equals zero.
- The cumulative mount excreted may be reported in absolute value and/or normalized in percentage of the administered dose.

7.3. PK TFLs Checklist

7.3.1. Individual data handling in listings

Concentration data below the lower limit of quantification (BLQ) should be labeled as such in the data listings. Several flagging options are possible for BLQ data, including:

- the actual numerical data with a flag (eg, "*"),
- a missing value,
- an imputed value such as zero, the LLOQ, the LLOQ/2.
- the labels "BLQ" or "<X" where X is the numerical value of the LLOQ established by the laboratory.

A footnote should be added to the listing in order indicating the LLOQ value and how BLQ data were reported.

Missing values should also be labeled as such in the data listings. Label such as "NV" (no value) or "." (dot) may be used.

Any missing sampling or concentration data that was imputed should be flagged in the concentration data listing.

Any individual data excluded from NCA or statistical analysis should be flagged in the listings.

7.3.2. Individual plots

Depending on the design of the study (e.g., crossover, parallel, sequential), individual graphs can be presented per treatment, as in spaghetti plots, and/or by subject.

Plasma concentration vs. time profiles are often reported both on linear and semi-logarithmic scales.

For urine, amount excreted, cumulative or not, is usually presented on a linear scale.

In general, it is recommended to display the time scale for individual plots according to the method that was chosen for PK parameters determination. The actual times are most often reported. The protocol time may be used as an alternative when actual times are missing or when they do not differ greatly, by more than 5%.

The plot axis scales can be optimized per treatment, for the entire study, per subject or per occasion, as deemed appropriate.

Most often, individual plots present all available data. Data points flagged for exclusion, or BLQ values that have been imputed, may be identified using different symbols and/or colors in the plots. For BLQ values, a footnote is often added that details how these data were managed in the plots. A horizontal reference line at the BLQ value may also be added to indicate the threshold in the plots.

7.3.3. Descriptive statistics in tables

Unless otherwise specified in the protocol or SAP, the following descriptive statistics are often calculated for PK concentrations and PK parameters: N, arithmetic mean, SD, coefficient of variation (CV%), minimum, median, maximum, geometric mean and geometric CV%.

The geometric mean is computed as:

Geo-mean = exp(arithmetic mean of log transformed data).

The geometric CV% is computed as:

CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100.

For t_{max} and t_{lag}, it is customary to report only the N, median, minimum and maximum statistics, but mean, SD and geometric mean can also be reported.

Additional statistics such as the number of missing observations, quartiles (Q1, Q3), specific percentiles, the standard error, the standard error of the mean (%SEM) and confidence intervals are less frequently reported.

In the presence of zero concentrations, the geometric mean and CV% geo-mean cannot be calculated, and should be reported as missing.

When there is only one non-missing value, the measures of precision (SD, CV%, geometric CV%, etc…) are not reported. The CV% is not reported when the mean is zero.

7.3.3.1. Statistics in the presence of BLQ data

The method used to handle BLQ values in statistical summaries of concentrations should be documented preferably in the SAP, or in the CSR.

Usually, BLQ values are either ignored (i.e., left missing) or imputed by a single particular value (e.g., 0, LLOQ, or LLOQ/2) prior to computing standard statistical summaries of PK concentrations.

However, standard descriptive results may be greatly biased when the total number of BLQ values is large, such as when it exceeds one-third of the total.

As an alternative option, the arithmetic mean and standard deviation may be adapted to the presence of left-censored values (values below the LLOQ), by reporting the maximum likelihood estimates from a parametric model for data that can be left-censored, using procedures such as SAS™ PROC LIFEREG.

The geometric mean and it CV% are calculated similarly, by applying the censoring method to log-concentrations and back-transforming the estimates to the original scale.

A similar approach considering right-censored data at the upper limit of quantification (ULOQ) is possible when there are values > ULOQ. However, this is more rarely the case in practice as samples may be diluted.

In the case of censoring, the empirical minimum (maximum) may not be quantified if there are values below the LLOQ (above the ULOQ).

In case of values below the LLOQ or above the ULOQ, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, may be reported as well.

7.3.4. Individual data handling in summary tables

In the presence of missing concentrations, if the missing values are critical for the calculation of selected PK parameters, the corresponding PK endpoints may still be calculated but they should be flagged for exclusion from the statistical summaries.

When any actual sampling time differs significantly from the protocol time by more than 10% but at least 5 minutes, the concentration should be excluded from calculation of descriptive statistics, but always kept in the determination of PK parameters (according to Section 6.2.5). A flag and a footnote should be presented in the concentration table describing what was done. The threshold of 10% may be increased in some specific studies, such as outpatient or target population trials where sampling occasions are limited, to a value determined by the pharmacokineticist.

The method used to handle BLQ data prior to the calculation of summary statistics should be presented in a footnote on the summary tables. If BLQ data have been imputed, the imputed value (eg, 0, LLOQ or LLOQ/2) should be indicated. If data have been ignored, if a censoring method has been used or if the actual numerical values were used, the approach should be indicated in a footnote.

In urine, only descriptive statistics on the amount excreted, fraction or cumulative amount excreted over time are usually computed; no descriptive statistics on concentration or volume are presented. When these amounts are not estimable they should be considered as missing.

In specific situations, it may not be possible to calculate PK parameters, either because some required input data are not available, or for there are justifiable calculation reasons. If the proportion of missing PK parameters is large (eg, larger than 1/3 of all data), the available data may not provide an unbiased representation of the parameters distribution in the entire population. Therefore, it is advisable not to report descriptive statistics in this context. Only the proportion of missing values should be reported and the specific reason for not reporting the statistics should be indicated.

7.3.5. Mean and median plots

Protocol times are used for generating the mean/median concentration-time data. When the actual sampling time differs significantly from the protocol time (e.g. when the deviation is greater than 10%), then the concentration should be excluded from mean and median plots.

Considering the inherently log-normal distribution of concentrations, plots of geometric mean concentration versus time may be generated in addition to or in replacement for the arithmetic mean plots. As geometric means cannot be calculated when there are zero values. Therefore, replacing values < LLOQ by zero is not recommended for the display of geometric mean plots.

Median plots are another robust alternative to mean plots in the presence of extreme, possibly influential observations. They do not assume any underlying parametric distribution for the data and can manage data with zero or BLQ concentration values.

Linear and log-linear displays are often produced side by side to clearly delineate the concentration-time profiles.

Error bars are usually added to the mean/median display in the linear-linear scale to characterize the data distribution in the population. In that case the standard deviation (SD) is often reported. Error bars may also be used in particular situations to characterize the precision of the mean, with either standard errors (SE) or confidence intervals (CI) reported. In general two-sided error bars are reported, unless the figure becomes too busy. In that case, one-sided bars may be considered. Both upper and lower bars may be shown in the same plots for different profiles in order to improve rendering of the graph. For instance, use a lower bar for groups having low concentrations and vice-versa.

Error bars SD in geometric mean plots are computed after back transformation from the log-scale of the mean +/- SD log-concentrations. In that case, the upper and lower bars are calculated according to the following formula:

- upper bar=gmean*exp(SDlogPK);
- lower bar=gmean/exp(SDlogPK), where gmean is the geometric mean and SDlogPK is the standard deviation of the log-concentrations.

The same approach applies to SE bars, by replacing SD by SE in the above formulas. For CI bars, calculate the CI for the log-concentrations in the usual way, then back transform the lower and upper bounds to present results in the original scale.

7.3.6. Formats for individual data and statistics

If possible, the actual values as provided from the bioanalytical laboratory should be displayed individual PK concentration listings. Derived PK parameters should be formatted to 3 significant figures in the individual data listings. Other formats or rounding presentations may be considered as deemed appropriate and defined in the SAP.

For statistical tables, the descriptive statistics are often rounded to one more digit than the individual values for the mean, and median, to one or two additional digits for the SD, and to the same number of digits for the minimum and maximum values. The CV% values are often reported as a percentage using one decimal place.

7.3.7. Symbols for units

Whenever possible, all units of measurement (uom) should be expressed according the set of symbols recommended for use in the international system of unit (SI) brochure. A non-exhaustive list is provided in Table 7-1. Units for PK parameters should be reported according to the CDISC controlled terminology for the *PK Parameter Units of Measure* variable in the PP and ADPP datasets.

Table 7-1 Recommended symbols for common units of measurements

Multiplying factor	Name	Symbol
$1000=10^3$	kilo	k
$100=10^2$	hecto	h
$10=10^1$	deca	da
$0.1=10^{-1}$	deci	d
$0.01=10^{-2}$	centi	c
$0.001=10^{-3}$	milli	m
10^{-6}	micro	µ (or u when Greek letters not supported)
10^{-9}	nano	n
10^{-12}	pico	p
Quantity	**Name**	**Symbol**
Time	day	d
	hour	h
	minute	min
	second	s
Mass	kilogram	kg
	gram	g
	milligram	mg
	microgram	µg (or ug when Greek letters not supported)
	nanogram	ng
	picogram	pg
Volume	litre	L
	decilitre	dL
	centilitre	cL
	millilitre	mL
Amount of substance	mole	mol
	millimole	mmol

8. Example SAP Language

8.1. Data to be analysed

All subjects who received treatment, with evaluable PK parameter data and no major protocol deviations with an impact on PK data will be included in the PK analysis set.

8.2. Pharmacokinetic methods

All subjects of the PK analysis set will be included in the pharmacokinetic data analysis.

Individual PK data for all randomized subjects will be listed.

Biofluid concentrations will be expressed in [uom]. All concentrations below the lower limit of quantification (LLOQ) or missing data will be labelled as such in the concentration data listings. Concentrations below the LLOQ will be treated as [zero or LLOQ or LLOQ/2 or missing or left-censored values] in summary statistics for concentration data. PK concentration profiles will be summarized by treatment and over time in tabular and graphical formats. Arithmetic [and/or geometric] [mean/median] +/-SD concentration-time plots will be produced.

The following pharmacokinetic parameters will be determined using non-compartmental methods, according to the standard rules defined [company SOP and/or Section 6.2 above]:

- Primary PK endpoints: AUC_{inf}, AUC_{last} for single dose studies, $AUC\tau$ for multiple dose studies, C_{max}.
- Secondary PK endpoints: t_{max}, t_{lag}, t½, AUMC, CL/F, V_z/F.

Descriptive statistics of pharmacokinetic parameters and concentrations will include mean, SD, CV%, minimum, median and maximum. When a geometric mean is presented it will be labelled as such. Since t_{max} and t_{lag} are generally evaluated by a nonparametric method, median, minimum and maximum values will be given for these parameters[, but mean, SD, and geometric mean may also be presented].

9. References

AGAH working group pharmacokinetics. Collection of terms, symbols, equations, and explanations of common pharmacokinetic and pharmacodynamic parameters and some statistical functions. 2004.

Rosario LA, Kropp TJ, Wilson SE, and Cooper CK. Join FDA/PhUSE working groups to help harness the power of computational science. Drug Information Journal 46 (5) 523-524, 2012.

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